

World Journal of *Rheumatology*

World J Rheumatol 2015 March 12; 5(1): 1-49





Editorial Board

2011-2015

The *World Journal of Rheumatology* Editorial Board consists of 191 members, representing a team of worldwide experts in rheumatology. They are from 38 countries, including Argentina (2), Australia (4), Belgium (3), Brazil (3), Canada (2), Chile (1), China (16), Egypt (1), Finland (2), France (9), Germany (5), Greece (6), Hungary (2), India (3), Iran (2), Israel (6), Italy (11), Japan (2), Kuwait (1), Mexico (4), Morocco (2), Netherlands (3), Peru (1), Poland (1), Portugal (2), Qatar (1), Saudi Arabia (2), Slovakia (1), South Korea (4), Spain (7), Sweden (2), Switzerland (2), Thailand (1), Tunisia (1), Turkey (14), United Arab Emirates (1), United Kingdom (13), and United States (48).

EDITOR-IN-CHIEF

Jörg HW Distler, *Erlangen*

GUEST EDITORIAL BOARD MEMBERS

Yih-Hsin Chang, *Taichung*
Jing-Long Huang, *Taoyuan*
Pi-Chang Lee, *Taipei*
Chin-San Liu, *Changhua*
Ko-Hsiu Lu, *Taichung*
Fuu-Jen Tsai, *Taichung*
Chih-Shung Wong, *Taipei*
Jeng-Hsien Yen, *Kaohsiung*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Javier Alberto Cavallasca, *Santa Fe*
Enrique Roberto Soriano, *Buenos Aires*



Australia

Chang-Hai Ding, *Melbourne*
Davinder Singh-Grewal, *Sydney*
Gethin Thomas, *Brisbane*
Yin Xiao, *Brisbane*



Belgium

Olivier Bruyère, *Liège*
Nijs Jo, *Brussels*
Jean-Yves Reginster, *Liège*



Brazil

Simone Appenzeller, *Cidade Universitaria*
Mittermayer Santiago, *Nazaré Salvador*
Samuel K Shinjo, *São paulo*



Canada

Hong-Yu Luo, *Montreal*
Guang-Ju Zhai, *St John's*



Chile

Iván Palomo, *Maule*



China

Jun-Min Chen, *Fuzhou*
Sheng-Ming Dai, *Shanghai*
Ai-Ping Lu, *Beijing*
Chi Chiu Mok, *Hong Kong*
Ling Qin, *Hong Kong*
Han-Shi Xu, *Guangzhou*
Qing-Yu Zeng, *Shantou*
Peng Zhang, *Shenzhen*



Egypt

Yasser Emad, *Cairo*



Finland

Yrjö T Konttinen, *Helsinki*

Rahman Shiri, *Helsinki*



France

Didier Attaix, *Theix*
Francis Berenbaum, *Paris*
Michel Jacques de Bandt, *Aulnay sous Bois*
Pascal Laugier, *Paris*
Pierre Miossec, *Lyon*
M Djavad Mossalayi, *Bordeaux*
Luc Mouthon, *Paris*
Aleth Perdriger, *Rennes*
Alain Saraux, *Brest*



Germany

Magali Cucchiari, *Homburg*
Thomas Jax, *Neuss*
Friedrich Paul Paulsen, *Erlangen*
Med H H Peter, *Freiburg*



Greece

Andrew P Andonopoulos, *Rion*
Dimitrios Daoussis, *Patras*
Kosmas I Paraskevas, *Athens*
Grigorios Sakellariou, *Thessaloniki*
Lazaros I Sakkas, *Larissa*
Michael Voulgarelis, *Athens*



Hungary

Laszlo Czirkak, *Pecs*
András Komócsi, *Pecs*

**India**

Vikas Agarwal, *Lucknow*
Srikantiah Chandrashekar, *Bangalore*
Rajesh Vijayvergiya, *Chandigarh*

**Iran**

Nima Rezaei, *Tehran*
Zahra Rezaeiyazdi, *Mashhad*

**Israel**

Boaz Amichai, *Ramat Gan*
George S Habib, *Nazareth Illit*
Leonid Kalichman, *Beer Sheva*
Igal Leibovitch, *Tel-Aviv*
Ami Schattner, *Rehovot*
Elias Toubi, *Haifa*

**Italy**

Silvano Adami, *Verona*
Giuseppe Barbaro, *Rome*
Mauro Cellini, *Bologna*
Nicola Giordano, *Siena*
Estrella Garcia Gonzalez, *Siena*
Giovanni La Montagna, *Napoli*
Claudio Lunardi, *Verona*
Francesco Oliva, *Rome*
Donato Rigante, *Rome*
Dario Roccatello, *Turin*
Maurizio Turiel, *Milano*

**Japan**

Yoshiya Tanaka, *Kitakyushu*
Takashi Usui, *Kyoto*

**Kuwait**

Adel M A Alawadhi, *Kuwait*

**Mexico**

Carlos Abud-Mendoza, *San Luis Potosi*
Monica Vazquez-Del Mercado, *Guadalajara*
José F Muñoz-Valle, *Zapopan*
José Alvarez Nemegeyi, *Mérida*

**Morocco**

Zoubida Tazi Mezalek, *Rabat*
Faissal Tarrass, *Larache*

**Netherlands**

Esmeralda Blaney Davidson, *Nijmegen*
Timothy Ruben Radstake, *Nijmegen*

Nico M Wulffraat, *Utrecht*

**Peru**

Claudia Selene Mora-Trujillo, *Lima*

**Poland**

Przemyslaw Kotyla, *Katowice*

**Portugal**

Elizabeth Benito-Garcia, *Oeiras*
Alexandrina Ferreira Mendes, *Coimbra*

**Qatar**

Mohammed Hammoudeh, *Doha*

**Saudi Arabia**

Almoallim Hani Mohammad, *Jeddah*
Mohammed Tikly, *Johannesburg*

**Slovakia**

Ivica Lazúrová, *Košice*

**South Korea**

Dae-Hyun Hahm, *Seoul*
Young Mo Kang, *Daegu*
Myeong Soo Lee, *Daejeon*
Chang-Hee Suh, *Suwon*

**Spain**

Pedro Carpintero Benítez, *Cordoba*
Francisco J Blanco, *Coruña*
Vicente Giner Galvañ, *Alcoy*
Segundo Gonzalez, *Oviedo*
Narcis Gusi, *Caceres*
Luis Martinez-Lostao, *Zaragoza*
Gusi Narcis, *Caceres*

**Sweden**

Aladdin Mohammad, *Lund*
Ronald van Vollenhoven, *Stockholm*

**Switzerland**

Daniel Aeberli, *Bern*
Hossein Hemmatazad, *Zurich*

**Thailand**

Prachya Kongtawelert, *Chiang Mai*

**Tunisia**

Ghazi Chabchoub, *Sfax*

**Turkey**

Aynur Akay, *İzmir*
Deniz Evcik, *Ankara*
Sibel Eyigor, *Izmir*
Ozgur Kasapcopur, *Istanbul*
Suleyman Serdar Koca, *Elazig*
Ugur Musabak, *Ankara*
Demet Oflluoglu, *Istanbul*
Salih Ozgocmen, *Kayseri*
Cagatay Ozturk, *Istanbul*
Mehmet Akif Ozturk, *Ankara*
Ismail Sari, *Izmir*
Mehmet Soy, *Bolu*
Yavuz Yakut, *Ankara*
Serap Yalin, *Mersin*

**United Arab Emirates**

Ashok Kumar, *Dubai*

**United Kingdom**

Ade O Adebajo, *Sheffield*
Khalid Binyamin, *Mersyside*
Dimitrios P Bogdanos, *London*
David D'Cruz, *London*
Magdalena Dziadzio, *London*
Edzard Ernst, *Exeter*
Elena A Jones, *Leeds*
Joseph G McVeigh, *Belfast*
Sanjay Mehta, *London*
Jonathan Rees, *London*
Anita Williams, *Salford*
Hazem M Youssef, *Aberdeen*
Wei-Ya Zhang, *Nottingham*

**United States**

Cynthia Aranow, *Manhasset*
Joseph R Berger, *Lexington*
Vance Berger, *Rockville*
Daniel Bikle, *San Francisco*
Marc R Blackman, *Washington*
Galina S Bogatkevich, *Charleston*
Charles R Brown, *Columbia*
Leigh F Callahan, *Chapel Hill*
Hamid Chalian, *Chicago*
Majid Chalian, *Baltimore*
Sean Patrick Curtis, *Rahway*
Barbara A Eberhard, *New Hyde Park*
Luis R Espinoza, *New Orleans*
Shu -Man Fu, *Charlottesville*
Daniel E Furst, *Los Angeles*
Reda Ebeid Girgis, *Baltimore*
Alexei A Grom, *Cincinnati*
Simon Helfgott, *Boston*
Howard J Hillstrom, *New York*
Gary S Hoffman, *Cleveland*
Seung Jae Hong, *Chicago*

Meenakshi Jolly, *Chicago*
M Firoze Khan, *Galveston*
Irving Kushner, *Shaker Heights*
Antonio La Cava, *Los Angeles*
Yi Li, *Gainesville*
Chuan-Ju Liu, *New York*
Charles J Malemud, *Cleveland*
Mahnaz Momeni, *Washington*
Swapan K Nath, *Oklahoma*

Ewa Olech, *Oklahoma*
Alicia Rodríguez Pla, *Dallas*
Chaim Putterman, *Bronx*
Robert James Quinet, *New Orleans*
Allison B Reiss, *Mineola*
Lisa Georgianne Rider, *Bethesda*
Bruce M Rothschild, *Lawrence*
Hee-Jeong Im Sampen, *Chicago*
Naomi Schlesinger, *New Brunswick*

H Ralph Schumacher, *Philadelphia*
Jasvinder A Singh, *Birmingham*
Jianxun (Jim) Song, *Hershey*
Yu-Bo Sun, *Charlotte*
Thomas H Taylor, *Norwich*
George C Tsokos, *Boston*
Yu-Cheng Yao, *Los Angeles*
Ping Zhang, *Indianapolis*
Xiao-Dong Zhou, *Houston*

**REVIEW**

- 1 Interstitial lung disease in rheumatoid arthritis: Current concepts in pathogenesis, diagnosis and therapeutics

Olivas-Flores EM, Bonilla-Lara D, Gamez-Nava JI, Rocha-Muñoz AD, Gonzalez-Lopez L

- 23 Osteoporosis in rheumatic diseases

Gao LX, Jin HT, Xue XM, Wang J, Liu DG

MINIREVIEWS

- 36 Classification, diagnosis and treatment of ANCA-associated vasculitis

Moiseev SV, Novikov PI

- 45 Orofacial pain and fibromyalgia pain: Being aware of comorbid conditions

Alpaslan C

Contents

World Journal of Rheumatology
Volume 5 Number 1 March 12, 2015

ABOUT COVER

Editorial Board Member of *World Journal of Rheumatology*, Faissal Tarrass, MD, Department of Hemodialysis, Hospital Princess Lala Meryem, 92000 Larache, Morocco

AIM AND SCOPE

World Journal of Rheumatology (*World J Rheumatol*, *WJR*, online ISSN 2220-3214, DOI: 10.5499) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJR covers topics concerning osteoarthritis, metabolic bone disease, connective tissue diseases, antiphospholipid antibody-associated diseases, spondyloarthropathies, acute inflammatory arthritis, fibromyalgia, polymyalgia rheumatica, vasculitis syndromes, periarticular rheumatic disease, pediatric rheumatic disease, miscellaneous rheumatic diseases, and rheumatology-related therapy, pain management, rehabilitation.

We encourage authors to submit their manuscripts to *WJR*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ ABSTRACTING

World Journal of Rheumatology is now indexed in Digital Object Identifier.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Yue-Li Tian*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL

World Journal of Rheumatology

ISSN

ISSN 2220-3214 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Four-monthly

EDITOR-IN-CHIEF

Jörg HW Distler, MD, Department of Internal Medicine 3, University of Erlangen-Nuremberg, Universitätsstr. 29, 91054 Erlangen, Germany

EDITORIAL OFFICE

Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Rheumatology

Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLICATION DATE

March 12, 2015

COPYRIGHT

© 2015 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/2220-3214/g_info_20100722180909.htm

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Interstitial lung disease in rheumatoid arthritis: Current concepts in pathogenesis, diagnosis and therapeutics

Eva M Olivas-Flores, David Bonilla-Lara, Jorge I Gamez-Nava, Alberto D Rocha-Muñoz, Laura Gonzalez-Lopez

Eva M Olivas-Flores, Hospital General Regional 180 Instituto Mexicano del Seguro Social (IMSS), Tlajomulco 45640, Mexico
 David Bonilla-Lara, Jorge I Gamez-Nava, Alberto D Rocha-Muñoz, Laura Gonzalez-Lopez, Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara, Guadalajara, Jalisco 44280, Mexico

Jorge I Gamez-Nava, Hospital de Especialidades Centro Medico Nacional de Occidente, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jalisco 44340, Mexico

Laura Gonzalez-Lopez, Hospital General Regional 110 Departamento de Medicina Interna-Reumatología, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jalisco 48520, Mexico

Author contributions: All the authors equally contributed to this work.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Laura Gonzalez-Lopez, MD, MSc, PhD, Hospital General Regional 110 Departamento de Medicina Interna-Reumatología, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jalisco 48520, Mexico. dr.lauragonzalez@prodigy.net.mx
 Telephone: +52-33-38541369

Received: July 21, 2014

Peer-review started: July 22, 2014

First decision: July 22, 2014

Revised: September 27, 2014

Accepted: December 10, 2014

Article in press: December 10, 2014

Published online: March 12, 2015

articular complication and causes symptoms that lead to a deterioration in the quality of life, high utilization of health resources, and an increased risk of earlier mortality. Early in the course of RA-ILD, symptoms are highly variable, making the diagnosis difficult. Therefore, a rational diagnostic strategy that combines an adequate clinical assessment with the appropriate use of clinical tests, including pulmonary function tests and high-resolution computed tomography, should be used. In special cases, lung biopsy or bronchioalveolar lavage should be performed to achieve an early diagnosis. Several distinct histopathological subtypes of RA-ILD are currently recognized. These subtypes also have different clinical presentations, which vary in therapeutic response and prognosis. This article reviews current evidence about the epidemiology of RA-ILD and discusses the varying prevalence rates observed in different studies. Additionally, aspects of RA-ILD pathogenesis, including the role of cytokines and other molecules such as autoantibodies, as well as the evidence linking several drugs used to treat RA with lung damage will be discussed. Some aspects of the clinical characteristics of RA-ILD are noted, and diagnostic strategies are reviewed. Finally, this article analyzes current treatments for RA-ILD, including immunosuppressive therapies and biologic agents, as well as other therapeutic modalities. The prognosis of this severe complication of RA is discussed. Additionally, this paper examines updated evidence from studies identifying an association between drugs used for the treatment of RA and the development of ILD.

Key words: Rheumatoid arthritis; Interstitial lung disease; Pathogenesis; Diagnosis; Therapeutic

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Abstract

Rheumatoid arthritis (RA) is the most common chronic autoimmune inflammatory joint disease. RA-associated interstitial lung disease (RA-ILD) is a major extra-

Core tip: This review analyzes current evidence regarding the epidemiology, pathogenesis, diagnosis and treatment of interstitial lung disease associated with

rheumatoid arthritis (RA-ILD). Data regarding differences in the prevalence of RA-ILD in different populations are presented. Updates regarding the pathogenesis of RA-ILD, including genetics, environmental factors, cytokines and autoantibodies, are presented. The paper also reviews the different tests used to diagnose RA-ILD, describes RA-ILD treatment, and discusses studies that were designed to identify a therapeutic response to immunosuppressive drugs or biological agents.

Olivas-Flores EM, Bonilla-Lara D, Gamez-Nava JI, Rocha-Muñoz AD, Gonzalez-Lopez L. Interstitial lung disease in rheumatoid arthritis: Current concepts in pathogenesis, diagnosis and therapeutics. *World J Rheumatol* 2015; 5(1): 1-22 Available from: URL: <http://www.wjnet.com/2220-3214/full/v5/i1/1.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i1.1>

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that involves synovial joints and extra-articular organs. Worldwide, the prevalence of RA has small variations. In Mexico, Peláez-Ballestas *et al*^[1] reported a prevalence of RA of 1.6% (95%CI: 1.4-1.8). Extra-articular manifestations in RA (ExRA) are a frequent complication, affecting approximately 40% of patients with RA^[2]. Pulmonary involvement is an important ExRA manifestation, as it is associated with a decrease in survival rates^[3]. Pulmonary involvement can present in a number of ways, such as pleural disease, pulmonary nodules, Caplan's syndrome, bronchiectasis, bronchiolitis, and airway or interstitial disease^[4]. Of these presentations, interstitial lung disease (ILD) is the most relevant pulmonary complication in terms of morbidity, impairment in quality of life (QoL), and mortality. ILD heterogeneously affects the lung parenchyma; its clinical spectrum ranges from an incidental subclinical finding of diffuse inflammation to a rapidly progressive, life-threatening, end-stage pulmonary fibrosis (PF). Therefore, ILD is a complex extra-articular complication that is classified according to specific clinical, serological, radiological, and histopathological features^[5].

EPIDEMIOLOGY

The prevalence of ILD in RA varies widely and is affected by factors such as country, race, clinical setting, study design, and intensity of assessment. In their study, Bongartz *et al*^[6] reported a lifetime risk for the development of ILD of 7.7%. Detection of RA-associated ILD (RA-ILD) in the disease's early stages can be difficult and requires a high level of diagnostic suspicion, as well as a systematic strategy for patient evaluation. One diagnostic problem is that in its early stages, RA-ILD can be asymptomatic or have non-specific symptoms, rendering suspicion of this entity

Table 1 Prevalence of rheumatoid arthritis-interstitial lung disease

Ref.	Number of patients	Study type	ILD (%)
Perez-Dorame <i>et al</i> ^[111]	34	Cross-sectional	34
Giles <i>et al</i> ^[154]	177	Cross-sectional	33
Yin <i>et al</i> ^[29]	71	Retrospective	24.9
Chen <i>et al</i> ^[10]	103	Cross-sectional	61
Solomon <i>et al</i> ^[155]	48	Retrospective	31
Richman <i>et al</i> ^[156]	274	Cross-sectional	3.6
Zou <i>et al</i> ^[157]	110	Cross-sectional	42.7
Mohd <i>et al</i> ^[158]	63	Cross-sectional	44
Al-Ghamdi <i>et al</i> ^[159]	74	Retrospective	10
Teh <i>et al</i> ^[160]	154	Cross-sectional	6.5
Bharadwaj <i>et al</i> ^[161]	140	Cross-sectional	9.29
Zrour <i>et al</i> ^[162]	75	Cross-sectional	49.3

ILD: Interstitial lung disease.

unlikely. Therefore, in these patients, a high level of diagnostic suspicion and a systematic assessment for this complication are mandatory, especially in patients with risk factors for RA-ILD. Some authors have reported that plain X-rays identified RA-ILD in < 5%^[7] of patients, whereas our group reported a prevalence at routine rheumatology consultation of only 2.7%^[8]. This prevalence has increased by 20%-30% with systematic evaluation using high-resolution computed tomography (HRCT)^[9]. On the other hand, when a combination of tests is employed, an increase is observed in the frequency of RA-ILD diagnosis. Chen *et al*^[10] described a 61% increase in the diagnosis of ILD using a combination of HRCT and pulmonary function tests (PFT). Table 1 illustrates the variability in the prevalence of RA-ILD, according to recent studies.

Although ILD prevalence has been evaluated in a series of studies, only a few studies have identified the incidence of ILD in patients with RA. Cumulative incidence rates for ILD in RA have been observed to be 3.5% over 10 years of follow-up, increasing to 6.3% at 20 years and to 7.7% at 30 years. After adjusting for the risk of death, the lifetime risk of developing RA-ILD is approximately 10%. In a population-based study, the risk of developing ILD among patients with RA is significantly higher than in patients without RA (HR = 8.96); an elevated risk of ILD in RA patients remained after adjusting for age, gender, and smoking^[6]. Koduri *et al*^[11], in a cohort study, reported that the annual incidence rate for the development of RA-ILD was 4.1/1000 person-years (95%CI: 3.0-5.4), with a cumulative ILD incidence at 15 years of 62.9/1000 individuals (95%CI: 43.0-91.7).

PATHOGENESIS

RA-ILD is considered a multifactorial complication, attributable to a number of factors. Several hypotheses have been formulated to explain its development. To date, the factors most consistently involved in the development of RA-ILD are shown in Table 2 and those

Table 2 Risk factors for interstitial lung disease in rheumatoid arthritis

Factors	
Environmental	Cigarette smoking Occupational exposure (silica)
Demographic	Male sex Age (≥ 65 yr)
Genetic	HLA-DRB1 alleles
Clinical	RA duration Anti-CCP (high titers) RF (high titers)
Medications	Methotrexate Leflunomide Sulfasalazine TNF- α inhibitors

RF: Rheumatoid factor; HLA-DRB1: Human leukocyte antigen-DRB-1; Anti-CCP: Anti-cyclic citrullinated peptide; Anti-TNF: Anti-tumor necrosis factor; RA: Rheumatoid arthritis.

can be classified as follows: (1) environmental; (2) genetic; (3) autoimmune (cytokines, autoantibodies); and (4) drug-related^[12].

Environmental factors

Epidemiological factors associated with ILD in RA include aging, smoking, and RA duration. Mori *et al.*^[12], in a prospective cohort study, observed a 4.58-fold increase in the risk for development of ILD in patients aged ≥ 65 years ($P = 0.003$); additionally, the risk of ILD was higher in males than in females (50% vs 23.2%, respectively; OR = 3.31, $P = 0.004$). A relationship between smoking and an increase in the prevalence of ILD has been identified in several studies. Miyake *et al.*^[13] observed, in a case-control study, that smoking increases the risk for ILD 2.21-fold. Saag *et al.*^[14] found a relationship between smoking and ILD, reporting an approximately 3.8-fold increase in the risk for ILD among patients with a smoking history of ≥ 25 pack-years. Baumgartner *et al.*^[15] reported, in a case-control study, that patients with a history of ever smoking or former smoking have 1.6- and 1.9-fold increases in the risk of ILD, respectively. Occupational exposure, such as silica inhalation, contributes to the development of chronic lung inflammation-related ILD^[16].

Genetic factors

Coultas *et al.*^[17] reported that the prevalence of ILD is approximately 20% higher in males than in females. Aubart *et al.*^[18] observed that male gender increases the risk for ILD in RA by 3.29-fold ($P = 0.0013$).

Several alleles are associated with an increased susceptibility for RA-ILD; susceptibility to RA-ILD can be triggered by environmental factors, leading to the development of ILD. Mori *et al.*^[12], in a prospective cohort study, observed that patients with RA who were carriers of the HLA-DRB1*1501 and *1502 alleles had an increased risk for ILD. Michalski *et al.*^[19] observed that α_1 -antitrypsin-variant phenotypes, particularly non-M₁M₁ α_1 -antitrypsin, are significantly associated

with PF in patients with RA.

Charles *et al.*^[20] found an association between antigen HLA-B40 and pulmonary involvement of RA. The authors observed an enhanced risk of approximately 40.54-fold in pulmonary involvement, compared with other ExRA manifestations. Sugiyama *et al.*^[21] reported an increase in the frequency of HLA-B54 (63.2%) and HLA-DR4 (60%) polymorphisms in patients with ILD-RA compared with controls (11.4% and 37.9%, respectively).

Cytokines and autoantibodies related to ILD in RA

Several cytokines have been linked to ILD. Chaudhary *et al.*^[22] observed, in an experimental model of PF, the pro-fibrotic effects of platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF)- β . The authors observed that targeting these molecules leads to an attenuation of lung fibrosis, suggesting that these cytokines may constitute a possible target for novel therapeutic approaches. Gochuico *et al.*^[23] quantified concentrations of TGF- β_1 , TGF- β_2 , PDGF-AA, PDGF-AB, PDGF-BB, and interferon gamma (IFN)- γ in fluids obtained by bronchoalveolar lavage (BAL) from 3 different group of patients: (1) RA without lung involvement; (2) RA with pulmonary fibrosis (RAPF); and (3) RA with preclinical ILD (RA preclinical-ILD). They observed significantly higher concentrations of PDGF-AB and PDGF-BB in patients with RA-ILD compared with RA patients without PF, suggesting a pro-fibrotic effect of the alveolar microenvironment in RA preclinical-ILD. Interestingly, when the RA-ILD group was sub-categorized into RA with progressive preclinical ILD and RA with stable preclinical ILD, the authors observed significantly higher concentrations of TGF- β_1 and IFN- γ in patients with RA with progressive preclinical ILD vs patients with RA with stable lung disease ($P = 0.038$ and $P = 0.044$, respectively). TGF- β is one of the strongest profibrotic cytokines; it triggers lung fibrosis, interacting with connective tissue growth factor (CTGF) to increase the fibrotic process. Ponticos *et al.*^[24] demonstrated, in an experimental model, that CTGF exerts a direct profibrotic effect on the development of PF through transcriptional activation of collagen gene type 1 α_2 (Col1 α_2). Pro-inflammatory cells, such as macrophages and mononuclear cells, also contribute to the activation of fibrosis by means of interleukin (IL)-4 and IL-13, inducing TGF- β production. Jakubczik *et al.*^[25] observed, in an experimental model of PF, that IL-4 and IL-13 expression was increased in macrophages and mononuclear cells in regions of active fibrosis. Monocyte chemotactic protein (MCP)-1 is also a profibrotic cytokine that exerts its action through chemokine receptor type 2 (CCR2). Moore *et al.*^[26] observed increased levels of MCP-1 in the CCR2^{-/-} model compared with the wild-type ($P = 0.004$) after induction of PF in the wild-type and the CCR2^{-/-} experimental models. Furthermore, the authors reported that a lack of CCR2 is a protective

factor against PF. Wilson *et al.*^[27] described enhanced levels of IL-17 and IL-1 β in the BALF of patients with PF, suggesting that these cytokines play a profibrotic role in the lung fibrosis pathway. On the other hand, IL-10, a well-recognized anti-inflammatory cytokine with immunosuppressive effects, has also been related to the induction of PF. Sun *et al.*^[28] observed, in an experimental model, that overexpression of IL-10 in lung tissue promoted collagen production and induced recruitment of fibrocytes into the lung, leading to the development of PF in mice.

Antibodies to cyclic citrullinated peptides (anti-CCP) and rheumatoid factor (RF) have also been associated with ILD. Yin *et al.*^[29], in a retrospective study, observed that serum levels of anti-CCP2 and RF were significantly enhanced in RA-ILD patients compared with RA patients ($P < 0.001$ and $P = 0.02$, respectively). Kelly *et al.*^[30] identified positive titers for anti-CCP and RF in 94% and 89%, respectively, of RA-ILD patients compared with RA patients (55%, $P = 0.006$; 58%, $P = 0.01$). Furthermore, they reported that anti-CCP and RF act as predictors of ILD in patients with RA ($P < 0.003$ and $P < 0.008$, respectively). Citrullinated proteins are not only restricted to synovial tissue; they have also been detected at extra-articular sites in patients with RA. Bongartz *et al.*^[31] observed that citrullination occurs inside mononuclear cells in lung tissue in open-lung biopsy specimens from patients with RA-associated interstitial pneumonia. The authors also reported that despite the high specificity of anti-CCP for RA, citrullination was also found in lung tissue from patients with idiopathic interstitial pneumonia. It remains unclear whether distinct citrullinated RA-specific proteins play a key role in the pathophysiological process in RA-ILD.

Pharmacological agents as risk factors for RA-ILD:

Presently, there is controversy regarding the actual effects of some medications on the development of ILD in patients with RA. Drug-induced ILD can develop within days of treatment initiation or many years after treatment. The major drugs that have been strongly associated with the induction of ILD are methotrexate (MTX), leflunomide (LFN), sulfasalazine (SFZ), and tumor necrosis factor- α (TNF- α) inhibitors, such as etanercept, infliximab, and adalimumab. However, other drugs, including d-penicillamine and gold compounds, are also associated with lung damage. There have been recent case reports of the induction or exacerbation of ILD by the newer anti-TNF agents, as well as other biologic agents that act by different mechanisms. This part of the review attempts to highlight the evidence linking these drugs to lung damage, primarily ILD.

Methotrexate and ILD

MTX is considered by the European League Against Rheumatism to be part of the first-line treatment of RA^[32], and several studies have reported an

association between MTX and the development of RA-ILD. Conway *et al.* reported, in a meta-analysis of randomized controlled trials from 1990-2013 that included 22 studies, that MTX treatment is a risk factor for the development of pneumonitis (RR = 7.81; 95%CI: 1.76-34.72)^[33]. Bongartz *et al.*^[6] also reported that treatment with MTX confers a 2.3-fold risk for ILD development. However, Sathi *et al.*^[34] reported, in a prospective study of 223 patients, that the incidence of MTX-induced pneumonitis after 2 years of follow-up was only ~1%, suggesting that pneumonitis is an uncommon complication. Assessing the actual incidence of MTX-induced ILD is difficult because ILD can be observed in patients with RA independently of MTX treatment; furthermore, MTX is frequently used with other drugs that can also be associated with ILD. Therefore, the most useful data regarding MTX-induced ILD come from studies that evaluated this drug as monotherapy. In a systematic review, Salliot *et al.*^[35] examined the long-term safety of MTX as monotherapy in 21 prospective studies and reported that only 15 of 3463 patients developed pneumonitis, yielding a frequency of 0.43%. Criteria have been proposed for the diagnosis of MTX-induced pneumonitis. In 1987, Searles *et al.*^[36] proposed the following 9 criteria for the diagnosis of MTX-induced pneumonitis, which include: (1) acute onset of dyspnea; (2) fever $> 38^{\circ}\text{C}$; (3) tachypnea; (4) radiological evidence of pulmonary interstitial or alveolar infiltrates; (5) white blood cell count $< 15000/\text{cu mm}$, with or without eosinophilia; (6) negative blood and sputum cultures (mandatory); (7) the finding of a restrictive pattern and decreased diffusing capacity of the lung for carbon monoxide (DLCO) on PFT; (8) $\text{PO}_2 < 60$ mmHg on room air; and (9) histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection. MTX-induced pneumonitis is considered definite if ≥ 6 criteria are present, probable if 5 of 9 criteria are present, and possible if 4 of 9 criteria are present. Subsequently, new guidelines have been developed that include 3 major criteria, which are: (1) hypersensitivity pneumonitis by histopathology without evidence of a pathogenic organism; (2) radiologic evidence of pulmonary interstitial or alveolar infiltrates; and (3) negative blood and initial sputum cultures. The guidelines also include 5 minor criteria, which are (1) shortness of breath for less than 8 wk; (2) nonproductive cough; (3) oxygen saturation $\leq 90\%$ on room air at the initial evaluation; (4) DLCO $\leq 70\%$ of predicted for age; and (5) leukocyte count ≤ 15000 cells/cu mm³. The diagnosis is considered certain when a patient meets the first major criterion and at least 3 of the minor criteria, or when a patient meets major criteria 2 and 3 as well as 3 minor criteria. In this system, the diagnosis is considered probable when a patient meets only the major criteria 2 and 3 and 2 of the minor criteria^[37]. Sidhu *et al.*^[4] reported that chest X-ray findings included diffuse, bilateral, basal interstitial, or

alveolar infiltrates. The authors also observed that the most frequent radiographic pattern shown on HRCT of RA-ILD is the non-specific interstitial pneumonia (NSIP) pattern. MTX-associated pneumonitis is described as a type-IV delayed-hypersensitivity pneumonitis dominated by lymphocytic proliferation and alveolitis^[38]; it is associated with a specific cellular immune response involving the release of cytokines^[39]. Chikura *et al.*^[40], in a retrospective study, observed that the following two forms of ILD have been attributed to MTX. Type 1 MTX-related ILD appears shortly after treatment initiation (< 6 mo) and is characterized by neutrophil infiltration, lung fibrosis, lower time of MTX to low-dose exposure, and a high mortality rate. Type 2 MTX-related ILD occurs later in MTX treatment (> 6 mo) and is associated with lymphocyte-dominated infiltrates, low levels of lung fibrosis, a higher MTX dose exposure, and a low mortality rate. Type II pneumocyte hyperplasia and fibroblast proliferation have been reported as being suggestive of, but not pathognomonic for, MTX-induced lung toxicity^[37]. A combination of a recent history of MTX initiation, clinical characteristics such as dyspnea, cough and fever, plus the findings of patchy ground-glass opacities on HRCT, increased lymphocytes and eosinophils in the BAL, and (if available) a lung biopsy showing interstitial pneumonitis with non-necrotizing granulomas and eosinophils, supports the diagnosis of MTX-induced ILD. To date, the optimal cost-effective strategy for detecting ILD changes in patients who are beginning MTX treatment has not been identified. Khadadah *et al.*^[41] have suggested that periodic monitoring with PFT in patients with RA starting MTX therapy could be a rational strategy. Nevertheless, the findings of other authors do not support these recommendations. For example, Dawson *et al.*^[42] did not observe differences in PFT or HRCT findings between patients with RA who had been treated with MTX versus other drugs, concluding that serial PFT in patients receiving MTX has no significant advantages. Therefore, there is presently no conclusive information about whether to perform PFT or HRCT in patients who are receiving MTX and do not have clinical symptoms or signs suggesting lung toxicity. However, the use of MTX in patients with pre-existing RA-ILD constitutes a significant risk factor for the development of pulmonary toxicity. Therefore, we recommend avoiding, if possible, the use of this drug in patients with a previous diagnosis of ILD. Other factors related to MTX-induced lung toxicity include elderly age, diabetes mellitus, and hypoalbuminemia, among others^[43]. Once MTX-induced ILD is suspected, the treatment must include the immediate suspension of MTX and corticosteroid treatment, with the corticosteroid dosage depending on the severity of the lung involvement and other relevant clinical characteristics. In severe cases, supplementary oxygen, antibiotics or assisted ventilation should be considered. Once the patient is stabilized, MTX must be avoided, and alternative agents that do not increase the risk of

developing subsequent episodes of ILD should be considered. Among these options are the antimalarials. The prognosis of MTX-induced lung toxicity is usually good for the majority of patients, although a mortality rate of 13% has been reported in a review of MTX-induced pneumonitis in patients with a variety of different diseases (approximately 50% of whom had RA)^[44].

LFN and lung damage

Establishing a clear association between LFN treatment and the development of ILD has been difficult, as LFN is frequently used after MTX failure; it can therefore be difficult to distinguish whether the development of ILD was secondary to LFN, MTX, or both drugs. Sawada *et al.*^[45] analyzed the results of a cohort of 5054 Japanese RA patients and observed the development of ILD in 1.2% of patients. Suissa *et al.*^[46] reported that LFN may enhance the risk of ILD by 1.9-fold. Chikura *et al.*^[47] described, in a systematic review, that LFN-induced interstitial pneumonia occurs within the first 20 wk of LFN treatment initiation. Additionally, the authors reported a 19% mortality rate in patients with LFN-associated ILD. The factors associated with LFN-induced ILD were also analyzed by Sawada *et al.*^[45] and included the use of LFN in patients with pre-existing ILD (OR = 8.17, 95%CI: 4.63-14.41, $P < 0.001$), the use of an LFN loading dose (OR = 3.97, 95%CI: 1.22-12.92, $P = 0.02$), cigarette smoking (OR = 3.12, 95%CI: 1.73-5.597, $P = 0.001$) and low body weight < 40 kg (OR = 2.91, 95%CI: 1.15-7.37, $P = 0.02$). Sato *et al.*^[48], in a retrospective study of patients with LFN-induced pulmonary injury, observed that an oxygen saturation level of < 90% is a marker for greater mortality in RA-ILD patients. The authors also found that serum C-reactive protein level were higher ($P = 0.03$) and that the albumin level decreased ($P = 0.03$) at the outset of lung injury in patients with fatal outcomes in comparison with patients who recovered. It is relevant to highlight that the main histopathological finding reported in this study in the two autopsied patients was diffuse alveolar damage (DAD), in contrast to the alveolitis with lymphocyte infiltration observed in patients who recovered. The mechanism of the development of ILD in patients exposed to LFN could be related to the effects of the active metabolite A771726, which induces the transition of lung epithelial cells to myofibroblasts^[49]. In addition to other established therapeutic strategies for ILD, such as corticosteroids and (if required) mechanical ventilation, some authors recommend the immediate suspension of LFN and the addition of cholestyramine as wash-out therapy, constituting a rational intervention for these patients^[50].

Sulfasalazine and lung damage

Numerous case reports have been published associating sulfasalazine (SSZ) with lung toxicity; a review of 50 cases^[51] reported that most cases occurred

in patients with ulcerative colitis, although some cases were reported in RA patients. These authors noted that the clinical characteristics of SSZ-induced lung toxicity include dyspnea of recent onset that is associated with lung infiltrates and, in more than half of cases, with peripheral eosinophilia and a variable spectrum of pathological findings; the most common pathologic findings were eosinophilic pneumonia and interstitial inflammation in some patients with lung fibrosis. To date, it is not conclusively known which drug component is primarily responsible for lung toxicity, although it is believed that the major culprit is sulfapyridine. Once SSZ lung toxicity is suspected, the drug should be withdrawn immediately. Stopping the drug is followed by the rapid improvement of symptoms and signs of lung toxicity in most cases, although some patients with SSZ-induced lung toxicity may die, mainly if the drug is not withdrawn. Although a number of patients with SSZ-induced lung toxicity have been managed with corticosteroids, evidence for the benefit of corticosteroids in this setting is not definitive, and further studies are required.

Azathioprine and lung damage

Lung toxicity associated with azathioprine (AZA) has been observed primarily in patients with kidney transplants and may result from both allergic and dose-dependent toxicities. To date, there is only limited, case report-based information suggesting that AZA may induce lung toxicity in patients with previous ILD. Ishida *et al.*^[52] reported the case of a male patient who developed interstitial pneumonia, was subsequently treated with AZA, and suffered worsening symptoms. The patient developed lung infiltrate and ground-glass opacities on lung HRCT after only 6 d of treatment with AZA. These pulmonary infiltrates resolved after the suspension of AZA treatment. As a small proportion of patients may die, physicians should be aware of this complication in patients who have initiated treatment with AZA and have a recent onset of cough, fever and dyspnea.

Other synthetic disease-modifying antirheumatic drugs and lung damage

Currently, gold salts and d-penicillamine are infrequently used to treat RA. Gold-induced lung damage is a challenging diagnosis in RA. Tomioka *et al.*^[53] performed a review of published information regarding the clinical features and prognosis of gold-induced pulmonary disease in RA, identifying 140 cases of patients treated with gold, 81% of whom had RA. These authors reported that patients with gold-induced pulmonary damage frequently have other side effects associated with toxicity to gold salts, such as skin rash (38%), peripheral eosinophilia (38%), proteinuria (22%) and liver dysfunction (15%). In this review, factors frequently associated with gold-induced pulmonary disease included female sex, fever, skin rash, absence of rheumatoid nodules, low titers of rheumatoid factor,

lymphocytosis in BAL, and alveolar opacities along the broncho-vascular bundles visualized on chest computed tomography. Patients generally improve after withdrawal of the gold salts and may require treatment with corticosteroids. Currently, d-penicillamine is rarely used. Chakravarty *et al.*^[54] reported that after 2 years of follow-up, 21% of their patients treated with d-penicillamine developed a restrictive pattern on PFT. Nevertheless, the incidence of severe pulmonary adverse reactions to d-penicillamine is relatively rare. Grove *et al.*^[55] evaluated common adverse reactions to synthetic disease-modifying antirheumatic drugs (DMARDs) in 2170 patients with RA, who were followed for a total of 9378 treatment-years. Of these, 582 patients were exposed to d-penicillamine during a total of 1889 monitored treatment years. Although this was an important series of patients treated with d-penicillamine, the authors were able to find only one patient who stopped d-penicillamine due to a severe pulmonary reaction.

Regarding synthetic DMARD-induced ILD, it is important to take into account the following points: (1) the age-adjusted incidence of MTX-induced pneumonitis is approximately 3.78 cases per 1000 patients treated with MTX^[56]; (2) factors associated with MTX-induced ILD include: male gender, impairment in functioning, and elevated ESR^[56]; (3) the initiation of MTX treatment, along with clinical manifestations including dyspnea, cough, fever, and patchy ground-glass opacities on HRCT may suggest the diagnosis of MTX-induced ILD; (4) if MTX-induced ILD is suspected, the drug must be immediately discontinued; (5) the use of LFN increases the risk of ILD, which usually occurs within the first 20 wk after beginning this therapy^[46,47]; (6) a relevant marker for mortality in LFN-induced ILD patients is a < 90% oxygen saturation level^[48]; (7) patients with LFN-induced ILD must immediately stop treatment with LFN, begin corticosteroids, undergo mechanical ventilation if required, and receive cholestyramine wash-out treatment^[50]; and (8) similar guidelines can be used to manage ILD induced by other synthetic DMARDs.

Biologic agents and lung damage

TNF- α inhibitors are commonly used for the treatment of RA and offer a good alternative in patients who have failed treatment with MTX or other synthetic DMARDs with high response rates. There are two major concerns with the use of anti-TNF agents and RA-ILD: (1) the possible association between the use of anti-TNF agents and the new onset of clinically significant ILD; and (2) the possibility of exacerbating preexisting ILD when an anti-TNF agent is used for controlling disease activity in RA (despite reports that treatment with anti-TNF agents may stabilize or improve ILD in some patients). The paradoxical effects of anti-TNF agents in ILD are interesting, and further studies are required to identify why some patients improve while others develop worsening disease. We will briefly review some of the evidence regarding ILD related to

the use of anti-TNF agents in RA.

Presently, there is increasing evidence suggesting that the use of TNF- α inhibitors is associated with the development of ILD. Ramos-Casals *et al.*^[57], in a case series of 233 patients treated with anti-TNF agents (71% of whom had RA), observed that 10% of patients developed ILD after initiation of anti-TNF therapy; the mean time for developing ILD after receiving anti-TNF drugs was 42 wk, and mortality was reported in 32% of patients with ILD.

There are a significant number of studies reporting the development of new cases of ILD or the worsening of pre-existing ILD following the use of anti-TNF agents, including infliximab^[58-60], etanercept^[61-64], and adalimumab^[65-68], as well as the newer anti-TNF agents such as golimumab^[69] and certolizumab pegol^[70-72].

The development of ILD with etanercept treatment has been described in approximately 0.6% of patients (77 cases from 13894 patients treated with etanercept)^[73]. For infliximab, one study^[74] reported an incidence of 0.5% for ILD (25 cases of ILD from 5000 patients treated). In another study, the incidence of ILD in patients receiving tocilizumab was 0.48%^[75]. However, for abatacept the incidence in one study has been reported to range from 0.1% (short-term) to 0.3% (long-term)^[76].

Perez-Alvarez *et al.*^[77] analyzed 122 cases of new onset or exacerbated ILD secondary to biologic agents. Of these, 58 cases were observed in patients receiving etanercept and 56 cases in those treated with infliximab. The majority of these patients had RA. ILD developed at a mean of 26 wk after initiation of the biologic agent. Fifty-two patients had detailed follow-up; 29% died, 70% of these during the first weeks after the initiation of biologic agents.

Several mechanisms may explain the development of ILD associated with anti-TNF agents. It is unclear whether TNF blockers can potentiate the pulmonary toxicity of MTX^[78]. However, some of these agents, such as infliximab, bind to TNF that is expressed on the surface of macrophages and CD4⁺ and T cells, resulting in cell lysis^[79]. It is thus conceivable that the local release of macrophage-derived proteolytic enzymes may contribute to MTX toxicity. Other potential mechanisms for the development or progression of ILD and lung fibrosis in some patients receiving anti-TNF agents may involve the down-regulation of TNF α (due to TNF blockade), which causes the up-regulation of anti-inflammatory cytokines including transforming growth factor β , leading to a profibrotic state^[80].

In the study by Perez-Alvarez^[77], patients with antecedents of ILD before being treated with biologic agents had a high mortality rate, which was associated with worsening ILD after the initiation of biologic therapy. Other factors associated with mortality were age > 65 years, later onset of ILD, and use of immunosuppressive drugs.

Ramos-Casals *et al.*^[81] analyzed 379 cases of autoimmune diseases secondary to anti-TNF agents.

Using data obtained from the BIOGEAS project (www.biogeas.org), a study with the aim of collecting data on the use of biological agents in patients with systemic autoimmune diseases, Ramos-Casals reported cases of ILD induced by biological agents. These authors described 34 patients who developed ILD after the initiation of anti-TNF agents, 30 of whom had RA. The most commonly used anti-TNF agents were infliximab in 20 cases (59%), etanercept in 11 cases (32%) and adalimumab in 3 cases (9%). Interestingly, although the majority of the patients had received MTX, 11/31 patients (35%) of these patients had no history of MTX use. The use of anti-TNF agents, particularly in the lung, has poor efficacy in controlling collagenosis-associated ILD and can lead to other complications, such as reactivation of mycobacterial and fungal infections, as well as to sarcoidosis and other ILD^[81].

Most recently, the rate of mortality has been evaluated in patients with RA who had ILD before beginning treatment with anti-TNF agents. The British Society for Rheumatology Biologics Register^[82] followed 299 patients with pre-existing RA-ILD who were treated with anti-TNF agents, as well as 68 patients who were treated with synthetic DMARDs. In this cohort, 70/299 patients with pre-existing ILD who were treated with anti-TNF agents died, with RA-ILD being the underlying cause of death in 15/70 (21%) patients. However, 14/68 patients treated with synthetic DMARDs died; in only one patient (7%) was the cause of death related to ILD. Although the proportion of deaths attributable to RA-ILD in this study was higher in patients receiving anti-TNF agents, the authors recognized the possibility of reporting bias that may have influenced the validity of their results.

Other biologic agents associated with ILD

To date, there has been one case report of a patient with RA who was treated with abatacept and developed worsening ILD^[83]. Weinblatt *et al.*^[76] analyzed the data from 8 clinical trials of abatacept in RA and observed a rate of 0.1% (2 cases of 3173 patients analyzed) for the development of ILD in the short-term period (\leq 12 mo). This rate increased to 0.3% (11 cases of 4149 abatacept-treated patients) in the pooled long-term period.

Some isolated cases of new ILD or exacerbations of pre-existing ILD have been associated with the use of tocilizumab (TCZ). Kawashiri *et al.*^[84] described an exacerbation of pre-existing ILD in a 68-year-man with RA after 10 mo of treatment with TCZ. This patient died despite treatment with pulsed-dose steroids and antibiotics. The main pharmacological agents related to ILD in RA patients are summarized in Table 3.

Some points to remember in ILD-associated biologic agents include the following: (1) the incidence of new-onset ILD with anti-TNF agents is low, and in some studies probably does not differ from the incidence observed with MTX^[85]; (2) although a higher incidence of new-onset ILD is expected in RA patients

Table 3 Pharmacological agents implicated in the development of interstitial lung disease in rheumatoid arthritis patients

Pharmacological agent	Relevant information
DMARDs	
MTX	Long-term frequency of MTX-induced ILD is 0.43% ^[35]
	Incidence is 3.78/1000 patients ^[56]
LFN	Risk factor for ILD in RA patients (RR = 7.81) ^[33]
	Increases the risk of developing ILD ^[46]
	Mortality of 19% in patients with LFN-induced ILD ^[47]
AZA	Complication of interstitial pneumonia after treatment with AZA ^[52]
TNF- α inhibitors	Mortality is 32% in patients with ILD treated with TNF- α inhibitors ^[57]
Etanercept	Incidence of etanercept-induced ILD is 0.6% ^[73]
Infliximab	Incidence of infliximab-induced ILD is 0.5% ^[74]

DMARDs: Disease-modifying antirheumatic drugs; MTX: Methotrexate; ILD: Interstitial lung disease; RA: Rheumatoid arthritis; RR: Relative risk; LFN: Leflunomide; AZA: Azathioprine; TNF- α : Tumor necrosis factor- α .

treated with anti-TNF agents (compared with other CTD that are also treated with anti-TNF therapy), this rate is approximately 7 times higher in RA compared with other diseases such as ankylosing spondylitis or psoriatic arthritis; (3) most reported cases of new-onset or worsening ILD with anti-TNF therapies are secondary to etanercept or infliximab^[77]; (4) always suspect a worsening of ILD in patients with previous ILD who develop cough, dyspnea and fever; (5) most reported cases of new-onset ILD or worsening of a previous ILD appear in the first year after initiation of biologics; in one report, the mean was 26 wk^[77]; (6) in patients with baseline (before treatment initiation) ILD, the mortality attributable to ILD in patients treated with anti-TNF agents is higher than those treated with synthetic DMARDs^[82]; (7) characteristics supporting an association between ILD and treatment with biologics include recent initiation of therapy with a biologic agent, usually in elderly patients; most such patients show clinical improvement after the suspension of biologic agents and the addition of steroids; and (8) Treatment for patients with a suspicion for ILD induced or worsened by synthetic or biologic DMARDs should include the following elements: if there is a suspicion of drug-induced pulmonary damage, the agent must be rapidly discontinued; the use of other drugs that may potentially be implicated in lung damage should be avoided; smokers should stop smoking; patients may receive supportive therapy, such as supplementary oxygen, treatment of concurrent respiratory infection with antibiotics or mechanical ventilation, as indicated; and corticosteroids are the most commonly used drug for the management of drug-induced pulmonary damage and can be administered orally or intravenously at variable dosages. (In severe cases, prednisone should be administered at a dosage of 1 mg/kg. Other corticosteroids can be given at equivalent dosages, and, if required, a steroid pulse can be

used, particularly intravenous methylprednisolone at dosages of 1 g/d over 3 to 5 d). In patients with acute episodes, a clinical and symptomatic response can be observed around 24-48 h after withdrawal of the offending drugs. However, in cases of chronic damage, this response can be delayed.

One study^[77] described response rates in 52 cases of biologic-associated ILD: complete resolution was achieved in 40%, improvement or partial resolution in 25%, and no resolution in 35%. In this study, 29% of patients died during follow-up, with 70% of deaths occurring during the first 5 wk after the development or worsening of a previous biologic-associated ILD.

Importance of hepatitis C virus and lung damage in RA: Maillefert *et al.*^[86]

observed that the prevalence of hepatitis C virus (HCV) in patients with RA was approximately 0.65% (taking into account both history of HCV or active infection) and did not differ from the prevalence of HCV infection in the general population. Nevertheless, HCV infection is relevant because patients with concurrent HCV and RA may have an increased prevalence of lung damage. Aliannejad *et al.*^[87] in a review, observed a discrepancy between studies evaluating the frequency of HCV in idiopathic pulmonary fibrosis (IPF) patients, which might be attributed to geographical differences for the prevalence of HCV infection or selection bias in choosing the control group. HCV infection is associated with increased counts of lymphocytes and neutrophils in BAL fluid. These studies have shown that HCV infection is associated with nonspecific pulmonary inflammatory reactions that lead in some patients to pulmonary fibrosis. The treatment of HCV infection, especially with interferon therapy, has also been implicated in the development of lung damage in HCV patients. Complications associated with INF therapy include interstitial pneumonia and pulmonary sarcoidosis. Ueda *et al.*^[88] reported a higher prevalence of HCV antibodies in patients with IPF (28.8%) compared with that observed in age-matched control subjects (3.6%). Ferri *et al.*^[89], in a cohort of 300 HCV-positive patients, observed eight patients with interstitial lung involvement. In 6 patients, the presence of lung involvement was suspected on the basis of dyspnea with dry cough or digital clubbing. Different degrees of reduction in DLCO were observed; spirometric abnormalities, consistent with a global restrictive pattern, were found less frequently. The presence of parenchymal radiotracer uptake on G67 scan and an increased percentage of neutrophils and lymphocytes on BAL suggested active lung involvement. The treatment of HCV infection is associated with decreased pulmonary function. Foster *et al.*^[90] reported the results of a controlled clinical trial of 391 patients with HCV infection who received 24 wk of treatment with alb-IFN- α -2b or pegylated IFN- α -2a (peg-IFN α -2a) and ribavirin. Patients were followed over 6 mo with spirometry, DLCO, and chest

Table 4 Histological and clinical classification of idiopathic interstitial pneumonias

Histologic pattern	Clinical-Radiological-Pathological Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/COP
NSIP	NSIP
Organizing pneumonia	COP
Diffuse alveolar damage	Acute interstitial pneumonia
LIP	LIP

From: ref.^[107], American Thoracic Society; European Respiratory Society. *Am J Respir Crit Care Med* 2002; 165: 277-304. COP: Cryptogenic fibrosing alveolitis; NSIP: Non-specific interstitial pneumonia; LIP: Lymphoid interstitial pneumonia.

X-ray. During follow-up, DLCO declines of < 15% were observed in 173 (48%) of patients, whereas one patient developed new interstitial chest X-ray abnormalities. The underlying mechanisms for this decline in pulmonary function in patient's treatment with alb-IFN- α -2b or pegylated IFN- α -2a require further investigation.

BIOMARKERS FOR RA-ILD

To date, the use of RF and anti-CCP as predictive biomarkers for ILD development in patients with RA remains controversial. Some evidence indicates that there is a clear association between high RF and anti-CCP titer levels and RA-ILD^[29]. However, other authors have not identified an association between anti-CCP and RA-ILD^[31].

In serum from patients with RA-ILD, Harlow *et al*^[91] identified citrullinated heat shock proteins (Hsp) 90 α and Hsp90 β as potential biomarkers for ILD in patients with RA (Sensitivity, 0.29; Specificity, 0.96). Serum ferritin has been proposed as a prognostic marker in scleroderma-ILD based on the finding that patients with higher ferritin levels at baseline (> 1500 μ g/L) had a significantly increased risk of fatal outcomes^[92]. To date, there has been a lack of information about serum ferritin in RA-ILD. However, in a cross-sectional study, Rosas *et al*^[93] observed significantly increased matrix metalloproteases (MMP)-7 and MMP-1 concentrations in the serum of patients with IPF ($P = 0.01$ and $P < 0.001$, respectively). Additionally, the authors reported that a combination of enhanced concentrations of MMP-7 and MMP-1 could discriminate IPF from hypersensitivity pneumonitis, with a sensitivity of 96.3% and a specificity of 87.2%^[93]. Further studies of these metalloproteases in RA-ILD are required.

Ascherman *et al*^[94] reviewed potential biomarkers implicated in RA-ILD. To date, the following cytokines have been considered as potential biomarkers of ILD: platelet derived growth factor isoforms AB and BB, interferon-alpha, and profibrotic cytokine transforming growth factor-B1. Elevated levels of these cytokines have been observed in BAL. High levels of Krebs von den Lungen-6 protein (KL-6) have been identified

in serum, reflecting alveolar damage. KL-6 protein levels have demonstrated a correlation with the severity of ILD, as evaluated by HRCT^[95]. The role of other potential biomarkers, such as surfactant protein-D (SP-D), surfactant protein-A (SP-A), and YKL-40 chitinase-3-like protein 1, or cytokines such as chemokine motif ligand 18, which have been identified in other CTD complicated by lung involvement, should be evaluated in RA-ILD^[96].

HISTOPATHOLOGY

Five main histological patterns of ILD have been characterized, including NSIP, usual interstitial pneumonia (UIP), DAD, organizing pneumonia (OP), and lymphocytic interstitial pneumonia (LIP)^[97]. The histological patterns of ILD and their relationship to clinical and radiological features are summarized in Table 4. The most frequent histological pattern of RA-ILD is UIP, followed by NSIP. In terms of severity, Kim *et al*^[98] reported in 2010 that the UIP pattern in RA-ILD was associated with worse survival than the non-UIP pattern. In patients with UIP, the mean survival was 3.2 years; in patients with the non-UIP pattern, mean survival time was 6.6 years ($P = 0.04$). The severity and high mortality of the DAD pattern has been recognized. Tsuchiya *et al*^[99] reported that patients with the DAD histological pattern of RA-ILD had the highest mortality, with a median survival time of 0.2 years.

DIAGNOSIS

Clinical features

The clinical symptoms of RA-ILD are non-specific. Dyspnea on exertion is the most frequent symptom, and cough, sputum production, wheezing, and chest pain have also been reported^[100]. However, dyspnea and physical limitations may not be apparent in the early stages of disease.

Core set of domains in clinical trials

Using Delphi and nominal group techniques, a group of experts recently proposed a preliminary core set of outcome measures in connective tissue disease-associated ILD (CTD-ILD) and idiopathic pulmonary fibrosis for use in clinical trials^[101]. The results of this study included identification of the following domains to be measured in clinical trials: (1) dyspnea; (2) health-related quality of Life (HRQoL); (3) lung imaging; (4) lung physiology/function; (5) survival; and (6) medications.

The instruments accepted for each domain were derived from the Delphi Technique and are depicted in Figure 1^[101]. Selection of this core of domains and instruments is very useful in diverse contexts in order to standardize the assessment of clinical responses across studies, rendering these results useful for systematic reviews or meta-analyses, and to facilitate

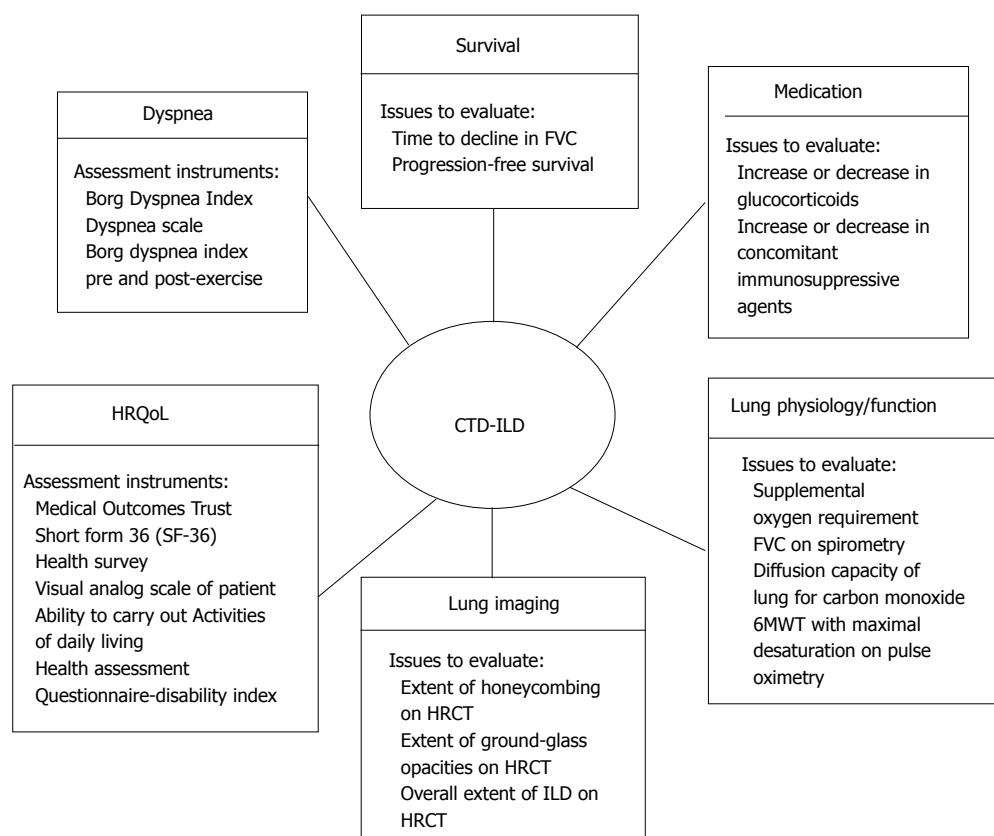


Figure 1 Suggested instruments to assess connective tissue disease associated interstitial lung disease, based on the Delphi Technique^[101]. CTD-ILD: Connective tissue disease associated-interstitial lung disease; FVC: Forced vital capacity; HRQoL: Health-related quality of life; HRCT: High-resolution computed tomography.

the selection of outcome measures in multicenter randomized controlled trials.

The treatment of RA-ILD can be classified into supportive measures and treatment against the inflammatory processes that are responsible for ILD. To date, there is no specific treatment for RA-ILD. The best therapeutic strategy is believed to be a multidisciplinary approach that evaluates the severity of lung involvement, the type of pneumonitis, concomitant organs involved, and associated comorbidities. At our center, this therapeutic approach is performed by a rheumatologist, a pulmonologist, and a specialist in internal medicine. Included among supportive measures are supplementary therapy with oxygen, pulmonary rehabilitation, anti-reflux therapy, and treatment of comorbidities^[102]. Many patients may have coexisting infections, and appropriate antimicrobial agents should be considered in such cases.

Six-minute walk test

The six-minute walk test (6MWT) measures the distance that a patient can walk quickly on a flat, hard surface over a period of 6 min (6MWD). It evaluates the global and integrated responses of all of the systems involved in exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units,

and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or on the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing^[103]. Changes in 6MWD after therapeutic interventions correlate with subjective improvements in dyspnea^[104].

St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire was originally developed to assess the health status of patients with chronic obstructive pulmonary disease and asthma^[105]. It has also been used for patients with other diseases, such as bronchiectasis and ILD^[106]. Chang *et al.*^[106] observed that forced vital capacity (FVC)% was more strongly correlated with activity score than with symptom score. Similarly, on the chronic respiratory questionnaire, the dyspnea score was significantly correlated with FVC%, whereas the fatigue and emotional scores were not correlated.

PFT

Patients with RA-ILD usually demonstrate a restrictive pattern on PFT with reduced total lung capacity (TLC), or a diminished FVC with a normal or increased forced expiratory volume at 1 second/forced vital capacity (FEV1/FVC) ratio and/or impaired gas exchange, which is characterized by an increased P (A-a) O₂ (Alveolar-

arterial pressure difference for O₂), decreased PaO₂ at rest or exertion, or decreases in the DLCO^[107]. Chen *et al*^[10] observed, in a cross-sectional study of patients with RA-ILD, the presence of severe respiratory impairment [lower percent predicted FVC (74.9 ± 12.2 vs 86.9 ± 11.3; *P* < 0.001), TLC (87.8 ± 15.7 vs 98.4 ± 11.3; *P* = 0.001), FEV1 (74.1 ± 14.6 vs 88.0 ± 12.9; *P* < 0.001), and DLCO (68.1 ± 19.5 vs 96.2 ± 17.7; *P* < 0.001)] compared to RA patients without ILD. Saag *et al*^[14], in a cross-sectional study, found that worse functioning as evaluated by the Health Assessment Questionnaire Disability-Index (HAQ-DI), was a risk factor for declines in both the DLCO and FVC. However, Kim *et al*^[98], in a retrospective study, observed that variables associated with a decrease in survival time in patients with RA-ILD included baseline FVC (HR = 0.98; *P* = 0.01), baseline DLCO (HR = 0.97; *P* = 0.002), and the presence of a UIP pattern on HRCT (HR = 2.09; *P* = 0.04).

Radiological findings

Radiographically, changes observed in RA-ILD are indistinguishable from those observed in IPF or ILD associated with other connective-tissue diseases. Plain chest X-rays mainly demonstrate reticular and fine nodular opacities. These findings are commonly concentrated in the lower lung zones. Early on, these changes may appear as a patchy, alveolar-filling infiltrate. Disease progression results in a more reticulonodular pattern. Plain chest X-ray is an insensitive means for identifying ILD, which has a prevalence rate of only 6%^[9]. Progression to nodular, patchy infiltrates may develop. Rarely, lymphadenopathy, rheumatoid nodules, and pleural effusions may be present^[107]. Gabbay *et al*^[9], in a cross-sectional study, observed the prevalence of RA-ILD (14%) by employing a number of sensitive techniques in patients with RA for < 2 years.

High resolution computed tomography and histological correlation

One of the varied manifestations of ILD is asymptomatic disease that is detected by HRCT of the chest and PFT^[108]. The American Thoracic Society and the European Respiratory Society (ATS/ERS), in collaboration with the Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT), published HRCT criteria for the diagnosis of UIP. The following are the main criteria for UIP in HRCT (all four features must be present): subpleural, basal predominance; reticular abnormality; honeycombing with or without traction bronchiectasis, and the absence of features listed as inconsistent with the UIP pattern. The criteria for possible UIP pattern include all features for the UIP pattern listed above, except for honeycombing. Inconsistent with the UIP pattern are any of the following seven features: upper or mid-lung predominance; peribronchovascular predominance; extensive ground-glass abnormality (extent >

reticular abnormality); profuse micronodules (bilateral, predominantly upper lobes); discrete cysts (multiple, bilateral, at a distance from areas of honeycombing); diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes); and consolidation in bronchopulmonary segment(s)/lobe(s)^[109].

Assayag *et al*^[110] compared, in a cohort of 69 patients with RA-ILD, the usefulness of two computed tomography (CT) criteria and their correspondence with histopathologic patterns. Using the strict criteria, a definite UIP pattern on a CT scan had 96% specificity with histopathological findings and a positive predictive value of 95%. However, the sensitivity of the UIP pattern on CT scan was 45%, and when the broad criteria were used, the sensitivity of CT scan increased to 81%, with a decrease in specificity to 85%. Kim *et al*^[98], in a retrospective study that included bivariate survival analysis of specific HRCT features in patients with RA-ILD, found that reticulation, traction bronchiectasis, and honeycombing were significantly associated with worse survival time. Cox regression modeling found that the presence and extent of traction bronchiectasis were significant independent predictors of worse survival time, with a hazard ratio (HR) 2.6; honeycombing had a HR for death of 2.1.

Pérez-Dórame *et al*^[111] observed, in a cross-sectional study, the likelihood of NSIP being the most prevalent pattern on HRCT scans (29%). UIP patterns were observed in 13% of the patients. However, there was considerable overlap among tomographic patterns: 42% of patients had two ILD tomographic patterns, and 20% of patients also had small airway disease, defined as the presence of mosaic attenuation and air-trapping images.

Correlation between PFT and HRCT

McDonagh *et al*^[112], in a cross-sectional study, calculated the sensitivity and specificity of PFT, using HRCT as the gold standard. These authors observed that reduced FEV and low total lung capacity (TLC) [both > 1 Standard (SD) deviation below that predicted] were highly sensitive markers for the presence of ILD on HRCT (88% and 90%, respectively). However, the specificity of each was relatively low (59% and 71%, respectively). The most sensitive test appeared to be measurement of residual volume (RV). A reduction of > 1 SD below the predicted RV was 83%- specific for ILD.

Figure 2 describes a diagnosis strategy for patients with suspicion of RA-ILD. This strategy is based on the findings of clinical features and/or presence of risk factors for ILD in patients with a recognized RA. A recommendation is to perform a systematic assessment of the arterial blood gas, PFT and chest radiograph. If there is evidence in any of these tests that justify further investigation, we recommend a HRCT as the next step. HRCT may exclude or confirm the diagnosis of ILD, nevertheless in case of a reasonable suspicion justified by the clinical findings

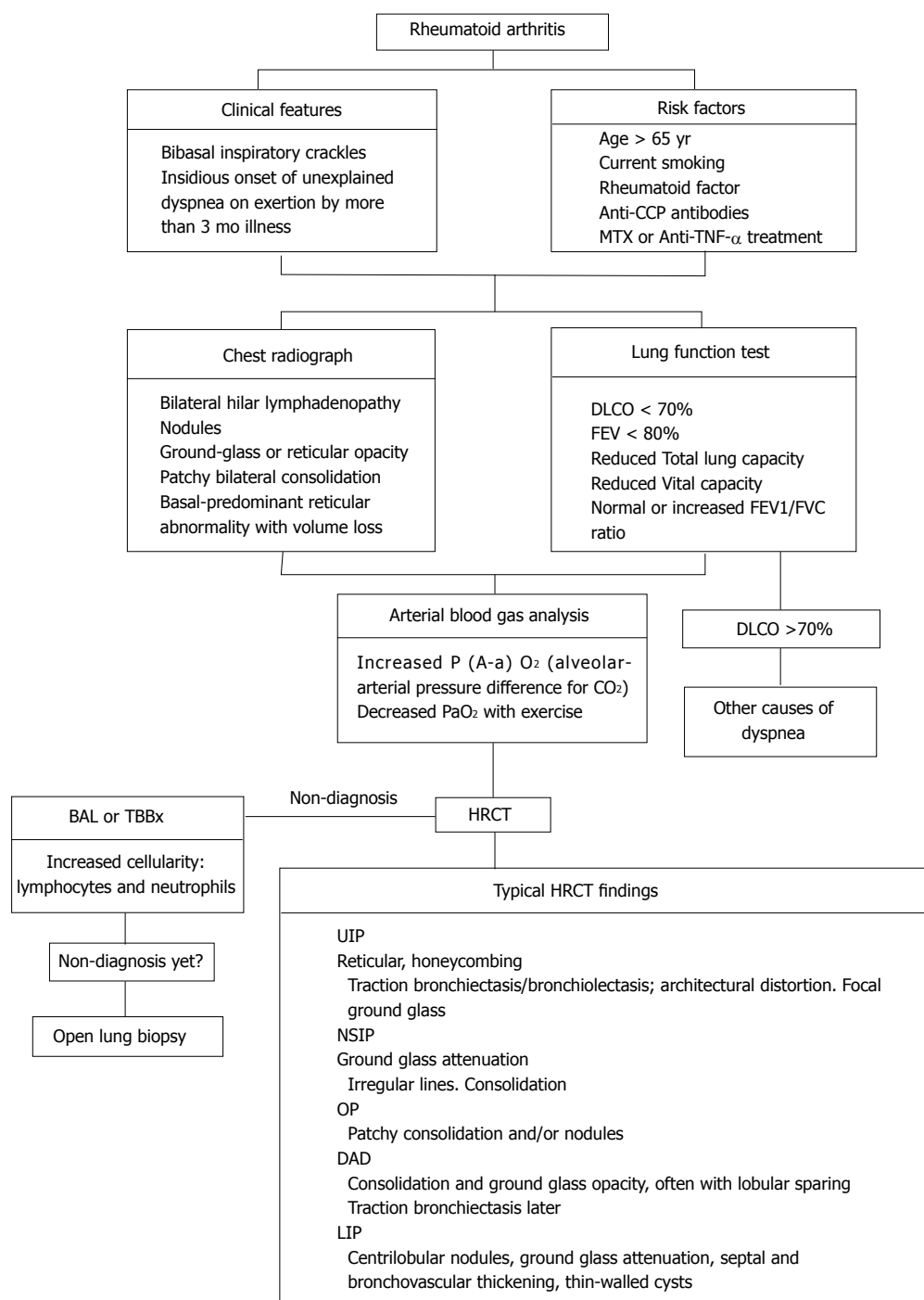


Figure 2 Recommendations for the diagnosis of interstitial lung disease in rheumatoid arthritis patients. Anti-CCP: Anti-cyclic citrullinated peptide; MTX: methotrexate; Anti-TNF- α : Anti-tumor necrosis factor- α ; DLCO: Diffusing capacity of the lung for carbon monoxide; FEV: Forced expiratory volume; FVC: Forced vital capacity; BAL: Bronchoalveolar lavage; TBBx: Transbronchial lung biopsy; HRCT: High-resolution computed tomography; UIP: Usual interstitial pneumonia; NSIP: Non-specific interstitial pneumonia; OP: Organizing pneumonia; DAD: Diffuse alveolar damage; LIP: Lymphocytic interstitial pneumonia.

with a HRCT that is not conclusive, probably invasive approaches, such as BAL or open lung biopsy should be considered.

Positron emission tomography and interstitial lung disease

HRCT is an exclusively structural imaging technique from which only indirect inferences in relation to metabolism can be made. Recent technologic advances have led to the integration of positron emission

tomography (PET) with CT, allowing molecular imaging to be combined with the fine structural detail of CT. PET/CT has profoundly affected the management of cancer^[113]. However, to date, PET/CT has not been used in patients with IPF and ILD^[114]. PET with [18F]-Fluorodeoxyglucose ([18F]-FDG) can be used to quantify pulmonary inflammation. [18F]-FDG, a glucose analog, is taken up by the same transporters that take up glucose into the cell; therefore, [18F]-FDG uptake tracks cellular glucose transport, which

is highly correlated with the rate of cellular glucose metabolism^[115]. Increased pulmonary [18F]-FDG metabolism in all patients with IPF and other forms of diffuse parenchymal lung disease was observed. Pulmonary 18F-FDG uptake predicts measurements of health and lung physiology in these patients. 18F-FDG metabolism was higher when the site of maximal uptake corresponded to areas of reticulation/honeycombing on HRCT, rather than to areas with ground-glass patterns. To date, there are, to our knowledge, no studies evaluating lung metabolism in patients with RA-ILD, and longitudinal studies evaluating treatment based on pulmonary metabolism are required.

PULMONARY ARTERIAL HYPERTENSION AND RA-ILD

Pulmonary arterial hypertension (PAH) may be an extra-articular manifestation of RA or may be associated with RA-ILD^[116]. PAH in patients with RA-ILD who have either dyspnea or lung dysfunction [reduced carbon monoxide transfer factor (TLCO) or desaturation on exercise] can appear disproportionate to the extent of parenchymal lung disease. Trans-thoracic echocardiography is a suitable screening tool for detection of pulmonary hypertension in patients with ILD^[102], and PAH can be confirmed with cardiac catheterization.

PHARMACOLOGICAL TREATMENT

There is only limited information derived from well-designed clinical trials or prospective cohort studies regarding the efficacy of immunosuppressive or biological therapy for RA-ILD. Current understanding suggests that the therapeutic response depends on several factors, such as early detection of involvement, the radiological-histological subset (with lower rates of therapeutic response in fibrotic UIP compared with *Bronchiolitis obliterans* organizing pneumonia and non-fibrotic NSIP), and other comorbidities such as renal failure. There are several common clinical scenarios. The first scenario is an asymptomatic patient in whom ILD is discovered incidentally. In this patient, the decision to start treatment is not always easy, because ILD may remain stable in some of these patients for years, and aggressive therapy may cause severe, life-threatening side effects. On the other hand, an incidental finding of ILD represents a window of opportunity for initiating treatment prior to clinical worsening. In this scenario, patients should initially be closely monitored monthly, and thereafter, at 3-6 mo intervals with PFT and 6MWT; in case of deterioration, immunosuppressive therapy should be considered. The second scenario is that of a patient with symptoms and clinical signs of ILD and a confirmed diagnosis based on PFT and HRCT. In these patients, immunosuppressive therapy against the inflammatory

process should be initiated. The third scenario involves a patient who has failed treatment with immunosuppressive drugs, has severe lung fibrosis, and has very few or absent signs of inflammation on HRCT. These patients generally do not benefit greatly from immunosuppressive therapy. If, after a course of corticosteroids and immunosuppressive drugs, such patients suffer rapid deterioration of FVC, diffuse PaO₂ capacity of the lung for carbon dioxide (DLCO₂), or clinical parameters, other therapies including lung transplantation should be considered (see later). In patients with moderate or severe symptoms and who have rapid progression of ILD (as reflected by a rapid deterioration of FVC and DLCO₂ with an increase in dyspnea), corticosteroids are considered first-line treatment.

However, there is a lack of evidence from controlled studies regarding the effect size of corticosteroid treatment on the therapeutic response in RA-ILD. This lack of clinical trials is explained because ILD is a life-threatening complication and ethically is not suitable for evaluation in placebo-controlled trials. One of the most recent studies evaluating the effect of corticosteroids on the therapeutic response was performed by Rojas-Serrano *et al.*^[117]. These authors, in a retrospective cohort design of 40 patients with RA-ILD treated with prednisone 1 mg/kg per day for 6 wk followed by tapering of 10 mg/d for approximately 6-8 mo, observed significant improvement in FVC at the final evaluation (compared with baseline values). However, the lack of a comparison group and the fact that the majority of these 40 patients with ILD concomitantly received MTX, AZA, or LFN limit the study's usefulness in understanding the true effect of corticosteroids in these patients.

Ineffective agents

Some medications have been used in CTD-ILD but have not demonstrated significant efficacy. These drugs include d-penicillamine and colchicine, which have been tested in systemic sclerosis but not in RA-ILD^[118,119]. In an original study, Steen *et al.*^[118] evaluated the effects of d-penicillamine in 44 patients with systemic sclerosis compared with patients who did not receive this drug; while patients who received d-penicillamine had no further progression of dyspnea or fibrosis in chest X-rays during follow-up, there were no significant modifications in vital capacity (VC). In an open trial, van der Schee *et al.*^[120] evaluated the effects of d-penicillamine (750 mg/d) in seven patients with ILD-RA. Patients also received prednisone 60 mg/d during month 1 with a gradual taper; VC and CO diffusion were measured prior to treatment, at 1 mo, and annually. Anecdotal reports have described some cases of patients with ILD-RA who exhibited improvement after receiving cyclosporine^[121].

Immunosuppressive agents

Azathioprine: Since the late 1970s, azathioprine and

corticosteroid therapy have been used for the treatment of RA-ILD in order to improve functional parameters and to stabilize lung inflammation. Cohen *et al.*^[122] published one of the first case reports, which discussed a patient with RA-ILD who had been treated for 5 years with azathioprine; improvements in pulmonary function and clinical symptoms were observed. Interestingly, there is also a lack of evidence from controlled studies regarding the efficacy of azathioprine in RA-ILD.

Cyclophosphamide: Cyclophosphamide (CYC) is an immunosuppressive drug commonly used to treat patients with ILD. A recent study^[123] evaluated the effects of CYC on serum and bronchoalveolar lavage (BALF), TNF- α , TGF- β 1, and MMP-9 levels, as well as TNF- α and TGF- β 1 messenger RNA (mRNA) levels, in the peripheral blood of patients with primary Sjögren's syndrome with ILD. The results of this study showed that TNF- α , TGF- β 1, and MMP-9 levels decreased significantly after CYC treatment.

The majority of evidence published on CYC in ILD has been derived from patients with systemic sclerosis who were treated with CYC. Although CYC is the "gold standard" immunosuppressant for the treatment of CTD-ILD, a meta-analysis^[124] evaluating the evidence of three randomized clinical trials and six prospective cohorts evaluating the effect of CYC on systemic sclerosis and ILD did not observe significant changes in the FVC or DLCO after 12 mo of therapy, concluding that CYC treatment did not result in a clinically significant improvement of pulmonary function in these patients. However, when the individual studies are examined, there was wide variability in CYC doses and administration, with some studies evaluating oral CYC whereas others employed intravenous (*iv*) administration. The studies also differ in concurrent interventions; patients in some studies also received high doses of corticosteroids, others low corticosteroid doses, and in one study, corticosteroids were not used. Therefore, new studies with similar designs, inclusion criteria, and concurrent interventions are required to support the results of this meta-analysis. CYC therapy has also been used in patients with suspected drug-induced ILD. In a case report, an RA patient with MTX-induced pneumonitis was considered resistant to withdrawal of MTX, oxygen administration, and pulse-dose corticosteroids. This patient was treated with an *iv* CYC pulse, resulting in a substantial improvement in hypoxemia and X-ray findings. The authors suggest that CYC should be considered in patients with MTX-induced pneumonitis without response to corticosteroids^[125].

Mycophenolate mofetil: Mycophenolate mofetil (MMF) has been studied in patients with CTD-ILD. In a case series^[126], 10 patients with autoimmune disorders complicated by ILD (three of whom had RA) received MMF. Symptomatic improvement was observed in 10/11 patients, and 4/5 discontinued oxygen. There

was stabilization or improvement in HRCT lesions in 8/8 patients, only 1/9 had worsening PFT, and patients were able to significantly decrease the dose of prednisone. The authors concluded that MMF is probably safer and more effective than CYC and should be considered as a first-line agent or a maintenance therapy after CYC treatment. However, these data are very preliminary and require corroboration in a controlled study that compares CYC vs MMF in ILD-RA.

Combined therapy with methylprednisolone pulses: Combined therapy with methylprednisolone and CYC has been evaluated mainly in patients with systemic sclerosis-associated ILD. Yiannopoulos *et al.*^[127] evaluated 13 patients with systemic sclerosis-associated ILD, observing that 66.6% had stable or improved pulmonary function parameters. However, ILD worsened in some individuals after stopping treatment. The authors concluded that this combination is effective and well-tolerated and helps to stabilize respiratory function in ILD. Airò *et al.*^[128] described the results of an observational study evaluating the results of the combination of CYC and 6-methylprednisolone in 13 patients with systemic sclerosis and active alveolitis, observing an increase in FVC ($P = 0.005$) at 6 mo compared to baseline.

Biologic agents

Tocilizumab: Tocilizumab is an interleukin (IL)-6 receptor blocker useful in the treatment of joint symptoms and some systemic manifestations in RA. Excessive production of IL-6 is associated with fibrosis in ILD; therefore, IL-6 constitutes a potential target in the treatment of RA-ILD. Gallelli *et al.*^[129] have observed, in an *in vitro* study that used primary cultures of normal and fibrotic human lung fibroblasts, that the proliferative mechanisms induced by TGF- β 1 are in part mediated by an increased release of IL-6, leading to phosphorylation-dependent mitogen-activated protein kinase (MAPK) activation. These findings help to understand the effects of therapies that are based on IL-6 inhibition and their effects on lung fibroblasts. Mohr *et al.*^[130] described the results of tocilizumab in one patient with ILD-RA, observing an improvement in alveolitis and ground-glass opacities. Although the existing evidence is clearly insufficient to establish strong conclusions, it indicates the necessity of performing controlled studies to evaluate the efficacy of tocilizumab in these patients.

Anti-TNF agents and ILD: Only few case reports and case series have been published regarding patients with RA-ILD who may have benefited from anti-TNF treatment. Bargagli *et al.*^[131] described the case of one patient with RA and pulmonary fibrosis, refractory to corticosteroids and azathioprine, who was treated with infliximab. These authors observed an improvement in vital capacity, TLCO and FEV1 after 15 mo of infliximab therapy. Similarly, Vassallo *et al.*^[132]

described a response to infliximab in a patient with RA and pulmonary fibrosis refractory to corticosteroids. After 12 mo of infliximab treatment, this patient had symptomatic improvement with stabilization of PFT. Additionally, Antoniou *et al.*^[133] identified responses to infliximab in a case series of 4 patients with CTD-associated pulmonary fibrosis (3 with RA and 1 with systemic sclerosis). The authors observed a stabilization of pulmonary fibrosis in terms of PFT results and HRCT findings after at least 12 mo of treatment. Etanercept is another anti-TNF agent where a therapeutic response in ILD has been observed. Schultz *et al.*^[134] described a girl with juvenile chronic arthritis and pulmonary interstitial and intra-alveolar cholesterol granulomas, in whom treatment with etanercept improved symptoms and physical capacities. Wang *et al.*^[135] described a therapeutic response to etanercept in a 52-year-old woman with RA-ILD that was refractory to corticosteroids and azathioprine. These authors observed a sustained improvement in symptoms, PFT results, and HRCT findings.

There is controversy concerning whether anti-TNF agents are associated with an increase in the prevalence of RA-ILD, and several case reports have been published on the development of RA in patients receiving anti-TNF agents^[65,66,70-72,136]. In addition, cases have also been reported of patients with RA-ILD experiencing exacerbations of lung disease after receiving anti-TNF therapy^[61]. Perez-Alvarez *et al.*^[77] analyzed 122 cases of new-onset ILD or exacerbation of ILD in connective tissue diseases after administration of biological agents. Among these, 108 (89%) patients had RA. The drugs that were most frequently associated with ILD were etanercept (58 patients) and infliximab (56 patients); ILD developed at a mean of 26 wk after starting biological agents.

Rituximab: B cells are probably involved in the pathogenesis of RA-ILD. Atkins *et al.*^[137] have observed the presence of follicular B-hyperplasia and infiltration of the interstitium with plasma cells in patients with interstitial pneumonia. Observational and open uncontrolled studies have described the effects of rituximab (RTX) in patients with RA-ILD. Matteson *et al.*^[138] described the effects of RTX (1000 mg given on day 1 and day 15 and again after 24 and 26 wk) on 10 patients with RA-ILD who were evaluated in a 48-wk, open clinical trial. At the end of the study, only 7/10 patients were assessed for therapeutic response. Among these patients, DLCO₂ increased > 15% of baseline in 2/7 patients, remained stable in 4/7 patients, and worsened in 1/7 patients. However, the FVC increased by at least 10% in 2/7 patients, was stable in 4/7 patients, and declined in 1/7 patients. In the six patients who had a follow-up HRCT, findings remained unchanged in 5/6 and improved in 1/6. These preliminary data suggest that RTX benefits only some patients with RA-ILD; nevertheless, further controlled studies are required to identify the possible

effects of RTX on patients with established RA-ILD. Dass *et al.*^[139] described the safety of RTX among 67 patients with RA and lung involvement; of these, 48 patients (71.6%) had ILD. The authors observed 3 deaths (2 patients with ILD and 1 patient with chronic obstructive pulmonary disease), one of which was secondary to pneumonia and acute progression of ILD observed in the 4 wk after the first cycle of RTX. These authors conclude that treatment with RTX in patients with RA and lung involvement apparently does not increase the rate of expected severe side effects.

Romero *et al.*^[140] described the safety of RTX in a series of 14 patients with CTD-ILD, 29 of whom had RA-ILD. They observed a decreased incidence of ILD relapse during rituximab therapy (0.745/100 patient-months) compared to 5.56/100 patient-months during the pre-treatment period. Only 12 patients had PFT results available during follow-up, demonstrating an increase in FVC and DLCO. Radiographic studies were available in 6 patients and demonstrated stabilization of ILD in 5/6 and improvement in 1/6. These authors conclude that RTX was safe in the sample studied, although there was 1 death secondary to neutropenia and a disseminated fungal infection during follow-up. Becerra *et al.*^[141] described the results of treatment with RTX in 38 patients with RA and lung involvement, 19 of whom had ILD. They observed that lung disease remained stable, although one patient with severe UIP developed progressive lung disease. Interestingly, 66% of the patients had respiratory infections, 2 of which required hospitalization. There were 2 deaths in this series, neither of which was related to RTX treatment. These authors conclude that RTX is a relatively safe therapy in patients with RA and lung involvement; however, there is no significant evidence to demonstrate improvement in lung disease.

Abatacept: Abatacept is a promising biologic agent for RA; nevertheless, there is a lack of studies evaluating the safety of abatacept in RA-ILD, and most information about this medication has been obtained from observational studies, particularly case reports. In a mice model of hypersensitivity pneumonitis characterized by T cell-mediated lung inflammation, the administration of abatacept significantly decreased the extent of lung damage and decreased the number of inflammatory cells in the BAL^[142]. Wada *et al.*^[83] reported the case of a 55-year-old man with RA and interstitial pneumonia who deteriorated early after the administration of abatacept. This patient had a rapid clinical and radiographic deterioration of ILD that improved after abatacept was stopped. Nevertheless, other causes of ILD besides the abatacept should be considered, and additional information is required before establishing definite conclusions about the safety of abatacept in patients with RA-ILD.

Lung transplantation and RA-ILD

Several studies have demonstrated that patients with

systemic sclerosis had similar rates of survival after lung transplantation compared with patients who had idiopathic pulmonary fibrosis or idiopathic pulmonary arterial hypertension^[143]. Nevertheless, there are only few studies evaluating outcomes in patients with RA-ILD who underwent lung transplantation. Yazdani *et al.*^[144] performed a retrospective study to examine survival in 10 patients with RA-ILD who received a lung transplant, compared with 53 patients with IPF and 17 with systemic sclerosis-ILD (SSc-ILD). The authors reported similar cumulative survival rates in RA-ILD compared to IPF (67% vs 69%, respectively), although the cumulative survival rate was higher in SSc-ILD (82%). These data suggest that RA-ILD patients have a similar cumulative survival rate compared to other recipient of lung transplant, and therefore lung transplant should be considered in patients with refractory ILD who have not responded to other therapeutic strategies.

Other treatments

Some treatments used for idiopathic pulmonary fibrosis have been infrequently investigated in patients with rheumatic disorders associated ILD. These treatments include (1) pirfenidone; (2) bosentan and sildenafil; (3) imatinib; and (4) warfarin. Pirfenidone is an antifibrotic drug that inhibits fibroblast proliferation and collagen synthesis and clinically is used for IPF. In an open-label trial, Nagai *et al.*^[145] evaluated the effects of one year of treatment with oral pirfenidone (40 mg/kg body weight) in patients with advanced pulmonary fibrosis secondary to systemic sclerosis without observing a survival benefit, although these patients had no significant deterioration in chest radiographic findings or arterial oxygen pressure. To date, there have been no studies evaluating pirfenidone in RA-ILD. Therefore, new evidence derived from such studies is required. Bosentan is an endothelin-1 antagonist used in patients with pulmonary arterial hypertension. However, most of the information of bosentan's effects on CTD-ILD is derived from patients with systemic sclerosis. Mittoo *et al.*^[146] performed a retrospective assessment of 13 patients with CTD-ILD and pulmonary hypertension. Only 2/13 of these patients had RA-ILD. These patients received bosentan alone, sildenafil alone or bosentan plus sildenafil. This study found that the drugs used to treat pulmonary hypertension were well tolerated, with higher mortality rates among patients with systemic sclerosis compared with other CTD. New studies evaluating bosentan in RA-ILD are required to draw definite conclusions. Imatinib mesylate inhibits the activation of the PDGF receptor, as well as the c-Abl, Bcr-Abl and c-Kit tyrosine kinases. Consequently, imatinib mesylate suppresses the activation and proliferation of fibroblasts, requiring this drug to be evaluated in RA-ILD^[147]. Warfarin has been only evaluated in retrospective studies. Watanabe *et al.*^[148] performed a retrospective analysis of 20 patients with

rapidly progressive interstitial pneumonia, 11 cases of which were secondary to CTD (2/11 were due to rheumatoid arthritis). These authors classified the patients into 2 groups: group A, which included 11 patients treated with anticoagulant therapy (warfarin or dalteparin), and group B, which included 9 patients who did not receive anticoagulation. At the end of the study, patients treated with anticoagulation had a better survival rate compared with the non-anticoagulated group ($P = 0.038$). Nevertheless, this evidence is too weak to recommend the use of warfarin in patients with RA-ILD. N-acetylcysteine is an antioxidant, acts as a scavenger for free radicals and has anti-inflammatory properties. This agent also suppresses the production of TNF- α and TGF- β by alveolar macrophages in patients with idiopathic pulmonary fibrosis^[149]. N-acetylcysteine is an interesting drug in idiopathic pulmonary fibrosis, where it is widely used as an adjuvant therapy, although recent data did not demonstrate significant differences between N-acetylcysteine vs placebo in terms of FVC, frequency of exacerbations or mortality rates^[150]. To date, limited information exists about the effects of N-acetylcysteine in CTD-ILD. Rosato *et al.*^[151] evaluated, in a retrospective study, the effects of intravenous N-acetylcysteine in patients with systemic sclerosis, observing a decrease in the rate of deterioration of DLCO, VC and TLC. Nevertheless, to date, no studies have reported the effects of N-acetylcysteine in RA-ILD. Evidence against the use of this drug has appeared in one study that demonstrated an increased risk of death and hospitalization in patients with idiopathic pulmonary fibrosis who received a combination of prednisone, azathioprine and N-acetylcysteine compared with patients who received placebo.

PROGNOSIS

Predictors of mortality include older age, male sex, lower socioeconomic status, decreased lung function, the presence of fibrosis, the extent of disease, the presence of a lung-injury pattern of usual interstitial pneumonia, higher disease activity scores, higher erythrocyte sedimentation rates, higher lactate dehydrogenase levels, greater baseline pain, and worse health assessment questionnaire scores^[152]. Average survival in patients with RA is 10-11 years shorter than that of the general population. Lung disease is especially common in RA and is directly responsible for 10%-20% of all RA-associated mortality^[153]. A retrospective study by Kelly *et al.*^[30] demonstrated that mortality rates were related to the subtype of lung disease; patients with a UIP/OS pattern had an RR of death from any cause of 3.9 compared with patients who had a pattern of NSIP/cryptogenic organizing pneumonia (COP). These authors observed during follow-up that, compared with limited disease, extensive disease was associated with an RR of death from any cause of 2.17.

Gochuico *et al*^[23] examined the differences between progressive RA-ILD and stable RA-ILD. Higher alveolar concentrations of IFN- γ and TGF- β 2 were observed in patients with progressive RA-ILD versus stable RA-ILD. Additionally, patients with progressive RA-ILD were more likely to be treated with MTX, suggesting that treatment with this agent may constitute a risk factor for progression of preclinical RA-ILD. Assayag *et al*^[152] performed a systematic review evaluating predictors of mortality in RA-ILD. Factors associated with higher mortality rates were older age, male gender, lower DLCO, extent of fibrosis and UIP pattern. Nevertheless, the authors recognized that the review was limited by the low quality of some of the included studies; therefore, larger, well-designed, multicenter studies evaluating prognostic factors in RA-ILD are still required.

CONCLUSION

Recent evidence indicates that ILD is presently observed more frequently in RA than was the case a decade ago. Establishing an early diagnosis of this complication depends on the level of clinical suspicion, as well as the strategy used to assess patients at risk of ILD. The adequate assessment of patients with suspected ILD should be based on a combination of tests, including clinical assessments, PFT, HRCT, and in some cases BAL or lung biopsy. Currently, distinct clinical subtypes of RA-ILD are recognized that may differ importantly in terms of prognosis and therapeutic response. Efforts to identify the subtype of RA-ILD should be made in order to design a therapeutic strategy that will be of the greatest benefit to a particular patient. In terms of treatment, recently identified therapeutic targets have produced new drugs for evaluation. Nevertheless, most of the information about these treatments is derived from observational or uncontrolled open studies. Therefore, evidence about the effectiveness of these agents is too weak to establish definite conclusions in patients with RA-ILD. New well-designed, randomized, multicenter, double-blinded clinical trials are needed to evaluate the use of novel therapeutic agents in RA-ILD. This represents an important opportunity for future research.

REFERENCES

- 1 Peláez-Ballestas I, Sanin LH, Moreno-Montoya J, Alvarez-Nemegyei J, Burgos-Vargas R, Garza-Elizondo M, Rodríguez-Amado J, Goycochea-Robles MV, Madariaga M, Zamudio J, Santana N, Cardiel MH. Epidemiology of the rheumatic diseases in Mexico. A study of 5 regions based on the COPCORD methodology. *J Rheumatol Suppl* 2011; **86**: 3-8 [PMID: 21196592 DOI: 10.3899/jrheum.100951]
- 2 Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis* 2003; **62**: 722-727 [PMID: 12860726 DOI: 10.1136/ard.62.8.722]
- 3 Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, Murphy J, Cohen M, Raghu G, Brown KK. Rheumatoid arthritis-interstitial lung disease-associated mortality. *Am J Respir Crit Care Med* 2011; **183**: 372-378 [PMID: 20851924 DOI: 10.1164/rccm.201004-0622OC]
- 4 Sidhu HS, Bhatnagar G, Bhogal P, Riordan R. Imaging features of the pleuropulmonary manifestations of rheumatoid arthritis: pearls and pitfalls. *J Clin Imaging Sci* 2011; **1**: 32 [PMID: 21966629 DOI: 10.4103/2156-7514.82244]
- 5 American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000; **161**: 646-664 [PMID: 10673212 DOI: 10.1164/ajrccm.161.2.ats3-00]
- 6 Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, Vassallo R, Gabriel SE, Matteson EL. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2010; **62**: 1583-1591 [PMID: 20155830 DOI: 10.1002/art.27405]
- 7 Morrison SC, Mody GM, Benatar SR, Meyers OL. The lungs in rheumatoid arthritis--a clinical, radiographic and pulmonary function study. *S Afr Med J* 1996; **86**: 829-833 [PMID: 8764910]
- 8 Gonzalez-Lopez L, Rocha-Muñoz AD, Ponce-Guarneros M, Flores-Chavez A, Salazar-Paramo M, Nava A, Cardona-Muñoz EG, Fajardo-Robledo NS, Zavaleta-Muñoz SA, Garcia-Cobian T, Gamez-Nava JJ. Anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) relation with extra-articular manifestations in rheumatoid arthritis. *J Immunol Res* 2014; **2014**: 536050 [PMID: 24804270 DOI: 10.1155/2014/536050]
- 9 Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, Lake FR. Interstitial lung disease in recent onset rheumatoid arthritis. *Am J Respir Crit Care Med* 1997; **156**: 528-535 [PMID: 9279235 DOI: 10.1164/ajrccm.156.2.9609016]
- 10 Chen J, Shi Y, Wang X, Huang H, Ascherman D. Asymptomatic preclinical rheumatoid arthritis-associated interstitial lung disease. *Clin Dev Immunol* 2013; **2013**: 406927 [PMID: 23983768 DOI: 10.1155/2013/406927]
- 11 Koduri G, Norton S, Young A, Cox N, Davies P, Devlin J, Dixey J, Gough A, Prouse P, Winfield J, Williams P. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. *Rheumatology (Oxford)* 2010; **49**: 1483-1489 [PMID: 20223814 DOI: 10.1093/rheumatology/keq035]
- 12 Mori S, Koga Y, Sugimoto M. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. *Respir Med* 2012; **106**: 1591-1599 [PMID: 22867979 DOI: 10.1016/j.rmed.2012.07.006]
- 13 Miyake Y, Sasaki S, Yokoyama T, Chida K, Azuma A, Suda T, Kudoh S, Sakamoto N, Okamoto K, Kobashi G, Washio M, Inaba Y, Tanaka H. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. *Ann Occup Hyg* 2005; **49**: 259-265 [PMID: 15640309 DOI: 10.1093/annhyg/meh090]
- 14 Saag KG, Kolluri S, Koehnke RK, Georgou TA, Rachow JW, Hunninghake GW, Schwartz DA. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. *Arthritis Rheum* 1996; **39**: 1711-1719 [PMID: 8843862 DOI: 10.1002/art.1780391014]
- 15 Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1997; **155**: 242-248 [PMID: 9001319 DOI: 10.1164/ajrccm.155.1.9001319]
- 16 Cavagna L, Monti S, Grosso V, Boffini N, Scorletti E, Crepaldi G, Caporali R. The multifaceted aspects of interstitial lung disease in rheumatoid arthritis. *Biomed Res Int* 2013; **2013**: 759760 [PMID: 24205507 DOI: 10.1155/2013/759760]
- 17 Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994; **150**: 967-972 [PMID: 7921471 DOI: 10.1164/ajrccm.150.4.7921471]
- 18 Aubart F, Crestani B, Nicaise-Roland P, Tubach F, Bollet C, Dawidowicz K, Quintin E, Hayem G, Palazzo E, Meyer O, Chollet-Martin S, Dieudé P. High levels of anti-cyclic citrullinated peptide

- autoantibodies are associated with co-occurrence of pulmonary diseases with rheumatoid arthritis. *J Rheumatol* 2011; **38**: 979-982 [PMID: 21362759 DOI: 10.3899/jrheum.101261]
- 19 **Michalski JP**, McCombs CC, Scopelitis E, Biundo JJ, Medsger TA. Alpha 1-antitrypsin phenotypes, including M subtypes, in pulmonary disease associated with rheumatoid arthritis and systemic sclerosis. *Arthritis Rheum* 1986; **29**: 586-591 [PMID: 3487321 DOI: 10.1002/art.1780290502]
- 20 **Charles PJ**, Sweatman MC, Markwick JR, Maini RN. HLA-B40: a marker for susceptibility to lung disease in rheumatoid arthritis. *Dis Markers* 1991; **9**: 97-101 [PMID: 1782749]
- 21 **Sugiyama Y**, Ohno S, Kano S, Maeda H, Kitamura S. Diffuse pan-bronchiolitis and rheumatoid arthritis: a possible correlation with HLA-B54. *Intern Med* 1994; **33**: 612-614 [PMID: 7827377 DOI: 10.2169/internalmedicine.33.612]
- 22 **Chaudhary NI**, Roth GJ, Hilberg F, Müller-Quernheim J, Prasse A, Zissel G, Schnapp A, Park JE. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. *Eur Respir J* 2007; **29**: 976-985 [PMID: 17301095 DOI: 10.1183/09031936.00152106]
- 23 **Gochuico BR**, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, MacDonald SD, Travis WD, Stylianou MP, Rosas IO. Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med* 2008; **168**: 159-166 [PMID: 18227362 DOI: 10.1001/archinternmed.2007.59]
- 24 **Ponticos M**, Holmes AM, Shi-wen X, Leoni P, Khan K, Rajkumar VS, Hoyles RK, Bou-Gharios G, Black CM, Denton CP, Abraham DJ, Leask A, Lindahl GE. Pivotal role of connective tissue growth factor in lung fibrosis: MAPK-dependent transcriptional activation of type I collagen. *Arthritis Rheum* 2009; **60**: 2142-2155 [PMID: 19565505 DOI: 10.1002/art.24620]
- 25 **Jakubczik C**, Kunkel SL, Puri RK, Hogaboam CM. Therapeutic targeting of IL-4- and IL-13-responsive cells in pulmonary fibrosis. *Immunol Res* 2004; **30**: 339-349 [PMID: 15531774 DOI: 10.1385/ir]
- 26 **Moore BB**, Paine R, Christensen PJ, Moore TA, Sitterding S, Ngan R, Wilke CA, Kuziel WA, Toews GB. Protection from pulmonary fibrosis in the absence of CCR2 signaling. *J Immunol* 2001; **167**: 4368-4377 [PMID: 11591761 DOI: 10.4049/jimmunol.167.8.4368]
- 27 **Wilson MS**, Madala SK, Ramalingam TR, Gochuico BR, Rosas IO, Cheever AW, Wynn TA. Bleomycin and IL-1beta-mediated pulmonary fibrosis is IL-17A dependent. *J Exp Med* 2010; **207**: 535-552 [PMID: 20176803 DOI: 10.1084/jem.20092121]
- 28 **Sun L**, Louie MC, Vannella KM, Wilke CA, LeVine AM, Moore BB, Shanley TP. New concepts of IL-10-induced lung fibrosis: fibrocyte recruitment and M2 activation in a CCL2/CCR2 axis. *Am J Physiol Lung Cell Mol Physiol* 2011; **300**: L341-L353 [PMID: 21131395 DOI: 10.1152/ajplung.00122.2010]
- 29 **Yin Y**, Liang D, Zhao L, Li Y, Liu W, Ren Y, Li Y, Zeng X, Zhang F, Tang F, Shan G, Zhang X. Anti-cyclic citrullinated Peptide antibody is associated with interstitial lung disease in patients with rheumatoid arthritis. *PLoS One* 2014; **9**: e92449 [PMID: 24743261 DOI: 10.1371/journal.pone.0092449]
- 30 **Kelly CA**, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, Dawson J, Sathi N, Ahmad Y, Koduri G, Young A. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics-a large multicentre UK study. *Rheumatology* (Oxford) 2014; **53**: 1676-1682 [PMID: 24758887 DOI: 10.1093/rheumatology/keu165]
- 31 **Bongartz T**, Cantaert T, Atkins SR, Harle P, Myers JL, Turesson C, Ryu JH, Baeten D, Matteson EL. Citrullination in extra-articular manifestations of rheumatoid arthritis. *Rheumatology* (Oxford) 2007; **46**: 70-75 [PMID: 16782731 DOI: 10.1093/rheumatology/kel202]
- 32 **Smolen JS**, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, Emery P, Gaujoux-Viala C, Gossec L, Nam J, Ramiro S, Winthrop K, de Wit M, Aletaha D, Betteridge N, Bijlsma JW, Boers M, Buttgerit F, Combe B, Cutolo M, Damjanov N, Hazes JM, Kouloumas M, Kvien TK, Mariette X, Pavelka K, van Riel PL, Rubbert-Roth A, Scholte-Voshaar M, Scott DL, Sokka-Isler T, Wong JB, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; **73**: 492-509 [PMID: 24161836 DOI: 10.1136/annrheum-dis-2013-204573]
- 33 **Conway R**, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheumatol* 2014; **66**: 803-812 [PMID: 24757133 DOI: 10.1002/art.38322]
- 34 **Sathi N**, Chikura B, Kaushik VV, Wiswell R, Dawson JK. How common is methotrexate pneumonitis? A large prospective study investigates. *Clin Rheumatol* 2012; **31**: 79-83 [PMID: 21638023 DOI: 10.1007/s10067-011-1758-6]
- 35 **Salliot C**, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis* 2009; **68**: 1100-1104 [PMID: 19060002 DOI: 10.1136/ard.2008.093690]
- 36 **Searles G**, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and a review of the literature. *J Rheumatol* 1987; **14**: 1164-1171 [PMID: 3325643]
- 37 **Kremer JM**, Alarcón GS, Weinblatt ME, Kaymakcian MV, Macaluso M, Cannon GW, Palmer WR, Sundy JS, St Clair EW, Alexander RW, Smith GJ, Axiotis CA. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. *Arthritis Rheum* 1997; **40**: 1829-1837 [PMID: 9336418 DOI: 10.1002/1529-0131(199710)40]
- 38 **Mornex JF**, Cordier G, Pages J, Vergnon JM, Lefebvre R, Brune J, Revillard JP. Activated lung lymphocytes in hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1984; **74**: 719-727 [PMID: 6209321 DOI: 10.1016/0091-6749(84)90236-7]
- 39 **Akoun GM**, Gauthier-Rahman S, Mayaud CM, Touboul JL, Denis MF. Leukocyte migration inhibition in methotrexate-induced pneumonitis. Evidence for an immunologic cell-mediated mechanism. *Chest* 1987; **91**: 96-99 [PMID: 3539547 DOI: 10.1378/chest.91.1.96]
- 40 **Chikura B**, Sathi N, Lane S, Dawson JK. Variation of immunological response in methotrexate-induced pneumonitis. *Rheumatology* (Oxford) 2008; **47**: 1647-1650 [PMID: 18812430 DOI: 10.1093/rheumatology/ken356]
- 41 **Khadadah ME**, Jayakrishnan B, Al-Gorair S, Al-Mutairi M, Al-Maradni N, Onadeko B, Malaviya AN. Effect of methotrexate on pulmonary function in patients with rheumatoid arthritis--a prospective study. *Rheumatol Int* 2002; **22**: 204-207 [PMID: 12215867 DOI: 10.1007/s00296-002-0227-6]
- 42 **Dawson JK**, Graham DR, Desmond J, Fewins HE, Lynch MP. Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT scanning and pulmonary function tests. *Rheumatology* (Oxford) 2002; **41**: 262-267 [PMID: 11934961]
- 43 **Roubille C**, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDs and biologic agents in rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum* 2014; **43**: 613-626 [PMID: 24231065 DOI: 10.1016/j.semarthrit.2013.09.005]
- 44 **Imokawa S**, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J* 2000; **15**: 373-381 [PMID: 10706507]
- 45 **Sawada T**, Inokuma S, Sato T, Otsuka T, Saeki Y, Takeuchi T, Matsuda T, Takemura T, Sagawa A. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2009; **48**: 1069-1072 [PMID: 19321513 DOI: 10.1093/rheumatology/kep052]
- 46 **Suissa S**, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum* 2006; **54**: 1435-1439 [PMID: 16645972 DOI: 10.1002/art.21806]
- 47 **Chikura B**, Lane S, Dawson JK. Clinical expression of leflunomide-induced pneumonitis. *Rheumatology* (Oxford) 2009; **48**: 1065-1068 [PMID: 19321511 DOI: 10.1093/rheumatology/kep050]
- 48 **Sato T**, Inokuma S, Sagawa A, Matsuda T, Takemura T, Otsuka T, Saeki Y, Takeuchi T, Sawada T. Factors associated with fatal outcome of leflunomide-induced lung injury in Japanese patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2009; **48**: 1265-1268

- [PMID: 19651883 DOI: 10.1093/rheumatology/kep227]
- 49 **Namba T**, Tanaka KI, Ito Y, Hoshino T, Matoyama M, Yamakawa N, Isohama Y, Azuma A, Mizushima T. Induction of EMT-like phenotypes by an active metabolite of leflunomide and its contribution to pulmonary fibrosis. *Cell Death Differ* 2010; **17**: 1882-1895 [PMID: 20489727 DOI: 10.1038/cdd.2010.64]
 - 50 **Wong SP**, Chu CM, Kan CH, Tsui HS, Ng WL. Successful treatment of leflunomide-induced acute pneumonitis with cholestyramine wash-out therapy. *J Clin Rheumatol* 2009; **15**: 389-392 [PMID: 19955995 DOI: 10.1097/RHU.0b013e3181c3f87e]
 - 51 **Parry SD**, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. *Eur Respir J* 2002; **19**: 756-764 [PMID: 11999006]
 - 52 **Ishida T**, Kotani T, Takeuchi T, Makino S. Pulmonary toxicity after initiation of azathioprine for treatment of interstitial pneumonia in a patient with rheumatoid arthritis. *J Rheumatol* 2012; **39**: 1104-1105 [PMID: 22550011 DOI: 10.3899/jrheum.111415]
 - 53 **Tomioaka R**, King TE. Gold-induced pulmonary disease: clinical features, outcome, and differentiation from rheumatoid lung disease. *Am J Respir Crit Care Med* 1997; **155**: 1011-1020 [PMID: 9116980 DOI: 10.1164/ajrccm.155.3.9116980]
 - 54 **Chakravarty K**, Webley M. A longitudinal study of pulmonary function in patients with rheumatoid arthritis treated with gold and D-penicillamine. *Br J Rheumatol* 1992; **31**: 829-833 [PMID: 1458289]
 - 55 **Grove ML**, Hassell AB, Hay EM, Shadforth MF. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. *QJM* 2001; **94**: 309-319 [PMID: 11391029]
 - 56 **Shidara K**, Hoshi D, Inoue E, Yamada T, Nakajima A, Taniguchi A, Hara M, Momohara S, Kamatani N, Yamanaka H. Incidence of and risk factors for interstitial pneumonia in patients with rheumatoid arthritis in a large Japanese observational cohort, IORRA. *Mod Rheumatol* 2010; **20**: 280-286 [PMID: 20217173 DOI: 10.1007/s10165-010-0280-z]
 - 57 **Ramos-Casals M**, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine* (Baltimore) 2007; **86**: 242-251 [PMID: 17632266 DOI: 10.1097/MD.0b013e3181441a68]
 - 58 **Mori S**, Imamura F, Kiyofuji C, Sugimoto M. Development of interstitial pneumonia in a rheumatoid arthritis patient treated with infliximab, an anti-tumor necrosis factor alpha-neutralizing antibody. *Mod Rheumatol* 2006; **16**: 251-255 [PMID: 16906378 DOI: 10.1007/s10165-006-0491-5]
 - 59 **Ostör AJ**, Chilvers ER, Somerville MF, Lim AY, Lane SE, Crisp AJ, Scott DG. Pulmonary complications of infliximab therapy in patients with rheumatoid arthritis. *J Rheumatol* 2006; **33**: 622-628 [PMID: 16511933]
 - 60 **Taki H**, Kawagishi Y, Shinoda K, Hounoki H, Ogawa R, Sugiyama E, Tobe K. Interstitial pneumonitis associated with infliximab therapy without methotrexate treatment. *Rheumatol Int* 2009; **30**: 275-276 [PMID: 19373466 DOI: 10.1007/s00296-009-0931-6]
 - 61 **Hagiwara K**, Sato T, Takagi-Kobayashi S, Hasegawa S, Shigihara N, Akiyama O. Acute exacerbation of preexisting interstitial lung disease after administration of etanercept for rheumatoid arthritis. *J Rheumatol* 2007; **34**: 1151-1154 [PMID: 17444583]
 - 62 **Horai Y**, Miyamura T, Shimada K, Takahama S, Minami R, Yamamoto M, Suematsu E. Etanercept for the treatment of patients with rheumatoid arthritis and concurrent interstitial lung disease. *J Clin Pharm Ther* 2012; **37**: 117-121 [PMID: 21128990 DOI: 10.1111/j.1365-2710.2010.01234.x]
 - 63 **Lindsay K**, Melsom R, Jacob BK, Mestry N. Acute progression of interstitial lung disease: a complication of etanercept particularly in the presence of rheumatoid lung and methotrexate treatment. *Rheumatology* (Oxford) 2006; **45**: 1048-1049 [PMID: 16760195 DOI: 10.1093/rheumatology/ke1090]
 - 64 **Tournadre A**, Ledoux-Eberst J, Poujol D, Dubost JJ, Ristori JM, Soubrier M. Exacerbation of interstitial lung disease during etanercept therapy: Two cases. *Joint Bone Spine* 2008; **75**: 215-218 [PMID: 17977770 DOI: 10.1016/j.jbspin.2007.04.028]
 - 65 **Dascalu C**, Mrejen-Shakin K, Bandagi S. Adalimumab-induced acute pneumonitis in a patient with rheumatoid arthritis. *J Clin Rheumatol* 2010; **16**: 172-174 [PMID: 20511978 DOI: 10.1097/RHU.0b013e3181df8361]
 - 66 **Dias OM**, Pereira DA, Baldi BG, Costa AN, Athanasio RA, Kairalla RA, Carvalho CR. Adalimumab-induced acute interstitial lung disease in a patient with rheumatoid arthritis. *J Bras Pneumol* 2014; **40**: 77-81 [PMID: 24626274 DOI: 10.1590/s1806-37132014000100012]
 - 67 **Schoe A**, van der Laan-Baalbergen NE, Huizinga TW, Breedveld FC, van Laar JM. Pulmonary fibrosis in a patient with rheumatoid arthritis treated with adalimumab. *Arthritis Rheum* 2006; **55**: 157-159 [PMID: 16463430 DOI: 10.1002/art.21716]
 - 68 **Yamazaki H**, Isogai S, Sakurai T, Nagasaka K. A case of adalimumab-associated interstitial pneumonia with rheumatoid arthritis. *Mod Rheumatol* 2010; **20**: 518-521 [PMID: 20467775 DOI: 10.1007/s10165-010-0308-4]
 - 69 **Hadjinicolaou AV**, Nisar MK, Bhagat S, Parfrey H, Chilvers ER, Ostör AJ. Non-infectious pulmonary complications of newer biological agents for rheumatic diseases--a systematic literature review. *Rheumatology* (Oxford) 2011; **50**: 2297-2305 [PMID: 22019799 DOI: 10.1093/rheumatology/ker289]
 - 70 **Glaspole IN**, Hoy RF, Ryan PF. A case of certolizumab-induced interstitial lung disease in a patient with rheumatoid arthritis. *Rheumatology* (Oxford) 2013; **52**: 2302-2304 [PMID: 23661426 DOI: 10.1093/rheumatology/ket175]
 - 71 **Lager J**, Hilberg O, Løkke A, Bendstrup E. Severe interstitial lung disease following treatment with certolizumab pegol: a case report. *Eur Respir Rev* 2013; **22**: 414-416 [PMID: 23997067 DOI: 10.1183/09059180.00002013]
 - 72 **Pearce F**, Johnson SR, Courtney P. Interstitial lung disease following certolizumab pegol. *Rheumatology* (Oxford) 2012; **51**: 578-580 [PMID: 22116998 DOI: 10.1093/rheumatology/ker309]
 - 73 **Koike T**, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, Tanaka Y, Yamanaka H, Fujii K, Yoshinaga T, Freundlich B, Suzuki M. Postmarketing surveillance of safety and effectiveness of etanercept in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2011; **21**: 343-351 [PMID: 21264488 DOI: 10.1007/s10165-010-0406-3]
 - 74 **Takeuchi T**, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, Kamatani N, Harigai M, Ryu J, Inoue K, Kondo H, Inokuma S, Ochi T, Koike T. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2008; **67**: 189-194 [PMID: 17644554 DOI: 10.1136/ard.2007.072967]
 - 75 **Koike T**, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, Takei S, Tanaka Y, Sano Y, Yaguramaki H, Yamanaka H. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. *J Rheumatol* 2014; **41**: 15-23 [PMID: 24187110 DOI: 10.3899/jrheum.130466]
 - 76 **Weinblatt ME**, Moreland LW, Westhovens R, Cohen RB, Kelly SM, Khan N, Pappu R, Delaet I, Luo A, Gujrathi S, Hochberg MC. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol* 2013; **40**: 787-797 [PMID: 23588946 DOI: 10.3899/jrheum.120906]
 - 77 **Perez-Alvarez R**, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, Brito-Zeron P, Bosch X, Ramos-Casals M. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum* 2011; **41**: 256-264 [PMID: 21277618 DOI: 10.1016/j.semarthrit.2010.11.002]
 - 78 **Su X**, Zhou T, Yang P, Edwards CK, Mountz JD. Reduction of arthritis and pneumonitis in motheaten mice by soluble tumor necrosis factor receptor. *Arthritis Rheum* 1998; **41**: 139-149 [PMID: 9433879 DOI: 10.1002/1529-0131(199801)41]
 - 79 **Scallan BJ**, Moore MA, Trinh H, Knight DM, Ghayeb J. Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. *Cytokine* 1995; **7**: 251-259 [PMID: 7640345 DOI: 10.1006/cyto.1995.0029]
 - 80 **Wynn TA**. Fibrotic disease and the T(H)1/T(H)2 paradigm. *Nat*

- Rev Immunol* 2004; **4**: 583-594 [PMID: 15286725 DOI: 10.1038/nri1412]
- 81 **Ramos-Casals M**, Brito-Zerón P, Soto MJ, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. *Best Pract Res Clin Rheumatol* 2008; **22**: 847-861 [PMID: 19028367 DOI: 10.1016/j.berh.2008.09.008]
 - 82 **Dixon WG**, Hyrich KL, Watson KD, Lunt M, Symmons DP. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2010; **69**: 1086-1091 [PMID: 20444754 DOI: 10.1136/ard.2009.120626]
 - 83 **Wada T**, Akiyama Y, Yokota K, Sato K, Funakubo Y, Mimura T. [A case of rheumatoid arthritis complicated with deteriorated interstitial pneumonia after the administration of abatacept]. *Nihon Rinsho Meneki Gakkai Kaishi* 2012; **35**: 433-438 [PMID: 23124086 DOI: 10.2177/jsci.35.433]
 - 84 **Kawashiri SY**, Kawakami A, Sakamoto N, Ishimatsu Y, Eguchi K. A fatal case of acute exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab. *Rheumatol Int* 2012; **32**: 4023-4026 [PMID: 20480164 DOI: 10.1007/s00296-010-1525-z]
 - 85 **Herrinton LJ**, Harrold LR, Liu L, Raebel MA, Taharka A, Winthrop KL, Solomon DH, Curtis JR, Lewis JD, Saag KG. Association between anti-TNF- α therapy and interstitial lung disease. *Pharmacoevidemiol Drug Saf* 2013; **22**: 394-402 [PMID: 23359391 DOI: 10.1002/pds.3409]
 - 86 **Maillefert JF**, Muller G, Falgarone G, Bour JB, Ratovohery D, Dougados M, Tavernier C, Breban M. Prevalence of hepatitis C virus infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2002; **61**: 635-637 [PMID: 12079907]
 - 87 **Aliannejad R**, Ghanei M. Hepatitis C and pulmonary fibrosis: Hepatitis C and pulmonary fibrosis. *Hepat Mon* 2011; **11**: 71-73 [PMID: 22087122]
 - 88 **Ueda T**, Ohta K, Suzuki N, Yamaguchi M, Hirai K, Horiuchi T, Watanabe J, Miyamoto T, Ito K. Idiopathic pulmonary fibrosis and high prevalence of serum antibodies to hepatitis C virus. *Am Rev Respir Dis* 1992; **146**: 266-268 [PMID: 1320820 DOI: 10.1164/ajrccm/146.1.266]
 - 89 **Ferri C**, La Civita L, Fazzi P, Solfanelli S, Lombardini F, Begliomini E, Monti M, Longombardo G, Pasero G, Zignego AL. Interstitial lung fibrosis and rheumatic disorders in patients with hepatitis C virus infection. *Br J Rheumatol* 1997; **36**: 360-365 [PMID: 9133969]
 - 90 **Foster GR**, Zeuzem S, Pianko S, Sarin SK, Piratvisuth T, Shah S, Andreone P, Sood A, Chuang WL, Lee CM, George J, Gould M, Flisiak R, Jacobson IM, Komolmit P, Thongsawat S, Tanwandee T, Rasenack J, Sola R, Messina I, Yin Y, Cammarata S, Feutren G, Brown KK. Decline in pulmonary function during chronic hepatitis C virus therapy with modified interferon alfa and ribavirin. *J Viral Hepat* 2013; **20**: e115-e123 [PMID: 23490379 DOI: 10.1111/jvh.12020]
 - 91 **Harlow L**, Rosas IO, Gochuico BR, Mikuls TR, Dellaripa PF, Oddis CV, Ascherman DP. Identification of citrullinated hsp90 isoforms as novel autoantigens in rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheum* 2013; **65**: 869-879 [PMID: 23400887 DOI: 10.1002/art.37881]
 - 92 **Gono T**, Kawaguchi Y, Hara M, Masuda I, Katsumata Y, Shinozaki M, Ota Y, Ozeki E, Yamanaka H. Increased ferritin predicts development and severity of acute interstitial lung disease as a complication of dermatomyositis. *Rheumatology (Oxford)* 2010; **49**: 1354-1360 [PMID: 20385617 DOI: 10.1093/rheumatology/keq073]
 - 93 **Rosas IO**, Richards TJ, Konishi K, Zhang Y, Gibson K, Lokshin AE, Lindell KO, Cisneros J, Macdonald SD, Pardo A, Sciruba F, Dauber J, Selman M, Gochuico BR, Kaminski N. MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. *PLoS Med* 2008; **5**: e93 [PMID: 18447576 DOI: 10.1371/journal.pmed.0050093]
 - 94 **Ascherman DP**. Interstitial lung disease in rheumatoid arthritis. *Curr Rheumatol Rep* 2010; **12**: 363-369 [PMID: 20628839 DOI: 10.1007/s11926-010-0116-z]
 - 95 **Kinoshita F**, Hamano H, Harada H, Kinoshita T, Igishi T, Hagino H, Ogawa T. Role of KL-6 in evaluating the disease severity of rheumatoid lung disease: comparison with HRCT. *Respir Med* 2004; **98**: 1131-1137 [PMID: 15526815 DOI: 10.1016/j.rmed.2004.04.003]
 - 96 **Bonella F**, Costabel U. Biomarkers in connective tissue disease-associated interstitial lung disease. *Semin Respir Crit Care Med* 2014; **35**: 181-200 [PMID: 24668534 DOI: 10.1055/s-0034-1371527]
 - 97 **de Lauretis A**, Veeraraghavan S, Renzoni E. Review series: Aspects of interstitial lung disease: connective tissue disease-associated interstitial lung disease: how does it differ from IPF? How should the clinical approach differ? *Chron Respir Dis* 2011; **8**: 53-82 [PMID: 21339375 DOI: 10.1177/1479972310393758]
 - 98 **Kim EJ**, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, Lee JS, King TE, Collard HR. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2010; **35**: 1322-1328 [PMID: 19996193 DOI: 10.1183/09031936.00092309]
 - 99 **Tsuchiya Y**, Takayanagi N, Sugiura H, Miyahara Y, Tokunaga D, Kawabata Y, Sugita Y. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. *Eur Respir J* 2011; **37**: 1411-1417 [PMID: 20884744 DOI: 10.1183/09031936.0019210]
 - 100 **Skare TL**, Nakano I, Escuissati DL, Batistetti R, Rodrigues Tde O, Silva MB. Pulmonary changes on high-resolution computed tomography of patients with rheumatoid arthritis and their association with clinical, demographic, serological and therapeutic variables. *Rev Bras Reumatol* 2011; **51**: 325-330, 336-7 [PMID: 21779709 DOI: 10.1590/S0482-50042011000400005]
 - 101 **Saketkoo LA**, Mittoo S, Huscher D, Khanna D, Dellaripa PF, Distler O, Flaherty KR, Frankel S, Oddis CV, Denton CP, Fischer A, Kowal-Bielecka OM, LeSage D, Merkel PA, Phillips K, Pittrow D, Swigris J, Antoniou K, Baughman RP, Castellino FV, Christmann RB, Christopher-Stine L, Collard HR, Cottin V, Danoff S, Highland KB, Hummers L, Shah AA, Kim DS, Lynch DA, Miller FW, Proudman SM, Richeldi L, Ryu JH, Sandorfi N, Sarver C, Wells AU, Strand V, Matteson EL, Brown KK, Seibold JR. Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials. *Thorax* 2014; **69**: 428-436 [PMID: 24368713 DOI: 10.1136/thoraxjnl-2013-204202]
 - 102 **Bradley B**, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, Hirani N, Hubbard R, Lake F, Millar AB, Wallace WA, Wells AU, Whyte MK, Wilsher ML. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; **63** Suppl 5: v1-58 [PMID: 18757459 DOI: 10.1136/thx.2008.101691]
 - 103 **ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories**. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 1111-117 [PMID: 12091180 DOI: 10.1164/ajrccm.166.1.atl102]
 - 104 **Guyatt GH**, Townsend M, Keller J, Singer J, Nogradi S. Measuring functional status in chronic lung disease: conclusions from a randomized control trial. *Respir Med* 1991; **85** Suppl B: 17-21; discussion 33-37 [PMID: 1759016 DOI: 10.1016/S0954-6111(06)80164-2]
 - 105 **Jones PW**, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; **145**: 1321-1327 [PMID: 1595997 DOI: 10.1164/ajrccm/145.6.1321]
 - 106 **Chang JA**, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. *Chest* 1999; **116**: 1175-1182 [PMID: 10559073 DOI: 10.1378/chest.116.5.1175]
 - 107 **American Thoracic Society; European Respiratory Society**. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002; **165**: 277-304 [PMID: 11790668 DOI: 10.1164/

- ajrcm.165.2.ats01]
- 108 **Tanaka N**, Kim JS, Newell JD, Brown KK, Cool CD, Meehan R, Emoto T, Matsumoto T, Lynch DA. Rheumatoid arthritis-related lung diseases: CT findings. *Radiology* 2004; **232**: 81-91 [PMID: 15166329 DOI: 10.1148/radiol.2321030174]
- 109 **Raghu G**, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; **183**: 788-824 [PMID: 21471066 DOI: 10.1164/rccm.2009-040GL]
- 110 **Assayag D**, Elicker BM, Urbania TH, Colby TV, Kang BH, Ryu JH, King TE, Collard HR, Kim DS, Lee JS. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. *Radiology* 2014; **270**: 583-588 [PMID: 24126367 DOI: 10.1148/radiol.13130187]
- 111 **Pérez-Dórame R**, Mejía M, Mateos-Toledo H, Rojas-Serrano J. Rheumatoid arthritis-associated interstitial lung disease: Lung inflammation evaluated with high resolution computed tomography scan is correlated to rheumatoid arthritis disease activity. *Reumatol Clin* 2015; **11**: 12-16 [PMID: 24913966 DOI: 10.1016/j.reuma.2014.02.007]
- 112 **McDonagh J**, Greaves M, Wright AR, Heycock C, Owen JP, Kelly C. High resolution computed tomography of the lungs in patients with rheumatoid arthritis and interstitial lung disease. *Br J Rheumatol* 1994; **33**: 118-122 [PMID: 8162474 DOI: 10.1093/rheumatology/33.2.118]
- 113 **Lardinois D**, Weder W, Hany TF, Kamel EM, Korom S, Seifert B, von Schulthess GK, Steinert HC. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003; **348**: 2500-2507 [PMID: 12815135 DOI: 10.1056/NEJMoa022136]
- 114 **Groves AM**, Win T, Screaton NJ, Berovic M, Endozo R, Booth H, Kayani I, Menezes LJ, Dickson JC, Ell PJ. Idiopathic pulmonary fibrosis and diffuse parenchymal lung disease: implications from initial experience with 18F-FDG PET/CT. *J Nucl Med* 2009; **50**: 538-545 [PMID: 19289428 DOI: 10.2967/jnumed.108.057901]
- 115 **Chen DL**, Schuster DP. Imaging pulmonary inflammation with positron emission tomography: a biomarker for drug development. *Mol Pharm* 2006; **3**: 488-495 [PMID: 17009847 DOI: 10.1021/mp060050w]
- 116 **Gaine S**. Pulmonary hypertension. *JAMA* 2000; **284**: 3160-3168 [PMID: 11135781 DOI: 10.1001/jama.284.24.3160]
- 117 **Rojas-Serrano J**, González-Velásquez E, Mejía M, Sánchez-Rodríguez A, Carrillo G. Interstitial lung disease related to rheumatoid arthritis: evolution after treatment. *Reumatol Clin* 2012; **8**: 68-71 [PMID: 22341526 DOI: 10.1016/j.reuma.2011.12.008]
- 118 **Steen VD**, Owens GR, Redmond C, Rodnan GP, Medsger TA. The effect of D-penicillamine on pulmonary findings in systemic sclerosis. *Arthritis Rheum* 1985; **28**: 882-888 [PMID: 4026885 DOI: 10.1002/art.1780280807]
- 119 **Steen VD**, Medsger TA, Rodnan GP. D-Penicillamine therapy in progressive systemic sclerosis (scleroderma): a retrospective analysis. *Ann Intern Med* 1982; **97**: 652-659 [PMID: 7137731 DOI: 10.7326/0003-4819-97-5-652]
- 120 **van der Schee AC**, Dinkla BA, Festen JJ. Penicillamine for interstitial lung disease in rheumatoid arthritis. *Respiration* 1989; **56**: 134-136 [PMID: 2602667 DOI: 10.1159/000195788]
- 121 **Chang HK**, Park W, Ryu DS. Successful treatment of progressive rheumatoid interstitial lung disease with cyclosporine: a case report. *J Korean Med Sci* 2002; **17**: 270-273 [PMID: 11961317]
- 122 **Cohen JM**, Miller A, Spiera H. Interstitial pneumonitis complicating rheumatoid arthritis. Sustained remission with azathioprine therapy. *Chest* 1977; **72**: 521-524 [PMID: 908223 DOI: 10.1378/chest.72.4.521]
- 123 **Zhang L**, Mo H, Zhu M, Wang L. Effect of cyclophosphamide on cytokines in patients with primary Sjögren's syndrome-associated interstitial lung disease in South China. *Rheumatol Int* 2013; **33**: 1403-1407 [PMID: 23143555 DOI: 10.1007/s00296-012-2561-7]
- 124 **Nannini C**, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. *Arthritis Res Ther* 2008; **10**: R124 [PMID: 18937831 DOI: 10.1186/ar2534]
- 125 **Suwa A**, Hirakata M, Satoh S, Mimori T, Utsumi K, Inada S. Rheumatoid arthritis associated with methotrexate-induced pneumonitis: improvement with i.v. cyclophosphamide therapy. *Clin Exp Rheumatol* 1999; **17**: 355-358 [PMID: 10410272]
- 126 **Saketkoo LA**, Espinoza LR. Experience of mycophenolate mofetil in 10 patients with autoimmune-related interstitial lung disease demonstrates promising effects. *Am J Med Sci* 2009; **337**: 329-335 [PMID: 19295413 DOI: 10.1097/MAJ.0b013e31818d094b]
- 127 **Yiannopoulos G**, Pastromas V, Antonopoulos I, Katsiberis G, Kalliolias G, Liossis SN, Andonopoulos AP. Combination of intravenous pulses of cyclophosphamide and methylprednisolone in patients with systemic sclerosis and interstitial lung disease. *Rheumatol Int* 2007; **27**: 357-361 [PMID: 17021713 DOI: 10.1007/s00296-006-0217-1]
- 128 **Airò P**, Danieli E, Rossi M, Frassi M, Cavazzana I, Scarsi M, Grotto A, Franceschini F, Zambruni A. Intravenous cyclophosphamide for interstitial lung disease associated to systemic sclerosis: results with an 18-month long protocol including a maintenance phase. *Clin Exp Rheumatol* 2007; **25**: 293-296 [PMID: 17543156]
- 129 **Gallelli L**, Falcone D, Pelaia G, Renda T, Terracciano R, Malara N, Vatrella A, Sanduzzi A, D'Agostino B, Rossi F, Vancheri C, Maselli R, Marsico SA, Savino R. Interleukin-6 receptor superantagonist Sant7 inhibits TGF-beta-induced proliferation of human lung fibroblasts. *Cell Prolif* 2008; **41**: 393-407 [PMID: 18435790 DOI: 10.1111/j.1365-2184.2008.00538.x]
- 130 **Mohr M**, Jacobi AM. Interstitial lung disease in rheumatoid arthritis: response to IL-6R blockade. *Scand J Rheumatol* 2011; **40**: 400-401 [PMID: 21961704 DOI: 10.3109/03009742.2011.599072]
- 131 **Bargagli E**, Galeazzi M, Rottoli P. Infliximab treatment in a patient with rheumatoid arthritis and pulmonary fibrosis. *Eur Respir J* 2004; **24**: 708 [PMID: 15459153 DOI: 10.1183/09031936.04.00076904]
- 132 **Vassallo R**, Matteson E, Thomas CF. Clinical response of rheumatoid arthritis-associated pulmonary fibrosis to tumor necrosis factor-alpha inhibition. *Chest* 2002; **122**: 1093-1096 [PMID: 12226061 DOI: 10.1378/chest.122.3.1093]
- 133 **Antonίου KM**, Mamoulaki M, Malagari K, Kritikos HD, Bouros D, Siafakas NM, Boumpas DT. Infliximab therapy in pulmonary fibrosis associated with collagen vascular disease. *Clin Exp Rheumatol* 2007; **25**: 23-28 [PMID: 17417986]
- 134 **Schultz R**, Mattila J, Gappa M, Verronen P. Development of progressive pulmonary interstitial and intra-alveolar cholesterol granulomas (PICG) associated with therapy-resistant chronic systemic juvenile arthritis (CJA). *Pediatr Pulmonol* 2001; **32**: 397-402 [PMID: 11596165 DOI: 10.1002/ppul.1149]
- 135 **Wang Y**, Xu SQ, Xu JH, Ding C. Treatment with etanercept in a patient with rheumatoid arthritis-associated interstitial lung disease. *Clin Med Insights Case Rep* 2011; **4**: 49-52 [PMID: 22084614 DOI: 10.4137/CCRep.S8150]
- 136 **Sakaida H**, Komase Y, Takemura T. Organizing pneumonia in a patient with rheumatoid arthritis treated with etanercept. *Mod Rheumatol* 2010; **20**: 611-616 [PMID: 20585825 DOI: 10.1007/s10165-010-0327-1]
- 137 **Atkins SR**, Turesson C, Myers JL, Tazelaar HD, Ryu JH, Matteson EL, Bongartz T. Morphologic and quantitative assessment of CD20+ B cell infiltrates in rheumatoid arthritis-associated nonspecific interstitial pneumonia and usual interstitial pneumonia. *Arthritis Rheum* 2006; **54**: 635-641 [PMID: 16447242 DOI: 10.1002/art.21758]
- 138 **Matteson EL**, Bongartz T, Ryu JH, Crowson CS, Hartman TE, Dellaripa PF. Open-Label, Pilot Study of the Safety and Clinical Effects of Rituximab in Patients with Rheumatoid Arthritis-Associated

- Interstitial Pneumonia. *Open J Rheumatol Autoimmune Dis* 2012; **2**: 53-58 [DOI: 10.4236/ojra.2012.23011]
- 139 **Dass SF**, Atzeni F, Vital E, Bingham S, Buch M, Beirne P, Emery P. Safety of rituximab in patients with rheumatoid arthritis and concomitant lung disease. *Ann Rheum Dis* 2011; **70** Suppl 3: 71
 - 140 **Romero FI**, Recuero S, Gomez-Seco J, Rodriguez-Nieto MJ, Presa T, Mahillo I, Serrano C, Herrero-Beaumont G, Sánchez-Pernaute O. Safety and clinical response to rituximab in patients with connective tissue disease-associated interstitial lung disease: Preliminary results. *Ann Rheum Dis* 2013; **71** Suppl 3: 684
 - 141 **Becerra E**, Cambridge G, Leandro MJ. Safety and efficacy of rituximab in patients with rheumatoid arthritis and lung involvement. [Abstract]. *Ann Rheum Dis* 2012; **64**: Suppl 10: 502 [DOI: 10.1002/art.38237]
 - 142 **Jiménez-Alvarez L**, Arreola JL, Ramírez-Martínez G, Ortiz-Quintero B, Gaxiola M, Reynoso-Robles R, Avila-Moreno F, Urrea F, Pardo A, Selman M, Zúñiga J. The effect of CTLA-4lg, a CD28/B7 antagonist, on the lung inflammation and T cell subset profile during murine hypersensitivity pneumonitis. *Exp Mol Pathol* 2011; **91**: 718-722 [PMID: 21945736 DOI: 10.1016/j.yexmp.2011.09.010]
 - 143 **Schachna L**, Medsger TA, Dauber JH, Wigley FM, Braunstein NA, White B, Steen VD, Conte JV, Yang SC, McCurry KR, Borja MC, Plaskon DE, Orens JB, Gelber AC. Lung transplantation in scleroderma compared with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension. *Arthritis Rheum* 2006; **54**: 3954-3961 [PMID: 17133609 DOI: 10.1002/art.22264]
 - 144 **Yazdani A**, Singer LG, Strand V, Gelber AC, Williams L, Mittoo S. Survival and quality of life in rheumatoid arthritis-associated interstitial lung disease after lung transplantation. *J Heart Lung Transplant* 2014; **33**: 514-520 [PMID: 24630861 DOI: 10.1016/j.healun.2014.01.858]
 - 145 **Nagai S**, Hamada K, Shigematsu M, Taniyama M, Yamauchi S, Izumi T. Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. *Intern Med* 2002; **41**: 1118-1123 [PMID: 12521199 DOI: 10.2169/internalmedicine.41.1118]
 - 146 **Mittoo S**, Jacob T, Craig A, Bshouty Z. Treatment of pulmonary hypertension in patients with connective tissue disease and interstitial lung disease. *Can Respir J* 2010; **17**: 282-286 [PMID: 21165350]
 - 147 **Kameda H**, Suzuki M, Takeuchi T. Platelet-derived growth factor as a therapeutic target for systemic autoimmune diseases. *Drug Target Insights* 2007; **2**: 239-247 [PMID: 21901078 DOI: 10.4137/DTI.S0]
 - 148 **Watanabe K**, Tajima S, Tanaka J, Moriyama H, Nakayama H, Terada M, Takada T, Suzuki E, Narita I. Effects of anticoagulant therapy for rapidly progressive interstitial pneumonias. *Nihon Kokyuki Gakkai Zasshi* 2011; **49**: 407-412 [PMID: 21735740]
 - 149 **Cu A**, Ye Q, Sarria R, Nakamura S, Guzman J, Costabel U. N-acetylcysteine inhibits TNF-alpha, sTNFR, and TGF-beta1 release by alveolar macrophages in idiopathic pulmonary fibrosis in vitro. *Sarcoidosis Vasc Diffuse Lung Dis* 2009; **26**: 147-154 [PMID: 20560295]
 - 150 **Martínez FJ**, de Andrade JA, Anstrom KJ, King TE, Raghu G. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; **370**: 2093-2101 [PMID: 24836309 DOI: 10.1056/NEJMoa1401739]
 - 151 **Rosato E**, Rossi C, Molinaro I, Giovannetti A, Pisarri S, Salsano F. Long-term N-acetylcysteine therapy in systemic sclerosis interstitial lung disease: a retrospective study. *Int J Immunopathol Pharmacol* 2011; **24**: 727-733 [PMID: 21978705]
 - 152 **Assayag D**, Lubin M, Lee JS, King TE, Collard HR, Ryerson CJ. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. *Respirology* 2014; **19**: 493-500 [PMID: 24372981 DOI: 10.1111/resp.12234]
 - 153 **Brown KK**. Rheumatoid lung disease. *Proc Am Thorac Soc* 2007; **4**: 443-448 [PMID: 17684286 DOI: 10.1513/pats.200703-045MS]
 - 154 **Giles JT**, Danoff SK, Sokolove J, Wagner CA, Winchester R, Pappas DA, Siegelman S, Connors G, Robinson WH, Bathon JM. Association of fine specificity and repertoire expansion of anticitrullinated peptide antibodies with rheumatoid arthritis associated interstitial lung disease. *Ann Rheum Dis* 2014; **73**: 1487-1494 [PMID: 23716070 DOI: 10.1136/annrheumdis-2012-203160]
 - 155 **Solomon JJ**, Ryu JH, Tazelaar HD, Myers JL, Tuder R, Cool CD, Curran-Everett D, Fischer A, Swigris JJ, Brown KK. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). *Respir Med* 2013; **107**: 1247-1252 [PMID: 23791462 DOI: 10.1016/j.rmed.2013.05.002]
 - 156 **Richman NC**, Yazdany J, Graf J, Chernitskiy V, Imboden JB. Extraarticular manifestations of rheumatoid arthritis in a multiethnic cohort of predominantly Hispanic and Asian patients. *Medicine (Baltimore)* 2013; **92**: 92-97 [PMID: 23429352 DOI: 10.1097/MD.0b013e318289ce01]
 - 157 **Zou YQ**, Li YS, Ding XN, Ying ZH. The clinical significance of HRCT in evaluation of patients with rheumatoid arthritis-associated interstitial lung disease: a report from China. *Rheumatol Int* 2012; **32**: 669-673 [PMID: 21132550 DOI: 10.1007/s00296-010-1665-1]
 - 158 **Mohd Noor N**, Mohd Shahrir MS, Shahid MS, Abdul Manap R, Shahizon Azura AM, Azhar Shah S. Clinical and high resolution computed tomography characteristics of patients with rheumatoid arthritis lung disease. *Int J Rheum Dis* 2009; **12**: 136-144 [PMID: 20374331 DOI: 10.1111/j.1756-185X.2009.01376.x]
 - 159 **Al-Ghamdi A**, Attar SM. Extra-articular manifestations of rheumatoid arthritis: a hospital-based study. *Ann Saudi Med* 2009; **29**: 189-193 [PMID: 19448378]
 - 160 **Teh CL**, Wong JS. The pattern and clinical manifestations of rheumatoid arthritis in Sarawak General Hospital. *Clin Rheumatol* 2008; **27**: 1437-1440 [PMID: 18773254 DOI: 10.1007/s10067-008-0945-6]
 - 161 **Bharadwaj A**, Haroon N. Interstitial lung disease and neuropathy as predominant extra-articular manifestations in patients with rheumatoid arthritis: a prospective study. *Med Sci Monit* 2005; **11**: CR498-CR502 [PMID: 16192902]
 - 162 **Zrour SH**, Touzi M, Bejia I, Golli M, Rouatbi N, Sakly N, Younes M, Tabka Z, Bergaoui N. Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis. Prospective study in 75 patients. *Joint Bone Spine* 2005; **72**: 41-47 [PMID: 15681247 DOI: 10.1016/j.jbspin.2004.02.001]

P- Reviewer: La Montagna G, Nas Kemal, Martinez-Lostao L, Saviola G, Turiel M, Xue ML **S- Editor:** Tian YL **L- Editor:** A **E- Editor:** Wu HL



Osteoporosis in rheumatic diseases

Li-Xia Gao, Hong-Tao Jin, Xiao-Mei Xue, Jia Wang, Dong-Gang Liu

Li-Xia Gao, Hong-Tao Jin, Department of Rheumatology, the Second Hospital of Hebei Medical University, Shijiazhuang 050011, Hebei Province, China

Xiao-Mei Xue, Jia Wang, Dong-Gang Liu, Biomedical Engineering Center of Hebei Medical University, Shijiazhuang 050011, Hebei Province, China

Author contributions: Gao LX wrote the paper and searched the literature; Jin HT performed literature retrieval and analysis; Xue XM and Wang J revised the paper; Liu DG designed the review.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dong-Gang Liu, PhD, Professor, Biomedical Engineering Center of Hebei Medical University, No. 9 Tiyu North Street, Shijiazhuang 050011, Hebei Province, China. dgliu_hb@163.com

Telephone: +86-311-85917868

Fax: +86-311-85917868

Received: June 24, 2014

Peer-review started: June 25, 2014

First decision: August 28, 2014

Revised: September 19, 2014

Accepted: October 28, 2014

Article in press: October 29, 2014

Published online: March 12, 2015

Abstract

Rheumatic diseases, characterized by chronic inflammation and damage to various organs and systems, include systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis and other connective tissue diseases. Bone is a target in many inflammatory rheumatic diseases. In recent years, the survival of patients with rheumatic diseases has increased markedly and the relationship between rheumatic diseases and osteoporosis (OP) has become more prominent. OP and related fragility fractures increase the morbidity

and mortality of rheumatic disease. The cause of OP in rheumatic diseases is complex. The pathogenesis of OP in rheumatic diseases is multifactorial, including disease and treatment-related factors. Osteoimmunology, a crosstalk between inflammatory and bone cells, provides some insight into the pathogenesis of bone loss in systematic inflammatory diseases. The aim of this article is to review different risk factors in rheumatic diseases. Several factors play a role, such as chronic inflammation, immunological factors, traditional factors, metabolism and drug factors. Chronic inflammation is the most important risk factor and drug treatment is complex in patients with OP and rheumatic disease. Attention should be paid to bone loss in rheumatic disease. Optimal treatment of the underlying rheumatic disease is the first step towards prevention of OP and fractures. Apart from that, a healthy lifestyle is important as well as calcium and vitamin D supplementation. Bisphosphonates or denosumab might be necessary for patients with a low T score.

Key words: Rheumatic diseases; Osteoporosis; Systemic lupus erythematosus; Rheumatoid arthritis; Spondyloarthritis; Chronic inflammation

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Osteoporosis (OP) and related fractures are one of important complications for patients with rheumatic diseases. The pathogenesis of OP in rheumatic diseases is multifactorial, including disease and treatment-related factors. Chronic inflammation is the most important risk factor and drug treatment is complex in patients with OP and rheumatic disease. Controlling rheumatic disease effectively is an important way to prevent OP.

Gao LX, Jin HT, Xue XM, Wang J, Liu DG. Osteoporosis in rheumatic diseases. *World J Rheumatol* 2015; 5(1): 23-35 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i1/23.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i1.23>

INTRODUCTION

Rheumatic diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), ankylosing spondylitis (AS) and other connective tissue diseases. The characteristics of rheumatic disease are chronic inflammation and damage to various organs and systems. Rheumatic diseases can affect bone, muscle, periarticular attachment and soft tissue. Osteoporosis (OP) is a systemic bone disease characterized by low bone mass and disruption of bone microstructure, increasing skeletal fragility and resulting in fractures occurring easily. Bone mineral density (BMD) is commonly detected by dual-energy X-ray absorptiometry (DEXA). OP is defined by a T score of -2.5 or lower, that is, > 2.5 SD below the average density of a young normal adult.

The survival of patients with rheumatic diseases has increased dramatically during the past few decades. Patients with rheumatic diseases have an increased prevalence of long-term complications, such as cardiovascular diseases and OP^[1,2]. Bone is always involved in many inflammatory rheumatic diseases. OP and related fractures are one of the most important complications for patients with rheumatic diseases. Osteoporotic fractures and osteonecrosis increase the morbidity and mortality of rheumatic diseases^[3]. The pathogenesis of OP in rheumatic diseases is multifactorial and includes disease and treatment-related factors. Rheumatic diseases could result in bone loss through several mechanisms: inflammation, traditional risk factors and drug-induced factors^[4]. OP significantly decreases the quality of life of the person with rheumatic disease but the clinical manifestations of OP are not typical. Glucocorticoid-induced osteoporosis (GIOP) accounts for 5.0%-61.9% of adult rheumatic disease^[5]. Although OP has a high rate of prevalence among rheumatic disease patients, most patients do not receive adequate diagnostic evaluation and drug therapy. This article focuses on the relationship between rheumatic diseases and OP.

DATA SOURCES AND SEARCHES

A systematic search of the literature (from January 1, 1990 to August 31, 2014) was performed using the PubMed and Cochrane databases. We also searched for previously published systematic literature reviews.

The following keywords were used for the search: "rheumatic disease" and "bone mineral mass" or "osteoporosis"; "rheumatoid arthritis" and "bone mineral mass" or "osteoporosis"; "systemic lupus erythematosus" and "bone mineral mass" or "osteoporosis"; "ankylosing spondylitis" and "bone mineral mass" or "osteoporosis"; "systemic sclerosis" and "bone mineral mass" or "osteoporosis".

Study inclusion/exclusion criteria

The literature search was performed independently

by two of the authors and a consensus reached. The inclusion criteria for papers were as follows: (1) studies in English; (2) full text of articles available; (3) human patients with rheumatic disease; (4) randomized controlled clinical trials; and (5) diagnostic criteria of different rheumatic diseases met respective international diagnostic criteria. The exclusion criteria were as follows: (1) case reports; (2) reader comments; (3) duplicate publications; (4) literature without original data; and (5) studies with < 20 patients.

OP IN SLE

Prevalence and sex

SLE is characterized by a variety of clinical manifestations, a spectrum of autoantibodies and a multisystem involvement. There are debates about OP in SLE. The main controversies are about the prevalence of OP and the secondary debate is the dependence of glucocorticoids (GCs). However, all studies have demonstrated that bone loss is more common in patients with SLE than in the healthy human. Several cross-sectional studies have evaluated BMD and the prevalence of OP in SLE patients. There was a difference in the prevalence of OP in these studies but the results suggest a generalized reduction in BMD^[6]. The reported prevalence of osteopenia is 25%-74%, while that of OP is 1.4%-68%^[7]. SLE influences mainly reproductive females and is affected by the change of sex hormones. For women, osteopenia was found in 40% of patients, while OP was found in only 5%. Low body mass index (BMI), long-term disease damage and corticosteroid treatment were risk factors for low BMD in premenopausal SLE patients. Lumbar and femoral BMD of premenopausal patients with SLE was decreased and related to disease damage and long-term corticosteroid therapy^[8-13]. For postmenopausal SLE patients with long-term GC treatment, OP is always a common and terrible problem. The prevalence of lumbar spine OP is as high as 48%^[14,15]. Recently, a cross-sectional study investigated BMD in 67 women with SLE in a Mediterranean region and reported that the prevalence of osteopenia was 28%-46% and OP was 3%-9%^[16]. For men, although a few studies of OP in SLE have been reported, they have come to different conclusions. Two studies showed that bone mass in men with SLE was not decreased despite corticosteroid therapy^[17,18]. Another study reported different results, that low BMD and low body mass were prevalent for males with SLE. When SLE patients were compared with healthy controls, the Z scores of BMD at the femoral neck and spine were significantly lower in SLE^[19]. A recent cross-sectional and longitudinal study indicated that juvenile SLE patients had low bone mass and a decreased peak bone mass and juvenile-onset SLE had a high risk of OP in early adulthood^[20]. Another longitudinal study of OP in juvenile SLE

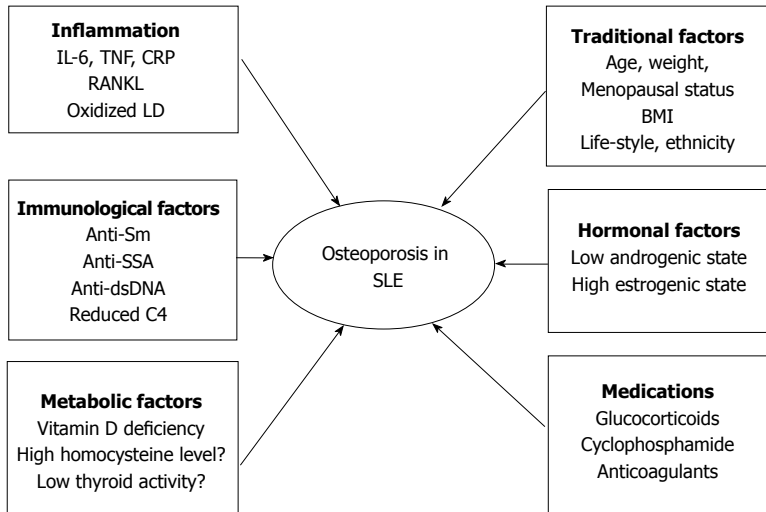


Figure 1 Risk factors of osteoporosis in systemic lupus erythematosus. SLE: Systemic lupus erythematosus; IL-6: Interleukin-6; TNF: Tumor necrosis factor; CRP: C-reactive protein; RANKL: Receptor activator of nuclear factor- κ B ligand; LDL: Low-density lipoprotein; BMI: Body mass index; Anti-Sm: Anti-Smith; Anti-dsDNA: Anti-double-stranded DNA.

indicated that BMD had a significant inverse correlation with the cumulative dose of corticosteroids^[21].

Risk factors

The reason for OP in SLE is considered to be multifactorial and includes inflammation, immune-mediated mechanisms, traditional OP risk factors, metabolic factors, serological factors and drug-induced adverse effects (Figure 1)^[7].

The inflammation associated with active disease contributes to the development of OP in SLE. Recent literature has affirmed an association between low BMD and the inflammatory feature of SLE. Several inflammation markers, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 and IL-6, can induce osteoclastogenesis which promotes the proliferation of precursor osteoclastic cells or activation of differentiated osteoclasts^[22]. Different studies have provided different views of the pathogenesis of inflammatory bone loss but now it is considered that the key osteoclastogenic cytokine, receptor activator of nuclear factor- κ B ligand (RANKL), plays an important role in the balance of osteoclasts and osteoblasts. Osteoprotegerin (OPG) is the physiological decoy receptor that moderates the biological activity of RANKL^[23]. SLE is a systemic autoimmune inflammatory disorder with increasing serum TNF- α , IL-1 and IL-6. These cytokines can increase and induce RANKL expression^[23,24]. The serum level of oxidized low-density lipoprotein (LDL) is increased in SLE^[25]. Oxidized lipids can induce increased production of RANKL and TNF by activating T cells. Both RANKL and TNF increase the activity and maturation of osteoclasts^[26]. A 5 year follow up study demonstrated that SLE patients had significant BMD loss in the femoral neck and hip. Disease activity and new organ damage could result in bone loss and new organ involvement was an independent predictor of bone loss at the femoral neck^[27].

Immune-mediated mechanisms are associated with OP of SLE and SLE *per se* contributes to the

deterioration in bone density, cortical microstructure and bone strength. SLE patients without GC treatment have a significantly lower real BMD at the femoral neck and hip and diminished radial total volumetric BMD and cortical area and thickness when compared with controls^[28]. SLE is marked by both humoral and cellular abnormalities, including multiple autoantibodies that may participate in the disease. The absence of anti-SSA and presence of anti-Sm were associated with higher BMD in the lumbar spine. The patients with positive anti-SSA were generally advised to avoid sun exposure, which may explain the relationship between the absence of anti-SSA and lower bone loss^[14]. Higher serum anti-double-stranded DNA level was an independent predictor of a higher 10 year probability of hip fracture and this reinforced the concept that the inflammatory state as reflected by high SLE disease activity might be an important driver for bone loss^[29]. Although clinical studies could not make a conclusion about an association between disease activity score and low BMD, low C4 levels could predict low spine BMD in SLE^[30]. The relationship between organ damage and bone loss was reported by several studies, organ damage resulted in bone loss at both the femoral and the lumbar level, and the relationship between cumulative disease damage and reduced BMD is independent of corticosteroid use^[31,32].

Metabolic factors are also risk factors for OP. Vitamin D deficiency, hyperhomocysteinemia and low thyroid activities are metabolic conditions that can induce bone loss in SLE. Vitamin D is a secosteroid hormone that regulates calcium homeostasis, bone mineralization and remodeling, as well as neuromuscular function. Many studies in the past decade have reported increased frequency of vitamin D deficiency among patients with SLE^[33-37]. The prevalence of vitamin D insufficiency in SLE patients ranged from 16% to 96% and the prevalence of vitamin D deficiency ranged from 4% to 54%^[38]. A number of factors contributed, such as avoidance of sunshine as a result of photosensitivity, dark skin

pigment, sun screen precautions, disease activity, renal failure, use of drugs, such as GCs, antimalarial and antiepileptic agents, and anti-vitamin D antibodies. Homocysteine (Hcy) modulates bone remodeling *via* several mechanisms, such as increased osteoclast activity, decreased osteoblast activity and direct action on the bone matrix^[39]. SLE patients have an increased level of plasma Hcy^[40,41] but no studies demonstrated an association between hyperhomocysteinemia and OP in SLE^[42].

The traditional factors, including age, low body weight and postmenopausal status, are all independent risk factors for OP in SLE. It is unclear if sex and ethnicity have an effect on bone loss in SLE; African-American women have lower hip and lumbar spine BMD compared with white women with SLE^[43]. The prevalence of OP in Chinese SLE patients with corticosteroids is 4%-6%, less than that reported in Caucasians (12%-18%)^[11]. Two studies have shown that white and non-African Caribbean races were a risk factor for OP in SLE patients^[44,45]. Daily dietary calcium intake did not correlate with BMD in premenopausal women with SLE^[46]. Smoking and alcohol have not been reported as risk factors for OP in lupus^[13,47] but alcohol use was associated with low BMD in Hong Kong men with lupus^[19].

Hormonal factors, for example, include the significant positive relationship between serum dehydroepiandrosterone sulfate and low BMD^[48].

The last factor is drug-induced adverse effects in SLE therapy. GCs are widely used for the therapy of SLE exacerbations and complications. GCs are a double-edged sword with respect to bone loss, are associated with the development of OP and fracture and can trigger significant bone loss. At the same time, they have good effects by controlling disease activity and systemic inflammation in bone^[7]. A dose-dependent relationship has been demonstrated between GC use and spinal bone loss in SLE. Significant bone loss was observed in the lumbar spine for SLE patients with a mean prednisolone dose of > 7.5 mg/d, but this phenomenon was not found in the hip^[12]. Hydroxychloroquine (HCQ) may act by inhibiting the change of 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D. An earlier study found that patients with SLE treated with HCQ had lower 1,25-dihydroxyvitamin D levels, although there were no differences in circulating 25-hydroxyvitamin D levels between treated and untreated patients^[34]. In contrast, some studies have shown that HCQ is a protecting factor for OP^[49]. It has been demonstrated that the treatment of HCQ is related to higher levels of 25-hydroxyvitamin D, which was probably a spurious effect of the drug at the expense of reducing the metabolically active form 1,25-dihydroxyvitamin D^[50]. Calcineurin inhibitors, such as cyclosporine A and tacrolimus, have been increasingly used in patients with SLE. The use of the calcineurin inhibitors may potentially lead to a vitamin D resistant state,

leading to impairment of the normal physiological effects of vitamin D^[51,52]. Other drugs used for SLE that play a role in bone loss are methotrexate (MTX), cyclophosphamide, anticonvulsants, oral anticoagulants and heparin^[53].

OP IN RA

Prevalence and sex

RA is a chronic inflammatory disorder in which an erosive, symmetric joint disorder maintains the center stage accompanied by a variable, but at times prominent, degree of extra-articular involvement. The inflammatory synovitis and damage of cartilage and bone is characteristic of RA patients. Bone involvement includes three types: periarticular osteopenia, bone erosion and systemic OP. There are two types of OP in RA: localized, occurring near to the site of inflamed joints, or generalized, involving the systemic bone. Local or periarticular bone loss is the typical radiographic sign in early RA. Systemic OP is prevalent in RA. So far, the use of biological therapy has not decreased the prevalence of OP in RA. RA patients have a lower bone mass in the appendicular and axial skeleton when compared with healthy controls, according to the conclusion of 10 cross-sectional studies^[54]. There was a twofold increase in RA in women aged 20-70 years. The prevalence of OP was 16.8% in the lumbar spine and 14.7% in the femur. It reached 31.5% in the lumbar spine and 28.6% in the femur for women aged 60-70 years^[55]. A multicenter cross-sectional study of RA and BMD indicated that the frequency of OP as assessed by DEXA was 28.8% at the lumbar spine and 36.2% at the femoral neck^[56]. A longitudinal study indicated that BMD loss was lower in men^[57]. A large study with 94 male RA patients concluded that a modest reduction in BMD was found only in patients aged 60-70 years. The percentage of BMD reduction in the femoral neck was 5.2% and the reduction in the hip was 6.9%, with no change in the spine. Despite a moderately low BMD, this report showed that the ratio of reduced BMD in men with RA was nearly twofold higher than in the control group^[58].

Risk factors

The reason for OP in RA patients is also multifactorial: factors related to the disease itself, antirheumatic drug use and traditional factors, such as low BMI, menopausal status, age and lack of physical exercise (Figure 2).

Local periarticular OP really reflects disease activity in early RA because the acute phase reactants are closely related to this phenomenon, but once periarticular OP appears, it is no longer a sign of disease activity^[59]. Generalized OP is a feature of established RA. Some literatures have shown an association between OP and proinflammatory cytokines, such as TNF- α , IL-1 and IL-6^[60], and these cytokines were independent risk factors of

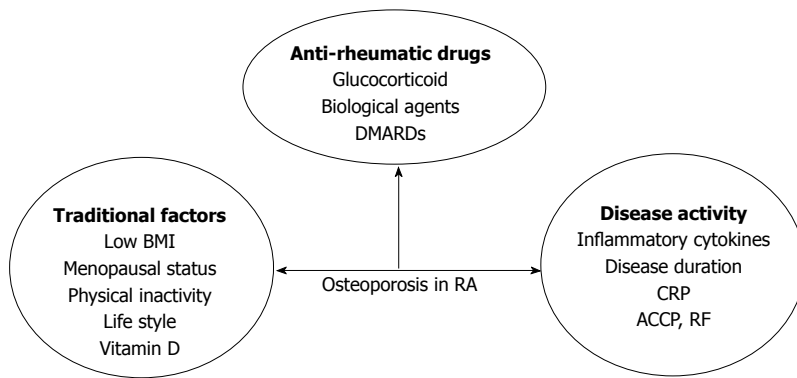


Figure 2 Risk factors for osteoporosis in rheumatoid arthritis. RA: Rheumatoid arthritis; BMI: Body mass index; DMARDs: Disease-modifying antirheumatic drugs; CRP: C-reactive protein; ACCP: Anti-cyclic citrullinated peptide; RF: Rheumatoid factor.

disease activity. IL-1 and IL-6, secreted by activated macrophages, synovial fibroblasts and T cells, result in synovial inflammation, bone damage and systemic manifestations of RA^[61,62]. Inflammation has an uncoupling effect on bone resorption and formation. In patients with active compared to inactive RA, bone resorption was increased, whereas bone formation was decreased. These cytokines are closely associated with osteoclast physiology as they extend survival and improve the activity of mature osteoclasts, mainly through RANKL-mediated and Wnt-signaling pathways^[63]. Anti-inflammatory treatment, especially with biological agents, in early RA reduces the rate of bone loss^[64]. However, there are some debates about the relationship between inflammation and bone loss in RA and recent data show that bone loss starts before inflammation and clinical disease^[65].

Osteoimmunology has attracted increased research attention and RA is also an autoimmune disease. There are many autoantibodies in RA, such as those against citrullinated proteins antibody (ACPA) and rheumatoid factor (RF). There are many data supporting the role of autoimmunity in bone destruction in RA. In RA, ACPA is an important prognostic factor. ACPA has a direct and independent stimulating effect on osteoclasts and induces elevated bone resorption^[66]. Bone loss occurs in RA patients displaying ACPA without signs of inflammation^[67]. ACPA-positive patients generally have not only higher disease activity and disability, but also more radiological damage^[67,68]. Healthy individuals with ACPA have low BMD compared with controls without ACPA and the thickness of cortical bone is significantly lower in healthy individuals positive for ACPA^[67]. The frequency of OP and lower BMD is higher in RF-positive patients^[55,69] and patients with high C-reactive protein (CRP) levels (> 20 mg/dL) are more likely to have a low BMD in the spine and hips^[57]. Immobility related to joint pain or damage aggravates bone loss^[70]. Disease-related disability, assessed by Health Assessment Questionnaire (HAQ) score, has nothing to do with BMD in the lumbar spine but is inversely related to BMD in the femoral neck and whole body^[71,72]. Disease activity and duration are also risk factors in RA and disease activity is the only reason for BMD loss in the lumbar spine. When active RA lasting more than 2

years is compared to inactive RA, mean bone loss in the former is higher.

The use of antirheumatic drugs plays an important role in OP in RA. There are some debates about the role of GCs in RA: on the one hand, low-dose corticosteroid therapy is associated with increased bone loss and fracture risk, but on the other hand, it effectively controls systemic inflammation. GIOP is the most common form of secondary OP. GCs can affect bone by several direct and indirect ways and affect both bone formation and resorption. Although high doses of GCs are related to bone loss, it is well known that GCs have a strong anti-inflammatory effect and low-dose GCs reduce localized bone loss in the hands. In RA patients with low doses of GCs or with rapidly tapered high-to-moderate dose induction therapy, the direct adverse effect of GCs on bone is counteracted by strong suppression of inflammation by GCs^[73-75]. The accumulative dose of steroids is more important for OP and there is no threshold dose. Disease-modifying antirheumatic drugs (DMARDs) have anti-inflammatory and structure-modifying properties, leading to better disease control in RA. Traditional DMARDs include MTX, leflunomide (LEF), sulfasalazine (SSZ), HCQ and gold agents. MTX is considered to be the cornerstone of RA treatment and is the most widely used agent. Osteopathy is reported in patients with malignant diseases treated with high-dose MTX; mostly reported in children with long-term maintenance therapy of MTX for acute leukemia^[76]. For postmenopausal women, MTX may be associated with OP because bone biopsy samples are consistent with osteoblast inhibition as a consequence of MTX action on the bone cells in RA patients when given at low doses for prolonged periods^[77]. Recently, more and more studies have shown no association between low-dose MTX and bone loss and multivariate covariance analysis has shown that reduced BMD is due to disease severity and activity and not to a direct negative effect of MTX on bone^[78-80]. The use of low-dose MTX was not associated with any change in BMD in patients without corticosteroid treatment^[81]. MTX seems to have some direct effects on bone metabolism and its anti-inflammatory effects reduce the negative effect of RA on bone. LEF is an isoxazole derivative that

inhibits the mitochondrial enzyme dihydroorotate dehydrogenase and prevents bone loss by its active metabolite that can inhibit osteoclastogenesis and osteoclast function^[82]. LEF can slow radiographic progression, both in terms of erosion and joint space narrowing. *In vitro*, SSZ inhibited osteoclastogenesis by acting on osteoclast precursor cells and regulating the RANKL-RANK-OPG interaction, primarily by reducing expression of RANKL on synovial fibroblasts and increasing expression of OPG^[83]. No studies have investigated whether LEF and SSZ have a sparing effect on BMD or bone strength in RA. Biological DMARDs dramatically improve inflammatory arthritis treatment and prognosis. Biological agents include TNF- α blockers (infliximab, adalimumab, etanercept, certolizumab and golimumab), agents counteracting B cell activity (rituximab) and T cell activation (abatacept), and anti-IL-6 agents (tocilizumab). All TNF- α blockers reduce the progression and formation of joint erosion and joint space narrowing. Infliximab^[84,85], adalimumab^[86-88], etanercept^[89-91] and rituximab^[92] can counteract local bone erosion and generalized bone loss. Tocilizumab has a positive, corrective effect on bone balance. It induces a significant decrease in bone resorption, rebalances bone turnover and increases the BMD of RA patients who have osteopenia at baseline^[93,94]. Fundamental studies have elucidated that inflammatory cytokines induce osteoclastogenesis through upregulation of RANKL, with subsequent activation of osteoclastogenesis which plays key role in bone loss in RA. Biological agents improve bone formation and reduce bone resorption by controlling active disease and inflammatory cytokine production^[95].

Traditional factors result in osteoporosis in RA. Both postmenopausal women and men with RA have a prevalence of OP. The percentage of OP in postmenopausal women is 55.7% and 50.5% in men, with the prevalence of OP higher than in premenopausal women (18%). OP risk factors are strongly dependent on gender and menopausal state^[96]. Female sex, increasing age, years since menopause, low weight, familial OP and low BMI are risk factors for osteopenia in patients with RA^[57,97-99].

OP IN SPONDYLOARTHRITIS

Spondyloarthritis (SpA) comprises a group of inflammatory diseases, such as psoriatic arthritis (PsA), reactive arthritis (Reiter's syndrome), enteropathic arthritis, undifferentiated spondyloarthropathy and AS. These diseases have some common characteristics, including imaging features, clinical manifestation and laboratory findings. Both sacroiliac joints and spine can be involved and to different degrees, peripheral joints.

Prevalence and sex

AS is the prototype of SpA and the most frequent subtype. AS mainly involves the axial joints, especially the sacroiliac joints. The spine, peripheral joints

and entheses can be affected to various degrees. Extraosseous new bone formation is considered a hallmark of AS. Although bone formation may affect the detection of BMD, OP always occurs in the early period of AS. The reported prevalence of OP varies from 19% to 62% in AS maybe because new bone formation and age distribution of the study cohorts make detecting BMD difficult^[100]. It was reported that the prevalence of OP in patients with early AS within 10 years after diagnosis was unexpected; 13% in the femoral neck and 16% in the lumbar spine^[101]. AS mainly affects young men and men with AS have had an annual total bone mass loss of 2.2% in longitudinal studies^[102]. Male patients with AS have decreased BMD in their lumbar spine and femoral neck, and femoral neck BMD in male AS patients is 10% lower than in age-matched male controls^[103,104].

In women, one study found a slight reduction in BMD in premenopausal women with early AS, but the difference was not significant^[105]. Another study to assess BMD of the hip and spine by DEXA and calcaneal quantitative ultrasound in women with AS showed that women with AS had reduced hip BMD and significantly fewer markers of bone formation than controls^[106]. In summary, OP is a significant complication in AS and significant OP can occur even in early disease. The spine is more likely to be damaged than the femur, with the spine still the most important site to diagnose OP in AS.

Risk factors

There are several reasons for OP in AS, such as proinflammatory cytokines, acute phase reactants, immobility, vitamin D, sex hormones, age and disease duration.

The systemic inflammatory cytokines are the core of OP during AS. Maybe inflammation of the entheses and synovium increase secretion of proinflammatory cytokines. Cytokines are a link between local and systemic inflammation on the one hand and result in bone resorption and BMD reduction on the other hand. IL-6, IL-1 and TNF- α are well-known osteoclast activators and play an important role in inflammation in AS. The RANK-RANKL system and its natural inhibitor OPG may be the key in bone-cytokine interrelationships. There is a strong correlation between bone turnover, proinflammatory cytokines and acute-phase reactants, for example erythrocyte sedimentation rate (ESR)^[107]. Low BMD is related to high biochemical markers of bone resorption, inflammatory activity and low OPG serum levels in AS patients^[108]. Longer disease duration, Bath AS Functional Index (BASFI) and Bath AS Disease Activity Index are also factors associated with OP^[100]. Low hip BMD was related to low BMI and high BASFI and Bath AS Radiology Index-total (BASRI-t) score and low lateral spinal BMD was associated with BASRI-t score^[109]. In addition, high disease burden, immobility and syndesmophyte formation increased the risk of

OP^[110].

Genetic factors and FokI genotypes of the vitamin D receptor gene were significantly associated with the spine as independent predictors of low BMD, which was also affected by BMI, inflammatory level and degree of pain. CRP and ESR values were also closely related to FokI genotypes in male AS patients^[111].

Metabolic factors are also risk factors for OP in AS. Bone loss is correlated with low serum sex steroid hormone levels in AS^[107,108,112]. Bone loss in AS is associated with endocrine mechanisms such as parathyroid hormone, impaired calcium and vitamin D absorption^[113].

In AS, traditional risk factors including a positive family history, older age, low BMI, Caucasian race, postmenopausal status in women or low androgen levels in men, low dietary calcium intake and vitamin D deficiency are risk factors for OP^[107].

Therapy for AS mainly involves nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, biological agents including infliximab, etanercept, adalimumab and anakinra, and conventional DMARDs, including MTX, SSZ and LEF. Some NSAIDs inhibit prostaglandin synthesis which has anabolic effects on bone and is thought to be related to higher BMD in men and women^[16,114]. However, 16 patients continued NSAIDs during the 24 mo follow-up period and data were inconclusive on the effect of NSAID use on BMD^[115]. Studies have shown that TNF- α blockers prevent systemic inflammation-induced bone loss in AS or SpA^[116-119]. In a larger cohort of 106 patients with SpA receiving infliximab or etanercept, patients had great improvement in the spine and hip BMD scores; the mean BMD scores in the lumbar spine reached 5.8% and increased by 2.3% in the total femur after 2 years follow-up^[120]. A recent study included seven longitudinal studies and one randomized control trial and studied the effect of TNF inhibitors on BMD in 568 AS patients with a minimum follow-up period of 1 year. They found that lumbar spine BMD increased by 5.1% and total hip BMD increased by 1.8% after 1 year of treatment with TNF inhibitors and lumbar spine BMD increased by 8.6% and total hip BMD increased by 2.5% after 2 years. So, they concluded that TNF inhibitors maintain femoral neck BMD homeostasis and increase BMD in the lumbar spine and hip for up to 2 years^[121]. Corticosteroids are used less often in AS so there have been few studies about GCs and OP in AS. We have not searched the literature about change of BMD in AS after using DMARDs treatment until now. Drug-related factors play an important role in OP for AS.

OP in other types of SpA

There are only a few studies about bone loss in other forms of SpA such as PsA in OP. The involvement of bone in PsA affects not only mechanisms of bone loss but also bone formation. Periarticular bone loss and

general bone loss are present. PsA patients were found to have periarticular bone loss in early disease but overall BMD values are higher than in RA patients^[122]. There are conflicting data about bone loss and bone turnover markers in patients with PsA, with some studies showing evidence of association with low BMD and some not, especially systemic OP^[123]. Some clinical studies conclude that BMD in patients with PsA has no significant decrease^[124-126], but bone biopsies suggest a latent high osteopathy^[127]. Recently, some literatures have indicated that the prevalence of OP increased in PsA patients, especially those with longer disease duration and disability^[128,129]. When PsA patients were compared with age-matched controls, BMD in the femoral neck and lumbar spine was found to be reduced^[130]. Bone demineralization occurs in 11% of young women, 47% of postmenopausal women and 29% men with non-axial PsA. OP is related to HAQ score, reflecting articular function^[131].

OP IN OTHER RHEUMATIC DISEASES

SSc, dermatomyositis (DM)/polymyositis (PM) and Behcet's disease (BD) are also rheumatic diseases associated with OP.

OP in SSc

SSc is characterized by skin thickening and fibrosis. SSc can be classified into two subsets: diffuse and limited cutaneous SSc. Before 2004, a review concluded that it was unknown if patients with scleroderma have an increased prevalence of OP^[132]. Recently, another review analyzed 19 studies about BMD in SSc. Fifteen studies found that the prevalence of BMD was 27%-53.3% and that of OP was 3%-51.1% in SSc patients compared to controls. Ten studies reported a lower BMD in SSc patients and two studies suggested no difference. It was concluded that SSc patients had a risk of low BMD and fracture. The cause of OP was complex, involving traditional factors, SSc-specific risk factors and drug-related factors^[133]. After 2012, a Chinese study indicated that the whole body BMD of SSc patients was much lower than controls and there was no association between BMD and the severity of involvement of the skin and other systems, while advanced age, sex, menopause and low BMI were independently correlated with bone loss in the spine or hip in SSc patients^[134]. An Italian study reported that the BMD of SSc patients was significantly lower than controls in the lumbar spine, femoral neck and total femur and serum 25 hydroxyvitamin D3 was significantly lower. In scleroderma patients, serum levels of 25 hydroxyvitamin D3 were greatly associated with parathyroid hormone levels, BMD, stiffness index and bone turnover markers^[135]. A study about Spanish SSc patients showed that the prevalence of OP/osteopenia was high, reaching 77% in SSc patients, but there was no relationship between vitamin D and

low BMD^[136]. A cross-sectional study suggested that the prevalence of OP was 30% and fractures was 35% in SSc patients, they were higher than healthy controls (11% and 10%) and the degree was very similar to RA (32% and 33%). Age and vitamin D deficiency were thought to be risk factors for fracture in SSc^[137]. So far, SSc patients have a high risk of OP but the risk factors need further study.

OP in DM/PM

DM/PM are uncommon idiopathic and autoimmune myopathies with characteristic clinical symptoms of proximal symmetric muscle weakness, rashes and fatigue. OP/fracture is found in about one quarter of adult DM/PM patients. This bone alteration was correlated with lower BMI^[138]. Most studies support decreased bone density in juvenile DM patients^[139,140]. Low lean body mass and GC pulse treatment were the important factors for low hip BMD in juvenile DM patients^[141] and the RANKL/OPG ratio is elevated in children with juvenile DM^[142].

OP in BD

BD is a multisystem vasculitis. BD may be a risk factor for OP because the BMD in the lumbar spine is lower than in healthy controls. The serum levels of cytokines such as IL-1, IL-6, IL-2 and TNF- α are increased in BD and there is a negative correlation between IL-1 levels and femur neck BMD^[143]. On the contrary, two studies showed no significant BMD reduction in the lumbar spine and hip of BD patients^[144,145].

CONCLUSION

In summary, inflammatory rheumatic diseases are always accompanied by elevated bone loss and increased fracture rates. Attention should be paid to bone loss in rheumatic disease. OP in rheumatic disease is complex. Several factors take part in this process, such as the disease itself and traditional, metabolic and drug-related factors. Osteoimmunology, a crosstalk between inflammatory and skeletal component cells, has given some perceptions to the pathogenic mechanism of OP in systemic inflammatory diseases. Chronic inflammation plays a key role in OP for rheumatic disease and inflammatory cytokines regulate the homeostasis between bone formation and resorption. Fundamental studies have demonstrated that the RANKL-OPG system plays a major role in bone loss and inflammatory cytokines upregulate RANKL, which further activates osteoclastogenesis, resulting in OP. Clinical studies have shown that effective immunosuppressive therapy prevents bone loss. Thus, the first step to prevent OP and fractures is to control primary rheumatic disease activity. Apart from that, a healthy lifestyle is important with calcium and vitamin D supplementation and prevention of falls. Bisphosphonates or denosumab might be necessary

for patients with a low T score.

REFERENCES

- Dougados M**, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, Casado G, Detert J, El-Zorkany B, Emery P, Hajjaj-Hassouni N, Harigai M, Luo SF, Kurucz R, Maciel G, Mola EM, Montecucco CM, McInnes I, Radner H, Smolen JS, Song YW, Vonkeman HE, Winthrop K, Kay J. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis* 2014; **73**: 62-68 [PMID: 24095940 DOI: 10.1136/annrheumdis-2013-204223]
- Sineglazova AV**. Coronary atherosclerosis and osteoporosis in rheumatoid arthritis. *Vestn Rentgenol Radiol* 2013; **(1)**: 25-28 [PMID: 23700922]
- Gladman DD**, Chaudhry-Ahluwalia V, Ibañez D, Bogoch E, Urowitz MB. Outcomes of symptomatic osteonecrosis in 95 patients with systemic lupus erythematosus. *J Rheumatol* 2001; **28**: 2226-2229 [PMID: 11669161]
- Bultink IE**, Vis M, van der Horst-Bruinsma IE, Lems WF. Inflammatory rheumatic disorders and bone. *Curr Rheumatol Rep* 2012; **14**: 224-230 [PMID: 22477520 DOI: 10.1007/s11926-012-0252-8]
- Pereira RM**, Carvalho JF, Canalis E. Glucocorticoid-induced osteoporosis in rheumatic diseases. *Clinics (Sao Paulo)* 2010; **65**: 1197-1205 [PMID: 21243296 DOI: 10.1590/S1807-59322010001100024]
- García-Carrasco M**, Mendoza-Pinto C, Escárcega RO, Jiménez-Hernández M, Etchegaray Morales I, Munguía Realpozo P, Rebollo-Vázquez J, Soto-Vega E, Delezé M, Cervera R. Osteoporosis in patients with systemic lupus erythematosus. *Isr Med Assoc J* 2009; **11**: 486-491 [PMID: 19891237]
- Bultink IE**. Osteoporosis and fractures in systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2012; **64**: 2-8 [PMID: 22213721 DOI: 10.1002/acr.20568]
- Pons F**, Peris P, Guañabens N, Font J, Huguet M, Espinosa G, Ingelmo M, Muñoz-Gomez J, Setoain J. The effect of systemic lupus erythematosus and long-term steroid therapy on bone mass in pre-menopausal women. *Br J Rheumatol* 1995; **34**: 742-746 [PMID: 7551659 DOI: 10.1093/rheumatology/34.8.742]
- Kipen Y**, Buchbinder R, Forbes A, Strauss B, Littlejohn G, Morand E. Prevalence of reduced bone mineral density in systemic lupus erythematosus and the role of steroids. *J Rheumatol* 1997; **24**: 1922-1929 [PMID: 9330933]
- Formiga F**, Moga I, Nolla JM, Pac M, Mitjavila F, Roig-Escofet D. Loss of bone mineral density in premenopausal women with systemic lupus erythematosus. *Ann Rheum Dis* 1995; **54**: 274-276 [PMID: 7763104 DOI: 10.1136/ard.54.4.274]
- Li EK**, Tam LS, Young RP, Ko GT, Li M, Lau EM. Loss of bone mineral density in Chinese pre-menopausal women with systemic lupus erythematosus treated with corticosteroids. *Br J Rheumatol* 1998; **37**: 405-410 [PMID: 9619891 DOI: 10.1093/rheumatology/37.4.405]
- Jardinet D**, Lefebvre C, Depresseux G, Lambert M, Devogelaer JP, Houssiau FA. Longitudinal analysis of bone mineral density in pre-menopausal female systemic lupus erythematosus patients: deleterious role of glucocorticoid therapy at the lumbar spine. *Rheumatology (Oxford)* 2000; **39**: 389-392 [PMID: 10817771 DOI: 10.1093/rheumatology/39.4.389]
- Mendoza-Pinto C**, García-Carrasco M, Sandoval-Cruz H, Escárcega RO, Jiménez-Hernández M, Etchegaray-Morales I, Soto-Vega E, Muñoz-Guarneros M, López-Colombo A, Delezé-Hinojosa M, Cervera R. Risks factors for low bone mineral density in premenopausal Mexican women with systemic lupus erythematosus. *Clin Rheumatol* 2009; **28**: 65-70 [PMID: 18670734 DOI: 10.1007/s10067-008-0984-z]
- Mok CC**, Mak A, Ma KM. Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. *Lupus* 2005; **14**: 106-112 [PMID: 15751814 DOI: 10.1191/0961203305lu2039oa]

- 15 **Bhattoa HP**, Bettembuk P, Balogh A, Szegedi G, Kiss E. Bone mineral density in women with systemic lupus erythematosus. *Clin Rheumatol* 2002; **21**: 135-141 [PMID: 12086164 DOI: 10.1007/s10067-002-8272-9]
- 16 **Salman-Monte TC**, Torrente-Segarra V, Muñoz-Ortego J, Mojal S, Carbonell-Abelló J. Prevalence and predictors of low bone density and fragility fractures in women with systemic lupus erythematosus in a Mediterranean region. *Rheumatol Int* 2015; **35**: 509-515 [PMID: 25030324 DOI: 10.1007/s00296-014-3087-y]
- 17 **Formiga F**, Nolla JM, Mitjavila F, Bonnin R, Navarro MA, Moga I. Bone mineral density and hormonal status in men with systemic lupus erythematosus. *Lupus* 1996; **5**: 623-626 [PMID: 9116708 DOI: 10.1177/096120339600500612]
- 18 **Bhattoa HP**, Kiss E, Bettembuk P, Balogh A. Bone mineral density, biochemical markers of bone turnover, and hormonal status in men with systemic lupus erythematosus. *Rheumatol Int* 2001; **21**: 97-102 [PMID: 11765229 DOI: 10.1007/s00296-001-0149-8]
- 19 **Mok CC**, Ying SK, To CH, Ma KM. Bone mineral density and body composition in men with systemic lupus erythematosus: a case control study. *Bone* 2008; **43**: 327-331 [PMID: 18515206 DOI: 10.1016/j.bone.2008.04.003]
- 20 **Stagi S**, Cavalli L, Bertini F, Matucci Cerinic M, Luisa Brandi M, Falcini F. Cross-sectional and longitudinal evaluation of bone mass and quality in children and young adults with juvenile onset systemic lupus erythematosus (JSLE): role of bone mass determinants analyzed by DXA, PQCT and QUS. *Lupus* 2014; **23**: 57-68 [PMID: 24218395 DOI: 10.1177/0961203313511679]
- 21 **Trapani S**, Civinini R, Ermini M, Paci E, Falcini F. Osteoporosis in juvenile systemic lupus erythematosus: a longitudinal study on the effect of steroids on bone mineral density. *Rheumatol Int* 1998; **18**: 45-49 [PMID: 9782532 DOI: 10.1007/s002960050056]
- 22 **Manolagas SC**, Jilka RL. Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. *N Engl J Med* 1995; **332**: 305-311 [PMID: 7816067 DOI: 10.1056/NEJM199502023320506]
- 23 **Weitzmann MN**. The Role of Inflammatory Cytokines, the RANKL/OPG Axis, and the Immunosteletal Interface in Physiological Bone Turnover and Osteoporosis. *Scientifica* (Cairo) 2013; **2013**: 125705 [PMID: 24278766 DOI: 10.1155/2013/125705]
- 24 **Robak E**, Sysa-Jedrzejewska A, Dzikowska B, Torzecka D, Chojnowski K, Robak T. Association of interferon gamma, tumor necrosis factor alpha and interleukin 6 serum levels with systemic lupus erythematosus activity. *Arch Immunol Ther Exp* (Warsz) 1998; **46**: 375-380 [PMID: 9883317]
- 25 **Frostegård J**, Svenungsson E, Wu R, Gunnarsson I, Lundberg IE, Klareskog L, Hörkö S, Witztum JL. Lipid peroxidation is enhanced in patients with systemic lupus erythematosus and is associated with arterial and renal disease manifestations. *Arthritis Rheum* 2005; **52**: 192-200 [PMID: 15641060 DOI: 10.1002/art.20780]
- 26 **Svenungsson E**, Fei GZ, Jensen-Ustad K, de Faire U, Hamsten A, Frostegård J. TNF-alpha: a link between hypertriglyceridaemia and inflammation in SLE patients with cardiovascular disease. *Lupus* 2003; **12**: 454-461 [PMID: 12873047 DOI: 10.1191/0961203303lu4120a]
- 27 **Qian BP**, Qiu Y, Wang B, Zhu ZZ, Wang WJ, Ma WW. Unusual association of ankylosing spondylitis with congenital spinal deformity. *Spine* (Phila Pa 1976) 2010; **35**: E1512-E1515 [PMID: 21102281 DOI: 10.1097/BRS.0b013e3181f3cf63]
- 28 **Tang XL**, Griffith JF, Qin L, Hung VW, Kwok AW, Zhu TY, Kun EW, Leung PC, Li EK, Tam LS. SLE disease per se contributes to deterioration in bone mineral density, microstructure and bone strength. *Lupus* 2013; **22**: 1162-1168 [PMID: 23884986 DOI: 10.1177/0961203313498802]
- 29 **Mak A**, Lim JQ, Liu Y, Cheak AA, Ho RC. Significantly higher estimated 10-year probability of fracture in lupus patients with bone mineral density comparable to that of healthy individuals. *Rheumatol Int* 2013; **33**: 299-307 [PMID: 22441963 DOI: 10.1007/s00296-012-2389-1]
- 30 **Petri M**. Musculoskeletal complications of systemic lupus erythematosus in the Hopkins Lupus Cohort: an update. *Arthritis Care Res* 1995; **8**: 137-145 [PMID: 7654797 DOI: 10.1002/art.1790080305]
- 31 **Lee C**, Almagor O, Dunlop DD, Manzi S, Spies S, Chadha AB, Ramsey-Goldman R. Disease damage and low bone mineral density: an analysis of women with systemic lupus erythematosus ever and never receiving corticosteroids. *Rheumatology* (Oxford) 2006; **45**: 53-60 [PMID: 16278288 DOI: 10.1093/rheumatology/kei079]
- 32 **Mendoza-Pinto C**, García-Carrasco M, Sandoval-Cruz H, Muñoz-Guarneros M, Escárcega RO, Jiménez-Hernández M, Munguía-Realpozo P, Sandoval-Cruz M, Delezé-Hinojosa M, López-Colombo A, Cervera R. Risk factors of vertebral fractures in women with systemic lupus erythematosus. *Clin Rheumatol* 2009; **28**: 579-585 [PMID: 19224131 DOI: 10.1007/s10067-009-1105-3]
- 33 **Borba VZ**, Vieira JG, Kasamatsu T, Radominski SC, Sato EI, Lazaretti-Castro M. Vitamin D deficiency in patients with active systemic lupus erythematosus. *Osteoporos Int* 2009; **20**: 427-433 [PMID: 18600287 DOI: 10.1007/s00198-008-0676-1]
- 34 **Huisman AM**, White KP, Algra A, Harth M, Vieth R, Jacobs JW, Bijlsma JW, Bell DA. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. *J Rheumatol* 2001; **28**: 2535-2539 [PMID: 11708429]
- 35 **Tolosa SM**, Cole DE, Gladman DD, Ibañez D, Urowitz MB. Vitamin D insufficiency in a large female SLE cohort. *Lupus* 2010; **19**: 13-19 [PMID: 19897520]
- 36 **Yeap SS**, Othman AZ, Zain AA, Chan SP. Vitamin D levels: its relationship to bone mineral density response and disease activity in premenopausal Malaysian systemic lupus erythematosus patients on corticosteroids. *Int J Rheum Dis* 2012; **15**: 17-24 [PMID: 22324943 DOI: 10.1111/j.1756-185X.2011]
- 37 **Sumethkul K**, Boonyaratavej S, Kitumnuaypong T, Angthararuk S, Cheewasat P, Manadee N, Sumethkul V. The predictive factors of low serum 25-hydroxyvitamin D and vitamin D deficiency in patients with systemic lupus erythematosus. *Rheumatol Int* 2013; **33**: 1461-1467 [PMID: 23179257 DOI: 10.1007/s00296-012-2537-7]
- 38 **Mok CC**. Vitamin D and systemic lupus erythematosus: an update. *Expert Rev Clin Immunol* 2013; **9**: 453-463 [PMID: 23634739 DOI: 10.1586/eci.13.19]
- 39 **Vacek TP**, Kalani A, Voor MJ, Tyagi SC, Tyagi N. The role of homocysteine in bone remodeling. *Clin Chem Lab Med* 2013; **51**: 579-590 [PMID: 23449525 DOI: 10.1515/cclm-2012-0605]
- 40 **Sabio JM**, Vargas-Hitos JA, Martinez-Bordonado J, Navarrete-Navarrete N, Díaz-Chamorro A, Olvera-Porcel C, Zamora-Pasadas M, Jiménez-Alonso J. Relationship between homocysteine levels and hypertension in systemic lupus erythematosus. *Arthritis Care Res* (Hoboken) 2014; **66**: 1528-1535 [PMID: 24692389 DOI: 10.1002/acr.22340]
- 41 **Lazzerini PE**, Capecchi PL, Selvi E, Lorenzini S, Bisogno S, Galeazzi M, Laghi Pasini F. Hyperhomocysteinemia: a cardiovascular risk factor in autoimmune diseases? *Lupus* 2007; **16**: 852-862 [PMID: 17971357 DOI: 10.1177/0961203307084176]
- 42 **Rhew EY**, Lee C, Eksarko P, Dyer AR, Tily H, Spies S, Pope RM, Ramsey-Goldman R. Homocysteine, bone mineral density, and fracture risk over 2 years of followup in women with and without systemic lupus erythematosus. *J Rheumatol* 2008; **35**: 230-236 [PMID: 18203323]
- 43 **Lee C**, Almagor O, Dunlop DD, Chadha AB, Manzi S, Spies S, Ramsey-Goldman R. Association between African American race/ethnicity and low bone mineral density in women with systemic lupus erythematosus. *Arthritis Rheum* 2007; **57**: 585-592 [PMID: 17471525 DOI: 10.1002/art.22668]
- 44 **Lakshminarayanan S**, Walsh S, Mohanraj M, Rothfield N. Factors associated with low bone mineral density in female patients with systemic lupus erythematosus. *J Rheumatol* 2001; **28**: 102-108 [PMID: 11196509]
- 45 **Yee CS**, Crabtree N, Skan J, Amft N, Bowman S, Situnayake D, Gordon C. Prevalence and predictors of fragility fractures in systemic lupus erythematosus. *Ann Rheum Dis* 2005; **64**: 111-113 [PMID: 15608308 DOI: 10.1136/ard.2003.018127]

- 46 **Chong HC**, Chee SS, Goh EM, Chow SK, Yeap SS. Dietary calcium and bone mineral density in premenopausal women with systemic lupus erythematosus. *Clin Rheumatol* 2007; **26**: 182-185 [PMID: 16565892 DOI: 10.1007/s10067-006-0258-6]
- 47 **Almehed K**, Forsblad d'Elia H, Kvist G, Ohlsson C, Carlsten H. Prevalence and risk factors of osteoporosis in female SLE patients-extended report. *Rheumatology* (Oxford) 2007; **46**: 1185-1190 [PMID: 17500075 DOI: 10.1093/rheumatology/kem105]
- 48 **Formiga F**, Moga I, Nolla JM, Navarro MA, Bonnin R, Roig-Escofet D. The association of dehydroepiandrosterone sulphate levels with bone mineral density in systemic lupus erythematosus. *Clin Exp Rheumatol* 1997; **15**: 387-392 [PMID: 9272299]
- 49 **Boyanov M**, Robeva R, Popivanov P. Bone mineral density changes in women with systemic lupus erythematosus. *Clin Rheumatol* 2003; **22**: 318-323 [PMID: 14579164 DOI: 10.1007/s10067-003-0743-0]
- 50 **Ruiz-Irastorza G**, Egurbide MV, Olivares N, Martinez-Berriotxo A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. *Rheumatology* (Oxford) 2008; **47**: 920-923 [PMID: 18411213 DOI: 10.1093/rheumatology/ken121]
- 51 **Lee CT**, Ng HY, Lien YH, Lai LW, Wu MS, Lin CR, Chen HC. Effects of cyclosporine, tacrolimus and rapamycin on renal calcium transport and vitamin D metabolism. *Am J Nephrol* 2011; **34**: 87-94 [PMID: 21691056 DOI: 10.1159/000328874]
- 52 **Grenet O**, Bobadilla M, Chibout SD, Steiner S. Evidence for the impairment of the vitamin D activation pathway by cyclosporine A. *Biochem Pharmacol* 2000; **59**: 267-272 [PMID: 10609555 DOI: 10.1016/S0006-2952(99)00321-4]
- 53 **Di Munno O**, Mazzantini M, Delle Sedie A, Mosca M, Bombardieri S. Risk factors for osteoporosis in female patients with systemic lupus erythematosus. *Lupus* 2004; **13**: 724-730 [PMID: 15485112 DOI: 10.1191/0961203303lu1097oa]
- 54 **Deodhar AA**, Woolf AD. Bone mass measurement and bone metabolism in rheumatoid arthritis: a review. *Br J Rheumatol* 1996; **35**: 309-322 [PMID: 8624634 DOI: 10.1093/rheumatology/35.4.309]
- 55 **Haugeberg G**, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum* 2000; **43**: 522-530 [PMID: 10728744 DOI: 10.1002/1529-0131(200003)43]
- 56 **Sinigaglia L**, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, Frediani B, Cantatore F, Pellerito R, Bartolone S, La Montagna G, Adami S. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. *J Rheumatol* 2000; **27**: 2582-2589 [PMID: 11093437]
- 57 **Gough AK**, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. *Lancet* 1994; **344**: 23-27 [PMID: 7912297 DOI: 10.1016/S0140-6736(94)91049-9]
- 58 **Haugeberg G**, Uhlig T, Falch JA, Halse JI, Kvien TK. Reduced bone mineral density in male rheumatoid arthritis patients: frequencies and associations with demographic and disease variables in ninety-four patients in the Oslo County Rheumatoid Arthritis Register. *Arthritis Rheum* 2000; **43**: 2776-2784 [PMID: 11145036 DOI: 10.1002/1529-0131(200012)43]
- 59 **Dequeker J**, Maenaut K, Verwilghen J, Westhovens R. Osteoporosis in rheumatoid arthritis. *Clin Exp Rheumatol* 1995; **13** Suppl 12: S21-S26 [PMID: 8846540]
- 60 **Dischereit G**, Lange U. Osteoporosis - inflammatory effects on bone metabolism and fracture risk. *Z Orthop Unfall* 2014; **152**: 170-176 [PMID: 24760457 DOI: 10.1055/s-0034-1368247]
- 61 **Abdel Meguid MH**, Hamad YH, Swilam RS, Barakat MS. Relation of interleukin-6 in rheumatoid arthritis patients to systemic bone loss and structural bone damage. *Rheumatol Int* 2013; **33**: 697-703 [PMID: 22531887 DOI: 10.1007/s00296-012-2375-7]
- 62 **Abramson SB**, Amin A. Blocking the effects of IL-1 in rheumatoid arthritis protects bone and cartilage. *Rheumatology* (Oxford) 2002; **41**: 972-980 [PMID: 12209029]
- 63 **Maeda K**, Takahashi N, Kobayashi Y. Roles of Wnt signals in bone resorption during physiological and pathological states. *J Mol Med* (Berl) 2013; **91**: 15-23 [PMID: 23111637 DOI: 10.1007/s00109-012-0974-0]
- 64 **Haugeberg G**, Helgetveit KB, Førre Ø, Garen T, Sommerseth H, Proven A. Generalized bone loss in early rheumatoid arthritis patients followed for ten years in the biologic treatment era. *BMC Musculoskelet Disord* 2014; **15**: 289 [PMID: 25182527]
- 65 **Kleyer A**, Schett G. Arthritis and bone loss: a hen and egg story. *Curr Opin Rheumatol* 2014; **26**: 80-84 [PMID: 24276089 DOI: 10.1097/BOR.0000000000000007]
- 66 **Mustila A**, Korpela M, Haapala AM, Kautiainen H, Laasonen L, Möttönen T, Leirisalo-Repo M, Ilonen J, Järvenpää S, Luukkainen R, Hannonen P. Anti-citrullinated peptide antibodies and the progression of radiographic joint erosions in patients with early rheumatoid arthritis treated with FIN-RACo combination and single disease-modifying antirheumatic drug strategies. *Clin Exp Rheumatol* 2011; **29**: 500-505 [PMID: 21640044]
- 67 **Kleyer A**, Finzel S, Rech J, Manger B, Krieter M, Faustini F, Araujo E, Hueber AJ, Harre U, Engelke K, Schett G. Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies. *Ann Rheum Dis* 2014; **73**: 854-860 [PMID: 23520034 DOI: 10.1136/annrheumdis-2012-202958]
- 68 **Syversen SW**, Goll GL, van der Heijde D, Landewé R, Lie BA, Odegård S, Uhlig T, Gaarder PI, Kvien TK. Prediction of radiographic progression in rheumatoid arthritis and the role of antibodies against mutated citrullinated vimentin: results from a 10-year prospective study. *Ann Rheum Dis* 2010; **69**: 345-351 [PMID: 19648126 DOI: 10.1136/ard.2009.113092]
- 69 **Güler-Yüksel M**, Bijsterbosch J, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Roday HK, Peeters AJ, de Jonge-Bok JM, Breedveld FC, Dijkmans BA, Allaart CF, Lems WF. Bone mineral density in patients with recently diagnosed, active rheumatoid arthritis. *Ann Rheum Dis* 2007; **66**: 1508-1512 [PMID: 17456523 DOI: 10.1136/ard.2007.070839]
- 70 **Laan RF**, Buijs WC, Verbeek AL, Draad MP, Corstens FH, van de Putte LB, van Riel PL. Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. *Ann Rheum Dis* 1993; **52**: 21-26 [PMID: 8427509 DOI: 10.1136/ard.52.1.21]
- 71 **Dao HH**, Do QT, Sakamoto J. Bone mineral density and frequency of osteoporosis among Vietnamese women with early rheumatoid arthritis. *Clin Rheumatol* 2011; **30**: 1353-1361 [PMID: 21547438 DOI: 10.1007/s10067-011-1762-x]
- 72 **Book C**, Karlsson M, Akesson K, Jacobsson L. Disease activity and disability but probably not glucocorticoid treatment predicts loss in bone mineral density in women with early rheumatoid arthritis. *Scand J Rheumatol* 2008; **37**: 248-254 [PMID: 18612924 DOI: 10.1080/03009740801998747]
- 73 **Boers M**, Verhoeven AC, Markuse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A, van der Linden S. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; **350**: 309-318 [PMID: 9251634 DOI: 10.1016/S0140-6736(97)01300-7]
- 74 **Haugeberg G**, Morton S, Emery P, Conaghan PG. Effect of intra-articular corticosteroid injections and inflammation on periarticular and generalised bone loss in early rheumatoid arthritis. *Ann Rheum Dis* 2011; **70**: 184-187 [PMID: 20805297 DOI: 10.1136/ard.2009.128124]
- 75 **Haugeberg G**, Strand A, Kvien TK, Kirwan JR. Reduced loss of hand bone density with prednisolone in early rheumatoid arthritis: results from a randomized placebo-controlled trial. *Arch Intern Med* 2005; **165**: 1293-1297 [PMID: 15956010 DOI: 10.1001/archinte.165.11.1293]
- 76 **Ragab AH**, Frech RS, Vietti TJ. Osteoporotic fractures secondary to methotrexate therapy of acute leukemia in remission. *Cancer* 1970; **25**: 580-585 [PMID: 5264439 DOI: 10.1002/1097-0142(197003)25]

- 77 **Preston SJ**, Diamond T, Scott A, Laurent MR. Methotrexate osteopathy in rheumatic disease. *Ann Rheum Dis* 1993; **52**: 582-585 [PMID: 8215620 DOI: 10.1136/ard.52.8.582]
- 78 **Cranney AB**, McKendry RJ, Wells GA, Ooi DS, Kanigsberg ND, Kraag GR, Smith CD. The effect of low dose methotrexate on bone density. *J Rheumatol* 2001; **28**: 2395-2399 [PMID: 11708409]
- 79 **di Munno O**, Mazzantini M, Sinigaglia L, Bianchi G, Minisola G, Muratore M, la Corte R, di Matteo L, Canesi B, Caminiti M, Brogginini M, Adami S. Effect of low dose methotrexate on bone density in women with rheumatoid arthritis: results from a multicenter cross-sectional study. *J Rheumatol* 2004; **31**: 1305-1309 [PMID: 15229948]
- 80 **Kita K**, Sierakowski S. The effect of low dose methotrexate treatment on bone mineral density in patients with rheumatoid arthritis. *Pol Merkur Lekarski* 2002; **12**: 122-125 [PMID: 11995248]
- 81 **Buckley LM**, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. *J Rheumatol* 1997; **24**: 1489-1494 [PMID: 9263140]
- 82 **Kobayashi Y**, Ueyama S, Arai Y, Yoshida Y, Kaneda T, Sato T, Shin K, Kumegawa M, Hakeda Y. The active metabolite of leflunomide, A771726, inhibits both the generation of and the bone-resorbing activity of osteoclasts by acting directly on cells of the osteoclast lineage. *J Bone Miner Metab* 2004; **22**: 318-328 [PMID: 15221489 DOI: 10.1007/s00774-003-0489-4]
- 83 **Lee CK**, Lee EY, Chung SM, Mun SH, Yoo B, Moon HB. Effects of disease-modifying antirheumatic drugs and antiinflammatory cytokines on human osteoclastogenesis through interaction with receptor activator of nuclear factor kappaB, osteoprotegerin, and receptor activator of nuclear factor kappaB ligand. *Arthritis Rheum* 2004; **50**: 3831-3843 [PMID: 15593184 DOI: 10.1002/art.20637]
- 84 **Korcowska I**, Lacki JK, Hrycaj P. Influence of infliximab on cytokines network and markers of bone remodeling in rheumatoid arthritis patients. *Yonsei Med J* 2013; **54**: 183-188 [PMID: 23225817 DOI: 10.3349/ymj.2013.54.1.183]
- 85 **Musacchio E**, Valvason C, Botsios C, Ostuni F, Furlan A, Ramonda R, Modesti V, Sartori L, Punzi L. The tumor necrosis factor- α -blocking agent infliximab inhibits interleukin 1 β (IL-1 β) and IL-6 gene expression in human osteoblastic cells. *J Rheumatol* 2009; **36**: 1575-1579 [PMID: 19567627 DOI: 10.3899/jrheum.081321]
- 86 **Krieckaert CL**, Nurmohamed MT, Wolbink G, Lems WF. Changes in bone mineral density during long-term treatment with adalimumab in patients with rheumatoid arthritis: a cohort study. *Rheumatology (Oxford)* 2013; **52**: 547-553 [PMID: 23221326 DOI: 10.1093/rheumatology/kes320]
- 87 **Hoff M**, Kvien TK, Kälvesten J, Elden A, Haugeberg G. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. *Ann Rheum Dis* 2009; **68**: 1171-1176 [PMID: 18801760 DOI: 10.1136/ard.2008.091264]
- 88 **Wijbrandts CA**, Klaasen R, Dijkgraaf MG, Gerlag DM, van Eck-Smit BL, Tak PP. Bone mineral density in rheumatoid arthritis patients 1 year after adalimumab therapy: arrest of bone loss. *Ann Rheum Dis* 2009; **68**: 373-376 [PMID: 18408246 DOI: 10.1136/ard.2008.091611]
- 89 **Tanida A**, Kishimoto Y, Okano T, Hagino H. Etanercept Promotes Bone Formation via Suppression of Dickkopf-1 Expression in Rats with Collagen-Induced Arthritis. *Yonago Acta Med* 2013; **56**: 13-19 [PMID: 24031147]
- 90 **Lisbona M**, Maymó J, Solano A, Almirall M, Navallas M, Ares J, Carbonell J. Repair of erosions in patients with rheumatoid arthritis treated with etanercept: magnetic resonance imaging findings after 1 year of follow-up. *Scand J Rheumatol* 2013; **42**: 437-444 [PMID: 23607571 DOI: 10.3109/03009742.2013.776104]
- 91 **Ozaki T**, Hashizume K, Nakahara R, Nishida K. Radiographic remodeling of the shoulder joint in a patient with rheumatoid arthritis after 4 years of treatment with etanercept. *Mod Rheumatol* 2012; **22**: 635-637 [PMID: 22318335 DOI: 10.1007/s10165-012-0599-8]
- 92 **Hein G**, Eidner T, Oelzner P, Rose M, Wilke A, Wolf G, Franke S. Influence of Rituximab on markers of bone remodeling in patients with rheumatoid arthritis: a prospective open-label pilot study. *Rheumatol Int* 2011; **31**: 269-272 [PMID: 20661741 DOI: 10.1007/s00296-010-1560-9]
- 93 **Kume K**, Amano K, Yamada S, Kanazawa T, Ohta H, Hatta K, Amano K, Kuwaba N. The effect of tocilizumab on bone mineral density in patients with methotrexate-resistant active rheumatoid arthritis. *Rheumatology (Oxford)* 2014; **53**: 900-903 [PMID: 24441151 DOI: 10.1093/rheumatology/ket468]
- 94 **Karsdal MA**, Schett G, Emery P, Harari O, Byrjalsen I, Kenwright A, Bay-Jensen AC, Platt A. IL-6 receptor inhibition positively modulates bone balance in rheumatoid arthritis patients with an inadequate response to anti-tumor necrosis factor therapy: biochemical marker analysis of bone metabolism in the tocilizumab RADIATE study (NCT00106522). *Semin Arthritis Rheum* 2012; **42**: 131-139 [PMID: 22397953 DOI: 10.1016/j.semarthrit.2012.01.004]
- 95 **Vis M**, Güler-Yüksel M, Lems WF. Can bone loss in rheumatoid arthritis be prevented? *Osteoporos Int* 2013; **24**: 2541-2553 [PMID: 23775419]
- 96 **Oelzner P**, Schwabe A, Lehmann G, Eidner T, Franke S, Wolf G, Hein G. Significance of risk factors for osteoporosis is dependent on gender and menopause in rheumatoid arthritis. *Rheumatol Int* 2008; **28**: 1143-1150 [PMID: 18446340 DOI: 10.1007/s00296-008-0576-x]
- 97 **Tourinho TF**, Stein A, Castro JA, Brenol JC. Rheumatoid arthritis: evidence for bone loss in premenopausal women. *J Rheumatol* 2005; **32**: 1020-1025 [PMID: 15940761]
- 98 **Ørstavik RE**, Haugeberg G, Uhlig T, Mowinckel P, Falch JA, Halse JI, Kvien TK. Self reported non-vertebral fractures in rheumatoid arthritis and population based controls: incidence and relationship with bone mineral density and clinical variables. *Ann Rheum Dis* 2004; **63**: 177-182 [PMID: 14722207 DOI: 10.1136/ard.2003.005850]
- 99 **Lodder MC**, de Jong Z, Kostense PJ, Molenaar ET, Staal K, Voskuyl AE, Hazes JM, Dijkmans BA, Lems WF. Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. *Ann Rheum Dis* 2004; **63**: 1576-1580 [PMID: 15547081 DOI: 10.1136/ard.2003.016253]
- 100 **Ghozlan I**, Ghazi M, Nouijai A, Mounach A, Rezqi A, Achemlal L, Bezza A, El Maghraoui A. Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. *Bone* 2009; **44**: 772-776 [PMID: 19442629 DOI: 10.1016/j.bone.2008.12.028]
- 101 **van der Weijden MA**, Claushuis TA, Nazari T, Lems WF, Dijkmans BA, van der Horst-Bruinsma IE. High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. *Clin Rheumatol* 2012; **31**: 1529-1535 [PMID: 22706444 DOI: 10.1007/s10067-012-2018-0]
- 102 **Bronson WD**, Walker SE, Hillman LS, Keisler D, Hoyt T, Allen SH. Bone mineral density and biochemical markers of bone metabolism in ankylosing spondylitis. *J Rheumatol* 1998; **25**: 929-935 [PMID: 9598894]
- 103 **Will R**, Palmer R, Bhalla AK, Ring F, Calin A. Osteoporosis in early ankylosing spondylitis: a primary pathological event? *Lancet* 1989; **2**: 1483-1485 [PMID: 2574769 DOI: 10.1016/S0140-6736(89)92932-2]
- 104 **Jun JB**, Joo KB, Her MY, Kim TH, Bae SC, Yoo DH, Kim SK. Femoral bone mineral density is associated with vertebral fractures in patients with ankylosing spondylitis: a cross-sectional study. *J Rheumatol* 2006; **33**: 1637-1641 [PMID: 16881119]
- 105 **Juanola X**, Mateo L, Nolla JM, Roig-Vilaseca D, Campoy E, Roig-Escofet D. Bone mineral density in women with ankylosing spondylitis. *J Rheumatol* 2000; **27**: 1028-1031 [PMID: 10782832]
- 106 **Speden DJ**, Calin AI, Ring FJ, Bhalla AK. Bone mineral density, calcaneal ultrasound, and bone turnover markers in women with ankylosing spondylitis. *J Rheumatol* 2002; **29**: 516-521 [PMID: 11908565]

- 107 **Magrey M**, Khan MA. Osteoporosis in ankylosing spondylitis. *Curr Rheumatol Rep* 2010; **12**: 332-336 [PMID: 20680529 DOI: 10.1007/s11926-010-0122-1]
- 108 **Franck H**, Meurer T, Hofbauer LC. Evaluation of bone mineral density, hormones, biochemical markers of bone metabolism, and osteoprotegerin serum levels in patients with ankylosing spondylitis. *J Rheumatol* 2004; **31**: 2236-2241 [PMID: 15517638]
- 109 **Ulu MA**, Batmaz İ, Dilek B, Çevik R. Prevalence of osteoporosis and vertebral fractures and related factors in patients with ankylosing spondylitis. *Chin Med J (Engl)* 2014; **127**: 2740-2747 [PMID: 25146606]
- 110 **Klingberg E**, Lorentzon M, Mellström D, Geijer M, Göthlin J, Hilme E, Hedberg M, Carlsten H, Forsblad-d'Elia H. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. *Arthritis Res Ther* 2012; **14**: R108 [PMID: 22569245 DOI: 10.1186/ar3833]
- 111 **Obermayer-Pietsch BM**, Lange U, Tauber G, Frühauf G, Fahrleitner A, Dobnig H, Hermann J, Aglas F, Teichmann J, Neeck G, Leb G. Vitamin D receptor initiation codon polymorphism, bone density and inflammatory activity of patients with ankylosing spondylitis. *Osteoporos Int* 2003; **14**: 995-1000 [PMID: 14530911 DOI: 10.1007/s00198-003-1501-5]
- 112 **Aydin T**, Karacan I, Demir SE, Sahin Z. Bone loss in males with ankylosing spondylitis: its relation to sex hormone levels. *Clin Endocrinol (Oxf)* 2005; **63**: 467-469 [PMID: 16181241 DOI: 10.1111/j.1365-2265.2005.02369.x]
- 113 **Lange U**, Jung O, Teichmann J, Neeck G. Relationship between disease activity and serum levels of vitamin D metabolites and parathyroid hormone in ankylosing spondylitis. *Osteoporos Int* 2001; **12**: 1031-1035 [PMID: 11846329 DOI: 10.1007/s001980170013]
- 114 **Morton DJ**, Barrett-Connor EL, Schneider DL. Nonsteroidal anti-inflammatory drugs and bone mineral density in older women: the Rancho Bernardo study. *J Bone Miner Res* 1998; **13**: 1924-1931 [PMID: 9844111 DOI: 10.1359/jbmr.1998.13.12.1924]
- 115 **Kaya A**, Ozgocmen S, Kamanli A, Ardicoglu O. Bone loss in ankylosing spondylitis: does syndesmophyte formation have an influence on bone density changes? *Med Princ Pract* 2009; **18**: 470-476 [PMID: 19797924 DOI: 10.1159/000235897]
- 116 **Visvanathan S**, van der Heijde D, Deodhar A, Wagner C, Baker DG, Han J, Braun J. Effects of infliximab on markers of inflammation and bone turnover and associations with bone mineral density in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; **68**: 175-182 [PMID: 18495735 DOI: 10.1136/ard.2007.084426]
- 117 **Briot K**, Garnero P, Le Henanff A, Dougados M, Roux C. Body weight, body composition, and bone turnover changes in patients with spondyloarthritis receiving anti-tumour necrosis factor {alpha} treatment. *Ann Rheum Dis* 2005; **64**: 1137-1140 [PMID: 15642695 DOI: 10.1136/ard.2004.028670]
- 118 **Allali F**, Breban M, Porcher R, Maillefert JF, Dougados M, Roux C. Increase in bone mineral density of patients with spondyloarthritis treated with anti-tumour necrosis factor alpha. *Ann Rheum Dis* 2003; **62**: 347-349 [PMID: 12634235 DOI: 10.1136/ard.62.4.347]
- 119 **Brandt J**, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J, Thriene W, Sieper J, Braun J. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000; **43**: 1346-1352 [PMID: 10857793 DOI: 10.1002/1529-0131(200006)43]
- 120 **Briot K**, Gossec L, Kolta S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthritis receiving anti-tumor necrosis factor-alpha treatment. *J Rheumatol* 2008; **35**: 855-861 [PMID: 18381782]
- 121 **Haroon NN**, Sriganthan J, Al Ghanim N, Inman RD, Cheung AM. Effect of TNF-alpha inhibitor treatment on bone mineral density in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2014; **44**: 155-161 [PMID: 24909809 DOI: 10.1016/j.semarthrit.2014.05.008]
- 122 **Harrison BJ**, Hutchinson CE, Adams J, Bruce IN, Herrick AL. Assessing periarticular bone mineral density in patients with early psoriatic arthritis or rheumatoid arthritis. *Ann Rheum Dis* 2002; **61**: 1007-1011 [PMID: 12379525 DOI: 10.1136/ard.61.11.1007]
- 123 **Husni ME**, Mease PJ. Managing comorbid disease in patients with psoriatic arthritis. *Curr Rheumatol Rep* 2010; **12**: 281-287 [PMID: 20589485 DOI: 10.1007/s11926-010-0112-3]
- 124 **Dheda K**, Cassim B, Patel N, Mody GM. A comparison of bone mineral density in Indians with psoriatic polyarthritis and healthy Indian volunteers. *Clin Rheumatol* 2004; **23**: 89 [PMID: 14749995 DOI: 10.1007/s10067-003-0818-y]
- 125 **Grisar J**, Bernecker PM, Aringer M, Redlich K, Sedlak M, Wolozczuk W, Spitzauer S, Grampp S, Kainberger F, Ebner W, Smolen JS, Pietschmann P. Ankylosing spondylitis, psoriatic arthritis, and reactive arthritis show increased bone resorption, but differ with regard to bone formation. *J Rheumatol* 2002; **29**: 1430-1436 [PMID: 12136902]
- 126 **Nolla JM**, Fiter J, Rozadilla A, Gomez-Vaquero C, Mateo L, Rodriguez-Moreno J, Roig-Escofet D. Bone mineral density in patients with peripheral psoriatic arthritis. *Rev Rhum Engl Ed* 1999; **66**: 457-461 [PMID: 10567973]
- 127 **Hein G**, Abendroth K, Müller A, Wessel G. Studies on psoriatic osteopathy. *Clin Rheumatol* 1991; **10**: 13-17 [PMID: 2065500 DOI: 10.1007/BF02208026]
- 128 **Grazio S**, Cvijetić S, Vlak T, Grubišić F, Matijević V, Nemčić T, Punda M, Kusić Z. Osteoporosis in psoriatic arthritis: is there any? *Wien Klin Wochenschr* 2011; **123**: 743-750 [PMID: 22127468 DOI: 10.1007/s00508-011-0095-8]
- 129 **Pedreira PG**, Pinheiro MM, Szejnfeld VL. Bone mineral density and body composition in postmenopausal women with psoriasis and psoriatic arthritis. *Arthritis Res Ther* 2011; **13**: R16 [PMID: 21299865 DOI: 10.1186/ar3240]
- 130 **Borman P**, Babaoğlu S, Gur G, Bingol S, Bodur H. Bone mineral density and bone turnover in patients with psoriatic arthritis. *Clin Rheumatol* 2008; **27**: 443-447 [PMID: 17876648 DOI: 10.1007/s10067-007-0725-8]
- 131 **Frediani B**, Allegri A, Falsetti P, Storri L, Bisogno S, Baldi F, Filippini P, Marcolongo R. Bone mineral density in patients with psoriatic arthritis. *J Rheumatol* 2001; **28**: 138-143 [PMID: 11196516]
- 132 **Loucks J**, Pope JE. Osteoporosis in scleroderma. *Semin Arthritis Rheum* 2005; **34**: 678-682 [PMID: 15692961 DOI: 10.1016/j.semarthrit.2004.08.006]
- 133 **Omair MA**, Pagnoux C, McDonald-Blumer H, Johnson SR. Low bone density in systemic sclerosis. A systematic review. *J Rheumatol* 2013; **40**: 1881-1890 [PMID: 24037552 DOI: 10.3899/jrheum.130032]
- 134 **Mok CC**, Chan PT, Chan KL, Ma KM. Prevalence and risk factors of low bone mineral density in Chinese patients with systemic sclerosis: a case-control study. *Rheumatology (Oxford)* 2013; **52**: 296-303 [PMID: 23006511 DOI: 10.1093/rheumatology/kes240]
- 135 **Atteritano M**, Sorbara S, Bagnato G, Miceli G, Sangari D, Morgante S, Visalli E, Bagnato G. Bone mineral density, bone turnover markers and fractures in patients with systemic sclerosis: a case control study. *PLoS One* 2013; **8**: e66991 [PMID: 23818972 DOI: 10.1371/journal.pone.0066991]
- 136 **Rios-Fernández R**, Callejas-Rubio JL, Fernández-Roldán C, Simeón-Aznar CP, García-Hernández F, Castillo-García MJ, Fonollosa Pla V, Barnosí Marín AC, González-Gay MÁ, Ortego-Centeno N. Bone mass and vitamin D in patients with systemic sclerosis from two Spanish regions. *Clin Exp Rheumatol* 2012; **30**: 905-911 [PMID: 22935485]
- 137 **Avouac J**, Koumakis E, Toth E, Meunier M, Maury E, Kahan A, Cormier C, Allanore Y. Increased risk of osteoporosis and fracture in women with systemic sclerosis: a comparative study with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012; **64**: 1871-1878 [PMID: 22730393 DOI: 10.1002/acr.21761]
- 138 **de Andrade DC**, de Magalhães Souza SC, de Carvalho JF, Takayama L, Borges CT, Aldrich JM, Pereira RM. High frequency of osteoporosis and fractures in women with dermatomyositis/polymyositis. *Rheumatol Int* 2012; **32**: 1549-1553 [PMID: 21327426 DOI: 10.1007/s00296-011-1821-2]

- 139 **Alsufyani KA**, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Nadel H, Malleson PN. Bone mineral density in children and adolescents with systemic lupus erythematosus, juvenile dermatomyositis, and systemic vasculitis: relationship to disease duration, cumulative corticosteroid dose, calcium intake, and exercise. *J Rheumatol* 2005; **32**: 729-733 [PMID: 15801032]
- 140 **Castro TC**, Terreri MT, Szejnfeld VL, Len C, Fonseca AS, Hilário MO. Bone mineral density of Brazilian girls with juvenile dermatomyositis. *Braz J Med Biol Res* 2005; **38**: 309-313 [PMID: 15785843 DOI: 10.1590/S0100-879X2005000200020]
- 141 **Santiago RA**, Silva CA, Caparbo VF, Sallum AM, Pereira RM. Bone mineral apparent density in juvenile dermatomyositis: the role of lean body mass and glucocorticoid use. *Scand J Rheumatol* 2008; **37**: 40-47 [PMID: 18189194 DOI: 10.1080/03009740701687226]
- 142 **Rouster-Stevens KA**, Langman CB, Price HE, Seshadri R, Shore RM, Abbott K, Pachman LM. RANKL: osteoprotegerin ratio and bone mineral density in children with untreated juvenile dermatomyositis. *Arthritis Rheum* 2007; **56**: 977-983 [PMID: 17328075 DOI: 10.1002/art.22433]
- 143 **Kirnap M**, Calis M, Kaya N, Muhtaroglu S. Is the Behçet's disease a risk factor for osteoporosis and is relation to cytokines? *Bratisl Lek Listy* 2010; **111**: 340-344 [PMID: 20635679]
- 144 **Tekin NS**, Ozdolap S, Sarikaya S, Esturk E, Gumustas S. Bone mineral density and bone turnover markers of patients with Behçet's disease. *J Eur Acad Dermatol Venereol* 2007; **21**: 25-29 [PMID: 17207163 DOI: 10.1111/j.1468-3083.2006.01845.x]
- 145 **Bicer A**, Tursen U, Kaya TI, Ozer C, Camdeviren H, Ikizoglu G, Erdogan C. Bone mineral density in patients with Behçet's disease. *Rheumatol Int* 2004; **24**: 355-358 [PMID: 14556035 DOI: 10.1007/s00296-003-0381-5]

P- Reviewer: Korovessis P, Luo XH **S- Editor:** Tian YL

L- Editor: Roemmele A **E- Editor:** Wu HL



Classification, diagnosis and treatment of ANCA-associated vasculitis

Sergey V Moiseev, Pavel I Novikov

Sergey V Moiseev, Pavel I Novikov, Clinic of Nephrology, Internal and Occupational Diseases, The Sechenov First Moscow State Medical University, Moscow 119435, Russia

Author contributions: Both the authors contributed to this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Sergey V Moiseev, MD, Professor, Clinic of Nephrology, Internal and Occupational Diseases, The Sechenov First Moscow State Medical University, Rossolimo, 11/5, Moscow 119435, Russia. clinpharm@mtu-net.ru
 Telephone: +7-495-2482544

Fax: +7-901-5904491

Received: June 25, 2014

Peer-review started: June 26, 2014

First decision: August 14, 2014

Revised: October 29, 2014

Accepted: November 7, 2014

Article in press: November 10, 2014

Published online: March 12, 2015

Abstract

Diagnosis of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is usually not difficult in patient with systemic disease, including lung and kidneys involvement, and laboratory signs of inflammation. The presence of ANCA and the results of histological investigation confirm diagnosis of ANCA-associated vasculitis. Cyclophosphamide/azathioprine in combination with high dose steroids are used to induce and maintain remission of systemic vasculitis. The clinical trials also showed efficacy of rituximab that induces depletion of B-cells. Our understanding and management of ANCA-associated vasculitis improved significantly over the last decades but there is still a

lot of debate over its classification, diagnostic criteria, assessment of activity and optimum treatment.

Key words: Systemic vasculitis; Anti-neutrophil cytoplasmic antibodies; Granulomatosis with polyangiitis; Microscopic polyangiitis

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The diagnosis and treatment of anti-neutrophil cytoplasmic antibodies-associated vasculitis are a challenge for physicians. This article presents an updated information about these uncommon diseases.

Moiseev SV, Novikov PI. Classification, diagnosis and treatment of ANCA-associated vasculitis. *World J Rheumatol* 2015; 5(1): 36-44 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i1/36.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i1.36>

INTRODUCTION

Systemic vasculitides associated with anti-neutrophil cytoplasmic autoantibodies (ANCA) include granulomatosis with polyangiitis (Wegener's; GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss; EGPA). The annual incidence of ANCA-associated vasculitides is 10 to 20 cases per 1000000 of the general population^[1,2]. The relative incidence depends on the geographic region, e.g., in Europe GPA is more prevalent than MPA while the opposite is true in Japan^[3]. The circulation of ANCA is the distinctive feature of all three ANCA-associated vasculitides though these autoantibodies are present only in part of patients, are not obligatory classification criterium and may be detected in patients with other diseases, including infective endocarditis^[4]. *In vitro*

and *in vivo* studies suggest that ANCA are essential for the development of ANCA-associated vasculitis. Interaction of autoantibodies with antigens expressed by neutrophils (and mononuclear cells) induces activation of cells and inflammatory response that ultimately leads to necrotic changes in vascular walls and surrounding tissues^[5]. In this review we focused on GPA and MPA that have many common features and do not discuss EGPA.

CLASSIFICATION AND NOMENCLATURE OF ANCA-ASSOCIATED VASCULITIDES

The modern nomenclature of systemic vasculitides was developed in 2012 at the consensus conference in Chapel-Hill (United States)^[6]. According to the current definition ANCA-associated vasculitis is predominantly small-vessel necrotizing vasculitis associated with autoantibodies for myeloperoxidase (MPO) or proteinase-3 (PR3)^[7]. In patients with MPA inflammation involves practically exclusively vessels walls, mainly in kidneys and lungs, while in GPA (as is in EGPA) vasculitis is associated with extravascular necrotizing granulomatous inflammation of tissues, *e.g.*, of upper and/or lower respiratory tract. Necrotizing glomerulonephritis is common in patients with both ANCA-associated vasculitides, especially in MPA.

The current classification of ANCA-associated vasculitides may be revised in the future. Lionaki *et al.*^[7] showed in 502 patients with ANCA-associated vasculitides that ANCA-specificity predicted the risk of relapse while the clinical phenotype had lower predictive value^[7]. In patients with PR3-ANCA the risk of relapse was almost twice higher than in patients with MPO-ANCA (OR = 1.89; 95%CI: 1.33-2.69) though ANCA-specificity did not predict the resistance to standard treatment or the risk of end-stage renal failure and death. These data suggest that ANCA-specificity may be a valuable classification criterium, *e.g.*, PR3-ANCA- and MPO-ANCA-associated vasculitis, though the obvious limitation of such approach is the absence of autoantibodies in significant number of patients.

The genetic studies confirmed the possible significance of ANCA-specificity for MPO and PR3 in disease recognition and prognosis. Lyons *et al.*^[8] in a large-scale study in 2687 patients with GPA or MPA and 7550 control patients have detected close association of PR3-ANCA with HLA-DP and genes that coded α_1 -antitrypsin (SERPINA1) and PR3 (PRTN3), while MPO-ANCA were associated with HLA-DQ^[8]. Meanwhile the association of clinical syndromes with genetic factors was less significant.

Recently the researchers from the French Vasculitis Study Group (FVSG) and the European Vasculitis Society (EUVAS) have performed cluster analysis in 673 subjects with GPA (59%) and MPA (41%)^[9].

Five partially redundant clusters were found, *e.g.*, "renal vasculitis with PR3-ANCA" (40% of subjects), "renal vasculitis without PR3-ANCA" (32%), "nonrenal vasculitis" (12%), "cardiovascular vasculitis" (9%) and "gastrointestinal vasculitis" (7%). The five phenotypes had distinct relapse rates and mortality. The non-renal ANCA-associated vasculitis class (this group predominantly consisted of patients with GPA) was characterized by the lowest risk of death and the highest risk of relapse and was chosen as the reference group. Kidney disease was associated with 2 to 4-fold lower relapse risk compared to reference group while the death risk was increased significantly only in patients with renal vasculitis without PR3-ANCA. Cardiovascular disease had unfavorable prognosis and was associated with the highest risk of death and the relapse rate comparable to that in non-renal ANCA-associated vasculitis. The authors suggested that a classification based on kidney involvement and ANCA specificity, and perhaps also gastrointestinal and cardiovascular diseases, may lead to more accurate stratification of patients into homogeneous disease groups though the clinical relevance of this approach requires further validation.

DIAGNOSTIC CRITERIA

There are no accepted criteria for the diagnosis of ANCA-associated vasculitis. The criteria developed by the American College of Rheumatology (ACR) in 1990^[10] can be used for classification of systemic vasculitides, while the categories that were defined in Chapel-Hill represent the nomenclature of these systemic diseases^[6]. The ACR criteria performed badly in 198 patients who have been referred to rheumatologists with probable systemic vasculitis^[11]. Moreover ACR classification did not include MPA. The Diagnostic and Classification Criteria for Vasculitis (DCVAS) study is a multinational observational study that was designed to develop diagnostic criteria for primary systemic vasculitis according to the guidelines of the ACR and the European League against Rheumatism (EULAR)^[12]. The researchers anticipate to recruit > 2000 patients with primary systemic vasculitis and 1500 patients with other conditions that can mimic vasculitis. The study incorporates detailed clinical data, evaluation of ANCA and other laboratory parameters, biopsy and imaging data. As of April 2014 more than 115 medical centers in Europe, North America, Russia, Asia, Australasia, and South America were contributing data to this study.

Though diagnostic criteria for systemic vasculitis are not established, ANCA-associated vasculitis can be usually suspected in patients with typical clinical manifestations, *e.g.*, fever, joint pain, disease of upper and lower respiratory tract, kidney and other organs, and laboratory signs of inflammation (high ESR and C-reactive protein)^[13]. GPA and MPA have overlapping features but show certain differences, *e.g.*,

ear, nose and throat involvement is more common in GPA than in MPA. In addition, patients with GPA frequently present with extravascular granulomatous lesions that are not seen in MPA. Not all patients with ANCA-associated vasculitides will have biopsy, while the results of histological examination may be difficult to interpretate. Thus, the clinical equivalents of granulomatous inflammation should be taken into account, *e.g.*, the following ones^[14,15]: (1) lower respiratory tract and lung disease: persisting infiltrates, nodules and cavities, stenosis of bronchi; (2) upper respiratory tract disease: necrotising rhinitis with nasal bleedings and crusting, saddle nose deformity, chronic sinusitis (> 3 mo) and radiological damage, otitis media and mastoiditis; subglottic stenosis of trachea; and (3) orbital inflammatory pseudotumour.

ANCA-specificity has no decisive diagnostic value though PR3-ANCA are usually detected in GPA patients while MPO-ANCA are more common in MPA. In clinical practice it may be difficult to differentiate GPA and MPA but it is worth noting that nosological form, especially at the time of diagnosis, is less important for treatment decisions than the extent and severity of target organs damage.

Diagnosis is usually more complicated in patients with localised GPA (up to 25% of cases) that involves ear, nose and throat, eyes and/or ears, especially if imaging methods show the presence of pseudotumour with destruction of orbital and nasal sinuses walls. In patients with isolated orbital mass that is not associated with systemic manifestations the diagnosis of GPA may be established only with biopsy or after resection of "tumour". The presence of ANCA that can be detected with immunofluorescence method or ELISA contributes significantly to the diagnosis of ANCA-associated vasculitis^[16] though these autoantibodies can be negative or disappear during immunosuppressive treatment. Biopsy (nose, lung, kidney, *etc.*) can be used to confirm the diagnosis of systemic vasculitis but histological study is not necessary for all patients.

ASSESSMENT OF ACTIVITY AND PROGNOSIS

The detection of ANCA is a valuable diagnostic test but their role as a marker of activity has not been established. Birck *et al.*^[17] in meta-analysis of 22 studies in 950 patients with ANCA-associated vasculitides failed to confirm the value of serial ANCA titers for evaluation of activity^[17]. In the cohort study PR3-ANCA levels also did not correlate with disease activity in 156 patients with GPA^[18]. Nevertheless, the results of several studies suggest that detection of ANCA can predict relapse in patients with ANCA-associated vasculitis. In 87 patients with GPA or MPA and PR3-antibodies ANCA-positivity at 18 and 24 mo of immunosuppressive treatment was associated with 2.7 (95%CI: 1.1-4.3) and 4.6 (95%CI: 1.2-6.3)-fold

increased risk of relapse during 5-year follow-up^[19]. Tomasson *et al.*^[20] evaluated the predictive value of ANCA detection in meta-analysis of 18 trials that measured the levels of autoantibodies during follow-up of patients. The persistence of ANCA-positivity increased the risk of relapse 2.84-fold (95%CI: 1.65-4.90) while increase in ANCA level during treatment was associated with 1.97-fold (95%CI: 1.43-2.70) higher relapse rate. These data suggest that ANCA detection during immunosuppressive treatment may predict the relapse of ANCA-associated vasculitis though predictive power of a rise in or a persistence of ANCA is probably modest^[4]. In at least 25% of patients there is no correlation between clinical signs of vasculitis and immunological parameters^[21]. Thus treatment decisions cannot be based only on ANCA titers^[21].

Monach *et al.*^[22] measured 28 serum proteins, including cytokines, soluble receptors, chemokines, markers of tissue damage and inflammation, at baseline and at 6 mo in 186 patients with active ANCA-associated vasculitis who received immunosuppressive agents in RAVE study. At 6 mo 137 patients have achieved remission of vasculitis and showed significant declines in 24 of the 28 studied biomarkers. ROC analysis suggested that CXCL13 (BCA-1), matrix metalloproteinase-3 and tissue inhibitor of metalloproteinases-1 levels best discriminated active vasculitis from remission (AUC > 0.8) and from healthy controls (AUC > 0.9). These proteins are the promising candidates for the future studies that would probably identify more reliable markers of activity and predictors of relapse of ANCA-associated vasculitis. Poor correlation of these markers with ESR or C-reactive protein (CRP) confirmed the low predictive value of the latter. Nevertheless the changes in ESR and CRP level during treatment should be taken into account especially if patients present with clinical signs of vasculitis relapse.

In 1994, Luqmani *et al.*^[23] in a study of 213 consecutive patients with different forms of vasculitis have devised the Birmingham Vasculitis Activity Score (BVAS) as the clinical index of activity in systemic necrotizing vasculitis^[23]. BVAS is widely used in clinical studies in patients with ANCA-associated vasculitides^[24]. BVAS 3.0 includes 56 clinical signs and symptoms in nine separate organ systems^[25]. Disease signs and symptoms are scored only when they are attributable to active systemic vasculitis and to other causes, such as infection, hypertension, toxic effects of treatment, and when they are new or deteriorate in the previous 28 d. BVAS 3.0 was recently validated in 238 patients from 7 European countries^[26]. Higher BVAS value reflects activity and severity of systemic vasculitis and indicates unfavorable prognosis^[27].

Vasculitis damage index (VDI) was developed to assess the irreversible tissue damage in systemic vasculitis and to account for the consequences of

immunosuppressive treatment (*e.g.*, osteoporosis, diabetes, hypertension *etc.*) and other factors such as atherosclerosis^[28]. Each feature is scored only if it persists for more than 3 mo. Patients with at least five items of damage on the VDI score had 7- to 11-fold higher risk of death, as compared with those with lower VDI score^[29]. Irreversible damage develops in 80% to 90% of patients with ANCA-associated vasculitis and usually progresses with time. In 302 patients who were followed in four European Vasculitis Study group trials at 7.3 years post-diagnosis the most frequent items of vasculitis damage were proteinuria, impaired glomerular filtration rate, hypertension, nasal crusting, hearing loss and peripheral neuropathy while the most commonly reported items of treatment-related damage included hypertension (41.5%), osteoporosis (14.1%), malignancy (12.6%), and diabetes (10.4%)^[30]. At long-term follow-up around one-third of patients had ≥ 5 items of damage. VDI does not measure functional disability related to systemic vasculitis or its treatment. For example, in patient with chronic nasal discharge and mild arterial hypertension VDI will be higher (2 items) than in disabled patient with persistent palsy associated with transverse myelitis (1 item) or end stage renal failure requiring dialysis (1 item).

Five-factor score (FFS) was developed by the French Vasculitis Study Group in 1996 as a prognostic index^[31]. FFS was revised in 2009 in a study in 1108 consecutive patients with 4 systemic necrotizing vasculitides (GPA, polyarteritis nodosa, MPA and EGPA)^[32]. This score is based on five factors that were associated with higher 5-year death rate, *e.g.*, age (> 65 years), heart disease, gastrointestinal involvement and renal failure (creatinine level ≥ 150 $\mu\text{mol/L}$) and an additional criteria for GPA and EGPA-the absence of ENT symptoms. In patients with FFS of 0, 1 and ≥ 2 the 5-year mortality was 9%, 21% and 40%, respectively.

CURRENT TREATMENT

Without treatment majority of patients with ANCA-associated vasculitis die within two years after diagnosis. Treatment with corticosteroids and cyclophosphamide significantly increased patients survival but also induced the changes in the causes of death, *e.g.*, increased the risk of cardiovascular outcomes and the complications of prolonged immunosuppression. In 535 patients with GPA and MPA who had been enrolled at the time of diagnosis to four randomised controlled trials in 1995-2002 overall survival at five years of follow-up was 75%^[27]. Compared with an age- and sex-matched general population there was a mortality ratio of 2.6 (95%CI: 2.2-3.1). Within the first year of follow-up patients mainly died from infection (48%) and active vasculitis (19%) while later the death was more frequently attributed to cardiovascular disease (26%) and malignancy (22%) and more rarely to

infections (20%). Multivariable analysis showed an end-stage kidney disease, advancing age and higher BVAS were negative prognostic factors for patient survival.

In spite of considerable advances in treatment there is a high need in new immunosuppressive regimens as a significant proportion of patients are refractory to current therapies and around 50% develop a relapse within 5 years while more than 90% of patients accumulate irreversible damage associated with both vasculitis and prolonged immunosuppression^[33].

The aim of treatment for ANCA-associated vasculitis is to induce (usually within 3 to 6 mo) and to maintain remission. Maintenance treatment should be continued for at least 2 years or frequently life-long. The choice of the immunosuppressive regimen depends on activity, extent of damage and severity of visceral manifestations (*e.g.*, kidney or lung disease) that can be fatal or disabling. It worth noting that patients with localised GPA can also require intensive immunosuppressive treatment taking into account the risk of serious outcomes (*e.g.*, loss of vision or hearing, destruction of tissues) and/or generalization of vasculitis. In patients with active ANCA-associated vasculitis the current standard of care is cyclophosphamide oral (2 mg/kg daily) or intravenous (15 mg/kg every 2 wk for the first three doses and thereafter every 3 wk) administration in combination with high-dose glucocorticoids (0.5 to 1 mg/kg orally \pm one to three intravenous pulses of up to 1000 mg). Cyclophosphamide dose should be reduced by up to 25% in the elderly and in patients with renal impairment. Following induction of remission glucocorticoids should be tapered or discontinued while cyclophosphamide can be replaced with azathioprine or other immunosuppressive agents, *e.g.*, methotrexate or more rarely leflunomide or mycophenolate mofetil. Co-trimoxazole 960 mg three times per week is frequently administered for prevention of *Pneumocystis jiroveci* infections that can induce relapse of systemic vasculitis.

The efficacy of a sequential cyclophosphamide and azathioprine (2 mg/kg per day) treatment as an alternative to prolonged cyclophosphamide administration was established in the CYCAZAREM study^[34]. In this trial, 155 randomized patients received either oral cyclophosphamide for 1 year or 3 to 6 mo of oral cyclophosphamide followed by azathioprine. At 18 mo the relapse rates was not significantly different between the two regimens. The randomised CYCLOPS study showed similar efficacy (the time to remission and the rate of remission at 9 mo) of intravenous or oral cyclophosphamide in 149 patients with generalised ANCA-associated vasculitis. However, long-term follow-up (median 4.3 years) showed higher relapse rate in patients who were treated with pulsed intravenous cyclophosphamide^[35,36]. The potential advantages of intravenous cyclophosphamide included reduced exposure (8.2 g compared to 15.9 g with

oral administration) and the lower rate of leucopenia though the latter was not associated with reduced risk of infectious complications.

In the NORAM study methotrexate 25 mg weekly was not inferior to oral cyclophosphamide at inducing remission in 100 patients with early GPA (e.g., without serious visceral manifestations) but showed slower effect in patients with pulmonary disease^[37]. Methotrexate administration was associated with lower risk of leucopenia, but higher rate of liver impairment and relapse of systemic vasculitis. In the long-term first-line treatment with methotrexate was associated with less effective disease control than cyclophosphamide induction therapy^[38].

In the WEGENT study maintenance treatment with methotrexate was at least as effective as azathioprine in 126 patients with remission of ANCA-associated vasculitis that was induced by cyclophosphamide^[39]. Thus, methotrexate can be used as an alternative to azathioprine in patients with normal kidney function who do not tolerate the latter. The IMPROVE randomised study showed increased risk of relapses and shorter time to relapse in patients treated with mycophenolate mofetil after cyclophosphamide induction compared to those with azathioprine^[40], while efficacy of leflunomide for maintenance treatment remains uncertain. In the multicentre, randomized controlled clinical trial, 54 patients with generalized GPA were treated either with oral leflunomide 30 mg/d or oral methotrexate (7.5 to 20 mg/wk) for 2 years following induction of remission with cyclophosphamide^[41]. The rate of major relapses was significantly higher in the methotrexate group ($P = 0.037$), and the study was terminated prematurely. However, treatment with leflunomide was associated with an increased frequency of adverse events. Mycophenolate mofetil and leflunomide should not be used as a first-line treatment.

Rituximab was first studied in relapsing and refractory ANCA-associated vasculitis. Its efficacy for induction of remission in patients with GPA and MPA was shown in two randomised trials (RITUXVAS and RAVE)^[42,43] and numerous case series and uncontrolled studies^[44-46]. In the RITUXVAS study 44 patients with ANCA-associated renal vasculitis were randomised to a standard glucocorticoid regimen plus either rituximab at a dose of 375 mg/m² per week for 4 wk, with two intravenous cyclophosphamide pulses, or 3 to 6 mo intravenous cyclophosphamide^[42]. Following induction of remission at 3 to 6 mo patients in the control group continued treatment with azathioprine, while in the rituximab group patients received only glucocorticoids for maintenance treatment. Sustained remission at 12 mo was achieved in 76% and 82% of patients in rituximab and control groups, respectively. The safety of two regimens was also comparable. Thus, a rituximab-based regimen was not inferior to intravenous cyclophosphamide in patients with severe ANCA-associated vasculitis. The use of rituximab

permitted to avoid of maintenance immunosuppression but was not associated with reduced rate of infectious complications.

In a multicenter, randomized, double-blind, noninferiority RAVE study rituximab (375 mg/m² once a week for 4 wk) followed by placebo was compared to cyclophosphamide for 3 to 6 mo followed by azathioprine for 12 to 15 mo in 197 patients with severe ANCA-associated vasculitis^[47]. Severe disease was defined as vital organ involvement that posed an immediate threat to the function of that organ or the patient's life. By 5 mo all patients who had a remission without disease flares had discontinued glucocorticoids. The primary end point was remission of disease without the use of prednisone at 6 mo. Primary end point was reached in 63 patients in the rituximab group (64%) and 52 patients in the control group (53%). Non-Inferiority was confirmed in this study ($P < 0.001$). Rituximab was more efficacious than cyclophosphamide for inducing remission in relapse of vasculitis: the primary end point was reached in 67% of patients in the rituximab group and in 42% of patients in the control group ($P = 0.01$). Rituximab was also as effective as cyclophosphamide in the treatment of patients with renal involvement or alveolar hemorrhage and in patients with both GPA and MPA. The rate of adverse events was not different between the two groups. The long-term follow-up of patients confirmed the comparable efficacy of the rituximab- and cyclophosphamide-based regimens^[47]. At 12 and 18 mo, the complete remissions was maintained in 48% and 39% of patients, respectively, in the rituximab group and 39% and 33% of patients in the control group. The duration of complete remission and the frequency or severity of relapses did not differ significantly between the two groups. In patients with relapsing disease, rituximab was superior to cyclophosphamide-based treatment at 12 mo ($P = 0.009$) but not at 18 mo ($P = 0.06$). At the latter point the majority of patients in the rituximab group had reconstituted B cells. The overall incidence of adverse events was not different between the two groups, with the exception of leukopenia and pneumonia that were less common in the rituximab group. Thus, at 18 mo a single course of rituximab was as effective as a standard immunosuppressive therapy for the induction and maintenance of remissions in patients with severe ANCA-associated vasculitis. Rituximab may be superior to conventional immunosuppressive regimen in relapsing disease.

The high efficacy of rituximab was also shown in retrospective studies in patients with ANCA-associated vasculitis refractory to standard treatment. Rituximab may be less effective for induction of remission in patients with predominant granulomatous lesions, e.g., orbital pseudotumour. In one uncontrolled study in 59 patients with refractory GPA complete remission or improvement following rituximab treatment were achieved in 89.2% of patients with kidney disease and

Table 1 Randomized controlled trials in patients with antineutrophil cytoplasmic antibody-associated vasculitis^[53]

Trial (n)	Inclusion criteria	Treatment groups (dose)	Primary end-points	Outcome
Induction of remission				
NORAM (100)	New diagnosis of GPA or MPA, and creatinine < 150 µmol/L	Methotrexate (0.3 mg/kg once weekly) <i>vs</i> daily oral cyclophosphamide	Remission Time to relapse	Methotrexate not inferior to cyclophosphamide Time to relapse shorter with methotrexate
CYCLOPS (149)	New diagnosis of GPA, MPA, or relapse with renal involvement, creatinine 150-500 µmol/L	Intravenous pulse cyclophosphamide (15 mg/kg) <i>vs</i> daily oral cyclophosphamide (2 mg/kg)	Remission Time to relapse	Pulse cyclophosphamide not inferior to oral cyclophosphamide Less leucopenia and trend towards more relapses with pulse cyclophosphamide
RITUXVAS (44)	New diagnosis of AAV and severe renal involvement	Rituximab (four 375 mg/m ² infusions) plus two intravenous pulses of cyclophosphamide, <i>vs</i> intravenous pulse cyclophosphamide only	Sustained remission	Rituximab not inferior to pulse cyclophosphamide
RAVE (198)	New or relapsing GPA or MPA	Rituximab (4 × 375 mg/m ² infusions) <i>vs</i> daily oral cyclophosphamide	Complete remission and cessation of glucocorticoids at 6 mo	Rituximab not inferior to oral cyclophosphamide Rituximab better in patients with relapse than after first diagnosis
MEPEX (137)	New diagnosis of GPA or MPA and creatinine > 500 µmol/L	Plasma exchange and oral cyclophosphamide <i>vs</i> 3 × intravenous methylprednisolone pulse and oral cyclophosphamide	Renal survival at 3 mo	Better renal survival with plasma exchange 24% risk reduction for ESRD with plasma exchange
MYCYC (140)	New diagnosis of GPA, MPA and major organ involvement	Mycophenolate mofetil (2-3 g daily) <i>vs</i> intravenous pulse cyclophosphamide (15 mg/kg)	Remission at 6 mo Relapse	Preliminary data: noninferiority not proven for mycophenolate mofetil <i>vs</i> pulse cyclophosphamide
CORTAGE (104)	New diagnosis of MPA, GPA, EGPA, PAN and age > 65 yr	Rapid glucocorticoid tapering and reduced-dose intravenous pulse cyclophosphamide (500 mg) <i>vs</i> standard intravenous pulse cyclophosphamide (500 mg/m ²)	Severe adverse events	Preliminary data: less severe adverse events with reduced immunosuppression, no difference in remission and relapse rates
Maintenance of remission				
CYCAZAREM (144)	GPA, MPA or relapse and renal or vital organ involvement	Oral azathioprine (2 mg/kg) <i>vs</i> oral cyclophosphamide (1.5 mg/kg daily)	Relapse Adverse events	No difference in relapse
IMPROVE (165)	New diagnosis of GPA or MPA	Oral mycophenolate mofetil (2 g daily) <i>vs</i> oral azathioprine (2 mg/kg)	Time without relapse Adverse events	More relapses with mycophenolate mofetil than azathioprine, trend towards more adverse events with azathioprine
WEGENT (126)	GPA or MPA and renal or multiorgan involvement	Methotrexate (0.3 mg/kg once weekly) <i>vs</i> azathioprine (2 mg/kg)	Adverse events with consecutive treatment cessation or death	No difference between groups in primary end point and relapses
LEM (54)	Generalized GPA and creatinine < 1.3 mg/dL	Leflunomide (30 mg daily) <i>vs</i> methotrexate (up to 20 mg per week)	Relapse	More relapses with methotrexate than leflunomide, trend towards more adverse events with leflunomide
WGET (174)	GPA and BVAS > 3	Etanercept and methotrexate or cyclophosphamide <i>vs</i> placebo and methotrexate or cyclophosphamide	Sustained remission for > 6 mo	No benefit with etanercept, more cancers in etanercept group

AAV: Antineutrophil cytoplasmic antibody-associated vasculitis; BVAS: Birmingham vasculitis activity score; EGPA: Eosinophilic granulomatosis with polyangiitis; ESRD: End-stage renal disease; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; PAN: Polyarteritis nodosa.

in only 44.4% of patients with orbital pseudotumor ($P = 0.003$)^[48]. The efficacy of rituximab for maintenance therapy was established in the retrospective studies^[46]. It is currently being evaluated in prospective, randomized MAINRITSAN trial, comparing 500 mg of rituximab every 6 mo for 18 mo *vs* azathioprine for 22 mo. Preliminary results indicate significantly fewer relapses in the rituximab arm^[49].

Recently the Recommendations Committee of

the FVSG developed guidelines for rituximab use to induce and maintain remission of ANCA-associated vasculitis^[50]. The main statements of these guidelines are summarised below: (1) rituximab is not inferior to conventional treatment and may be used to induce remission of GPA and MPA for the same indications as cyclophosphamide; (2) rituximab should preferentially be prescribed to women of childbearing age, especially when they are over 30 years old, taking into account

the risk of infertility with cyclophosphamide; (3) rituximab should not be administered as a first-line treatment in patients with predominant granulomatous lesions, *e.g.*, orbital pseudotumors, ENT manifestations, tracheal and bronchial stenosis; (4) rituximab should preferentially be chosen for patients with relapsing GPA or MPA who have received previously at least one full cyclophosphamide cycle; (5) rituximab is recommended to prescribe for failure or incomplete response to intravenous cyclophosphamide and in patients intolerant of cyclophosphamide or who developed complication(s) resulting from prior cyclophosphamide exposure (*e.g.*, hemorrhagic cystitis); (6) rituximab should not be combined with conventional immunosuppressive treatments (except glucocorticoids) though such option is possible in patients not responding or responding incompletely to immunosuppressant(s) or rituximab alone; and (7) rituximab can be prescribed for maintenance treatment.

The other promising biologic agents for the treatment of ANCA-associated vasculitis include ocrelizumab, afatumumab, epratimumab, belimumab, abatacept, C5a complement inhibitor. The efficacy of belimumab for maintenance treatment is currently being studied in the placebo-controlled BREVAS study (NCT01663623) that plans to enroll around 300 patients with GPA and MPA who have achieved remission with oral or intravenous cyclophosphamide.

The results of main randomized controlled trials in patients with ANCA-associated vasculitides are summarized in Table 1^[51].

CONCLUSION

The diagnosis and treatment of ANCA-associated vasculitis were always the challenge for physicians. The criteria of activity and approaches to classification also remain the subject for discussion. The conventional immunosuppressive treatment allows to achieve and to maintain remission in the majority of patients with ANCA-associated vasculitis. Nevertheless, there is a need for more effective therapies for patients who are refractory or intolerant to current immunosuppressive regimens, and for those who have a relapsing systemic vasculitis. Biologic agents may have advantages over conventional immunosuppressive agents for efficacy and/or safety. The controlled and uncontrolled studies showed that rituximab can be used for induction of remission in patients with GPA and MPA and is the treatment of choice in patients with refractory ANCA-associated vasculitis and in those who had incomplete response to or were intolerant of cyclophosphamide.

REFERENCES

- 1 **Ntatsaki E**, Watts RA, Scott DG. Epidemiology of ANCA-associated vasculitis. *Rheum Dis Clin North Am* 2010; **36**: 447-461 [PMID: 20688243 DOI: 10.1016/j.rdc.2010.04.002]
- 2 **Watts RA**, Mooney J, Skinner J, Scott DG, Macgregor AJ. The

- contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. *Rheumatology* (Oxford) 2012; **51**: 926-931 [PMID: 22258386]
- 3 **Fujimoto S**, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, Hashimoto H, Nuno H. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. *Rheumatology* (Oxford) 2011; **50**: 1916-1920 [PMID: 21798892 DOI: 10.1093/rheumatology/ker454]
- 4 **Millet A**, Pederzoli-Ribeil M, Guillemin L, Witko-Sarsat V, Mouthon L. Antineutrophil cytoplasmic antibody-associated vasculitides: is it time to split up the group? *Ann Rheum Dis* 2013; **72**: 1273-1279 [PMID: 23606701 DOI: 10.1136/annrheumdis-2013-203255]
- 5 **Jennette JC**, Falk RJ, Hu P, Xiao H. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. *Annu Rev Pathol* 2013; **8**: 139-160 [PMID: 23347350 DOI: 10.1146/annurev-pathol-011811-132453]
- 6 **Jennette JC**, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillemin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65**: 1-11 [PMID: 23045170 DOI: 10.1002/art.37715]
- 7 **Lionaki S**, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, Nachman PH, Jennette JC, Falk RJ. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis Rheum* 2012; **64**: 3452-3462 [PMID: 23023777 DOI: 10.1002/art.34562]
- 8 **Lyons PA**, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, Baslund B, Brechley P, Bruchfeld A, Chaudhry AN, Cohen Tervaert JW, Deloukas P, Feighery C, Gross WL, Guillemin L, Gunnarsson I, Harper L, Hrušková Z, Little MA, Martorana D, Neumann T, Ohlsson S, Padmanabhan S, Pusey CD, Salama AD, Sanders JS, Savage CO, Segelmark M, Stegeman CA, Tesaf V, Vaglio A, Wieczorek S, Wilde B, Zwerina J, Rees AJ, Clayton DG, Smith KG. Genetically distinct subsets within ANCA-associated vasculitis. *N Engl J Med* 2012; **367**: 214-223 [PMID: 22808956 DOI: 10.1056/NEJMoa1108735]
- 9 **Mahr A**, Katsahian S, Varet H, Guillemin L, Hagen EC, Höglund P, Merkel PA, Pagnoux C, Rasmussen N, Westman K, Jayne DR. Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. *Ann Rheum Dis* 2013; **72**: 1003-1010 [PMID: 22962314 DOI: 10.1136/annrheumdis-2012-201750]
- 10 **Leavitt RY**, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, Calabrese LH, Fries JF, Lie JT, Lightfoot RW. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990; **33**: 1101-1107 [PMID: 2202308]
- 11 **Rao JK**, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. *Ann Intern Med* 1998; **129**: 345-352 [PMID: 9735061]
- 12 **Craven A**, Robson J, Ponte C, Grayson PC, Suppiah R, Judge A, Watts R, Merkel PA, Luqmani RA. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DC-VAS). *Clin Exp Nephrol* 2013; **17**: 619-621 [PMID: 23996327 DOI: 10.1007/s10157-013-0854-0]
- 13 **Jennette JC**, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997; **337**: 1512-1523 [PMID: 9366584]
- 14 **Watts R**, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007; **66**: 222-227 [PMID: 16901958]
- 15 **Mueller A**, Holl-Ulrich K, Gross WL. Granuloma in ANCA-associated vasculitides: another reason to distinguish between syndromes? *Curr Rheumatol Rep* 2013; **15**: 376 [PMID: 24078103]

- DOI: 10.1007/s11926-013-0376-5]
- 16 **Schmitt WH**, van der Woude FJ. Clinical applications of antineutrophil cytoplasmic antibody testing. *Curr Opin Rheumatol* 2004; **16**: 9-17 [PMID: 14673383]
 - 17 **Birck R**, Schmitt WH, Kaelsch IA, van der Woude FJ. Serial ANCA determinations for monitoring disease activity in patients with ANCA-associated vasculitis: systematic review. *Am J Kidney Dis* 2006; **47**: 15-23 [PMID: 16377381]
 - 18 **Finkelmann JD**, Merkel PA, Schroeder D, Hoffman GS, Spiera R, St Clair EW, Davis JC, McCune WJ, Lears AK, Ytterberg SR, Hummel AM, Viss MA, Peikert T, Stone JH, Specks U. Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis. *Ann Intern Med* 2007; **147**: 611-619 [PMID: 17975183]
 - 19 **Sanders JS**, Huitma MG, Kallenberg CG, Stegeman CA. Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. *Rheumatology* (Oxford) 2006; **45**: 724-729 [PMID: 16399845]
 - 20 **Tomasson G**, Grayson PC, Mahr AD, Lavalley M, Merkel PA. Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis--a meta-analysis. *Rheumatology* (Oxford) 2012; **51**: 100-109 [PMID: 22039267 DOI: 10.1093/rheumatology/ker280]
 - 21 **Thai LH**, Charles P, Resche-Rigon M, Desseaux K, Guillevin L. Are anti-proteinase-3 ANCA a useful marker of granulomatosis with polyangiitis (Wegener's) relapses? Results of a retrospective study on 126 patients. *Autoimmun Rev* 2014; **13**: 313-318 [PMID: 24225075 DOI: 10.1016/j.autrev.2013.11.003]
 - 22 **Monach PA**, Warner RL, Tomasson G, Specks U, Stone JH, Ding L, Fervenza FC, Fessler BJ, Hoffman GS, Iklé D, Kallenberg CG, Krischer J, Langford CA, Mueller M, Seo P, St Clair EW, Spiera R, Tchao N, Ytterberg SR, Johnson KJ, Merkel PA. Serum proteins reflecting inflammation, injury and repair as biomarkers of disease activity in ANCA-associated vasculitis. *Ann Rheum Dis* 2013; **72**: 1342-1350 [PMID: 22975753]
 - 23 **Luqmani RA**, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, Savage C, Adu D. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM* 1994; **87**: 671-678 [PMID: 7820541 DOI: 10.1136/annrheumdis-2012-201981]
 - 24 **Merkel PA**, Aydin SZ, Boers M, Direskeneli H, Herlyn K, Seo P, Suppih R, Tomasson G, Luqmani RA. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. *J Rheumatol* 2011; **38**: 1480-1486 [PMID: 21724720 DOI: 10.3899/jrheum.110276]
 - 25 **Mukhtyar C**, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossmann O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani RA. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; **68**: 1827-1832 [PMID: 19054820]
 - 26 **Suppih R**, Mukhtyar C, Flossmann O, Alberici F, Baslund B, Batra R, Brown D, Holle J, Hruskova Z, Jayne DR, Judge A, Little MA, Palmisano A, Stegeman C, Tesar V, Vaglio A, Westman K, Luqmani R. A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis. *Rheumatology* (Oxford) 2011; **50**: 899-905 [PMID: 21156667 DOI: 10.1136/ard.2008.101279]
 - 27 **Flossmann O**, Berden A, de Groot K, Hagen C, Harper L, Heijl C, Höglund P, Jayne D, Luqmani R, Mahr A, Mukhtyar C, Pusey C, Rasmussen N, Stegeman C, Walsh M, Westman K. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; **70**: 488-494 [PMID: 21109517 DOI: 10.1136/ard.2010.137778]
 - 28 **Exley AR**, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, Adu D. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 1997; **40**: 371-380 [PMID: 9041949]
 - 29 **Bhamra K**, Luqmani R. Damage assessment in ANCA-associated vasculitis. *Curr Rheumatol Rep* 2012; **14**: 494-500 [PMID: 22983618 DOI: 10.1007/s11926-012-0291-1]
 - 30 **Robson J**, Doll H, Suppih R, Flossmann O, Harper L, Höglund P, Jayne D, Mahr A, Westman K, Luqmani R. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. *Ann Rheum Dis* 2015; **74**: 177-184 [PMID: 24243925 DOI: 10.1136/annrheumdis-2013-203927]
 - 31 **Guillevin L**, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibult N, Casassus P. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* (Baltimore) 1996; **75**: 17-28 [PMID: 8569467]
 - 32 **Guillevin L**, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* (Baltimore) 2011; **90**: 19-27 [PMID: 21200183 DOI: 10.1097/MD.0b013e318205a4c6]
 - 33 **Smith RM**, Jones RB, Jayne DR. Progress in treatment of ANCA-associated vasculitis. *Arthritis Res Ther* 2012; **14**: 210 [PMID: 22569190 DOI: 10.1186/ar3797]
 - 34 **Jayne D**, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniené J, Ekstrand A, Gaskin G, Gregorini G, de Groot K, Gross W, Hagen EC, Mirapeix E, Pettersson E, Siegert C, Sinico A, Tesar V, Westman K, Pusey C. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; **349**: 36-44 [PMID: 12840090]
 - 35 **de Groot K**, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, Luqmani R, Pusey CD, Rasmussen N, Sinico RA, Tesar V, Vanhille P, Westman K, Savage CO. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; **150**: 670-680 [PMID: 19451574]
 - 36 **Harper L**, Morgan MD, Walsh M, Höglund P, Westman K, Flossmann O, Tesar V, Vanhille P, de Groot K, Luqmani R, Flores-Suarez LF, Watts R, Pusey C, Bruchfeld A, Rasmussen N, Blockmans D, Savage CO, Jayne D. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 2012; **71**: 955-960 [PMID: 22128076 DOI: 10.1136/annrheumdis-2011-200477]
 - 37 **De Groot K**, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, Gross WL, Luqmani R, Jayne DR. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; **52**: 2461-2469 [PMID: 16052573]
 - 38 **Faurschou M**, Westman K, Rasmussen N, de Groot K, Flossmann O, Höglund P, Jayne DR. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012; **64**: 3472-3477 [PMID: 22614882 DOI: 10.1002/art.34547]
 - 39 **Pagnoux C**, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, Kyndt X, Lifermann F, Papo T, Lambert M, Le Noach J, Khellaf M, Merrien D, Puéchal X, Vinzio S, Cohen P, Mouthon L, Cordier JF, Guillevin L. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; **359**: 2790-2803 [PMID: 19109574 DOI: 10.1056/NEJMoa0802311]
 - 40 **Hiemstra TF**, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, Hauser T, Neumann I, Tesar V, Wissing KM, Pagnoux C, Schmitt W, Jayne DR. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 2010; **304**: 2381-2388 [PMID: 21060104 DOI: 10.1001/jama.2010.1658]
 - 41 **Metzler C**, Miehle N, Manger K, Iking-Konert C, de Groot K, Hellmich B, Gross WL, Reinhold-Keller E. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. *Rheumatology* (Oxford) 2007; **46**: 1087-1091 [PMID: 17519271]
 - 42 **Jones RB**, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D, Walsh M, Westman K, Jayne DR. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; **363**: 211-220 [PMID: 20647198 DOI: 10.1056/NEJMoa0909169]
 - 43 **Stone JH**, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman

- GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Weber L, Ding L, Sejismundo LP, Mieras K, Weitzkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; **363**: 221-232 [PMID: 20647199 DOI: 10.1056/NEJMoa0909905]
- 44 **Charles P**, Néel A, Tieulié N, Hot A, Pugnet G, Decaux O, Marie I, Khellaf M, Kahn JE, Karras A, Ziza JM, Deligny C, Tchérakian C, Guillevin L. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients. *Rheumatology (Oxford)* 2014; **53**: 532-539 [PMID: 24282319 DOI: 10.1093/rheumatology/ket381]
- 45 **Besada E**, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. *Rheumatology (Oxford)* 2013; **52**: 2041-2047 [PMID: 23934313 DOI: 10.1093/rheumatology/ket257]
- 46 **Cartin-Ceba R**, Golbin JM, Keogh KA, Peikert T, Sánchez-Menéndez M, Ytterberg SR, Fervenza FC, Specks U. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. *Arthritis Rheum* 2012; **64**: 3770-3778 [PMID: 22730028 DOI: 10.1002/art.34584]
- 47 **Specks U**, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Fessler BJ, Ding L, Viviano L, Tchao NK, Phippard DJ, Asare AL, Lim N, Ikle D, Jepson B, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh K, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Mueller M, Sejismundo LP, Mieras K, Stone JH. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; **369**: 417-427 [PMID: 23902481 DOI: 10.1056/NEJMoa1213277]
- 48 **Holle JU**, Dubrau C, Herlyn K, Heller M, Ambrosch P, Noelle B, Reinhold-Keller E, Gross WL. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. *Ann Rheum Dis* 2012; **71**: 327-333 [PMID: 22021864 DOI: 10.1136/ard.2011.153601]
- 49 **Guillevin L**, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, Decaux O, Desmurs-Clavel H, Gobert P, Quemeneur T, Blanchard-Delaunay C, Godmer P, Puechal X, Carron PL, Hatron PY, Limal N, Hamidou M, Bonnotte B, Ravaud P, Mouthon L. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. A prospective study in 117 patients. *Presse Med* 2013; **42**: 679 [DOI: 10.1016/j.lpm.2013.02.068]
- 50 **Charles P**, Bienvenu B, Bonnotte B, Gobert P, Godmer P, Hachulla É, Hamidou M, Harlé JR, Karras A, Lega JC, Le Quellec A, Mahr AD, Mouthon L, Papo T, Puéchal X, Pugnet G, Samson M, Sibilia J, Terrier B, Vanderghenst F, Guillevin L. Rituximab: Recommendations of the French Vasculitis Study Group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibody-associated necrotizing vasculitides. *Presse Med* 2013; **42**: 1317-1330 [PMID: 24095054 DOI: 10.1016/j.lpm.2013.08.003]
- 51 **Schönermarck U**, Gross WL, de Groot K. Treatment of ANCA-associated vasculitis. *Nat Rev Nephrol* 2014; **10**: 25-36 [PMID: 24189648 DOI: 10.1038/nrmeph.2013.225]

P- Reviewer: Cavallasca JA, Espinoza LR, Khan S
S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu HL



Orofacial pain and fibromyalgia pain: Being aware of comorbid conditions

Cansu Alpaslan

Cansu Alpaslan, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Gazi University, 06510 Ankara, Turkey
 Author contributions: Alpaslan C solely contributed to this manuscript.

Conflict-of-interest: The author confirms that the manuscript has no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Cansu Alpaslan, DDS, PhD, Professor, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Gazi Üniversitesi Dishekimligi Fakültesi Cerrahi Bolumu E Blok 5, Kat, 8, Cadde 82, Sokak Emek, 06510 Ankara, Turkey. cansu@gazi.edu.tr

Telephone: +90-312-2034329

Received: July 2, 2014

Peer-review started: July 3, 2014

First decision: August 30, 2014

Revised: November 13, 2014

Accepted: November 27, 2014

Article in press: November 27, 2014

Published online: March 12, 2015

Abstract

Orofacial pain originating from myofascial pain of temporomandibular disorders is the second most common source of pain, after tooth pain. However, diagnosis of myofascial pain is challenging due to its characteristic referral pattern. Furthermore, pain arising from structures in the orofacial region may be a presentation of fibromyalgia and treatment directed at temporomandibular disorders fails to alleviate the pain. Similarly, patients with fibromyalgia may present with pain in the orofacial region. The physician in this case should be aware of temporomandibular disorders, its

characteristic findings and treatment approaches that might be included in the treatment plan.

Key words: Orofacial pain; Fibromyalgia; Myofascial pain; Trigger point; Temporomandibular disorders

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The characteristic presentation of myofascial pain and fibromyalgia pain in the orofacial region and their comorbidity is covered in this review article.

Alpaslan C. Orofacial pain and fibromyalgia pain: Being aware of comorbid conditions. *World J Rheumatol* 2015; 5(1): 45-49
 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i1/45.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i1.45>

INTRODUCTION

Fibromyalgia (FM), characterized by widespread musculoskeletal pain, is the most common "rheumatic" disorder after osteoarthritis^[1]. It is a central pain disorder resulting from abnormal pain processing with increased pain transmission and perception in the central nervous system^[2,3]. Patients usually have episodic histories of pain throughout the body and have a familial history of FM^[1,3]. Fibromyalgia may develop after a traffic accident or viral infection and impaired socio-economic conditions like a low family income may contribute to the onset^[4,5]. The clinical diagnosis of FM is not easy as it has a myriad of symptoms. Its existence as an independent entity is not well accepted and it is usually co-morbid with other diseases^[6,7].

The characteristic symptom is generalized pain lasting more than 3 mo and described variously from burning, shooting to deep aching by verbal pain

descriptors. The pain described as hurting all over eases its differential diagnosis^[6]. Irritable bowel syndrome, stiffness, fatigue, sleep disturbance, headache and mood disorders may be the accompanying symptoms^[6,8].

Fibromyalgia patients may present with orofacial manifestations, including temporomandibular disorders (TMDs), headaches and oral complaints, in which case diagnosis is a challenge for dental professionals^[4,9-11].

Temporomandibular disorders have the highest prevalence among orofacial pain conditions involving disorders of the masticatory muscles and/or the temporomandibular joint (TMJ)^[12].

The purpose of this paper is to provide a review on the presentations, diagnoses and treatment of FM and TMDs, to raise awareness on comorbid conditions for both medical and dental professionals dealing with the management of pain.

EPIDEMIOLOGY, ETIOLOGY, PATHOPHYSIOLOGY

Temporomandibular joint and muscle disorders affect 5-12% of the population, with a higher prevalence rate among younger persons and in women^[13].

The overall prevalence of TMD type pain is around 4.6%, with a women: men ratio of 2:1^[14,15]. Marklund *et al*^[16] found that myofascial pain (MP) showed a preponderance among women in fertile ages than in men and both incidence rate and maintenance of orofacial pain for a one year follow-up period showed a gender difference.

Fibromyalgia has a female: male ratio of 2:1 with the newer diagnostic criteria which is similar to MP^[17]. Canadian prevalence rates have been reported as 2%-3% for FM, with females affected up to nine times more commonly than males^[18]. In a nationwide German population study, prevalence increased with age but rates did not differ significantly between males and females^[19]. Comparison of the rates of diagnoses by clinical examination with random survey results revealed a remarkable number of underdiagnosed cases, especially in men, that may explain the low rate of FM among males^[20].

The rate of new onset widespread pain is common in older adults, with some predictable factors like presence of pain at baseline and presence of diffuse osteoarthritis^[21]. However, FM can develop at any age, even in childhood^[1].

The real pathophysiology behind TMDs is not truly understood; trauma, either direct or indirect, micro or macro are blamed as a significant cause of TMDs. Poor posture, forward head position, sleep disorders, stress, eating disorders and psychosocial factors are counted as other possible etiological factors of TMDs, mostly believed to have a multifactorial etiology^[12,22].

The pathophysiology of FM, considered to be a centralized pain state, involves abnormal function of neuroendocrine and autonomic nervous systems,

genetic factors, environmental and psychosocial triggers like mechanical/physical/emotional trauma, and chronic stress^[23].

Psychological and psychosocial factors frequently accompany chronic pain syndromes; FM and MP have been suggested as occurring due to psychiatric distress and amplification of body sensations. Therefore, assessment may provide information about the relationship of TMDs and fibromyalgia^[24].

DIAGNOSTIC CRITERIA

Diagnostic criteria of temporomandibular disorders

There has been a long standing deficiency in establishing a common standard care for diagnosis and treatment of TMDs^[25]. For classification of TMDs, "research diagnostic criteria for temporomandibular disorders (RDC/TMD)" originally proposed by Dworkin *et al*^[26] have been used widely for both clinical and research purposes. This classification evaluates the patient in a dual axis, including both physical (Axis I) and psychosocial (Axis II) clinical assessment. Very recently, evidence-based "diagnostic criteria for temporomandibular disorders (DC/TMD)" were introduced by Schiffman *et al*^[27] and Peck *et al*^[28]. This classification included rarely seen but clinically apparent disorders to improve the diagnostic assessment of patients with temporomandibular disorders (Table 1).

The use of the DC/TMD protocol is appropriate for both clinical and research settings, permits multiple diagnoses and facilitates more individualized and customized care for each patient^[28]. Only masticatory muscle disorders will be reviewed here since it covers both fibromyalgia and myofascial pain.

Diagnostic criteria for fibromyalgia

Diagnosis of fibromyalgia is made based on the diagnostic criteria proposed by the American College of Rheumatology (ACR) in 1990 which was later modified in 2010; both have proven valid for diagnosis^[29]. According to ACR criteria, FM diagnosis can be made if the 3 conditions in the box (Table 2) below are met^[30].

CLINICAL PRESENTATIONS AND DIAGNOSIS

Clinical presentation and diagnosis of MP

Pain originating from masticatory muscles is considered to be musculoskeletal pains of the deep somatic category. A patient with myofascial pain presents with a history of pain in the orofacial region, mostly in the temple and cheek and aggravated with chewing and talking. Pain is not well localized, usually diffuse, with a dull, depressing quality^[12,26,27]. Pain is described as aching, tight, throbbing and tender^[31].

Myofascial pain is a condition in which pain originates from either the masseter muscle or temporalis muscle that may be duplicated by palpation for 5 s. Pain on palpation may be limited to the site of finger pressure,

Table 1 Diagnostic criteria for temporomandibular disorders^[27,28]

Temporomandibular joint disorders
Joint pain
Joint disorders
Joint diseases
Fractures
Congenital/developmental disorders
Masticatory muscle disorders
Muscle pain
Myalgia
Local myalgia
Myofascial pain
Myofascial pain with referral
Tendonitis
Myositis
Spasm
Contracture
Hypertrophy
Neoplasm
Movement disorders
Masticatory muscle pain attributed to systemic/central pain disorders
Fibromyalgia/widespread pain
Headache
Headache attributed to TMD
Associated structures
Coronoid hyperplasia

TMD: Temporomandibular disorders.

may exceed the site of palpation but stay within the boundaries of the muscle or may even spread beyond the boundaries of the muscle. Pain is mostly referred to anatomical parts in close proximity; mostly to teeth, ears and eyes when the boundaries of the palpated muscle are exceeded. The onset and severity of pain is highly attributed to jaw functions or parafunction. Limited mouth opening may accompany pain^[27,28].

If the patient has signs and symptoms of myofascial pain and also has a diagnosis of fibromyalgia, myofascial pain is considered to be related to fibromyalgia^[27]. These cases are characterized by the presence of widespread pain apart from the masticatory muscle pain. Localization of pain in the orofacial area is similar to those in myofascial pain. However, diverse pain complaints may be present, from back pain to headache^[27,28].

In the DC/TMD classification, diagnoses are made according to the signs and symptoms in the last 30 d rather than the etiologies and added further diagnoses for muscle pain disorders. However, the presence and number of trigger points is not mentioned in this classification.

In patients presenting with pain in the orofacial region, the differential diagnosis should be made based on detailed anamnesis, including the patient's history of signs, followed by clinical examination. Imaging should be considered if needed^[32].

Clinical presentation and diagnosis of FM

The American College of Rheumatology^[30] recognizes fibromyalgia as a true syndrome of diffuse body pain.

Table 2 American College of Rheumatology criteria for diagnosis of fibromyalgia^[30]

WPI > 7 and a symptom SS > 5 or WPI 3-6 and SS > 9
Symptoms have been present at a similar level for at least 3 mo
The patient does not have a disorder that would otherwise explain the pain

WPI: Widespread Pain Index; SS: Severity scale.

Pain is the primary complaint, with its presence for at least 3 mo required for verifying diagnosis. It is intermittent at the beginning and becomes more persistent as it progresses^[33]. Pain is described as aching, throbbing and/or stabbing^[4]. Sleep disturbance, fatigue, irritable bowel syndrome, headache and mood disturbance accompany this syndrome. The diagnosis is made by history, clinical evaluation and physical examination.

In the 2010 diagnostic criteria, FM is considered as a systemic somatic condition, a symptom complex, and its diagnosis does not rely on counting the tender points. A two part self-administered questionnaire, Part 1 assessing pain at 19 sites by the Widespread Pain Index (WPI) and Part 2 measuring intensity of symptoms like fatigue, headache and abdominal pain by the symptom severity (SS) scale, is used as the tools of the 2010 fibromyalgia diagnostic criteria^[3].

No confirmatory diagnostic test is required^[33].

Trigger points

Trigger points (TP), the taut bands, actually a contracted group of muscle fibers of skeletal muscles, tendons or ligaments, have long been believed to be present in myofascial pain syndrome. Pain occurs when the TP is palpated and can be irradiated to distant areas within myofascial structures. A reproducible duplication of a patient's pain complaint with palpation of the tender area is recognized as diagnostic^[3].

Differences in the prevalence and the anatomical localization of trigger points were compared in a study. Active trigger points were found to be 6 ± 1 for MP and 4 ± 1 for FM. A significant association with TPs and pain was found only in MP. Women with MP exhibited a greater number of active TPs in temporalis and masseter muscles than women with FM. On the other hand, larger referred pain from sternocleidomastoid and suboccipital muscles were found in women with FM than in those with MP. However, in the new classification, the term tender points replaces trigger points. It is emphasized that tender points in FM do not have taut bands and they do not refer pain to distant sites^[34].

In a Cochrane review dated 2012, myofascial pain syndrome is described as a regional muscular pain syndrome with painful trigger points in one or more muscles. The pain may either be localized to the site of trigger points or may extend away from the site of palpation^[35].

Relationship of MP with FM

Fibromyalgia and myofascial pain are two main musculoskeletal pain conditions that patients seek treatment for because of pain and fatigue^[2]. There are various opinions on the relationship of MP with FM or vice versa. While some authors believe that these disorders belong to the same spectrum of chronic widespread pain conditions, others accept that these two disorders belong to distinct types with similar underlying pathophysiology^[17,19].

Both conditions are associated with central sensitization. Fibromyalgia is a central pain disorder occurring because of abnormal pain processing within the central nervous system. Myofascial pain, which initially starts as a peripheral disorder with pain localized within muscle, progresses to central sensitization that causes referred pain. FM and MP which have similar pathophysiological processes may occur concomitantly^[2,3].

It has been found that 75% of patients with FM have signs and symptoms of MP, while 18% of patients with MP meet the FM criteria^[24]. Likewise, 59% of patients with TMD reported 2 or more comorbid pains in a large United States Health interview survey, whereas only 0.77% reported it without any comorbid conditions^[11].

Manfredini *et al*^[36] found that while 86.7% of patients with fibromyalgia have concomitantly reported signs and symptoms localized at the orofacial region, fibromyalgia affected only 10% of patients with temporomandibular disorders. In another study, 85% of FM patients reported facial pain, with 77.5% later receiving a diagnosis of myofascial TMD^[37].

The percentage of patients meeting the clinical RDC/TMD criteria among FM patients reporting face pain has been found to be 71%^[4], consistent with the finding of Plesh *et al*^[11]. Furthermore, almost half of FM patients have not reported facial pain, thinking that it is related to FM, and also met the diagnostic criteria for temporomandibular disorders^[4].

Both MP and FM may present with irritable bowel syndrome, with a ratio of 32%-80% for FM patients and 64% for TMD patients^[24]. Besides, different types of headaches like migraine or tension type headaches, irritable bowel syndrome, hypermobility syndromes, painful bladder syndrome, pelvic pain syndrome, vulvovaginitis, endometriosis, dysmenorrhea, prostatitis and hypothyroidism have been reported to be commonly associated with both FM and MP. Vitamin D and B12 deficiency, iron deficiency, parasitic infection and celiac disease of malabsorption have been reported to be more commonly associated with MP^[3].

Treatment

Since no exact causative factors responsible for MP and FM have been isolated so far, treatment of those conditions is directed towards restoring function of the descending nociceptive inhibitory system, restoring sleep patterns, alleviating pain and treating comorbid

medical conditions^[2,3].

A thorough patient history including the chief complaint of the patient, clinical exam and imaging if needed leads to a proper diagnosis of TMDs. Conservative, reversible and evidence-based therapeutic modalities should be attempted as the first step treatment of TMDs^[32].

The aim for the treatment of FM patients is to restore function. Like TMDs, patients with FM respond to simple and conservative interventions like stress reduction, cognitive behavioral therapy, restoring sleep pattern, treating comorbid medical conditions and exercise^[3].

Medical therapies and more advanced interventions are needed for an individual patient-based approach if initial interventions fail.

CONCLUSION

Patients with pain in the orofacial region mostly seek treatment from dentists, while patients with generalized pain go to medical doctors. Both professionals should be aware of the comorbidity between FM and MP when they examine patients. The importance of making a distinction between these 2 disorders is necessary, mostly for proper treatment and avoiding overtreatment.

REFERENCES

- 1 **Clauw DJ**. Fibromyalgia: a clinical review. *JAMA* 2014; **311**: 1547-1555 [PMID: 24737367 DOI: 10.1001/jama.2014.3266]
- 2 **Chandola HC**, Chakraborty A. Fibromyalgia and Myofascial Pain Syndrome-A Dilemma. *Indian J Anaestht* (serial online) 2009; **53**: 575-581. Available from: URL: <http://www.ijaweb.org/text.asp?2009/53/5/575/60336>
- 3 **Gerwin RD**. Diagnosing fibromyalgia and myofascial pain syndrome: a guide. *J Fam Pract* 2013; **62**: S19-S25 [PMID: 24340342]
- 4 **Balasubramaniam R**, de Leeuw R, Zhu H, Nickerson RB, Okeson JP, Carlson CR. Prevalence of temporomandibular disorders in fibromyalgia and failed back syndrome patients: a blinded prospective comparison study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **104**: 204-216 [PMID: 17482850 DOI: 10.1016/j.tripleo.2007.01.012]
- 5 **Toda K**. Comparison of Symptoms Among Fibromyalgia Syndrome, Chronic Widespread Pain, and an Incomplete Form of Chronic Widespread Pain. *J Musculoskel Pain* 2011; **19**: 52-55 [DOI: 10.3109/10582452.2010.502614]
- 6 **Atzeni F**, Cazzola M, Benucci M, Di Franco M, Salaffi F, Sarzi-Putini P. Chronic widespread pain in the spectrum of rheumatological diseases. *Best Pract Res Clin Rheumatol* 2011; **25**: 165-171 [PMID: 22094193 DOI: 10.1016/j.berh.2010.01.011]
- 7 **Cazzola M**, Sarzi-Putini P, Stisi S, Di Franco M, Bazzichi L, Carignola R, Gracely RH, Salaffi F, Marinangeli F, Torta R, Giamberardino MA, Buskila D, Spath M, Cazzola M, Di Franco M, Biasi G, Stisi S, Altomonte L, Arioli G, Alciati A, Marsico A, Ceccherelli F, Leardini G, Gorla R, Atzeni F. Fibromyalgia syndrome: definition and diagnostic aspects. *Reumatismo* 2008; **60** Suppl 1: 3-14 [PMID: 18852904]
- 8 **Cassisi G**, Sarzi-Putini P, Alciati A, Casale R, Bazzichi L, Carignola R, Gracely RH, Salaffi F, Marinangeli F, Torta R, Giamberardino MA, Buskila D, Spath M, Cazzola M, Di Franco M, Biasi G, Stisi S, Altomonte L, Arioli G, Leardini G, Gorla R, Marsico A, Ceccherelli F, Atzeni F. Symptoms and signs in fibromyalgia syndrome. *Reumatismo* 2008; **60** Suppl 1: 15-24 [PMID: 18852905]
- 9 **Aaron LA**, Burke MM, Buchwald D. Overlapping conditions

- among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med* 2000; **160**: 221-227 [PMID: 10647761 DOI: 10.1001/archinte.160.2.221]
- 10 **Rhodus NL**, Friction J, Carlson P, Messner R. Oral symptoms associated with fibromyalgia syndrome. *J Rheumatol* 2003; **30**: 1841-1845 [PMID: 12913944]
 - 11 **Plesh O**, Wolfe F, Lane N. The relationship between fibromyalgia and temporomandibular disorders: prevalence and symptom severity. *J Rheumatol* 1996; **23**: 1948-1952 [PMID: 8923373]
 - 12 **Okeson JP** (Ed.). Orofacial Pain. Guidelines for Assessment, Diagnosis and Management. Chicago, Ill: Quintessence, 1996: 119-127
 - 13 **National Institute of Dental and Craniofacial Research**. Facial Pain (accessed 2014 September 8). Available from: URL: <http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/FacialPain/>
 - 14 **Isong U**, Gansky SA, Plesh O. Temporomandibular joint and muscle disorder-type pain in U.S. adults: the National Health Interview Survey. *J Orofac Pain* 2008; **22**: 317-322 [PMID: 19090404]
 - 15 **LeResche L**. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. *Crit Rev Oral Biol Med* 1997; **8**: 291-305 [PMID: 9260045]
 - 16 **Marklund S**, Wänman A. Incidence and prevalence of myofascial pain in the jaw-face region. A one-year prospective study on dental students. *Acta Odontol Scand* 2008; **66**: 113-121 [PMID: 18446553 DOI: 10.1080/00016350802010372]
 - 17 **Wolfe F**, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011; **38**: 1113-1122 [PMID: 21285161 DOI: 10.3899/jrheum.100594]
 - 18 **McNally JD**, Matheson DA, Bakowsky VS. The epidemiology of self-reported fibromyalgia in Canada. *Chronic Dis Can* 2006; **27**: 9-16 [PMID: 16672135]
 - 19 **Wolfe F**, Brähler E, Hinz A, Häuser W. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. *Arthritis Care Res* (Hoboken) 2013; **65**: 777-785 [PMID: 23424058 DOI: 10.1002/acr.21931]
 - 20 **Vincent A**, Lahr BD, Wolfe F, Clauw DJ, Whipple MO, Oh TH, Barton DL, St Sauver J. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. *Arthritis Care Res* (Hoboken) 2013; **65**: 786-792 [PMID: 23203795 DOI: 10.1002/acr.21896]
 - 21 **McBeth J**, Lacey RJ, Wilkie R. Predictors of new-onset widespread pain in older adults: results from a population-based prospective cohort study in the UK. *Arthritis Rheumatol* 2014; **66**: 757-767 [PMID: 24574238 DOI: 10.1002/art.38284]
 - 22 **Licini F**, Nojelli A, Segù M, Collesano V. Role of psychosocial factors in the etiology of temporomandibular disorders: relevance of a biaxial diagnosis. *Minerva Stomatol* 2009; **58**: 557-566 [PMID: 20027126]
 - 23 **Bradley LA**. Pathophysiology of fibromyalgia. *Am J Med* 2009; **122**: S22-S30 [PMID: 19962493 DOI: 10.1016/j.amjmed.2009.09.008]
 - 24 **Plesh O**, Gansky SA. Fibromyalgia. In: Laskin DM, Greene CS, Hylander WL (eds) TMDs An evidence-based approach to diagnosis and treatment. Singapore: Quintessence books, 2006: 335-345
 - 25 **Greene CS**. Diagnosis and treatment of temporomandibular disorders: emergence of a new "standard of care". *Quintessence Int* 2010; **41**: 623-624 [PMID: 20677398]
 - 26 **Dworkin SF**, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *J Craniomandib Disord* 1992; **6**: 301-355 [PMID: 1298767]
 - 27 **Schiffman E**, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group †. *J Oral Facial Pain Headache* 2014; **28**: 6-27 [PMID: 24482784 DOI: 10.11607/jop.1151]
 - 28 **Peck CC**, Goulet JP, Lobbezoo F, Schiffman EL, Alstergren P, Anderson GC, de Leeuw R, Jensen R, Michelotti A, Ohrbach R, Petersson A, List T. Expanding the taxonomy of the diagnostic criteria for temporomandibular disorders. *J Oral Rehabil* 2014; **41**: 2-23 [PMID: 24443898 DOI: 10.1111/joor.12132]
 - 29 **Carrillo-de-la-Peña MT**, Triñanes Y, González-Villar A, Romero-Yuste S, Gómez-Perretta C, Arias M, Wolfe F. Convergence between the 1990 and 2010 ACR diagnostic criteria and validation of the Spanish version of the Fibromyalgia Survey Questionnaire (FSQ). *Rheumatol Int* 2015; **35**: 141-151 [PMID: 24952419 DOI: 10.1007/s00296-014-3074-3]
 - 30 **American College of Rheumatology**. 2010 Fibromyalgia Diagnostic Criteria - Excerpt. Available from: URL: http://www.rheumatology.org/practice/clinical/classification/fibromyalgia/fibro_2010.asp
 - 31 **Türp JC**, Kowalski CJ, Stohler CS. Pain descriptors characteristic of persistent facial pain. *J Orofac Pain* 1997; **11**: 285-290 [PMID: 9656903]
 - 32 **Türp JC**. What's new on the dental scene? Browsing through the dental literature. *J Orofac Orthop* 2011; **72**: 243-24, 246 [PMID: 21898194 DOI: 10.1007/s00056-011-0031-6]
 - 33 **Fitzcharles MA**, Ste-Marie PA, Goldenberg DL, Pereira JX, Abbey S, Choinière M, Ko G, Moulin DE, Panopalis P, Proulx J, Shir Y. Canadian Pain Society and Canadian Rheumatology Association recommendations for rational care of persons with fibromyalgia: a summary report. *J Rheumatol* 2013; **40**: 1388-1393 [PMID: 23818709 DOI: 10.3899/jrheum.130127]
 - 34 **Alonso-Blanco C**, Fernández-de-Las-Peñas C, de-la-Llave-Rincón AI, Zarco-Moreno P, Galán-Del-Río F, Svensson P. Characteristics of referred muscle pain to the head from active trigger points in women with myofascial temporomandibular pain and fibromyalgia syndrome. *J Headache Pain* 2012; **13**: 625-637 [PMID: 22935970 DOI: 10.1007/s10194-012-0477-y]
 - 35 **Soares A**, Andriolo RB, Atallah AN, da Silva EM. Botulinum toxin for myofascial pain syndromes in adults. *Cochrane Database Syst Rev* 2014; **7**: CD007533 [PMID: 25062018 DOI: 10.1002/14651858.CD007533.pub2]
 - 36 **Manfredini D**, Tognini F, Montagnani G, Bazzichi L, Bombardieri S, Bosco M. Comparison of masticatory dysfunction in temporomandibular disorders and fibromyalgia. *Minerva Stomatol* 2004; **53**: 641-650 [PMID: 15894939]
 - 37 **Pimentel MJ**, Gui MS, Martins de Aquino LM, Rizzatti-Barbosa CM. Features of temporomandibular disorders in fibromyalgia syndrome. *Cranio* 2013; **31**: 40-45 [PMID: 23461261]

P- Reviewer: Enlander D, Kapur S, Siqueira SRDT

S- Editor: Ji FF **L- Editor:** Roemmele A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Rheumatology*

World J Rheumatol 2015 July 12; 5(2): 50-126





Editorial Board

2011-2015

The *World Journal of Rheumatology* Editorial Board consists of 191 members, representing a team of worldwide experts in rheumatology. They are from 38 countries, including Argentina (2), Australia (4), Belgium (3), Brazil (3), Canada (2), Chile (1), China (16), Egypt (1), Finland (2), France (9), Germany (5), Greece (6), Hungary (2), India (3), Iran (2), Israel (6), Italy (11), Japan (2), Kuwait (1), Mexico (4), Morocco (2), Netherlands (3), Peru (1), Poland (1), Portugal (2), Qatar (1), Saudi Arabia (2), Slovakia (1), South Korea (4), Spain (7), Sweden (2), Switzerland (2), Thailand (1), Tunisia (1), Turkey (14), United Arab Emirates (1), United Kingdom (13), and United States (48).

EDITOR-IN-CHIEF

Jörg HW Distler, *Erlangen*

GUEST EDITORIAL BOARD MEMBERS

Yih-Hsin Chang, *Taichung*
Jing-Long Huang, *Taoyuan*
Pi-Chang Lee, *Taipei*
Chin-San Liu, *Changhua*
Ko-Hsiu Lu, *Taichung*
Fuu-Jen Tsai, *Taichung*
Chih-Shung Wong, *Taipei*
Jeng-Hsien Yen, *Kaohsiung*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Javier Alberto Cavallasca, *Santa Fe*
Enrique Roberto Soriano, *Buenos Aires*



Australia

Chang-Hai Ding, *Melbourne*
Davinder Singh-Grewal, *Sydney*
Gethin Thomas, *Brisbane*
Yin Xiao, *Brisbane*



Belgium

Olivier Bruyère, *Liège*
Nijs Jo, *Brussels*
Jean-Yves Reginster, *Liège*



Brazil

Simone Appenzeller, *Cidade Universitaria*
Mittermayer Santiago, *Nazaré Salvador*
Samuel K Shinjo, *São paulo*



Canada

Hong-Yu Luo, *Montreal*
Guang-Ju Zhai, *St John's*



Chile

Iván Palomo, *Maule*



China

Jun-Min Chen, *Fuzhou*
Sheng-Ming Dai, *Shanghai*
Ai-Ping Lu, *Beijing*
Chi Chiu Mok, *Hong Kong*
Ling Qin, *Hong Kong*
Han-Shi Xu, *Guangzhou*
Qing-Yu Zeng, *Shantou*
Peng Zhang, *Shenzhen*



Egypt

Yasser Emad, *Cairo*



Finland

Yrjö T Konttinen, *Helsinki*

Rahman Shiri, *Helsinki*



France

Didier Attaix, *Theix*
Francis Berenbaum, *Paris*
Michel Jacques de Bandt, *Aulnay sous Bois*
Pascal Laugier, *Paris*
Pierre Miossec, *Lyon*
M Djavad Mossalayi, *Bordeaux*
Luc Mouthon, *Paris*
Aleth Perdriger, *Rennes*
Alain Saraux, *Brest*



Germany

Magali Cucchiari, *Homburg*
Thomas Jax, *Neuss*
Friedrich Paul Paulsen, *Erlangen*
Med H H Peter, *Freiburg*



Greece

Andrew P Andonopoulos, *Rion*
Dimitrios Daoussis, *Patras*
Kosmas I Paraskevas, *Athens*
Grigorios Sakellariou, *Thessaloniki*
Lazaros I Sakkas, *Larissa*
Michael Voulgarelis, *Athens*



Hungary

Laszlo Czirkak, *Pecs*
András Komócsi, *Pecs*

**India**

Vikas Agarwal, *Lucknow*
Srikantiah Chandrashekara, *Bangalore*
Rajesh Vijayvergiya, *Chandigarh*

**Iran**

Nima Rezaei, *Tehran*
Zahra Rezaeiyazdi, *Mashhad*

**Israel**

Boaz Amichai, *Ramat Gan*
George S Habib, *Nazareth Illit*
Leonid Kalichman, *Beer Sheva*
Igal Leibovitch, *Tel-Aviv*
Ami Schattner, *Rehovot*
Elias Toubi, *Haifa*

**Italy**

Silvano Adami, *Verona*
Giuseppe Barbaro, *Rome*
Mauro Cellini, *Bologna*
Nicola Giordano, *Siena*
Estrella Garcia Gonzalez, *Siena*
Giovanni La Montagna, *Napoli*
Claudio Lunardi, *Verona*
Francesco Oliva, *Rome*
Donato Rigante, *Rome*
Dario Roccatello, *Turin*
Maurizio Turiel, *Milano*

**Japan**

Yoshiya Tanaka, *Kitakyushu*
Takashi Usui, *Kyoto*

**Kuwait**

Adel M A Alawadhi, *Kuwait*

**Mexico**

Carlos Abud-Mendoza, *San Luis Potosi*
Monica Vazquez-Del Mercado, *Guadalajara*
José F Muñoz-Valle, *Zapopan*
José Alvarez Nemegeyi, *Mérida*

**Morocco**

Zoubida Tazi Mezalek, *Rabat*
Faissal Tarrass, *Larache*

**Netherlands**

Esmeralda Blaney Davidson, *Nijmegen*
Timothy Ruben Radstake, *Nijmegen*

Nico M Wulffraat, *Utrecht*

**Peru**

Claudia Selene Mora-Trujillo, *Lima*

**Poland**

Przemyslaw Kotyla, *Katowice*

**Portugal**

Elizabeth Benito-Garcia, *Oeiras*
Alexandrina Ferreira Mendes, *Coimbra*

**Qatar**

Mohammed Hammoudeh, *Doha*

**Saudi Arabia**

Almoallim Hani Mohammad, *Jeddah*
Mohammed Tikly, *Johannesburg*

**Slovakia**

Ivica Lazúrová, *Košice*

**South Korea**

Dae-Hyun Hahm, *Seoul*
Young Mo Kang, *Daegu*
Myeong Soo Lee, *Daejeon*
Chang-Hee Suh, *Suwon*

**Spain**

Pedro Carpintero Benítez, *Cordoba*
Francisco J Blanco, *Coruña*
Vicente Giner Galvañ, *Alcoy*
Segundo Gonzalez, *Oviedo*
Narcis Gusi, *Caceres*
Luis Martinez-Lostao, *Zaragoza*
Gusi Narcis, *Caceres*

**Sweden**

Aladdin Mohammad, *Lund*
Ronald van Vollenhoven, *Stockholm*

**Switzerland**

Daniel Aeberli, *Bern*
Hossein Hemmatazad, *Zurich*

**Thailand**

Prachya Kongtawelert, *Chiang Mai*

**Tunisia**

Ghazi Chabchoub, *Sfax*

**Turkey**

Aynur Akay, *İzmir*
Deniz Evcik, *Ankara*
Sibel Eyigor, *Izmir*
Ozgur Kasapcopur, *Istanbul*
Suleyman Serdar Koca, *Elazig*
Ugur Musabak, *Ankara*
Demet Oflluoglu, *Istanbul*
Salih Ozgocmen, *Kayseri*
Cagatay Ozturk, *Istanbul*
Mehmet Akif Ozturk, *Ankara*
Ismail Sari, *Izmir*
Mehmet Soy, *Bolu*
Yavuz Yakut, *Ankara*
Serap Yalin, *Mersin*

**United Arab Emirates**

Ashok Kumar, *Dubai*

**United Kingdom**

Ade O Adebajo, *Sheffield*
Khalid Binyamin, *Mersyside*
Dimitrios P Bogdanos, *London*
David D'Cruz, *London*
Magdalena Dziadzio, *London*
Edzard Ernst, *Exeter*
Elena A Jones, *Leeds*
Joseph G McVeigh, *Belfast*
Sanjay Mehta, *London*
Jonathan Rees, *London*
Anita Williams, *Salford*
Hazem M Youssef, *Aberdeen*
Wei-Ya Zhang, *Nottingham*

**United States**

Cynthia Aranow, *Manhasset*
Joseph R Berger, *Lexington*
Vance Berger, *Rockville*
Daniel Bikle, *San Francisco*
Marc R Blackman, *Washington*
Galina S Bogatkevich, *Charleston*
Charles R Brown, *Columbia*
Leigh F Callahan, *Chapel Hill*
Hamid Chalian, *Chicago*
Majid Chalian, *Baltimore*
Sean Patrick Curtis, *Rahway*
Barbara A Eberhard, *New Hyde Park*
Luis R Espinoza, *New Orleans*
Shu -Man Fu, *Charlottesville*
Daniel E Furst, *Los Angeles*
Reda Ebeid Girgis, *Baltimore*
Alexei A Grom, *Cincinnati*
Simon Helfgott, *Boston*
Howard J Hillstrom, *New York*
Gary S Hoffman, *Cleveland*
Seung Jae Hong, *Chicago*

Meenakshi Jolly, *Chicago*
M Firoze Khan, *Galveston*
Irving Kushner, *Shaker Heights*
Antonio La Cava, *Los Angeles*
Yi Li, *Gainesville*
Chuan-Ju Liu, *New York*
Charles J Malemud, *Cleveland*
Mahnaz Momeni, *Washington*
Swapan K Nath, *Oklahoma*

Ewa Olech, *Oklahoma*
Alicia Rodríguez Pla, *Dallas*
Chaim Putterman, *Bronx*
Robert James Quinet, *New Orleans*
Allison B Reiss, *Mineola*
Lisa Georgianne Rider, *Bethesda*
Bruce M Rothschild, *Lawrence*
Hee-Jeong Im Sampen, *Chicago*
Naomi Schlesinger, *New Brunswick*

H Ralph Schumacher, *Philadelphia*
Jasvinder A Singh, *Birmingham*
Jianxun (Jim) Song, *Hershey*
Yu-Bo Sun, *Charlotte*
Thomas H Taylor, *Norwich*
George C Tsokos, *Boston*
Yu-Cheng Yao, *Los Angeles*
Ping Zhang, *Indianapolis*
Xiao-Dong Zhou, *Houston*



EDITORIAL

- 50 Use of biologic agents for rheumatic diseases in pregnancy
Garip Y

REVIEW

- 59 Pathogenetic mechanisms of antiphospholipid antibody production in antiphospholipid syndrome
Willis R, Gonzalez EB
- 69 Radiographic assessment of leg alignment and grading of knee osteoarthritis: A critical review
Sheehy L, Cooke TDV

MINIREVIEWS

- 82 Safety of biologic therapies during pregnancy in women with rheumatic disease
Mena-Vazquez N, Manrique-Arija S, Fernandez-Nebro A
- 90 Current review of trapeziometacarpal osteoarthritis (rhizarthrosis)
Bilge O, Karalezli N
- 96 Ins and outs of *Helicobacter pylori* association with autoimmune rheumatic diseases
Muhammad JS, Zaidi SF, Ishaq M
- 101 Pyoderma gangrenosum: An important dermatologic condition occasionally associated with rheumatic diseases
Yamamoto T

SYSTEMATIC REVIEWS

- 108 What is the best biological treatment for rheumatoid arthritis? A systematic review of effectiveness
dos Santos JB, Costa JO, Oliveira Junior HA, Lemos LLP, Araújo VE, Machado MAA, Almeida AM, Acurcio FA, Alvares J

Contents

World Journal of Rheumatology
Volume 5 Number 2 July 12, 2015

ABOUT COVER

Editorial Board Member of *World Journal of Rheumatology*, Luis Martinez-Lostao, MD, PhD, Assistant Professor, Department of Biochemistry, Molecular and Cell Biology, University of Zaragoza, C/ Pedro Cerbuna 12, 50009 Zaragoza, Spain

AIM AND SCOPE

World Journal of Rheumatology (*World J Rheumatol*, *WJR*, online ISSN 2220-3214, DOI: 10.5499) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJR covers topics concerning osteoarthritis, metabolic bone disease, connective tissue diseases, antiphospholipid antibody-associated diseases, spondyloarthropathies, acute inflammatory arthritis, fibromyalgia, polymyalgia rheumatica, vasculitis syndromes, periarticular rheumatic disease, pediatric rheumatic disease, miscellaneous rheumatic diseases, and rheumatology-related therapy, pain management, rehabilitation.

We encourage authors to submit their manuscripts to *WJR*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ ABSTRACTING

World Journal of Rheumatology is now indexed in Digital Object Identifier.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Xiao-Kang Jiao*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL

World Journal of Rheumatology

ISSN

ISSN 2220-3214 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Four-monthly

EDITOR-IN-CHIEF

Jörg HW Distler, MD, Department of Internal Medicine 3, University of Erlangen-Nuremberg, Universitätsstr. 29, 91054 Erlangen, Germany

EDITORIAL OFFICE

Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Rheumatology

Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLICATION DATE

July 12, 2015

COPYRIGHT

© 2015 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/2220-3214/g_info_20100722180909.htm

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Use of biologic agents for rheumatic diseases in pregnancy

Yesim Garip

Yesim Garip, Department of Physical Medicine and Rehabilitation,
06934 Sincan, Ankara, Turkey

Yesim Garip, Department of Physical Medicine and Rehabilitation,
Pinar Physical Therapy and Rehabilitation Center, 06010 Kecioren,
Ankara, Turkey

Author contributions: Garip Y solely contributed to this manuscript.

Conflict-of-interest statement: Yesim Garip declares that she has no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Yesim Garip, MD, Specialist, Department of Physical Medicine and Rehabilitation, Pinar Physical Therapy and Rehabilitation Center, Baglarbasi Mah Bursa Cad no 20, 06010 Kecioren, Ankara, Turkey. dryesimgarip@gmail.com
Telephone: +90-536-5844332
Fax: +90-312-2691718

Received: January 22, 2015
Peer-review started: January 24, 2015
First decision: February 7, 2015
Revised: April 29, 2015
Accepted: May 5, 2015
Article in press: May 6, 2015
Published online: July 12, 2015

Abstract

Biologic agents have ushered a new era in the treatment of inflammatory rheumatic diseases. In recent years, several biologic agents have been approved by food and drug administration and have significantly improved outcomes for patients with immune mediated

inflammatory disorders including rheumatic and inflammatory bowel diseases. The most common used biologic therapeutic agents are tumor necrosis factor inhibitors (etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab), an interleukin (IL)-6 inhibitor (tocilizumab), an IL-1 receptor antagonist (anakinra), an anti-CD-20 antibody (rituximab), and a T cell co-stimulation modulator (abatacept). Their use during pregnancy has been controversial because of absence of controlled studies which have enrolled pregnant women. This brief overview provides published data on use of biologic agents for the treatment of rheumatic diseases in pregnancy.

Key words: Ankylosing spondylitis; Rheumatoid arthritis; Pregnancy; Disease-modifying antirheumatic drugs

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Biologic agents are increasingly being used in the treatment of rheumatic diseases. This article presents published data on use of biologic agents in pregnant women with rheumatic diseases.

Garip Y. Use of biologic agents for rheumatic diseases in pregnancy. *World J Rheumatol* 2015; 5(2): 50-58 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i2/50.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i2.50>

INTRODUCTION

Most of the women with rheumatic diseases experience clinical remission during pregnancy, however in some cases, it is needed to continue the treatment throughout pregnancy^[1,2]. Few studies have suggested that high disease activity in rheumatic diseases throughout pregnancy may lead to increased risks for preeclampsia^[3], cesarean delivery^[4], prematurity^[5], low birth weight^[6,7], and intrauterine growth restriction^[4]. Owing to the fact

that important antirheumatic agents such as methotrexate and leflunomide have teratogenic effects, the treatment options are limited, and biological agents may be therapeutic alternative in pregnant women with high disease activity.

Since cytokines play a crucial role in host defense against infections, cytokine blockade is associated with increased risk of opportunistic infections. Previous studies have suggested an increased risk of bacterial, viral and fungal infections due to mycobacterium^[8], salmonella, listeria^[9], hepatitis B and C, herpes^[10], histoplasma, cryptococcus, coccidioides, candida, aspergillus and pneumocystis^[11]. Pregnancy is a period of relative immunosuppression, thus use of biologic agents during pregnancy may further increase the risk of infections^[12].

Since no drug trials have been performed in pregnant women to assess the risk of administration of biologic agents, safety of these agents during pregnancy is still a matter of debate. However, cumulative data suggest that frequency of birth defects after prenatal exposure to biologic agents does not seem to be higher than that occurs in the general population^[13].

Search strategy

A PubMed literature search (2000-2015) was performed to identify studies with human data on pregnancy outcomes after exposure to biologic agents during pregnancy. Search strategy was restricted to the articles published in English and Turkish and included the following search terms "tumor necrosis factor (TNF) inhibitors", "etanercept", "infliximab", "adalimumab", "certolizumab", "golimumab", "tocilizumab", "anakinra", "rituximab", "abatacept", and "pregnancy". First, titles and abstracts of all 931 references were screened; articles which have insufficient data or do not address the topic of the interest were excluded. Inclusion criteria were data on pregnancy outcomes in patients who were exposed to biologic agents before conception and throughout pregnancy. Additionally a hand-search was made looking for the reference lists of the applicable publications. Adequate documentation was found in 10 reviews, 10 registries, 17 case series and 18 case reports. Published data on reports of biologic therapies are summarized in Table 1.

USE OF ANTI-CYTOKINES DURING PREGNANCY

Tumor necrosis factor inhibitors

Efficacy of TNF inhibitors has been demonstrated in reducing disease activity and joint damage and improving health-related quality of life in the patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis^[14]. Most frequently used TNF inhibitors include etanercept, a soluble p75 TNF-receptor and IgG1 Fc fusion protein; infliximab, a human-murine IgG1 anti-TNF monoclonal antibody; adalimumab, a human IgG1

anti-TNF monoclonal antibody; certolizumab pegol, a pegylated Fab fragment of humanized anti-TNF monoclonal antibody; and golimumab, fully humanized TNF-alpha monoclonal antibody^[15].

TNF inhibitors have been rated as Food and Drug Administration (FDA) category B (No evidence of a risk to the fetus was found in animal toxicity studies; however there are no controlled studies which have enrolled pregnant women). TNF inhibitors do not actively cross the placenta during the first trimester and organogenesis, but they are transferred across the placenta during the late second and third trimester^[12]. These can be found in newborn's cord blood in levels that exceed those of the corresponding maternal serum^[16,17]. Additionally, they are detectable in blood of the infant for more than six months after the birth, reducing the safety of vaccination^[16]. Certolizumab does not contain Fc region, thus it does not actively cross the placenta^[18].

Use of TNF inhibitors has been reported in almost 2000 pregnancies of the patients with rheumatic diseases, inflammatory bowel diseases and psoriasis. Based on the published data from case reports^[19-29], case series^[30-34] and registries on etanercept, infliximab, adalimumab, golimumab and certolizumab^[35-37], it has been found that preconception exposure to biologic agents or use of them during pregnancy including first, second and third trimesters is not associated with increased risk of adverse pregnancy outcomes, malformations or birth defects compared with general population.

An FDA database review revealed 61 birth defects in 41 children born to mothers receiving TNF inhibitors^[38]. Of these mothers, 22 received etanercept and 19 received infliximab. The most common congenital anomalies were heart defects, spinal deformities, imperforate anus, tracheoesophageal fistula, renal anomalies and limb defects, which were the features of vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities association. These anomalies were found to be linked with use of TNF antagonists and it was suggested that these agents should not be administered during pregnancy.

British society for rheumatology biologics register (BSRBR) is a database which keeps information about RA patients taking TNF antagonists. Between 2005 and 2006, 11473 patients were registered with the BSRBR. Of these patients, 17 received etanercept, 3 received infliximab and 3 received adalimumab. No congenital malformation was observed^[37]. After this report, another BSRBR report which assesses the outcomes of 118 pregnancies in patients who were exposed to TNF antagonists was published in 2008^[39]. The rate of miscarriage was 27% in the patients who received anti-TNF at the time of conception (group 1), 17% in those with prior exposure to anti-TNF (group 2) and 10% in those who were never exposed to anti-TNF (group 3). The rate of premature delivery was 26% in group 1, 17% in group 2, and 20% in group 3. A perinatal death causing from hypoxia was reported in a patient who was

Table 1 An overview of published data from case reports, case series and registries on biologic agents

Ref.	Study design	No. of pregnancies	Diagnosis	Biologic agent	Time of exposure	Reported outcomes
Bortlik <i>et al</i> ^[6]	Case series	41	27 CD 14 UK	INF ETA	NR	5 spontaneous abortion 2 elective termination 1 congenital malformation (mild hip dysplasia) Healthy infant at 36 wk of gestation
Burt <i>et al</i> ^[9]	Case report	1	CD	INF	T1	Healthy term delivery
Sinha and Patient ^[20]	Case report	1	RA	ETA	C + T1 + T2 + T3	Healthy term delivery
Takayama <i>et al</i> ^[21]	Case report	1	BD	INF	T2 + T3 (discontinued at 32 wk of gestation)	Healthy term delivery
Coburn <i>et al</i> ^[22]	Case report	1	CD	ADA	T2 + T3	Healthy term delivery
Akinci <i>et al</i> ^[23]	Case report	1	AS	INF	T2 + T3	Healthy term delivery
Kraemer <i>et al</i> ^[24]	Case report	1	Takayasu arteritis	ADA	C + T1 + T2 + T3	Healthy term delivery
Hou <i>et al</i> ^[25]	Case report	1	CD	INF	T1 + T2 + T3 (discontinued at 33 wk of gestation)	Healthy term delivery
Umeda <i>et al</i> ^[26]	Case report	1	RA	ETA	T2 + T3	Healthy term delivery
Puig <i>et al</i> ^[27]	Case report	1	Psoriasis	INF	T1 + T2 + T3 (last infusion at 29 wk of gestation)	Healthy term delivery
Jang <i>et al</i> ^[28]	Case report	1	CD	INF	C + T1	Healthy term delivery
Vesga <i>et al</i> ^[29]	Case report	1	CD	ADA	C + T1 + T2 + T3	Healthy term delivery
Mahadevan <i>et al</i> ^[30]	Case series	10	CD	INF	NR	10 live birth 3 premature delivery 0 spontaneous abortion 0 elective termination 0 congenital malformation
Berthelot <i>et al</i> ^[31]	Case series	15	SpA, RA, IIA, PsA	3 INF 2 ADA 10 ETA	NR	2 spontaneous abortion (ETA) 1 elective termination (ETA)
Rump <i>et al</i> ^[33]	Case series	8 pregnancies in 5 women	4 RA 1 AS	ETA	NR	1 spontaneous abortion 1 megacolon congenitum 1 premature delivery
Arguelles-Arias <i>et al</i> ^[34]	Case series	12	8 CD 4 UK	INF	1 C 2 T1 3 T1 + T2 6 T1 + T2 + T3	No congenital malformation, IUGR, SGA
Diav-Citrin <i>et al</i> ^[35]	Registry	83	CD, RA, UK, UndA, PsA, AS, BD	35 INF 25 ETA 23 ADA	81 T1 2 T2 or T3	67 live birth 9 spontaneous abortion 5 elective termination 0 congenital malformation
Chakravarty <i>et al</i> ^[36]	Registry	17	RA	15 ETA 2 INF	NR	1 spontaneous abortion (ETA) 1 elective termination (ETA) No congenital malformation, IUGR, SGA
Hyrich <i>et al</i> ^[37]	Registry	23	RA	17 ETA 3 INF 3 ADA	NR	14 live births 6 spontaneous abortion (4 ETA, 1 INF, 1 ADA) 3 elective termination (all in patients receiving ETA, 2 also receiving MTX)
Carter <i>et al</i> ^[38]	Registry	41	Autoimmune diseases	22 ETA 19 INF	NR	24 (59%) children had one or more congenital deformities such as vertebral deformities, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal anomalies and limb defects, which were the features of VACTERL

Offiah <i>et al</i> ^[40]	Case report	1	PsA	INF	C + T1 + T2 + T3	Transient colloid membrane
Guidir <i>et al</i> ^[41]	Case series	4	UK	INF	T1 + T2 + T3	4 neonatal neutropenia
Grosen <i>et al</i> ^[42]	Case report	1	UK	INF	T3	Ten days after INF infusion serum sickness-like reaction in the mother
Ergaz <i>et al</i> ^[43]	Case report	1	RA	ETA (also receiving prednisone and hydroxychloroquine)	C + T1 + T2 + T3	Preterm infant without any congenital anomaly
Hultzsich <i>et al</i> ^[44]	Case series	26	19 RA 6 AS 1 PsA	ETA	T1	Congenital fulminant kaposiform hemangioendothelioma
Weber-Schoendorfer <i>et al</i> ^[47]	Case series	53	Autoimmune diseases	28 ADA 25 INF	T1	19 live birth 5 premature delivery 5 spontaneous abortion 2 elective termination 1 congenital renal agenesis 1 hypoplastic left heart syndrome + hypospadias 1 Wolff Parkinson White syndrome 46 live birth (24 ADA, 22 INF) 8 premature delivery (4 ADA, 4 INF) 4 spontaneous abortion (2 ADA, 2 INF) 3 elective termination (2 ADA, 1 INF) 1 autosomal disease inherited from his father (ADA)
Johnson <i>et al</i> ^[48]	Case series	34	RA	ADA	T1	1 ventricular septal defect (INF) 29 live birth 5 spontaneous abortion 1 undescended testicle 1 microcephaly 64 live birth
Katz <i>et al</i> ^[49]	Registry	64	82 CD 8 RA 2 JRA 1 UK	INF	53 within 3 mo of C 25 within 3 mo prior to C28 within 3 mo prior to C + T1 30 T1 7 > 3 mo prior to C 6 unknown C + T1 + T2 + T3	14 spontaneous abortion 18 therapeutic termination 0 congenital malformation
Cheent <i>et al</i> ^[50]	Case report	1	CD	INF	NR	No congenital malformation, IUGR BCG vaccination at age of 3 mo
Mahadevan <i>et al</i> ^[51]	Registry	190	124 CD 56 other diseases	CZP	NR	Died from disseminated BCG disease at age of 4.5 mo 132 live birth 36 spontaneous abortion 22 elective termination
Lau <i>et al</i> ^[56]	Case series	40	24 RA 1 PsA 5 AS 10 UK	GLM	NR	vesicoureteral reflux, congenital morbus, congenital megacolon, congenital talipes equinovarus, aortic arch anomaly, and unilateral hydronephrosis in four infants 19 live birth 13 spontaneous abortion 7 induced abortion 1 ectopic pregnancy
Berger <i>et al</i> ^[57]	Case report	1	AOSD	Anakinra	C + T1 + T2 + T3	1 unspecific congenital malformation leading to intrauterine death and induced abortion Term delivery complicated with placental retention

Chang <i>et al</i> ^[59]	Case series	9	CAPS	Anakinra	C + T1 + T2 + T3	No preterm birth or serious complication
Rubbert-Roth <i>et al</i> ^[60]	Registry	33	RA	TCZ	NR	Fetal loss of a twin due to renal agenesis. DNA testing revealed the same NLRP3 c.785T > C, p.V262A mutation as the mother 7 spontaneous abortion 13 elective termination 11 term delivery (1 infant died from ARDS 3 d after emergency cesarean section for intrapartum fetomaternal hemorrhage due to placenta previa) 3 healthy term delivery
Ojeda-Urbe <i>et al</i> ^[61]	Case series	3	Autoimmune diseases	2 RTX 1 abatacept	T1	90 live birth 33 spontaneous abortion 28 elective termination 22 premature delivery 1 maternal death from autoimmune thrombocytopenia
Chakravarty <i>et al</i> ^[64]	Registry	153	Autoimmune diseases	RTX	NR	11 perinatal hematologic anomalies 4 perinatal infections 1 congenital talipes equinovarus 1 cardiac malformation 4 healthy term delivery (3 SLE, 1 WG) 1 preterm low birth weight (SLE) 1 esophageal atresia (SLE)
Sangle <i>et al</i> ^[65]	Case series	6	5 SLE 1 WG	RTX	8-22 mo prior to C	Spontaneous abortion (Beckwith-Wiedemann Syndrome)
Pendergraft <i>et al</i> ^[66]	Case report	1	Autoimmune vasculitis	RTX	7.5 mo prior to C	

CD: Crohn's disease; RA: Rheumatoid arthritis; BD: Behcet disease; AS: Ankylosing spondylitis; SpA: Spondyloarthritis; JIA: Juvenile idiopathic arthritis; PsA: Psoriatic arthritis; UndA: Undifferentiated arthritis; JRA: Juvenile rheumatoid arthritis; SLE: Systemic lupus erythematosus; WG: Wegener granulomatosis; AOSD: Adult onset Still's disease; CAPS: Cryopyrin associated periodic syndromes; INF: Infliximab; ETA: Etanercept; ADA: Adalimumab; CZP: Certolizumab; GLM: Golimumab; RTX: Rituximab; TCZ: Tocilizumab; C: Conception; T1: First trimester; T2: Second trimester; T3: Third trimester; IUGR: Intrauterine growth restriction; SGA: Small for gestational age; BCG: Bacille Calmette-Guérin; ARDS: Acute respiratory distress syndrome; NR: Not reported; VACTERL: Vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities; UK: Ulcerative colitis; MTX: Methotrexate.

exposed to etanercept at the time of conception. Additionally four cases of congenital anomalies were reported. In group 1, congenital hip dysplasia and pylorostenosis, and in group 2 Marcus Gunn syndrome and infantile hemangioma were observed. The authors suggested that treatment with TNF inhibitors might be linked with an increased risk of spontaneous abortion, however the effects of disease activity and other antirheumatic agents could not be eliminated.

Offiah *et al*^[40] reported a transient collodion membrane in a 2-d-old infant born to mother receiving infliximab for severe psoriasis and PsA throughout pregnancy in United States. The skin turned to normal at age 1 year with mineral oil treatment.

Guidir *et al*^[41] reported four cases of severe neutropenia in newborn patients exposed to infliximab. High serum infliximab concentrations were detected several months after birth. It was suggested that the mononuclear phagocyte system of a newborn is inadequate to clear the antibody rapidly.

Tetralogy of Fallot, intestinal malrotation, hypothyroidism, intracranial and intrapulmonary hemorrhage, unilateral renal agenesis, serum sickness-like reaction (with infliximab)^[35,42-44], infantile kaposiform hemangioendothelioma, Kasabach-Merritt syndrome, renal agenesis, urethral defects, cardiac conduction system abnormalities, pylorostenosis, congenital megacolon (with etanercept)^[32,39,45,46], and ventricular septal defect, congenital hip dysplasia, spina bifida with hydrocephalus, aortic valve disease, corpus callosum agenesis, and congenital hypothyroidism (with adalimumab)^[47,48] have been reported in the babies born to mothers directly exposed to TNF inhibitors during pregnancy. However rates of these anomalies have been found to be similar to those expected for the general population^[35,46,49].

Cheent *et al*^[50] reported use of infliximab during pregnancy in a 28-year-old patient with Crohn's disease. Newborn had no congenital malformation or intrauterine growth

retardation. He was healthy until bacillus calmette-guerin (BCG) vaccine administered at the age of three months. One point five months later he died from disseminated BCG disease which was a rare life-threatening complication of BCG administration.

Certolizumab is different from other TNF inhibitors, it does not contain Fc region, thus it is not actively transported through the placenta^[16]. It has only minimal transplacental transmission to newborn *via* passive diffusion during first, second and third trimesters^[17].

The Union Chimique Belge Pharma global safety database revealed 69.5% live birth rate in 190 pregnant women exposed to certolizumab^[51]. The rates of spontaneous abortions and elective terminations were 18.9% and 11.6%, respectively. Six birth defects were observed in four infants among all live births: vesicoureteral reflux, congenital morbus, congenital megacolon, congenital talipes equinovarus, aortic arch anomaly, and unilateral hydronephrosis. However these congenital anomalies were not thought to be associated with exposure to certolizumab. These pregnancy outcomes were comparable to those reported for united states general population (65% live births, 17% spontaneous abortions, and 18% elective abortions)^[52]. In Pregnancy in Inflammatory Bowel Diseases and Neonatal Outcomes study^[53] where women with inflammatory bowel disease exposed to certolizumab in the third trimester of pregnancy were compared with unexposed group, it was suggested that use of certolizumab in the third trimester was not associated with increase in infant infection rates.

Golimumab is a newer TNF inhibitor and there is limited data on its use during pregnancy^[54]. In a study by Martin *et al*^[55] performed in cynomolgus monkeys received 25-50 mg/kg golimumab twice weekly during pregnancy, no effect was observed on pregnancy outcomes or fetal immune system. Experience with use of golimumab during pregnancy has been limited to conference abstracts. Lau *et al*^[56] reported pregnancy outcomes of 40 women exposed to golimumab at the American College of Rheumatology (ACR) Annual Meeting in 2013. Outcomes included one unspecific congenital anomaly, 19 live births, 13 spontaneous abortions and 7 induced abortions. Of 13 mothers with spontaneous abortion, 4 had concomitant methotrexate use.

Anakinra

Anakinra is a human IL-1 receptor antagonist certified by FDA for the therapy of RA patients with intermediate/high disease activity^[14]. It has been rated as FDA pregnancy category B. It has a half-life of 4-6 h. Because of its short half-life, discontinuance of anakinra before conception is not necessary^[18]. Experiences with use of anakinra during pregnancy are limited. Three pregnancies in patients received anakinra for the treatment of adult onset Still's disease resulted in term live births^[57,58]. Chang *et al*^[59] described outcomes of fifteen pregnancies in nine women receiving anakinra for the treatment of cryopyrin-associated periodic syndrome. Outcomes included 14

healthy term infants and one intrauterine fetal demise resulting from renal agenesis.

Tocilizumab

Tocilizumab is a humanized IL-6 receptor inhibitor used in the therapy of moderate to severe RA and polyarticular and systemic JIA. It is categorized as FDA pregnancy category C. Tocilizumab should be discontinued three months before conception^[18]. Experiences with use of tocilizumab during pregnancy were reported by Rubbert-Roth *et al*^[60] at the ACR Annual Meeting in 2010. Of 33 pregnancies, 13 resulted in induced abortion, 7 resulted in spontaneous abortion and 11 resulted in live births. Of 7 mothers with spontaneous abortion, 5 had concomitant methotrexate use.

ANTI-CELLULAR THERAPY DURING PREGNANCY

Rituximab

Rituximab is a chimeric monoclonal antibody against the B cell surface antigen CD20^[61]. It is indicated for the treatment of severe refractory RA with inadequate response to TNF inhibitors, certain types of vasculitis, non-Hodgkin's lymphoma and chronic lymphoid leukemia^[42]. It is classified as FDA category C, meaning "it has not been studied on pregnant women, however animal developmental toxicity studies have shown an adverse effects on the fetus". It has no active transplacental passage during the first trimester and organogenesis, but actively crosses the placenta during the late second and third trimester^[62], and may affect fetal and neonatal B cell development, causing increased risk for infections^[63]. Chakravarty *et al*^[64] reported pregnancy outcomes in 153 patients exposed to rituximab. Of these pregnancies, 90 resulted in live births, 22 resulted in prematurity and one resulted in perinatal death. 11 infants had hematologic abnormalities at birth (peripheral B-cell depletion, neutropenia, lymphopenia, thrombocytopenia and anemia) and four had perinatal infections. Two infants had congenital defects (congenital talipes equinovarus and cardiac malformation). Sangle *et al*^[65] reported pregnancy outcomes in 5 patients with systemic lupus erythematosus exposed to rituximab before conception. One of the infants was born with esophageal atresia, while the others were healthy. Pendergraft *et al*^[66] reported a miscarriage at 15 wk in a mother exposed to rituximab 7.5 mo prior to conception. Histologic and genetic evaluation of fetus revealed Beckwith-Wiedemann Syndrome. Ojeda-Urbe *et al*^[61] reported two successful outcomes in two women with autoimmune diseases received rituximab in the first trimester of pregnancy.

Preconception and first trimester exposure to rituximab seems not to indicate an excess risk of adverse fetal outcomes. Exposure during second and third trimesters causes decrease in B cells in the fetus^[18]. Further studies, especially prospective registries are needed to explore immune response to vaccines and perinatal infections in

infants born to mothers received rituximab during second and third trimesters.

Abatacept

Abatacept (CTLA4-Ig) is a recombinant fusion protein that modulates T cell costimulatory signal mediated through the CD28-CD80/86 pathway^[67]. It has been approved for the treatment of refractory RA^[4]. Abatacept therapy should be stopped three months before conception^[18]. Ojeda-Urbe *et al*^[61] reported a healthy infant born to a 33-year-old mother exposed to abatacept in the first trimester.

CONCLUSION

Since TNF inhibitors are classified in FDA category B, they are safer than synthetic Disease Modifying Anti Rheumatic Drugs such as methotrexate and leflunomide. Although sporadic cases of congenital malformations have been reported in newborns born to mothers exposed to biologics, these rates appear to be comparable with those expected in the general population. Maternal exposure to TNF inhibitors at conception seems not to be related to adverse pregnancy outcomes. TNF inhibitors do not pass through the placenta during the first trimester, but they cross the placenta during the late second and third trimester. They can be used in the first trimester if no therapeutic alternative is available. But use of these agents in late second and third trimester should be reconsidered more carefully because of high placental transfer. Collected experience does not suggest an increased risk of opportunistic infections in pregnant patients and fetus. However, in case of exposure to these agents in the late second and third trimester, live vaccines should not be administered in the first six months of life because of increased risk for infections.

Abatacept and tocilizumab are classified as FDA pregnancy category C, and they should be discontinued three months before conception. Experiences with use of anakinra and rituximab during pregnancy are limited, larger studies are needed to bring further clarity.

The decision to use biologic agents during pregnancy is difficult. The benefits of biologic agents must outweigh the risks to the fetus/embryo or the mother. Larger and further studies are needed to demonstrate the safety of these agents during pregnancy.

REFERENCES

- Hazes JM, Coulie PG, Geenen V, Vermeire S, Carbonnel F, Louis E, Masson P, De Keyser F. Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. *Rheumatology* (Oxford) 2011; **50**: 1955-1968 [PMID: 21890617 DOI: 10.1093/rheumatology/ker302]
- Nelson JL, Hughes KA, Smith AG, Nisperos BB, Branchaud AM, Hansen JA. Maternal-fetal disparity in HLA class II alloantigens and the pregnancy-induced amelioration of rheumatoid arthritis. *N Engl J Med* 1993; **329**: 466-471 [PMID: 8332151 DOI: 10.1016/0020-7292(94)90144-9]
- Reed SD, Vollan TA, Svec MA. Pregnancy outcomes in women with rheumatoid arthritis in Washington State. *Matern Child Health J* 2006; **10**: 361-366 [PMID: 16649008 DOI: 10.1007/s10995-006-0073-3]
- Skomsvoll JF, Ostensen M, Irgens LM, Baste V. Obstetrical and neonatal outcome in pregnant patients with rheumatic disease. *Scand J Rheumatol Suppl* 1998; **107**: 109-112 [PMID: 9759146]
- Wolfberg AJ, Lee-Parritz A, Peller AJ, Lieberman ES. Association of rheumatologic disease with preeclampsia. *Obstet Gynecol* 2004; **103**: 1190-1193 [PMID: 15172851 DOI: 10.1097/01.aog.0000126279.87151.e1]
- de Man YA, Hazes JM, van der Heide H, Willemsen SP, de Groot CJ, Steegers EA, Dolhain RJ. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009; **60**: 3196-3206 [PMID: 19877045 DOI: 10.1002/art.24914]
- Bowden AP, Barrett JH, Fallow W, Silman AJ. Women with inflammatory polyarthritis have babies of lower birth weight. *J Rheumatol* 2001; **28**: 355-359 [PMID: 11246676]
- Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, Kampmann B, Hellmich B, Groves R, Schreiber S, Wallis RS, Sotgiu G, Schölvinc EH, Goletti D, Zellweger JP, Diel R, Carmona L, Bartalesi F, Ravn P, Bossink A, Duarte R, Erkens C, Clark J, Migliori GB, Lange C. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J* 2010; **36**: 1185-1206 [PMID: 20530046 DOI: 10.1183/09031936.00028510]
- Davies R, Dixon WG, Watson KD, Lunt M, Symmons DP, Hyrich KL. Influence of anti-TNF patient warning regarding avoidance of high risk foods on rates of listeria and salmonella infections in the UK. *Ann Rheum Dis* 2013; **72**: 461-462 [PMID: 23076071 DOI: 10.1136/annrheumdis-2012-202228]
- Murdaca G, Spanò F, Contatore M, Guastalla A, Penza E, Magnani O, Puppo F. Infection risk associated with anti-TNF- α agents: a review. *Expert Opin Drug Saf* 2015; **14**: 571-582 [PMID: 25630559 DOI: 10.1517/14740338.2015.1009036]
- Desai SB, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. *Best Pract Res Clin Rheumatol* 2006; **20**: 757-790 [PMID: 16979537]
- Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. *Rheumatology* (Oxford) 2014; **53**: 1377-1385 [PMID: 24352337 DOI: 10.1093/rheumatology/ker409]
- Williams M, Chakravarty EF. Rheumatoid arthritis and pregnancy: impediments to optimal management of both biologic use before, during and after pregnancy. *Curr Opin Rheumatol* 2014; **26**: 341-346 [PMID: 24663107 DOI: 10.1097/BOR.0000000000000046]
- Vinet E, Pineau C, Gordon C, Clarke AE, Bernatsky S. Anti-TNF therapy and pregnancy outcomes in women with inflammatory arthritis. *Expert Rev Clin Immunol* 2009; **5**: 27-34 [PMID: 20476897 DOI: 10.1586/1744666X.5.1.27]
- Murdaca G, Colombo BM, Cagnati P, Gulli R, Spanò F, Puppo F. Update upon efficacy and safety of TNF- α inhibitors. *Expert Opin Drug Saf* 2012; **11**: 1-5 [PMID: 22010813 DOI: 10.1517/14740338.2012.630388]
- Bortlik M, Machkova N, Duricova D, Malickova K, Hrdlicka L, Lukas M, Kohout P, Shonova O, Lukas M. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF- α therapy during pregnancy: three-center study. *Scand J Gastroenterol* 2013; **48**: 951-958 [PMID: 23834232 DOI: 10.3109/00365521.2013.812141]
- Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, Ullman T, Glover S, Valentine JF, Rubin DT, Miller J, Abreu MT. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 286-292; quiz e24 [PMID: 23200982 DOI: 10.1016/j.cgh.2012.11.011]
- Ostensen M. Safety issues of biologics in pregnant patients with rheumatic diseases. *Ann N Y Acad Sci* 2014; **1317**: 32-38 [PMID: 24840548 DOI: 10.1111/nyas.12456]
- Burt MJ, Frizelle FA, Barbezat GO. Pregnancy and exposure to

- infliximab (anti-tumor necrosis factor-alpha monoclonal antibody). *J Gastroenterol Hepatol* 2003; **18**: 465-466 [PMID: 12653902 DOI: 10.1046/j.1440-1746.2003.02983.x]
- 20 **Sinha A**, Patient C. Rheumatoid arthritis in pregnancy: successful outcome with anti-TNF agent (Etanercept). *J Obstet Gynaecol* 2006; **26**: 689-691 [PMID: 17071443 DOI: 10.1080/01443610600930647]
 - 21 **Takayama K**, Ishikawa S, Enoki T, Kojima T, Takeuchi M. Successful treatment with infliximab for Behçet disease during pregnancy. *Ocul Immunol Inflamm* 2013; **21**: 321-323 [PMID: 23617408 DOI: 10.3109/09273948.2013.781655]
 - 22 **Coburn LA**, Wise PE, Schwartz DA. The successful use of adalimumab to treat active Crohn's disease of an ileoanal pouch during pregnancy. *Dig Dis Sci* 2006; **51**: 2045-2047 [PMID: 17009112 DOI: 10.1007/s10620-006-9452-2]
 - 23 **Akinci A**, Ozçakar L. Infliximab use during pregnancy revisited. *Acta Reumatol Port* 2008; **33**: 374-375 [PMID: 18846021]
 - 24 **Kraemer B**, Abele H, Hahn M, Rajab T, Kraemer E, Wallweiner D, Becker S. A successful pregnancy in a patient with Takayasu's arteritis. *Hypertens Pregnancy* 2008; **27**: 247-252 [PMID: 18696353 DOI: 10.1080/10641950801955741]
 - 25 **Hou JK**, Mahadevan U. A 24-year-old pregnant woman with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2009; **7**: 944-947 [PMID: 19410016 DOI: 10.1016/j.cgh.2009.04.022]
 - 26 **Umeda N**, Ito S, Hayashi T, Goto D, Matsumoto I, Sumida T. A patient with rheumatoid arthritis who had a normal delivery under etanercept treatment. *Intern Med* 2010; **49**: 187-189 [PMID: 20075588 DOI: 10.2169/internalmedicine.49.2439]
 - 27 **Puig L**, Barco D, Alomar A. Treatment of psoriasis with anti-TNF drugs during pregnancy: case report and review of the literature. *Dermatology* 2010; **220**: 71-76 [PMID: 19940453 DOI: 10.1159/000262284]
 - 28 **Jang YW**, Park YS, Kim SH, Jo YJ, Jo YK, Ahn SB, Seo YS, Hong YO. [A case of Crohn's disease having normal delivery after infliximab treatment during early pregnancy]. *Korean J Gastroenterol* 2013; **61**: 37-41 [PMID: 23354348]
 - 29 **Vesga L**, Terdiman JP, Mahadevan U. Adalimumab use in pregnancy. *Gut* 2005; **54**: 890 [PMID: 15888806 DOI: 10.1136/gut.2005.065417]
 - 30 **Mahadevan U**, Kane S, Sandborn WJ, Cohen RD, Hanson K, Terdiman JP, Binion DG. Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. *Aliment Pharmacol Ther* 2005; **21**: 733-738 [PMID: 15771759 DOI: 10.1111/j.1365-2036.2005.02405.x]
 - 31 **Berthelot JM**, De Bandt M, Goupille P, Solau-Gervais E, Lioté F, Goeb V, Azaïs I, Martin A, Pallot-Prades B, Maugars Y, Mariette X. Exposition to anti-TNF drugs during pregnancy: outcome of 15 cases and review of the literature. *Joint Bone Spine* 2009; **76**: 28-34 [PMID: 19059799 DOI: 10.1016/j.jbspin.2008.04.016]
 - 32 **Murashima A**. [Treatment of patients with rheumatoid arthritis who desire to become pregnant--successful pregnancy in three cases treated with etanercept]. *Nihon Rinsho* 2008; **66**: 2215-2220 [PMID: 19051745]
 - 33 **Rump JA**, Schönborn H. [Conception and course of eight pregnancies in five women on TNF blocker etanercept treatment]. *Z Rheumatol* 2010; **69**: 903-909 [PMID: 20532789 DOI: 10.1007/s00393-010-0652-y]
 - 34 **Argüelles-Arias F**, Castro-Laria L, Barreiro-de Acosta M, García-Sánchez MV, Guerrero-Jiménez P, Gómez-García MR, Cordero-Ruiz P, Iglesias-Flores E, Gómez-Camacho F, Domínguez-Muñoz EJ, Herreras-Gutiérrez JM. Is safety infliximab during pregnancy in patients with inflammatory bowel disease? *Rev Esp Enferm Dig* 2012; **104**: 59-64 [PMID: 22372798]
 - 35 **Diav-Citrin O**, Otcheretianski-Volodarsky A, Shechtman S, Ornoy A. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. *Reprod Toxicol* 2014; **43**: 78-84 [PMID: 24284028 DOI: 10.1016/j.reprotox.2013.11.004]
 - 36 **Chakravarty EF**, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. *J Rheumatol* 2003; **30**: 241-246 [PMID: 12563675]
 - 37 **Hyrich KL**, Symmons DP, Watson KD, Silman AJ. Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. *Arthritis Rheum* 2006; **54**: 2701-2702 [PMID: 16871549 DOI: 10.1002/art.22028]
 - 38 **Carter JD**, Ladhani A, Ricca LR, Valeriano J, Vasey FB. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. *J Rheumatol* 2009; **36**: 635-641 [PMID: 19132789 DOI: 10.3899/jrheum.080545]
 - 39 **Verstappen SM**, King Y, Watson KD, Symmons DP, Hyrich KL. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011; **70**: 823-826 [PMID: 21362710 DOI: 10.1136/ard.2010.140822]
 - 40 **Offiah M**, Brodell RT, Campbell LR, Wyatt JP. Collodion-like membrane in a newborn exposed to infliximab. *J Am Acad Dermatol* 2014; **71**: e22-e23 [PMID: 24947707 DOI: 10.1016/j.jaad.2014.01.856]
 - 41 **Guiddir T**, Frémond ML, Triki TB, Candon S, Croisille L, Leblanc T, de Pontual L. Anti-TNF- α therapy may cause neonatal neutropenia. *Pediatrics* 2014; **134**: e1189-e1193 [PMID: 25266439 DOI: 10.1542/peds.2014-0054]
 - 42 **Bogas M**, Leandro MJ. Biologic therapy and pregnancy. A systematic literature review. *Acta Reumatol Port* 2011; **36**: 219-232 [PMID: 22113598]
 - 43 **Srinivasan R**. Infliximab treatment and pregnancy outcome in active Crohn's disease. *Am J Gastroenterol* 2001; **96**: 2274-2275 [PMID: 11467677 DOI: 10.1016/s0002-9270(01)02550-3]
 - 44 **Grosen A**, Julsgaard M, Christensen LA. Serum sickness-like reaction due to Infliximab reintroduction during pregnancy. *J Crohns Colitis* 2013; **7**: e191 [PMID: 23102649 DOI: 10.1016/j.crohns.2012.10.006]
 - 45 **Ergaz Z**, Bar-Oz B, Vainer GW, Abu-Leil S, Simanovsky N, Diav-Citrin O. Congenital fulminant Kaposiform hemangioendothelioma of the leg. *Reprod Toxicol* 2014; **50**: 1-3 [PMID: 25277314 DOI: 10.1016/j.reprotox.2014.09.011]
 - 46 **Hultzs S**, Weber-Schoendorfer C, Schaefer C. Pregnancy outcomes after exposure to etanercept [abstract]. *Reprod Toxicol* 2011; **31**: 260 [DOI: 10.1016/j.reprotox.2010.12.033]
 - 47 **Weber-Schoendorfer C**, Fritzsche J, Schaefer C. Pregnancy outcomes in women exposed to adalimumab or infliximab: The experience of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy [abstract]. *Reprod Toxicol* 2011; **31**: 267-268 [DOI: 10.1016/j.reprotox.2010.12.052]
 - 48 **Johnson DJ**, Jones KL, Chambers CD, Salas E. Pregnancy outcomes in women exposed to adalimumab: the OTIS autoimmune diseases in pregnancy Project [abstract]. *Gastroenterol* 2009; **136** suppl1: A27 [DOI: 10.1016/S0016-5085(09)60125-6]
 - 49 **Katz JA**, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am J Gastroenterol* 2004; **99**: 2385-2392 [PMID: 15571587 DOI: 10.1111/j.1572-0241.2004.30186.x]
 - 50 **Cheent K**, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 2010; **4**: 603-605 [PMID: 21122568 DOI: 10.1016/j.crohns.2010.05.001]
 - 51 **Mahadevan U**, Vermeire S, Wolf DC, Forger F, Cush JJ, Golembesky A, Shaughnessy L, De Cuyper D, Abbas S, Clowse MEB. Pregnancy outcomes after certalizumab pegol: results from safety surveillance [abstract]. *J Crohn's Colitis* 2014; **8**: S26 [DOI: 10.1016/S1873-9946(14)60049-0]
 - 52 **Ventura SJ**, Curtin SC, Abma JC, Henshaw SK. Estimated pregnancy rates and rates of pregnancy outcomes for the United States, 1990-2008. *Natl Vital Stat Rep* 2012; **60**: 1-21 [PMID: 22970648]
 - 53 **Mahadevan U**, Martin CF, Dubinsky M, et al. Exposure to anti-TNF-alpha therapy in the third trimester of pregnancy is not

- associated with increased adverse outcomes: results from the PIANO registry [abstract]. *Gastroenterology* 2014; **146**: S170 [DOI: 10.1016/S0016-5085(14)60602-8]
- 54 **Khan N**, Asim H, Lichtenstein GR. Safety of anti-TNF therapy in inflammatory bowel disease during pregnancy. *Expert Opin Drug Saf* 2014; **13**: 1699-1708 [PMID: 25406728 DOI: 10.1517/14740338.2014.973399]
 - 55 **Martin PL**, Oneda S, Treacy G. Effects of an anti-TNF-alpha monoclonal antibody, administered throughout pregnancy and lactation, on the development of the macaque immune system. *Am J Reprod Immunol* 2007; **58**: 138-149 [PMID: 17631007 DOI: 10.1111/j.1600-0897.2007.00499.x]
 - 56 **Lau AG**, Clark M, Harrison DD, Geldhof A, Nissinen R, Sanders M. Pregnancy outcomes in women exposed to golimumab [abstract]. *Arthritis Rheum* 2013; **65** Suppl 10: 2041 [DOI: 10.1002/art.2013.65.issue-s10]
 - 57 **Berger CT**, Recher M, Steiner U, Hauser TM. A patient's wish: anakinra in pregnancy. *Ann Rheum Dis* 2009; **68**: 1794-1795 [PMID: 19822718 DOI: 10.1136/ard.2008.105833]
 - 58 **Fischer-Betz R**, Specker C, Schneider M. Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra). *Clin Exp Rheumatol* 2011; **29**: 1021-1023 [PMID: 22153586]
 - 59 **Chang Z**, Spong CY, Jesus AA, Davis MA, Plass N, Stone DL, Chapelle D, Hoffmann P, Kastner DL, Barron K, Goldbach-Mansky RT, Stratton P. Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). *Arthritis Rheumatol* 2014; **66**: 3227-3232 [PMID: 25223501 DOI: 10.1002/art.38811]
 - 60 **Rubbert-Roth A**, Goupille PM, Moosavi S, Hou A. First experiences with pregnancies in RA patients (pts) receiving tocilizumab (TCZ) therapy [abstract] *Arthritis Rheum* 2010; **62** Suppl 10: 384 [DOI: 10.1002/art.28153]
 - 61 **Ojeda-Urbe M**, Afif N, Dahan E, Sparsa L, Haby C, Sibilia J, Ternant D, Ardizzone M. Exposure to abatacept or rituximab in the first trimester of pregnancy in three women with autoimmune diseases. *Clin Rheumatol* 2013; **32**: 695-700 [PMID: 23292481 DOI: 10.1007/s10067-012-2156-4]
 - 62 **Ostensen M**, Förger F. Treatment with biologics of pregnant patients with rheumatic diseases. *Curr Opin Rheumatol* 2011; **23**: 293-298 [PMID: 21346578 DOI: 10.1097/BOR.0b013e328344a732]
 - 63 **Ton E**, Tekstra J, Hellmann PM, Nuver-Zwart IH, Bijlsma JW. Safety of rituximab therapy during twins' pregnancy. *Rheumatology (Oxford)* 2011; **50**: 806-808 [PMID: 21177333 DOI: 10.1093/rheumatology/keq403]
 - 64 **Chakravarty EF**, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. *Blood* 2011; **117**: 1499-1506 [PMID: 21098742 DOI: 10.1182/blood-2010-07-295444]
 - 65 **Sangle SR**, Lutalo PM, Davies RJ, Khamashta MA, D'Cruz DP. B-cell depletion therapy and pregnancy outcome in severe, refractory systemic autoimmune diseases. *J Autoimmun* 2013; **43**: 55-59 [PMID: 23608146 DOI: 10.1016/j.jaut.2013.03.001]
 - 66 **Pendergraft WF**, McGrath MM, Murphy AP, Murphy P, Laliberte KA, Greene MF, Niles JL. Fetal outcomes after rituximab exposure in women with autoimmune vasculitis. *Ann Rheum Dis* 2013; **72**: 2051-2053 [PMID: 23864238 DOI: 10.1136/annrheumdis-2013-203833]
 - 67 **Selmi C**, Ceribelli A, Naguwa SM, Cantarini L, Shoenfeld Y. Safety issues and concerns of new immunomodulators in rheumatology. *Expert Opin Drug Saf* 2015; **14**: 389-399 [PMID: 25518908 DOI: 10.1517/14740338.2015.993605]

P- Reviewer: Chizzolini C, Martinez-Lostao L, Nas K, Rothschild BM, Song J

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Jiao XK



Pathogenetic mechanisms of antiphospholipid antibody production in antiphospholipid syndrome

Rohan Willis, Emilio B Gonzalez

Rohan Willis, Emilio B Gonzalez, Antiphospholipid Standardization Laboratory, Division of Rheumatology, Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX 77555-1165, United States

Author contributions: Both authors contributed significantly to the literature review, writing of the article and final approval of the document.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest relevant to this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Emilio B Gonzalez, MD, FACP, FACR, Director and Chief, Division of Rheumatology, Department of Internal Medicine, University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77555-1165, United States. ebgonzal@utmb.edu
Telephone: +1-409-9387409
Fax: +1-409-9381479

Received: June 30, 2014
Peer-review started: July 1, 2014
First decision: July 18, 2014
Revised: March 24, 2015
Accepted: April 10, 2015
Article in press: April 14, 2015
Published online: July 12, 2015

Abstract

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the pathological action of antiphospholipid antibodies (aPL), that leads to recurrent

pregnancy loss and thrombosis. Despite limited evidence, it is clear that there are both inherited and acquired components of the ontogeny of these antibodies. Animal genetic studies and human familial and population studies highlight the influence of genetic factors in APS, particularly human leukocyte antigen associations. Similarly, both animal and human studies have reported the importance of acquired factors in APS development and infectious agents in particular have a great impact on aPL production. Bacterial and viral agents have been implicated in the induction of autoimmune responses by various mechanisms including molecular mimicry, cryptic autoantigens exposure and apoptosis. In this review we highlight the latest updates with regards to inherited and acquired factors leading to the manufacturing of pathogenic antibodies and APS.

Key words: Antiphospholipid; Autoimmune; Infections; Antibody production; Susceptibility; Genetic; Human leukocyte antigen; Environmental; Immune tolerance

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This article reviews the most up to date theories regarding the production of pathogenic antiphospholipid antibodies (aPL) in antiphospholipid syndrome. It focuses on both the genetic and environmental aspects related to aPL production. The genetic factors highlighted include human leukocyte antigen (HLA) and non-HLA associations and where available, data linking genes to clinical manifestations is presented. The key infectious agents linked to the formation of pathogenic aPL and those mechanisms by which these agents induce a break in immune tolerance are also discussed.

Willis R, Gonzalez EB. Pathogenetic mechanisms of antiphospholipid antibody production in antiphospholipid syndrome. *World J Rheumatol* 2015; 5(2): 59-68 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i2/59.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i2.59>

INTRODUCTION

Antiphospholipid syndrome (APS) is a multisystemic autoimmune disease, whose pathology is driven by the action of antiphospholipid antibodies (aPL), and is characterized by recurrent thrombosis and pregnancy morbidity^[1]. These antibodies are heterogenous, have numerous antigenic targets and interact with numerous negatively charged phospholipids (PLs) and protein complexes. However, during the 1990s, several groups showed simultaneously that β_2 -glycoprotein I (β_2 GP I), and prothrombin, are the major antigenic targets of aPL. More than 90% of binding activity in APS patients target these 2 antigens^[2-4].

The decades since APS was first described have seen an increased understanding of the pathological mechanisms of aPL that lead to the various clinical manifestations in the disease^[5]. In contrast, relatively little has been uncovered regarding the ontogeny of pathogenic aPL. However, various pathogenetic processes have been proposed based on the available evidence and what seems clear is that both inherited and acquired factors play roles in the initial induction of pathogenic aPL in APS patients.

Correlations of several genetic markers with the production of aPL and APS characteristic manifestations, such as thrombosis, have been highlighted using several APS human and animal studies. Major Histocompatibility Complex (MHC) genes could potentially affect both pathological aPL development and also the expression of disease in APS patients^[6]. Other studies highlight the effect of classical thrombogenic genetic risk factors on disease phenotype in APS patients^[7]. These various genetic markers are likely to confer a baseline risk with regards to aPL production and APS development, while exposure to various environmental factors augment and intensify this risk, in essence inducing the break in tolerance needed for autoantibody production^[8]. One of these key environmental factors seems to be infectious agents and indeed, most of the work done to elucidate the effect of environmental factors on aPL production has centered on viral and bacterial infectious agents^[8]. As was stated above, aPL represent a varied group of antibodies that target various antigens and clinical reports indicate that not all these antibodies cause disease. It is therefore very likely that only a select group of environmental agents, most likely infectious agents and even then only a select few viral or bacterial entities, are important in disease development^[8,9]. However, there is some limited evidence for other environmental factors such as malignancies, vaccinations and drugs being associated with aPL production^[8]. In this brief review, we outline the latest updates regarding proposed inherited and acquired factors contributing to the formation of pathogenic aPL.

GENETIC STUDIES-DATA FROM APS ANIMAL MODELS

The first evidence of a genetic component to the production of pathogenic aPL in APS was provided by studies in mice. In NZW x BXSB F1 (W/B F1) male mice, the spontaneous production of pathogenic aPL, namely IgG aCL that display β_2 GP I -dependent binding to cardiolipin, has been reported^[10]. Indeed, these W/B F1 male mice are SLE-prone mice that, in addition to aCL, develop autoantibodies to negatively charged PLs such as phosphatidylserine (PS) and phosphatidylinositol, circulating immune complexes, and nephritis. Thrombocytopenia and myocardial infarction on the background of degenerative coronary vascular disease is often found in these mice, which is akin to features of SLE and APS^[10-12]. The failure of either central or peripheral T-cell tolerance mechanisms is an important aspect of the production of self-reactive autoantibodies in autoimmune diseases. Gene analysis showed that the genes responsible for the development of pathogenic aCL in these mice used certain V_H and V_K genes preferentially, while those for non-pathogenic aCL utilized random V gene combinations. This indicates antigen-driven rather than germ-line encoded antibody production^[13]. In this study, the pathogenic aCL showed a 91.5% homology to a known germ-line V_H gene, suggesting that the pathogenic aPL were generated by somatic mutations. Similarly, in MRL-lpr/lpr mice (lupus prone mice), numerous somatic mutations in the V_H region of a gene encoding a monoclonal aCL compared to the related germ-line V_H gene were noted, indicating antigen-driven stimulation and a possible failure in peripheral tolerance mechanisms^[14]. aCL are also produced in normal C57BL/6J mice, with estrogen treatment increasing the incidence and levels of these antibodies, underscoring the role that environmental factors such as hormones may play in modifying genetic susceptibility in APS patients^[15]. However, the aCL that are produced in these mice are not β_2 GP I dependent but instead show diminished binding to cardiolipin in the presence of the β_2 GP I cofactor^[16]. Interestingly, an additional lupus murine model (NZW x NZB F1 mice) failed to produce aCL despite the production of other autoantibodies such as anti-dsDNA^[17].

A subsequent analysis of the clinical features present in NZW and BXSB mice and their offspring revealed that similar disease phenotypes were seen in both male BXSB parental mice and the male F1 progeny BXSB x NZW but these features were less frequent and intense in the parental mice. In stark contrast, the typical clinical features were not expressed in NZW parent female mice or female F1 BXSB x NZW female progeny^[18]. These results possibly indicated that BXSB genetic markers determine the disease expression while genes found in the NZW mice served to upregulate or modify the expression of manifestations of APS in their offspring. An additional consideration is that modifying alleles such as BXSB Y-linked autoimmune

accelerator gene may be an important factor in disease expression^[18-20]. A mapping of the BXSB alleles that contributed to the development of aCL, anti-platelet antibodies, thrombocytopenia, and myocardial infarction was subsequently achieved by analysis of the genome, focusing on microsatellite markers in NZW x (NZWxBXSB) male F1 backcross offspring^[18]. This genetic evaluation demonstrated that the complete expression of each feature was determined by the complementary activity of two independently segregating major dominant alleles. Full genetic concordance existed for antiplatelet antibodies and thrombocytopenia but different combinations of two dominant alleles acting independently were responsible for other features, suggesting that no single genetic factor can explain the pathogenesis of APS^[18].

The first direct evidence of certain MHC II alleles being involved in the induction of pathogenic aPL and development of APS clinical manifestations came from Papalardo *et al.*^[21] Utilizing a β_2 GP I –induced aPL production in mice, this group showed that thrombogenic aPL production and tissue factor upregulation occur in wild type mice after immunization with human β_2 GP I but do not occur in MHC- II knockout [MHC(-/-)] mice. Furthermore, the production of pathogenic aPL after inoculation with β_2 GP I was restored in MHC(-/-) that were modified to express human DQ6, DR4 or DQ8 genes. Interestingly, the quantity of pathogenic aPL that was produced varied among these 3 transgenic mouse groups. These studies confirm the involvement of certain haplotypes in the induction of aPL as well as their varied importance^[21].

HUMAN GENETIC ASSOCIATIONS IN APS

Human leukocyte antigen associations

Associations between several human leukocyte antigen (HLA)-DR and DQ haplotypes and aPL development have been reported but frequent logistical issues such as inappropriately matched control populations and small sample populations make interpretation problematic^[6,7]. The underlying problem is the difficulty in defining disease phenotypes appropriately due to variable clinical expression, the coexistence of clinical entities and variability in the progression of disease. Indeed, disease phenotypes may vary over time even in a single patient with APS, especially at advanced ages^[6]. Furthermore, these issues have made defining HLA associations with individual clinical features of APS extremely difficult. However, we discuss below the HLA genes which are associated with an increased susceptibility to the development of APS and the production of aPL antibodies.

Familial APS was initially described in a group of related individuals who consistently tested positive for syphilis in the absence of the infection and developed overt autoimmune disease years later^[22]. Since then, many studies have reported the high prevalence of PAPS

correlated with aPL such as lupus anticoagulant (LA) and aCL, and other autoantibodies in families^[23,24]. The frequent finding of aCL in first-degree relatives of patients with PAPS or secondary antiphospholipid syndrome (SAPS) has also been demonstrated^[25,26]. A dominant or co-dominant model for the inheritance of APS was suggested by segregation analysis studies in a group of seven families with a 30% prevalence of primary APS among them^[27]. However, the study failed to find any HLA associations or correlation with other putative genes including β_2 GP I and Fas. In an English-Canadian family, the paternal haplotype A30; Cw3; B60; DR4; DRw53; DQw3 was associated with aCL production in secondary APS patients and individuals without disease^[28]. DR4 and DR7 have also been reported to be associated with the presence of LA in families^[29,30]. Another study evaluated family members, all who had SLE and a myriad of APS clinical manifestations, and revealed that DR4, DRw53 and DQw7 composed a haplotype found in twins and their mother^[31].

Many HLA associations with APS have also been found in population studies of unrelated individuals. HLA-DQw7 (HLA-DQB1*0301) linked to HLA-DR4 and/or -DR5 was found to be associated with LA in a group of SLE patients^[32]. DR4 and DRw53 were found to occur more frequently in primary APS^[33]. Other primary APS associated HLA include DQB1*0301/4, DQB1*0604/5/6/7/9, DQA1*0102, DQA1*0301/2, DRB1*04 and DR7^[34-36]. Similar results were found in a large study of Italian SLE patients, in which HLA-DRB1*04, -DRB1*07, -DQA1*0201, -DQA1*0301, -DQB1*0302, -DRB3*0301 were associated with aCL and DQB1*0302 with anti- β_2 GP I^[37]. In Japanese patients, DRB1*09 has been reported to be associated with aCL production in patients with lupus-associated APS^[38]. A strong association exists between anti- β_2 GP I and HLA-DR4 haplotypes, particularly when linked to HLA-DQ8 (DQB1*0302) in Caucasian and Mexican Americans, while the association with anti- β_2 GP I was attributed to the HLA-DRB1*1302;DQB1*0604/0605 haplotype in African American and Caucasian British patients with primary APS^[34,39]. In black American populations, there is evidence that C4A or C4B null alleles are associated with the presence of aCL. It is interesting to note however, that in the Hopkins Lupus Cohort, composed of a significant number of African Americans, patients who were homozygous for C4A deficiency had a lower frequency of aCL and LA than patients without this deficiency^[40-42].

Non-HLA associations

Mutations in genes not associated with the MHC region, such as a substitution of valine for leucine at amino acid residue 247 in domain V of β_2 GP I, can contribute to APS development. This polymorphism is more prevalent in APS patients, especially those with arterial thrombosis, compared to matched controls and is linked to anti- β_2 GP I production in these patients^[43-45]. Other thrombophilia-related genetic factors like factor V Leiden (FVL), prothrombin mutations and deficiencies of antithrombin

Table 1 Candidate peptides with structural and functional similarity to the phospholipid-binding region of domain V of beta-2 glycoprotein I

Peptide	Source	Amino acid sequence	Inhibition of β_2 GP I binding to CL (%) ¹
GDKV	Gly ²⁷⁴ -Cys ²⁸⁸ in domain V of human B2GPI	GDKVSFFCKNKKC	43
GDKV ₂	Modified GDKV with all six residues between Lys ²⁸² -Lys ²⁸⁷ replaced with Lys	GDKVSFFCKKKKKKC	56
TADL	Thr ⁷⁷ -Glu ⁹⁶ of Adv type2 DNA binding protein	TADLAIAKKKKKKRPSKPKE	68
TIFI	Thr ¹⁰¹ -Thr ¹²⁰ of ULB0-HCMVA from human CMV	TIFILFCCSKEKRKKKQAAT	75
VITT	Val ⁵¹ -Ile ⁷⁰ of US27-HCMVA from human CMV	VITTILYYRRKKKSPSDT	83
SGDF	Ser ²³⁷ -Ser ²⁵⁶ of TLP-BACSU from <i>Bacillus subtilis</i>	SGDFEYTYKGKKKKMAFATS	NA

¹Refers to the percentage of inhibition of 100 nmol/L of beta-2 glycoprotein I binding to cardiolipin produced by 6uM of each peptide. CMV: Cytomegalovirus; NA: Not available; β_2 GP I : Beta-2 glycoprotein I ; CL: Cardiolipin.

III, protein C and protein S have also been linked to APS disease manifestations^[46].

The prevalence of the FVL G1691A mutation in Caucasian populations has been reported to range from 1% to as high as 15%^[47,48]. Studies have shown that persons homozygous for FVL have an approximately 80-fold increase and heterozygous individuals a seven-fold increase in the lifetime risk for a thrombotic event compared to the general population. However, FVL seems to have a milder effect on the development of thrombosis in APS patients than in the general population due to the effect of aPL, but this mutation may increase the thrombogenic effect of aPL in several patients^[49-51]. The G20210A prothrombin mutation (F2 G20210A) does confer an elevated risk of deep venous thromboembolism in the general population, although to a lesser degree than FVL, but in APS patients the effect seems to be less consistent. While it was first reported that the gene did not increase risk in Caucasian and Mexican mestizo APS patients^[52-54], studies that followed demonstrated that an elevated rate of thrombotic disease in patients with APS could be attributed to the presence of the gene. The initial report was of a young female patient with the homozygous G20210A mutation and lupus associated APS^[55-57]. However, reports that followed could not demonstrate an association between this mutation and thrombosis in APS^[51,58].

As a result of the rarity of deficiencies in antithrombin III and protein C and S it has proven difficult to accurately assess the role played by these mutations in increasing thrombotic risk in patients with aPL. However, studies have linked an elevated incidence of thrombotic disease with deficiencies of both protein C and S in APS^[59,60]. Polymorphisms in other relevant genes including thrombomodulin, annexin A5, methylenetetrahydrofolate reductase, plasminogen activator inhibitor-1, tumor necrosis factor α , platelet glycoproteins GP I a/II a and GP II b/III a, tissue factor pathway inhibitor, can also possibly increase the risk of thrombotic disease in APS but data is limited^[61].

ENVIRONMENTAL FACTORS IN APS

Infectious agents

Early efforts to induce aPL production in animal models

focused on immunization of animals with theorized antigenic targets. Initial experiments utilized cardiolipin antigens but these failed to allow for production of aPL in animal models^[62]. After the discovery that the main antigenic target of pathogenic aPL was in fact β_2 GP I, subsequent experiments utilized immunization with heterologous β_2 GP I rather than pure PLs. This led to the successful induction of aPL production in mice and these antibodies were able to induce pathogenic effects^[2,62]. Researchers then hypothesized that perhaps molecular mimicry played a key role in pathogenic aPL production. In essence, foreign PL-binding proteins that shared structural similarities to β_2 GP I could bind to self PLs in APS patients, and in so doing allow for the assembly of immunogenic complexes that stimulate aPL production.

Subsequent studies made use of a synthesized 15 amino acid peptide, GDKV, which spanned an area of the fifth domain of β_2 GP I known to be a major PL-binding site of the molecule. This peptide was able to induce pathogenic aPL and anti- β_2 GP I production in immunized mice^[63]. A monoclonal antibody with aPL and anti- β_2 GP I activity generated from these GDKV-immunized mice was shown to be pathogenic using *in vivo* models for thrombus enhancement and microcirculation^[64]. A search for candidate peptides with structural similarities to GDKV among libraries of peptides from viral and bacterial agents produced several candidates (Table 1). Similar results in experimental animal models were then reported using these candidate peptides^[65]. When compared to GDKV, peptides from cytomegalovirus (TIFI and VITT), from adenovirus (TADL) and from *Bacillus subtilis* (SGDF) all bound to PLs with greater affinity and induced higher anti- β_2 GP I levels in experimental animals. The thrombogenic and proinflammatory capacity of induced antibodies in mice immunized with TIFI was subsequently confirmed^[65,66].

An interesting set of experiments that focused on a hexapeptide, TLRVYK, which is a known antigen of pathogenic monoclonal anti- β_2 GP I, found in micro-organisms provided further evidence of molecular mimicry being involved in aPL production^[67]. BALB/c mice immunized with *Haemophilus influenzae*, *Neisseria gonorrhoeae* or tetanus toxoid produced high anti-TLRVYK and anti- β_2 GP I antibodies which were then isolated and passively transferred to naive mice at day 0 of pregnancy. These

antibodies induced a higher frequency of fetal loss, thrombocytopenia and prolonged activated partial thromboplastin times at day 15 after inoculation. Even further evidence comes from a study utilizing protein H found in *Streptococcus pyogenes* isolates. Protein H was able to bind to β_2 GP I, induce changes in the conformation of the protein, expose cryptic epitopes and consequently allow for the development of anti- β_2 GP I antibodies^[68].

Several infectious agents have been linked to aPL production and APS manifestations^[63]. Human immunodeficiency virus, Human T-cell lymphoma/leukemia virus, CMV, hepatitis B and C viruses, parvovirus B19 and Varicella Zoster Virus are a few for which these associations have been reported^[69]. It is clear that infectious agents play a major role in pathogenic aPL production but what remains uncertain is the mechanism which underlies the break in tolerance allowing for these autoantibodies to be produced. Additional methods of autoimmune induction by infectious agents include the release of cytokines and chemokines, selective activation or destruction of unique lymphocyte subsets or hidden epitope exposure during cell necrosis or apoptosis^[70-72].

The majority of circulating β_2 GP I exists in a reduced form containing unpaired cysteines (free thiols), which are involved in the interaction with platelets and endothelial cells. This abundant pool of free thiols may serve as an antioxidant reservoir protecting cells or critical molecules from oxidative stress and oxidation of β_2 GP I has been shown to confer an increase in its immunogenicity through a Th1 immunological mechanism. It is therefore possible that the generation of reactive oxidative and nitrosative species by certain infectious agents could allow for generation of an abundance of oxidized β_2 GP I and foster autoantibody production. Indeed, serum from patients with APS assessed by a novel enzyme linked immunoassay (ELISA) assay, have a significant increase in oxidized β_2 GP I^[73] (Figure 1).

The break in tolerance in APS patients is also likely to involve regulatory T-cell (Treg) function based on recent evidence. Peripheral blood mononuclear cells isolated from healthy donors were subjected to increasing concentrations of aPL and there was evidence of significant changes in T-cell subsets compared to controls^[74]. T-helper2 (Th2) and Th17 cell frequencies were increased, while Th1 and Treg cells were decreased. Subsequently, a study done in primary APS patients reported a reduced frequency of CD4+ CD25+ foxp3+ T-regulatory cells in these patients compared to controls^[75]. Taken together, these studies indicate that Th1/Th2 imbalance, Th17 upregulation and Treg dysfunction play potential roles in aPL production and APS development (Figure 1).

Rauch *et al.*^[76] have recently put forward a hypothesis that highlights the central part played by toll-like receptors (TLRs), especially TLR4, in inducing a break in tolerance, aPL production and epitope spread to several autoantigens based on their work^[76]. Quite recently, Aguilar-Valenzuela *et al.*^[77] demonstrated for the first

time that both TLR7 and TLR9 are involved in pathogenic aPL production by utilizing lupus prone mice treated with CMV derived peptides in the presence of TLR7 or TLR9 agonists and other lupus prone mice deficient in TLR7 or both TLR7 and TLR9.

Other environmental agents

Although there is only limited and often inconclusive data linking environmental agents such as vaccines, drugs and cancer to APS, these associations have been reported^[78,79]. Associations with acrylamide, silicone and vaccines have been outlined in case reports but remain unproven^[80,81].

Drugs are able to bind self-antigens, alter their processing and presentation to immune cells and in essence creating neopeptides or expose cryptic epitopes, facilitating autoimmune induction^[82]. Similar to other non-infectious environmental agents, several drugs have been reported to be associated with aPL production but conclusive evidence has not been presented. These drugs include antibiotics, propranolol, chlorpromazine, antiarrhythmic agents, quinine, amoxicillin, phenytoin, chlorothiazide, oral contraceptives, anti-hypertensive medications, alpha-interferon, and infliximab^[82-85].

Solid and hematologic cancers have been linked to aPL, which is perhaps most significant as it relates to an increased risk for thrombosis in patients with an already elevated risk and the potential for development of catastrophic antiphospholipid syndrome (CAPS). The underlying pathogenetic mechanisms of this association are as yet unclarified but may be related to an anti-tumor immune response or neoantigen formation during immunomodulatory drug therapy with agents like interferon- α ^[86].

APOPTOSIS IN APS DEVELOPMENT

Apoptosis is a normal regulatory process of tissue turnover in response to different homeostatic stimuli. However, as a result of this process there is continuous exposure of self-antigens to the immune system and so the key to prevention of autoimmune induction is efficient clearing of apoptotic debris. In the thymus and bone marrow, these clearance mechanisms are extremely efficient and since there is also a lack of co-stimulatory signals in these central lymphoid organs, no induction of autoantibodies occurs under normal circumstances. However, apoptosis results in disruption of intracellular boundaries and the clustering and structural modification of nuclear, cytoplasmic and membrane antigens. In the absence of efficient clearance mechanisms, normally unexposed antigens are subject to immune recognition, resulting in autoantibody production^[87].

During apoptosis, a negatively charged PL, PS, which is normally found almost entirely on the inner cytoplasmic leaflet, is transferred to the outer leaflet^[88,89]. This is important in APS as it provides an antigen for aPL binding and such autoantibodies that bind apoptotic cells *via* interaction with PL- β_2 GP I complexes have been

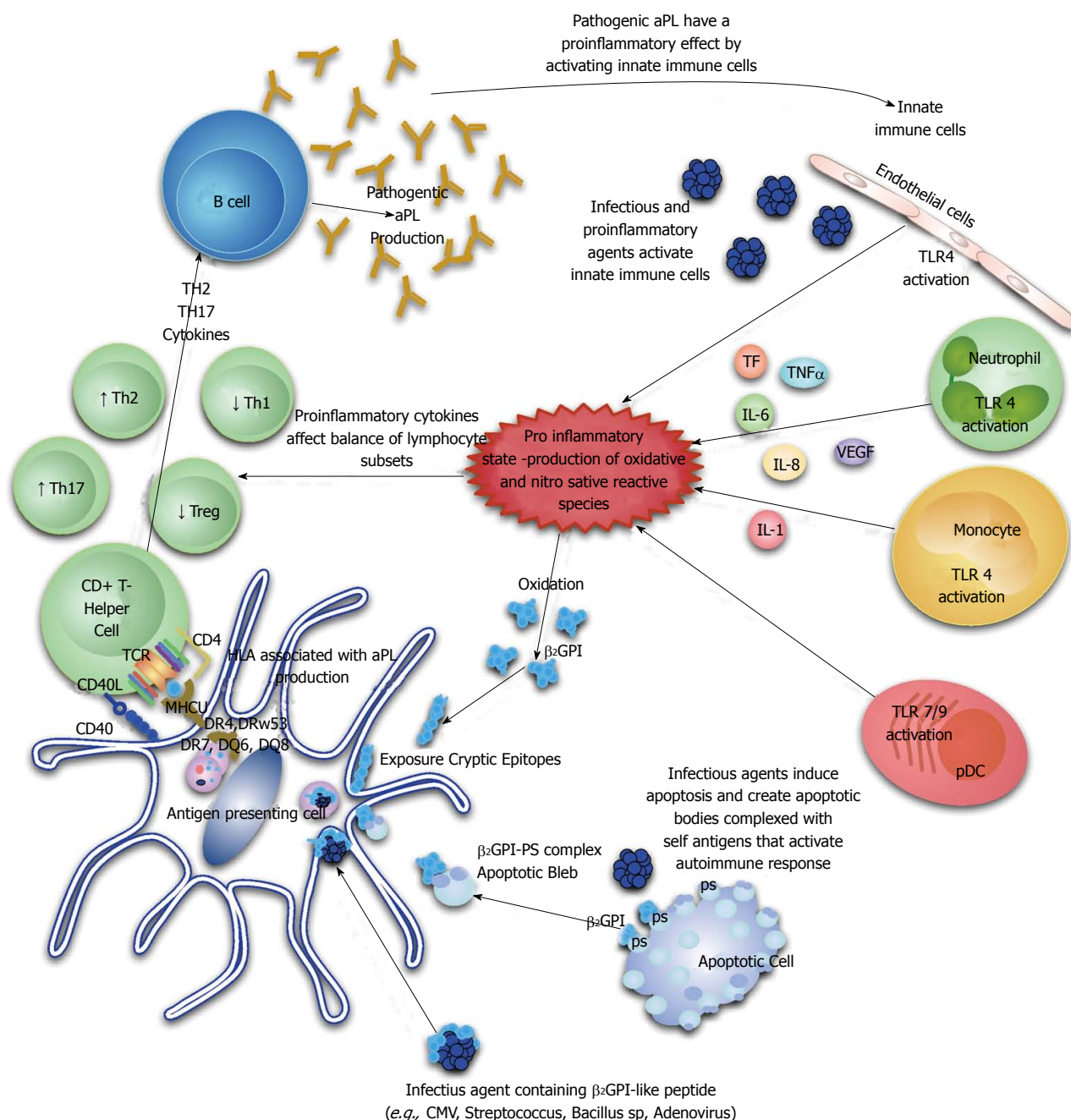


Figure 1 Proposed pathogenetic mechanisms leading to antiphospholipid antibody production in antiphospholipid syndrome. aPL: Antiphospholipid; TLR: Toll-like receptors.

identified^[90-92]. Indeed, the antigenic reactivity of several aPL with a complex formed between anionic phospholipid (e.g., PS) and β_2 GP I or β_2 GP I in isolation^[93]. During the apoptotic process in autoimmune patients, the sequestration of PS induces specific recognition by macrophages and subsequent removal^[94], and the PS/ β_2 GP I complex recruits anti- β_2 GP I, which then facilitates apoptotic cell clearance and preserves tissue homeostasis^[95].

The concept that apoptosis plays a role in the production of aPL was first proposed by Piroux *et al.*^[92]. Subsequent studies have provided evidence that apoptotic cells/ β_2 GP I complexes can act as a source of anti- β_2 GP I antibodies. Levine *et al.*^[96] reported that β_2 GP

I do not readily bind to the surface of viable cells but rather to the surface of apoptotic cells. Once bound, the exposure of an essential epitope facilitates recognition by aPL from patients with primary APS and SLE. Interestingly, increased aPL production can be induced in mice immunized with apoptotic cells alone or complexed to β_2 GP I. A recent study highlighted the importance of the Ro60 receptor in β_2 GP I precipitation in apoptotic bodies^[95-99].

CONCLUSION

The relative degree to which inherited and acquired factors determine the risk for developing aPL and APS

has not been fully elucidated. The most likely scenario is a complex interplay of a multitude of environmental factors in a genetically susceptible patient, which then induces autoantibody development and consequently typical disease manifestations. Once there is a more complete comprehension of the relative contributions of these varied factors, researchers and clinicians alike will be able to implement more effective preventive and therapeutic management guidelines for these patients. Future studies should focus on the elucidation of those specific immune factors leading to a break in tolerance and subsequent aPL production, as a stepping stone to the development of appropriate preventive and therapeutic modalities.

REFERENCES

- Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; **4**: 295-306 [PMID: 16420554 DOI: 10.1111/j.1538-7836.2006.01753.x]
- McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Antiphospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: beta 2-glycoprotein I (apolipoprotein H). *Proc Natl Acad Sci USA* 1990; **87**: 4120-4124 [PMID: 2349221 DOI: 10.1073/pnas.87.11.4120]
- Galli M, Comfurius P, Maassen C, Hemker HC, de Baets MH, van Breda-Vriesman PJ, Barbui T, Zwaal RF, Bevers EM. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. *Lancet* 1990; **335**: 1544-1547 [PMID: 1972485 DOI: 10.1016/0140-6736(90)91374-J]
- Amengual O, Atsumi T, Koike T. Antiproteolytic antibodies and the diagnosis of antiphospholipid syndrome. *Clin Immunol* 2004; **112**: 144-149 [PMID: 15240157 DOI: 10.1016/j.clim.2004.02.013]
- Willis R, Harris EN, Pierangeli SS. Pathogenesis of the antiphospholipid syndrome. *Semin Thromb Hemost* 2012; **38**: 305-321 [PMID: 22510982 DOI: 10.1055/s-0032-1311827]
- Sebastiani GDGM. Genetic aspects of the antiphospholipid syndrome: HLA associations. In: *Handbook of Systemic Autoimmune Diseases*; Vol 10, Chapter 6. Ed by Cervera, Reverter and Khamashta. Oxford, UK: Elsevier BC, 2009: 81-89 [DOI: 10.1111/j.1365-2141.2009.07831.x]
- Castro-Marrero J, Balada E, Vilardell-Tarrés M, Ordi-Ros J. Genetic risk factors of thrombosis in the antiphospholipid syndrome. *Br J Haematol* 2009; **147**: 289-296 [PMID: 19659549 DOI: 10.1016/S0889-857X(05)70219-2]
- Gharavi AE, Pierangeli SS, Harris EN. Origin of antiphospholipid antibodies. *Rheum Dis Clin North Am* 2001; **27**: 551-563 [PMID: 11534259]
- Gharavi AE, Pierangeli SS, Harris EN. Viral origin of antiphospholipid antibodies: endothelial cell activation and thrombus enhancement by CMV peptide-induced APL antibodies. *Immunobiology* 2003; **207**: 37-42 [PMID: 12638901 DOI: 10.1078/0171-2985-00216]
- Hashimoto Y, Kawamura M, Ichikawa K, Suzuki T, Sumida T, Yoshida S, Matsura E, Ikehara S, Koike T. Anticardiolipin antibodies in NZW x BXS F1 mice. A model of antiphospholipid syndrome. *J Immunol* 1992; **149**: 1063-1068 [PMID: 1634762]
- Hang LM, Izui S, Dixon FJ. (NZW x BXS)F1 hybrid. A model of acute lupus and coronary vascular disease with myocardial infarction. *J Exp Med* 1981; **154**: 216-221 [PMID: 7252427 DOI: 10.1084/jem.154.1.216]
- Oyaizu N, Yasumizu R, Miyama-Inaba M, Nomura S, Yoshida H, Miyawaki S, Shibata Y, Mitsuoka S, Yasunaga K, Morii S. (NZW x BXS)F1 mouse. A new animal model of idiopathic thrombocytopenic purpura. *J Exp Med* 1988; **167**: 2017-2022 [PMID: 3290385 DOI: 10.1084/jem.167.6.2017]
- Kita Y, Sumida T, Iwamoto I, Yoshida S, Koike T. V gene analysis of anti-cardiolipin antibodies from (NZW x BXS) F1 mice. *Immunology* 1994; **82**: 494-501 [PMID: 7959886]
- Kita Y, Sumida T, Ichikawa K, Maeda T, Yonaha F, Iwamoto I, Yoshida S, Koike T. V gene analysis of anticardiolipin antibodies from MRL-lpr/lpr mice. *J Immunol* 1993; **151**: 849-856 [PMID: 8335914]
- Ahmed SA, Verthelyi D. Antibodies to cardiolipin in normal C57BL/6J mice: induction by estrogen but not dihydrotestosterone. *J Autoimmun* 1993; **6**: 265-279 [PMID: 8397711 DOI: 10.1006/jaut.1993.1023]
- Verthelyi D, Ansar Ahmed S. Characterization of estrogen-induced autoantibodies to cardiolipin in non-autoimmune mice. *J Autoimmun* 1997; **10**: 115-125 [PMID: 9185873 DOI: 10.1006/jaut.1996.0121]
- Gharavi AE, Mellors RC, Elkon KB. IgG anti-cardiolipin antibodies in murine lupus. *Clin Exp Immunol* 1989; **78**: 233-238 [PMID: 12412755]
- Ida A, Hirose S, Hamano Y, Kodera S, Jiang Y, Abe M, Zhang D, Nishimura H, Shirai T. Multigenic control of lupus-associated antiphospholipid syndrome in a model of (NZW x BXS) F1 mice. *Eur J Immunol* 1998; **28**: 2694-2703 [PMID: 9754557]
- Izui S, Masuda K, Yoshida H. Acute SLE in F1 hybrids between SB/Le and NZW mice; prominently enhanced formation of gp70 immune complexes by a Y chromosome-associated factor from SB/Le mice. *J Immunol* 1984; **132**: 701-704 [PMID: 6690614]
- Izui S, Higaki M, Morrow D, Merino R. The Y chromosome from autoimmune BXS/MpJ mice induces a lupus-like syndrome in (NZW x C57BL/6)F1 male mice, but not in C57BL/6 male mice. *Eur J Immunol* 1988; **18**: 911-915 [PMID: 3260184 DOI: 10.1002/eji.1830180612]
- Papalardo ERPZ, Christodoss P, Pierangeli S. Induction of pathogenic antiphospholipid antibodies in vivo are dependent on expression of MHC-II genes. In: Pierangeli S, ed. *International Congress on Antiphospholipid Antibodies*. Vol 19. Galveston, Texas: Lupus, 2010: 496
- Harvey AM, Shulman LE. Connective tissue disease and the chronic biologic false-positive test for syphilis (BFP reaction). *Med Clin North Am* 1966; **50**: 1271-1279 [PMID: 6013230]
- Exner T, Barber S, Kronenberg H, Rickard KA. Familial association of the lupus anticoagulant. *Br J Haematol* 1980; **45**: 89-96 [PMID: 7378333 DOI: 10.1111/j.1365-2141.1980.tb03814.x]
- Jolidon RM, Knecht H, Humair L, de Torrente A. Different clinical presentations of a lupus anticoagulant in the same family. *Klin Wochenschr* 1991; **69**: 340-344 [PMID: 1909397 DOI: 10.1007/BF02115779]
- Mackworth-Young C, Chan J, Harris N, Walport M, Bernstein R, Batchelor R, Hughes G, Gharavi A. High incidence of anticardiolipin antibodies in relatives of patients with systemic lupus erythematosus. *J Rheumatol* 1987; **14**: 723-726 [PMID: 3668978]
- Goldberg SN, Conti-Kelly AM, Greco TP. A family study of anticardiolipin antibodies and associated clinical conditions. *Am J Med* 1995; **99**: 473-479 [PMID: 7485203 DOI: 10.1016/S0002-9343(99)80222-8]
- Goel N, Ortel TL, Bali D, Anderson JP, Gourley IS, Smith H, Morris CA, DeSimone M, Branch DW, Ford P, Berdeaux D, Roubey RA, Kostyu DD, Kingsmore SF, Thiel T, Amos C, Seldin MF. Familial antiphospholipid antibody syndrome: criteria for disease and evidence for autosomal dominant inheritance. *Arthritis Rheum* 1999; **42**: 318-327 [PMID: 10025927]
- Dagenais P, Urowitz MB, Gladman DD, Norman CS. A family study of the antiphospholipid syndrome associated with other autoimmune diseases. *J Rheumatol* 1992; **19**: 1393-1396 [PMID: 1433007]
- Rouget JP, Goudemand J, Montreuil G, Cosson A, Jaillard J. Lupus anticoagulant: a familial observation. *Lancet* 1982; **2**: 105

- [PMID: 6123796 DOI: 10.1016/S0140-6736(82)91726-3]
- 30 **Mackie IJ**, Colaco CB, Machin SJ. Familial lupus anticoagulants. *Br J Haematol* 1987; **67**: 359-363 [PMID: 3689698 DOI: 10.1111/j.1365-2141.1987.tb02358.x]
 - 31 **May KP**, West SG, Moulds J, Kotzin BL. Different manifestations of the antiphospholipid antibody syndrome in a family with systemic lupus erythematosus. *Arthritis Rheum* 1993; **36**: 528-533 [PMID: 8457227 DOI: 10.1002/art.1780360413]
 - 32 **Arnett FC**, Olsen ML, Anderson KL, Reveille JD. Molecular analysis of major histocompatibility complex alleles associated with the lupus anticoagulant. *J Clin Invest* 1991; **87**: 1490-1495 [PMID: 1673688 DOI: 10.1172/JCI115158]
 - 33 **Asherson RA**, Doherty DG, Vergani D, Khamashta MA, Hughes GR. Major histocompatibility complex associations with primary antiphospholipid syndrome. *Arthritis Rheum* 1992; **35**: 124-125 [PMID: 1731810 DOI: 10.1002/art.1780350119]
 - 34 **Caliz R**, Atsumi T, Kondeatis E, Amengual O, Khamashta MA, Vaughan RW, Lanchbury JS, Hughes GR. HLA class II gene polymorphisms in antiphospholipid syndrome: haplotype analysis in 83 Caucasian patients. *Rheumatology* (Oxford) 2001; **40**: 31-36 [PMID: 11157139 DOI: 10.1093/rheumatology/40.1.31]
 - 35 **Bertolaccini ML**, Atsumi T, Caliz AR, Amengual O, Khamashta MA, Hughes GR, Koike T. Association of antiphosphatidylserine/prothrombin autoantibodies with HLA class II genes. *Arthritis Rheum* 2000; **43**: 683-688 [PMID: 10728763]
 - 36 **Vargas-Alarcon G**, Granados J, Bekker C, Alcocer-Varela J, Alarcón-Segovia D. Association of HLA-DR5 (possibly DRB1*1201) with the primary antiphospholipid syndrome in Mexican patients. *Arthritis Rheum* 1995; **38**: 1340-1341 [PMID: 7575732 DOI: 10.1002/art.1780380925]
 - 37 **Galeazzi M**, Sebastiani GD, Tincani A, Piette JC, Allegri F, Morozzi G, Bellisai F, Scorza R, Ferrara GB, Carcassi C, Font J, Passiu G, Smolen J, Papasteriades C, Houssiau F, Nebro AF, Ramon Garrido ED, Jedryka-Goral A, Marcolongo R. HLA class II alleles associations of anticardiolipin and anti-beta2GPI antibodies in a large series of European patients with systemic lupus erythematosus. *Lupus* 2000; **9**: 47-55 [PMID: 10715100 DOI: 10.1177/09612033000900109]
 - 38 **Hashimoto H**, Yamanaka K, Tokano Y, Iida N, Takasaki Y, Kabasawa K, Nishimura Y. HLA-DRB1 alleles and beta 2 glycoprotein I-dependent anticardiolipin antibodies in Japanese patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 1998; **16**: 423-427 [PMID: 9706422]
 - 39 **Arnett FC**, Thiagarajan P, Ahn C, Reveille JD. Associations of anti-beta2-glycoprotein I autoantibodies with HLA class II alleles in three ethnic groups. *Arthritis Rheum* 1999; **42**: 268-274 [PMID: 10025920]
 - 40 **Wilson WA**, Perez MC, Michalski JP, Armatas PE. Cardiolipin antibodies and null alleles of C4 in black Americans with systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 1768-1772 [PMID: 3265959]
 - 41 **Wilson WA**, Scopelitis E, Michalski JP, Pierangeli SS, Silveira LH, Elston RC, Harris EN. Familial anticardiolipin antibodies and C4 deficiency genotypes that coexist with MHC DQB1 risk factors. *J Rheumatol* 1995; **22**: 227-235 [PMID: 7738943]
 - 42 **Petri M**, Watson R, Winkelstein JA, McLean RH. Clinical expression of systemic lupus erythematosus in patients with C4A deficiency. *Medicine* (Baltimore) 1993; **72**: 236-244 [PMID: 8341140]
 - 43 **Hirose N**, Williams R, Alberts AR, Furie RA, Chartash EK, Jain RI, Sison C, Lahita RG, Merrill JT, Cucurull E, Gharavi AE, Sammaritano LR, Salmon JE, Hashimoto S, Sawada T, Chu CC, Gregersen PK, Chiorazzi N. A role for the polymorphism at position 247 of the beta2-glycoprotein I gene in the generation of anti-beta2-glycoprotein I antibodies in the antiphospholipid syndrome. *Arthritis Rheum* 1999; **42**: 1655-1661 [PMID: 10446865]
 - 44 **Atsumi T**, Tsutsumi A, Amengual O, Khamashta MA, Hughes GR, Miyoshi Y, Ichikawa K, Koike T. Correlation between beta2-glycoprotein I valine/leucine247 polymorphism and anti-beta2-glycoprotein I antibodies in patients with primary antiphospholipid syndrome. *Rheumatology* (Oxford) 1999; **38**: 721-723 [PMID: 10501418 DOI: 10.1093/rheumatology/38.8.721]
 - 45 **Prieto GA**, Cabral AR, Zapata-Zuñiga M, Simón AJ, Villa AR, Alarcón-Segovia D, Cabiedes J. Valine/valine genotype at position 247 of the beta2-glycoprotein I gene in Mexican patients with primary antiphospholipid syndrome: association with anti-beta2-glycoprotein I antibodies. *Arthritis Rheum* 2003; **48**: 471-474 [PMID: 12571857 DOI: 10.1002/art.10771]
 - 46 **Reverter JCTM**. Genetic aspects of the antiphospholipid syndrome: associations with clinical manifestations. In: Asherson RA, ed. *Antiphospholipid Syndrome in Systemic Autoimmune Disease Vol 10*. Johannesburg, South Africa: Elsevier, 2009: 91-10 [DOI: 10.1016/S1571-5078(08)00407-8]
 - 47 **Rees DC**, Cox M, Clegg JB. World distribution of factor V Leiden. *Lancet* 1995; **346**: 1133-1134 [PMID: 7475606 DOI: 10.1016/S0140-6736(95)91803-5]
 - 48 **Franco RF**, Elion J, Tavella MH, Santos SE, Zago MA. The prevalence of factor V Arg306--> Thr (factor V Cambridge) and factor V Arg306--> Gly mutations in different human populations. *Thromb Haemost* 1999; **81**: 312-313 [PMID: 10064012]
 - 49 **Schütt M**, Klüter H, Hagedorn-Greife M, Fehm HL, Wiedemann GJ. Familial coexistence of primary antiphospholipid syndrome and factor VLeiden. *Lupus* 1998; **7**: 176-182 [PMID: 9607641 DOI: 10.1191/096120398678919967]
 - 50 **Brenner B**, Vulfsons SL, Lanir N, Nahir M. Coexistence of familial antiphospholipid syndrome and factor V Leiden: impact on thrombotic diathesis. *Br J Haematol* 1996; **94**: 166-167 [PMID: 8757529 DOI: 10.1046/j.1365-2141.1996.d01-1757.x]
 - 51 **Chopra N**, Koren S, Greer WL, Fortin PR, Rauch J, Fortin I, Senécal JL, Docherty P, Hanly JG. Factor V Leiden, prothrombin gene mutation, and thrombosis risk in patients with antiphospholipid antibodies. *J Rheumatol* 2002; **29**: 1683-1688 [PMID: 12180730]
 - 52 **Bentolila S**, Ripoll L, Drouet L, Crassard I, Tournier-Lasserre E, Piette JC. Lack of association between thrombosis in primary antiphospholipid syndrome and the recently described thrombophilic 3'-untranslated prothrombin gene polymorphism. *Thromb Haemost* 1997; **78**: 1415 [PMID: 9408029]
 - 53 **Bertolaccini ML**, Atsumi T, Hunt BJ, Amengual O, Khamashta MA, Hughes GR. Prothrombin mutation is not associated with thrombosis in patients with antiphospholipid syndrome. *Thromb Haemost* 1998; **80**: 202-203 [PMID: 9684813]
 - 54 **Ruiz-Argüelles GJ**, Garcés-Eisele J, Ruiz-Delgado GJ, Alarcón-Segovia D. The G20210A polymorphism in the 3'-untranslated region of the prothrombin gene in Mexican mestizo patients with primary antiphospholipid syndrome. *Clin Appl Thromb Hemost* 1999; **5**: 158-160 [PMID: 10726001 DOI: 10.1177/107602969900500303]
 - 55 **Sivera P**, Bosio S, Bertero MT, Demastri M, Mazza U, Camaschella C. G20210A homozygosity in antiphospholipid syndrome secondary to systemic lupus erythematosus. *Haematologica* 2000; **85**: 109-110 [PMID: 10629608]
 - 56 **Torresan M**, Machado TF, Siqueira LH, Ozelo MC, Arruda VR, Annichino-Bizzacchi JM. The impact of the search for thrombophilia risk factors among antiphospholipid syndrome patients with thrombosis. *Blood Coagul Fibrinolysis* 2000; **11**: 679-682 [PMID: 11085290 DOI: 10.1097/00001721-200010000-00014]
 - 57 **Forastiero R**, Martinuzzo M, Adamczuk Y, Varela ML, Pombo G, Carreras LO. The combination of thrombophilic genotypes is associated with definite antiphospholipid syndrome. *Haematologica* 2001; **86**: 735-741 [PMID: 11454529]
 - 58 **Galli M**, Finazzi G, Duca F, Norbis F, Moia M. The G1691--> A mutation of factor V, but not the G20210--> A mutation of factor II or the C677--> T mutation of methylenetetrahydrofolate reductase genes, is associated with venous thrombosis in patients with lupus anticoagulants. *Br J Haematol* 2000; **108**: 865-870 [PMID: 10792297 DOI: 10.1046/j.1365-2141.2000.01964.x]
 - 59 **de Visser MC**, Rosendaal FR, Bertina RM. A reduced sensitivity

- for activated protein C in the absence of factor V Leiden increases the risk of venous thrombosis. *Blood* 1999; **93**: 1271-1276 [PMID: 9949170]
- 60 **Erkan D**, Zhang HW, Shriky RC, Merrill JT. Dual antibody reactivity to beta2-glycoprotein I and protein S: increased association with thrombotic events in the antiphospholipid syndrome. *Lupus* 2002; **11**: 215-220 [PMID: 12043884 DOI: 10.1191/0961203302lu1780a]
 - 61 **Castro-Marrero J**, Balada E, Ordi-Rios J, Vilardell-Tarrés M. Genetics of Antiphospholipid Syndrome. In: Antiphospholipid Syndrome; Chapter 3. Ed by Buliková A. InTech, Croatia, 2012: 35-66 [DOI: 10.5772/31921]
 - 62 **Gharavi AE**, Sammaritano LR, Wen J, Elkon KB. Induction of antiphospholipid autoantibodies by immunization with beta 2 glycoprotein I (apolipoprotein H). *J Clin Invest* 1992; **90**: 1105-1109 [PMID: 1522219 DOI: 10.1172/JCI115927]
 - 63 **Gharavi AE**, Pierangeli SS, Colden-Stanfield M, Liu XW, Espinola RG, Harris EN. GDKV-induced antiphospholipid antibodies enhance thrombosis and activate endothelial cells in vivo and in vitro. *J Immunol* 1999; **163**: 2922-2927 [PMID: 10453040]
 - 64 **Gharavi AE**, Pierangeli SS, Gharavi EE, Hua T, Liu XW, Barker JH, Anderson GH, Harris EN. Thrombogenic properties of antiphospholipid antibodies do not depend on their binding to beta2 glycoprotein I (beta2GPI) alone. *Lupus* 1998; **7**: 341-346 [PMID: 9696138 DOI: 10.1191/096120398678920190]
 - 65 **Gharavi AE**, Pierangeli SS, Espinola RG, Liu X, Colden-Stanfield M, Harris EN. Antiphospholipid antibodies induced in mice by immunization with a cytomegalovirus-derived peptide cause thrombosis and activation of endothelial cells in vivo. *Arthritis Rheum* 2002; **46**: 545-552 [PMID: 11840458 DOI: 10.1002/art.10130]
 - 66 **Gharavi AE**, Vega-Ostertag M, Espinola RG, Liu X, Cole L, Cox NT, Romagnoli P, Labat K, Pierangeli SS. Intrauterine fetal death in mice caused by cytomegalovirus-derived peptide induced aPL antibodies. *Lupus* 2004; **13**: 17-23 [PMID: 14870913 DOI: 10.1191/0961203304lu4840a]
 - 67 **Blank M**, Krause I, Fridkin M, Keller N, Kopolovic J, Goldberg I, Tobar A, Shoenfeld Y. Bacterial induction of autoantibodies to beta2-glycoprotein-I accounts for the infectious etiology of antiphospholipid syndrome. *J Clin Invest* 2002; **109**: 797-804 [PMID: 11901188 DOI: 10.1172/JCI200212337]
 - 68 **van Os GM**, Meijers JC, Agar C, Seron MV, Marquart JA, Åkesson P, Urbanus RT, Derksen RH, Herwald H, Mörgelin M, D E Groot PG. Induction of anti-β2 -glycoprotein I autoantibodies in mice by protein H of Streptococcus pyogenes. *J Thromb Haemost* 2011; **9**: 2447-2456 [PMID: 21985124 DOI: 10.1111/j.1538-7836.2011.04532.x]
 - 69 **Sène D**, Piette JC, Cacoub P. [Antiphospholipid antibodies, antiphospholipid syndrome and viral infections]. *Rev Med Interne* 2009; **30**: 135-141 [PMID: 18926604 DOI: 10.1016/j.revmed.2008.05.020]
 - 70 **van de Berg PJ**, Heutink KM, Raabe R, Minnee RC, Young SL, van Donselaar-van der Pant KA, Bemelman FJ, van Lier RA, ten Berge IJ. Human cytomegalovirus induces systemic immune activation characterized by a type 1 cytokine signature. *J Infect Dis* 2010; **202**: 690-699 [PMID: 20632887]
 - 71 **Prandota J**. Possible pathomechanism of autoimmune hepatitis. *Am J Ther* 2003; **10**: 51-57 [PMID: 12522521 DOI: 10.1097/00045391-200301000-00012]
 - 72 **Nakagawa K**, Harrison LC. The potential roles of endogenous retroviruses in autoimmunity. *Immunol Rev* 1996; **152**: 193-236 [PMID: 8930674 DOI: 10.1111/j.1600-065X.1996.tb00917.x]
 - 73 **Passam FH**, Giannakopoulos B, Mirarabshahi P, Krilis SA. Molecular pathophysiology of the antiphospholipid syndrome: the role of oxidative post-translational modification of beta 2 glycoprotein I. *J Thromb Haemost* 2011; **9** Suppl 1: 275-282 [PMID: 21781264 DOI: 10.1111/j.1538-7836.2011.04301.x]
 - 74 **Xiao J**, Zhu F, Liu X, Xiong J. Th1/Th2/Th17/Treg expression in cultured PBMCs with antiphospholipid antibodies. *Mol Med Rep* 2012; **6**: 1035-1039 [PMID: 22941119]
 - 75 **Dal Ben ER**, do Prado CH, Baptista TS, Bauer ME, Staub HL. Decreased levels of circulating CD4+CD25+Foxp3+ regulatory T cells in patients with primary antiphospholipid syndrome. *J Clin Immunol* 2013; **33**: 876-879 [PMID: 23354908 DOI: 10.1007/s10875-012-9857-y]
 - 76 **Rauch J**, Dieudé M, Subang R, Levine JS. The dual role of innate immunity in the antiphospholipid syndrome. *Lupus* 2010; **19**: 347-353 [PMID: 20353968 DOI: 10.1177/0961203310361492]
 - 77 **Aguilar-Valenzuela R**, Nickerson K, Romay-Penabad Z, Shlomchik MJ, Vargas G, Shilagard T, Pierangeli S. Involvement of TLR7 and TLR9 in the production of antiphospholipid antibodies. *Arthritis Rheum* 2011; **63**: s281 (abstract 723). Available from: URL: <http://www.blackwellpublishing.com/acrmeeting/abstract.asp?MeetingID=781&id=95469>
 - 78 **Molina V**, Shoenfeld Y. Infection, vaccines and other environmental triggers of autoimmunity. *Autoimmunity* 2005; **38**: 235-245 [PMID: 16126512 DOI: 10.1080/08916930500050277]
 - 79 **Martinuc Porobic J**, Avcin T, Bozic B, Kuhar M, Cucnik S, Zupancic M, Prosenc K, Kveder T, Rozman B. Anti-phospholipid antibodies following vaccination with recombinant hepatitis B vaccine. *Clin Exp Immunol* 2005; **142**: 377-380 [PMID: 16232227 DOI: 10.1111/j.1365-2249.2005.02923.x]
 - 80 **Alusik S**, Jandová R, Gebauerová M, Tesárek B, Fabián J. [The anticardiolipin syndrome after breast reconstruction]. *Rozhl Chir* 1990; **69**: 298-301 [PMID: 2136447]
 - 81 **Rothschild B**. Acrylamine-induced autoimmune phenomena. *Clin Rheumatol* 2010; **29**: 999-1005 [PMID: 20544243]
 - 82 **Uetrecht J**. Current trends in drug-induced autoimmunity. *Autoimmun Rev* 2005; **4**: 309-314 [PMID: 15990079 DOI: 10.1016/j.autrev.2005.01.002]
 - 83 **El-Rayes BF**, Edelstein M. Unusual case of antiphospholipid antibody syndrome presenting with extensive cutaneous infarcts in a patient on long-term procainamide therapy. *Am J Hematol* 2003; **72**: 154 [PMID: 12555226 DOI: 10.1002/ajh.10274]
 - 84 **Sherer Y**, Blank M, Shoenfeld Y. Antiphospholipid syndrome (APS): where does it come from? *Best Pract Res Clin Rheumatol* 2007; **21**: 1071-1078 [PMID: 18068862 DOI: 10.1016/j.berh.2007.09.005]
 - 85 **Merrill JT**, Shen C, Guignani M, Lahita RG, Mongey AB. High prevalence of antiphospholipid antibodies in patients taking procainamide. *J Rheumatol* 1997; **24**: 1083-1088 [PMID: 9195513]
 - 86 **Uthman IW**, Gharavi AE. Viral infections and antiphospholipid antibodies. *Semin Arthritis Rheum* 2002; **31**: 256-263 [PMID: 11836658 DOI: 10.1053/sarh.2002.28303]
 - 87 **Sherer Y**, Gorstein A, Fritzler MJ, Shoenfeld Y. Autoantibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients. *Semin Arthritis Rheum* 2004; **34**: 501-537 [PMID: 15505768 DOI: 10.1016/j.semarthrit.2004.07.002]
 - 88 **Vermes I**, Haanen C, Steffens-Nakken H, Reutelingsperger C. A novel assay for apoptosis. Flow cytometric detection of phosphatidylserine expression on early apoptotic cells using fluorescein labelled Annexin V. *J Immunol Methods* 1995; **184**: 39-51 [PMID: 7622868 DOI: 10.1016/0022-1759(95)00072-I]
 - 89 **Verhoven B**, Schlegel RA, Williamson P. Mechanisms of phosphatidylserine exposure, a phagocyte recognition signal, on apoptotic T lymphocytes. *J Exp Med* 1995; **182**: 1597-1601 [PMID: 7595231 DOI: 10.1084/jem.182.5.1597]
 - 90 **Price BE**, Rauch J, Shia MA, Walsh MT, Lieberthal W, Gilligan HM, O'Laughlin T, Koh JS, Levine JS. Anti-phospholipid autoantibodies bind to apoptotic, but not viable, thymocytes in a beta 2-glycoprotein I-dependent manner. *J Immunol* 1996; **157**: 2201-2208 [PMID: 8757347]
 - 91 **Casciola-Rosen L**, Rosen A, Petri M, Schlissel M. Surface blebs on apoptotic cells are sites of enhanced procoagulant activity: implications for coagulation events and antigenic spread in systemic lupus erythematosus. *Proc Natl Acad Sci USA* 1996; **93**: 1624-1629 [PMID: 8643681 DOI: 10.1073/pnas.93.4.1624]
 - 92 **Piroux V**, Eschwège V, Freyssinet JM. Cell damage at the origin of antiphospholipid antibodies and their pathogenic potential in recurrent pregnancy loss. *Infect Dis Obstet Gynecol* 1997; **5**: 176-180 [PMID: 18476171 DOI: 10.1155/S1064744997000264]

- 93 **Koike T**, Bohgaki M, Amengual O, Atsumi T. Antiphospholipid antibodies: lessons from the bench. *J Autoimmun* 2007; **28**: 129-133 [PMID: 17383159 DOI: 10.1016/j.jaut.2007.02.009]
- 94 **Fadok VA**, Voelker DR, Campbell PA, Cohen JJ, Bratton DL, Henson PM. Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages. *J Immunol* 1992; **148**: 2207-2216 [PMID: 1545126]
- 95 **Manfredi AA**, Rovere P, Heltai S, Galati G, Nebbia G, Tincani A, Balestrieri G, Sabbadini MG. Apoptotic cell clearance in systemic lupus erythematosus. II. Role of beta2-glycoprotein I. *Arthritis Rheum* 1998; **41**: 215-223 [PMID: 9485079]
- 96 **Levine JS**, Subang R, Nasr SH, Fournier S, Lajoie G, Wither J, Rauch J. Immunization with an apoptotic cell-binding protein recapitulates the nephritis and sequential autoantibody emergence of systemic lupus erythematosus. *J Immunol* 2006; **177**: 6504-6516 [PMID: 17056583 DOI: 10.4049/jimmunol.177.9.6504]
- 97 **Mevorach D**, Zhou JL, Song X, Elkon KB. Systemic exposure to irradiated apoptotic cells induces autoantibody production. *J Exp Med* 1998; **188**: 387-392 [PMID: 9670050 DOI: 10.1084/jem.188.2.387]
- 98 **Levine JS**, Subang R, Koh JS, Rauch J. Induction of anti-phospholipid autoantibodies by beta2-glycoprotein I bound to apoptotic thymocytes. *J Autoimmun* 1998; **11**: 413-424 [PMID: 9802924 DOI: 10.1006/jaut.1998.0235]
- 99 **Rauch J**, Subang R, D'Agnillo P, Koh JS, Levine JS. Apoptosis and the antiphospholipid syndrome. *J Autoimmun* 2000; **15**: 231-235 [PMID: 10968916 DOI: 10.1006/jaut.2000.0396]

P- Reviewer: Blanco LP, Toubi E **S- Editor:** Ji FF

L- Editor: A **E- Editor:** Jiao XK



Radiographic assessment of leg alignment and grading of knee osteoarthritis: A critical review

Lisa Sheehy, T Derek V Cooke

Lisa Sheehy, Bruyère Research Institute, Ottawa, ON K1N 5C8, Canada

Lisa Sheehy, School of Rehabilitation Sciences, University of Ottawa, Roger-Guindon Hall, Ottawa, ON K1H 8M5, Canada

T Derek V Cooke, School of Rehabilitation Therapy, Queen's University, Perth, ON K7H 3A5, Canada

Author contributions: Sheehy L designed and wrote the initial draft of the paper and revised it; Cooke TDV conceived the paper and revised it for critically important content. Both authors approve the final version.

Conflict-of-interest statement: Cooke TDV is the president and shareholder of Orthopedic Alignment and Imaging Systems (OAISYS) Inc.; Cooke TDV has received salary support from OAISYS Inc.; Sheehy L declares no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Lisa Sheehy, PT, PhD, Bruyère Research Institute, 43 Bruyère St., Ottawa, ON K1N 5C8, Canada. lsheehy@bruyere.org
Telephone: +1-613-5626262-1593
Fax: +1-613-5624256

Received: November 18, 2014
Peer-review started: November 19, 2014
First decision: February 7, 2015
Revised: February 25, 2015
Accepted: May 5, 2015
Article in press: May 6, 2015
Published online: July 12, 2015

Abstract

Knee osteoarthritis (OA) is a progressive joint disease hallmarked by cartilage and bone breakdown and associated with changes to all of the tissues in the joint, ultimately causing pain, stiffness, deformity and disability in many people. Radiographs are commonly used for the clinical assessment of knee OA incidence and progression, and to assess for risk factors. One risk factor for the incidence and progression of knee OA is malalignment of the lower extremities (LE). The hip-knee-ankle (HKA) angle, assessed from a full-length LE radiograph, is ideally used to assess LE alignment. Careful attention to LE positioning is necessary to obtain the most accurate measurement of the HKA angle. Since full-length LE radiographs are not always available, the femoral shaft - tibial shaft (FS-TS) angle may be calculated from a knee radiograph instead. However, the FS-TS angle is more variable than the HKA angle and it should be used with caution. Knee radiographs are used to assess the severity of knee OA and its progression. There are three types of ordinal grading scales for knee OA: global, composite and individual feature scales. Each grade on a global scale describes one or more features of knee OA. The entire description must be met for a specific grade to be assigned. The Kellgren-Lawrence scale is the most commonly-used global scale. Composite scales grade several features of knee OA individually and sum the grades to create a total score. One example is the compartmental grading scale for knee OA. Composite scales can respond to change in a variety of presentations of knee OA. Individual feature scales assess one or more OA features individually and do not calculate a total score. They are most often used to monitor change in one OA feature, commonly joint space narrowing. The most commonly-used individual feature scale is the OA Research Society International atlas. Each type of scale has its advantages; however, composite scales may offer greater content validity.

Responsiveness to change is unknown for most scales and deserves further evaluation.

Key words: Osteoarthritis; Mechanical axis angle; Knee; Radiography; Alignment; Grading scales; Assessment; Hip-knee-ankle angle; Femoral shaft-tibial shaft angle; Anatomic axis angle

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Radiographs are commonly used for the clinical assessment of knee osteoarthritis (OA) and to assess for risk factors. One risk factor for knee OA is malalignment of the lower extremities (LE). LE alignment is ideally measured from a full-length LE radiograph. While knee radiographs are sometimes used, the resulting angle is much more variable and should be used with caution. Knee radiographs are also used to assess the severity of knee OA. Global, composite and individual feature grading scales may be used. Each type of scale has its advantages; however composite scales may offer greater content validity.

Sheehy L, Cooke TDV. Radiographic assessment of leg alignment and grading of knee osteoarthritis: A critical review. *World J Rheumatol* 2015; 5(2): 69-81 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i2/69.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i2.69>

INTRODUCTION

Osteoarthritis (OA) is a progressive joint disease hallmarked by cartilage and bone breakdown. In knee OA, excessive or prolonged force or instability leads to fibrillation and thinning of the articular cartilage^[1]. Associated with cartilage changes, the periarticular bone remodels, causes osteophytes. Erosion of the subchondral bone occurs as the cartilage continues to wear. Deeper into the bone structure, areas of sclerosis and cysts form. It has been acknowledged recently that other tissues, such as ligaments, menisci and synovium are also affected in knee OA. These whole joint changes ultimately cause pain, stiffness, deformity and disability in many people.

The prevalence of knee OA ranges from 5.4% in Italy to 38% in South Korea^[2-9]. These numbers show the rate at which the population is affected by knee OA, and suggest that a significant portion of older adults, at least one in twenty, and up to one in three, may be dealing with knee pain, stiffness and related disability.

Despite the increasing use of magnetic resonance imaging (MRI) for knee OA research, radiographs are most commonly used for the clinical assessment of knee OA incidence and progression. Articular features of knee OA such as osteophytes, joint space narrowing (JSN), sclerosis and bony deformity may be observed on a knee radiograph, which is simple and fast to obtain.

Radiographs are also used to assess frontal-plane alignment. This information may be used to identify the risk of knee OA incidence and progression and may be used for treatment planning. The first part of this review will address the measurement of tibiofemoral (TF) frontal-plane alignment. The measurement of knee OA severity and progression from knee radiographs will be discussed in the second part of this review.

Malalignment of the lower extremity (LE) has been identified as one factor associated with knee OA development^[10]. Being bow-legged (varus, genu varum) is the most common frontal-plane malalignment; it leads to increased loading in the medial TF compartment^[11]. Being knock-kneed (valgus, genu valgum) decreases the loading in the medial TF compartment but increases the loading in the lateral TF compartment. Increased loading is associated with an increased risk of OA in that TF compartment. Progression of existing knee OA is highly associated with varus [odds ratio (OR) 2.90 to 10.96, $P < 0.05$] and valgus (OR 3.42 to 10.44, $P < 0.05$) deformities^[11-17]. The risk for progression increases with the degree of deformity^[11,13,14,16,18]. The association of knee OA onset and malalignment is weaker (varus OR 2.1, $P < 0.05$; valgus OR 2.5, $P < 0.05$)^[16,17].

It is important that LE alignment is measured accurately, so that interventions can be prescribed appropriately, and research studies which include LE alignment can be compared to one another. The presence of varus or valgus alignment may suggest the need for early intervention, for example, orthotics, braces or surgical correction (tibial osteotomy)^[16,19]. An accurate measurement of alignment is also essential for proper placement of the implant during knee arthroplasty surgery. Proper placement resulting in restoration of neutral alignment ensures more even load distribution and prevention of premature wear and loosening of the implanted joints^[20-25].

The diagnosis of knee OA is based on symptoms of pain and stiffness, and the presence of OA changes on a knee radiograph. Assessment of the knee by plain radiographs is routinely done to define the presence and severity of knee OA for diagnosis, to monitor progression and to guide treatment decisions^[26-29]. In research studies, radiographic assessments are also used to guide participant eligibility and to stratify participants according to OA severity^[5,30]. Individual characteristics such as biometrics (body mass index, age, etc.), involvement of other joints, malalignment, family history and history of injury are commonly correlated to measures of knee OA severity to investigate risk factors^[30-36]. Studies of potentially disease-modifying OA drugs and other treatments also use knee OA assessments as outcome measures^[37,38].

Grading scales are applied to knee radiographs to rate the severity of OA (Table 1). Current scales vary from poor to excellent in their reliability^[26,39,40], poor to moderate in their sensitivity to change^[41,42] and negligible to moderate in their relationship to other knee OA features (pain, alignment, function)^[43-45]. Consistent use of a reliable, valid and responsive grading scale would

Table 1 Summary of knee osteoarthritis grading scales

Scale type	Ref.	Pros	Cons	Uses
Global	Kellgren and Lawrence ^[67,69]	Widely used Adopted by the World Health Organization (1961) and at the 3 rd International Symposium of Rheumatic Disease (1966) Moderate to excellent reliability	Multiple descriptions of the levels have been published Emphasizes osteophytes Poor sensitivity to change	Epidemiological studies Outcome measure (research) Clinical use
	Ahlbäck ^[65] Galli ^[91]	One version uses a template, placed over a radiograph, to show typical bone contour	Poor reliability Emphasizes joint space narrowing	Epidemiological studies
	Sundaram <i>et al</i> ^[68]		No psychometric testing Defines early OA as osteophytes only	Epidemiological study for knee OA after tibial dome osteotomy
	Brandt <i>et al</i> ^[66]	Good correlation to damage seen at arthroscopy	No reliability testing performed Emphasizes joint space narrowing	Classify participants for research studies
	Satku <i>et al</i> ^[97]	Includes a variety of features of knee OA	No psychometric testing	Used in research to describe OA development after anterior cruciate ligament tears
Composite	Kannus <i>et al</i> ^[96]	Includes many features of knee OA, in a variety of locations in the knee	Very complicated	Used in research to describe OA development after anterior cruciate ligament tears
	McAlindon <i>et al</i> ^[99]	Good reliability Moderate reliability Includes several compartments of the knee	Assesses both knees at once	Research on the association between knee pain, disability, strength and radiographic evidence of knee OA
	Merchant <i>et al</i> ^[98]	Includes several features of knee OA	No psychometric testing	Research on the onset of knee OA after ankle or lower leg injuries Epidemiological studies Part of the Knee Surgery Triage Tool
	Compartmental grading scale for knee OA (CG) Cooke <i>et al</i> ^[100]	Includes several features of knee OA Excellent reliability		
	Osteoarthritis Research Society International atlas Altman <i>et al</i> ^[26] Thomas <i>et al</i> ^[110] Cooper <i>et al</i> ^[105]	Most commonly-used individual OA feature scale Moderate reliability	Often used to assess only joint space narrowing No psychometric testing No psychometric testing	Epidemiological studies Monitor progression of knee OA
Individual	Spector <i>et al</i> ^[30,34,109] Braga <i>et al</i> ^[116] O'Reilly <i>et al</i> ^[117]	Fair to excellent reliability		Epidemiological studies Classify participants for intervention studies
	Scott feature based scoring system Scott <i>et al</i> ^[82]	Scores 8 different OA features Fair to excellent reliability		Epidemiological studies Outcome measure
	Nottingham logically derived line drawing atlas Nagaosa <i>et al</i> ^[107]	Line drawings are meant to avoid problems using radiographs in an atlas Moderate reliability		Epidemiological studies Outcome measure (research)
	Knee images digital analysis Marijnissen <i>et al</i> ^[130] Muraki <i>et al</i> ^[131]	Uses continuous scales Excellent reliability	Only good-quality radiographs can be used	Epidemiological studies
	Knee OA computer-aided diagnosis Oka <i>et al</i> ^[81]	Uses continuous scales Excellent reliability		Epidemiological studies

OA: Osteoarthritis.

ensure relevant longitudinal clinical evaluations and the ability to compare results between research studies.

FRONTAL-PLANE LE ALIGNMENT

Determination of LE alignment using full-length radiographs

The criterion standard measure of frontal-plane LE alignment is the hip-knee-ankle (HKA) angle, also known

as the mechanical axis angle, measured from a full-length LE radiograph^[46-48]. This is the angle subtended by a line drawn from the centre of the femoral head to the center of the knee (femoral mechanical axis) with a line drawn from the center of the knee to the centre of the tibial plafond or ankle talus (tibial mechanical axis) (Figure 1). Varus angles are commonly designated negative and valgus angles positive^[48]. "Normal" alignment in healthy adults is generally considered to be 1° to 1.5° of varus,

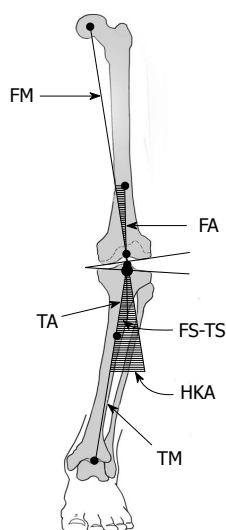


Figure 1 Diagram of a varus knee illustrating the mechanical and anatomic axes and angles. The FS-TS angle is 4° to 6° valgus compared to the HKA angle. (Modified from Cooke and Sled^[46]). FM: Femoral mechanical axis; TM: Tibial mechanical axis; FA: Femoral anatomic axis; TA: Tibial anatomic axis; HKA: Hip-knee-ankle angle (mechanical angle); FS-TS: Femoral shaft-tibial shaft angle (anatomic angle).

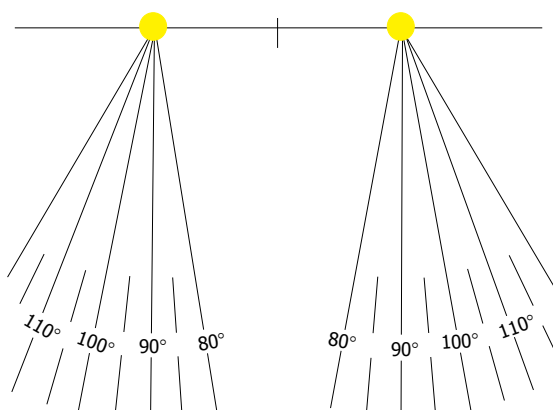


Figure 2 Calibrated template, used to position feet and to reliably measure lower extremity rotation. (Modified from Orthopedic Alignment and Imaging Systems, Inc.)

or -1° to -1.5° ^[49-51].

The points used for determining the HKA angle have varied, especially around the knee^[47,48]. The centre of the femoral head is found by placing a circle template over the femoral head on the radiograph, then marking the centre of this circle. There are several locations which may be used for the points at the knee. Many use a single point, often the centre of the tibial spines^[11,47,49]. Moreland *et al.*^[51] used a single point at the knee that was the average of several measured knee landmarks. Others used the centre of the femoral intercondylar notch as the distal point for the femoral mechanical axis, and the centre of the tibial interspinous groove as the knee point for the tibial mechanical axis^[11,48,52,53]. Using two points at the knee is preferred because it allows for the identification of the femoral and tibial contributions to deformity, and to define the extent of knee subluxation^[48].

(Figure 1). The centre of the talus or tibial plafond at the ankle is determined using a ruler placed on the radiographic image.

LE positioning

Use of a standardized and replicable approach for LE positioning is important for reliable and accurate alignment measurements. Changes in limb rotation, foot position and knee flexion alter the HKA angle^[46,48,54,55]. For example, external rotation has been shown to increase the appearance of varus malalignment^[56]. Some authors use a self-selected stance or the Romberg stance position (with medial borders of feet touching)^[57]. Others use anatomical landmarks based on such features as the patella and the tibial tubercle^[46]. None of these methods account for the variability between individuals with respect to rotation of the femur and tibia, position of the bony landmarks, flexibility of the feet (for example, pes planus leads to internal rotation of the tibia) and the relative length of the hip musculature (for example, a tight piriformis can lead to excessive external rotation of the hip when in a self-selected stance position).

The LE should be positioned in neutral alignment such that the knee flexion angle is directly in the sagittal plane^[46]. This is accomplished by positioning the patient or participant with the heels placed a standard distance apart (for example, 9 cm between the centres of the heels) and adjusting the rotation of the legs until the knee flexion axis, observed as the knee is flexed and extended, lies directly in the frontal plane. Foot position may be recorded from a template marked in degrees of internal and external rotation (Figure 2). Use of a template allows for reliable repositioning at subsequent assessments.

Determination of LE alignment using knee radiographs

Full-length LE radiographs are not always used. They require specialized equipment and technician training, are more costly and expose the patient to higher doses of radiation, particularly at the pelvis. As a result, knee radiographs are often used to estimate alignment and the HKA angle^[17,58]. The angle calculated on a knee radiograph is called the femoral shaft-tibial shaft (FS-TS) angle, or the anatomic axis angle^[47]. This is the angle subtended by a line drawn from the centre of the femoral shaft proximal to the knee (femoral anatomic axis) and a line drawn from the centre of the tibial shaft distal to the knee (tibial anatomic axis). The femoral and tibial shaft points are generally measured 10 cm from the knee joint, to accommodate the portion of the long-bone shafts commonly seen on a knee radiograph^[47,51]. The tibial anatomic axis is similar to the tibial mechanical axis (Figure 1). Similar to the definition of the HKA angle, one or two points at the knee may be chosen to determine the anatomic axes^[59]. The tibial interspinous point is frequently used as a single point reference at the knee^[47,49].

There are concerns that the FS-TS angle does not



Type of scale	Representative scale					
Global scale	Kellgren-lawrence scale ^[67]	Grade 2				
Composite scale	Compartmental grading scale for knee OA ^[100]	Joint space narrowing 1	Femoral osteophytes 2	Tibial erosion 0	Subluxation 0	Total score 3
Individual OA feature scale	Osteoarthritis Research Society International atlas ^[26]	Joint space narrowing 2				

Figure 3 Knee radiograph assessed with representative global, composite and individual feature osteoarthritis grading scales. The knee is in neutral rotation and slight varus alignment. The medial tibiofemoral compartment is most-affected. OA: Osteoarthritis.

produce an accurate estimate of the HKA angle^[53,60]. The FS-TS angle is offset towards valgus compared to the HKA angle by 4° to 6° for healthy individuals and 1.5° to 7° in individuals with knee OA^[47,49,52,59,61], with a low to high correlation between the two measurements, $r = 0.34$ to 0.88 , $P < 0.005$ in participants with knee OA^[47,58,59,61,62]. The offset between the HKA and FS-TS angles is significantly greater in individuals with knee OA compared to healthy controls (t -test, $P < 0.001$)^[52]. Two factors influence the relationship between the FS-TS and HKA angles. The first is the nature and severity of varus or valgus deformity^[52,63,64]. The second factor is the length of the femoral and tibial shafts used when calculating the FS-TS angle^[49,51]. In two studies, the FS-TS angle measured with a short femoral anatomic axis was 4.0° to 4.2° more valgus than the HKA angle, but with a long femoral anatomic axis the difference was 5.8° and when using the entire femoral shaft the difference was 4.9° to 5.9°^[49,51]. In another study, the FS-TS angle measured with a short femoral anatomic axis for individuals with moderate to severe varus alignment, was an average of 7.4° more valgus than the HKA angle while for individuals with moderate to severe valgus alignment, the FS-TS angle was an average of 2.3° more valgus^[60]. These studies illustrate how the shape of the femoral shaft impacts the relationship between the HKA and FS-TS angles. In order of importance, lateral bowing of the femoral shaft, tibial bowing and the angle between the tibial plateau and the tibial shaft all influence the relationship between these angles^[52]. The FS-TS angle also shows more variability than the HKA angle^[49,60]. The variability is increased when FS-TS angle measurements are calculated using a shorter amount of the femoral and tibial shaft lengths. Therefore it is recommended that the HKA angle, measured from a full-length LE radiograph, should be used to ensure an accurate measurement of LE alignment^[62].

Summary and recommendations

Because frontal-plane alignment is an important risk factor for the onset and especially the progression of knee OA, it is regularly assessed for research and clinical purposes. The "gold standard" evaluation of frontal-plane

alignment is the HKA angle measured from a full-length LE radiograph; however knee radiographs are often used to calculate the FS-TS angle, used to estimate the HKA angle. There is an offset between these angles of 4° to 6°, but this offset varies depending on the type and degree of malalignment of the individual, and the method used to calculate the FS-TS angle. For the above reasons, we strongly recommend that the HKA angle be used for clinical and research purposes whenever accurate information on alignment is needed. Attention to careful positioning of the limb with the knee flexion axis directly in the frontal plane will reduce rotational errors.

GRADING THE SEVERITY OF TF OA

Global scales

Global scales are ordinal scales that have specific descriptions for each grade^[65-68]. Each level describes one or more features of OA that must be met for that particular level to be ascribed to a radiographic image. Global scales require an individual's particular presentation of OA to "fit" all of the criteria for a given level of the scale. The earliest and by far the most commonly-used global scale is the Kellgren-Lawrence (KL) grading scale^[67] (Figure 3). Others include those developed by Ahlback^[65], Sundaram *et al.*^[68] and Brandt *et al.*^[66].

KL Grading scale

The KL scale, first described in 1957, gives an overall score of OA severity from zero to four^[67,69]. Their scale was applied widely for any joints affected by OA and served as an important screening tool in epidemiological studies. In their initial publication the authors considered the following features evidence of OA: osteophytes on the joint margins or the tibial spines; periarticular ossicles; narrowing of joint space associated with sclerosis of subchondral bone; small pseudocystic areas, usually in the subchondral bone; and altered shape of the bone ends^[67]. Both TF compartments of the knee were assessed using a standard set of radiographs for reference. Considering all features of OA, a grade of zero (no OA), one (doubtful OA), two (minimal OA), three

(moderate OA), or four (severe OA) was given. Inter-rater reliability was reported (Pearson's $r = 0.83$), but the authors acknowledged that one of the two readers consistently assessed the radiographs as showing more severe OA, illustrating the difficulty of using Pearson's correlation coefficients to adequately assess reliability. Intra-rater reliability was the same (Pearson's $r = 0.83$).

In 1963 an atlas (republished in 2005^[70]) was produced by Kellgren *et al.*^[69] which included written descriptions of each grade: Grade 1: doubtful narrowing of joint space and possible osteophytic lipping; Grade 2: definite osteophytes and possible narrowing of joint space; Grade 3: moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends; and Grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

Later, in a 1977 publication, Lawrence^[71] described the grades as such: Grade 1: minute osteophyte of doubtful significance the only feature; Grade 2: definite osteophyte, joint space unimpaired; Grade 3: moderate diminution of joint space; and Grade 4: joint space greatly impaired, subchondral sclerosis.

The KL scale was adopted by the World Health Organization in 1961 and has remained the most prominent scale for screening OA and grading disease severity^[72]. Its use as a standard evaluation for radiographic knee OA was reconfirmed at the third International Symposium on Rheumatic Disease in New York in 1966^[73]. OA incidence is defined by a KL grade of two^[67].

Despite its widespread use, there are continuing concerns about the KL scale^[72,74,75]. As evident in the above descriptions, osteophytes must be present for a KL grade greater than zero to be given. The radiographic presentations of knee OA vary. Some show JSN but lack osteophytes; they would be assessed as grade zero on the KL scale^[66]. For the Framingham OA Study, Felson *et al.*^[76] modified the KL scale by adding a second grade two category for radiographs showing JSN without osteophytes. None of their participants actually fit this new category, highlighting the difficulties of using the KL scale for assessment of knee OA^[76].

A second important issue is that there are multiple descriptions of the KL grades which create variability in their interpretation^[40,74,77,78]. This variability may allow individual research participants to be misidentified as having, or not having, OA, and creates difficulty in comparing research studies^[74,79].

Several authors have assessed the intra- and inter-rater reliability of the KL scale^[39,40,80-83]. Intra-rater reliability [Cohen's weighted kappa 0.50 to 0.88; Cohen's kappa 0.84 to 0.99; Spearman's correlation coefficient 0.89; Intraclass correlation coefficient (ICC) 0.85 to 0.93] and inter-rater reliability (Cohen's weighted kappa 0.56 to 0.80; Cohen's kappa 0.59 to 0.76; Spearman's correlation coefficient 0.85; ICC 0.68 to 0.84) generally fall in the moderate to excellent range^[39,40,80-85].

A lack of sensitivity to change using the KL scale has been reported^[41], and although it was not created to

follow change in OA severity over time, but rather to be used as a screening tool for epidemiological studies, it is frequently used for this purpose^[74,86]. There are only five grades, and the scale is not linear. Differentiating between grades zero and one, and one and two can be especially difficult^[74,79,87]. To illustrate this point, the border between "possible osteophytic lipping (grade one)" and "definite osteophytes (grade two)" is very subjective and the "narrowing of joint" in the grade three description can include joints with almost no joint narrowing to joints with almost no joint space left^[74]. In order to increase its sensitivity to change, Felson *et al.*^[74] proposed two changes to the KL scale: grade two to include the requirement of both osteophytes and JSN, and a new grade, two/osteophyte, which describes a knee with osteophytes but no JSN. They do admit that further changes, while addressing some of the problems, might also add to the confusion created because of different definitions of the scale.

KL grades are moderately to poorly correlated with cartilage lesions (Spearman's correlation $r = 0.55$, $P < 0.01$) and cartilage volume (Pearson's correlation $r = -0.30$ to -0.49 depending on location, $P < 0.01$) as measured from MRI^[44,88]. Correlations of KL grade to cartilage damage seen at arthroscopy are similar to those measured from MRI (Pearson's correlation $r = 0.49$, CI: 0.38 to 0.59), with a higher association for the medial compartment^[89,90]. These results suggest that the KL scale, with its emphasis on osteophytes, has significant limitations for the grading of knee OA severity.

Other Global scales

Global scales other than the KL scale tend to focus on one feature of knee OA. Ahlback^[65] published descriptions of six stages of knee OA based on the combination of JSN and bone attrition only^[65,91]. Stages zero to two describe JSN only, with progressive bone attrition described in stages three to five. Ahlback and Rydberg^[92] described the stages in a further publication with altered wording. Thirty five years after the initial description, two studies showed that intra-rater (Cohen's weighted kappa 0.17 to 0.35; Cohen's kappa 0.15 to 0.76) and inter-rater reliability (Cohen's weighted kappa 0.18 to 0.45; Cohen's kappa -0.01 to 0.21) of the Ahlback scale were variable but tended to be poor^[91,93]. Dieppe *et al.*^[94] subsequently improved the reliability by using a template showing typical bone contour, to be laid over a knee radiograph.

Sundaram *et al.*^[68] created a seven-point radiographic scale to assess the entire TF joint for knee OA after tibial dome osteotomy. Their grading system was very similar to the KL scale in that osteophytes were considered the initial presentation of the disease, with JSN being identified at grade three. Psychometric testing was not performed on this scale.

Finally, Brandt *et al.*^[66] created a JSN-weighted scale that they contrasted to the KL scale. Secondary features included subchondral sclerosis, geodes and osteophytes. Brandt scale scores were compared to cartilage damage

seen at arthroscopy; the Pearson's correlation coefficient was $r = 0.56$ (CI: 0.46 to 0.65)^[89]. This scale has been used to classify research participants for orthopaedic surgical outcomes research^[95].

Composite scales

Composite scales score several features of OA individually, then add them to create a total score^[96-100]. Felson *et al.*^[101] studied several radiographic features of OA and found that a combination of one or two features (osteophytes alone, or JSN and a bony feature such as a cyst, sclerosis or small osteophyte), each scored individually, correlated best with clinical symptoms of pain and crepitus, lending support to the usefulness of composite scales. Altman *et al.*^[26] also discovered that a sum of the individual scores for JSN, bone spurs, sclerosis, attrition and alignment was more sensitive to change over time than each individual score alone. Unlike global scales, composite scales are able to follow the course of several separate OA features, and can respond to change in individuals with a variety of radiographic presentations.

Two scales were designed to follow the development of knee OA in individuals with anterior cruciate ligament tears^[96,97]. Satku *et al.*^[97] scale grades osteophytes, peaking of the tibial spine, JSN and subchondral sclerosis or cysts in several locations in the knee, each on a scale of zero to one or two, to give a total score of 14. Kannus *et al.*^[96] created a complicated scale that measured osteophytes, subchondral sclerosis, flattening of the femoral condyles, subchondral cysts, ligament calcification, JSN and angular deformity at a variety of locations within the knee. Individual scores were out of three to 12, for a total score of 100^[96]. Lower scores denoted more severe disease. It was reported to have good to excellent intra-rater reliability (Cohen's kappa 0.70) and inter-rater reliability (Pearson's correlation 0.94; Spearman's correlation 0.90)^[102].

McAlindon *et al.*^[99] created a scale to investigate the association between knee pain, disability, knee strength and radiographic score. They scored JSN, osteophytes and sclerosis in several compartments of both knees to sum to a possible score of 30^[99]. Intra-rater reliability was moderate (Cohen's kappa of 0.57)^[99]. Another scale was created by Merchant *et al.*^[98] to follow individuals after ankle or lower leg injuries to investigate the onset of knee OA changes. A "normal" joint was given a score of ten and points were subtracted for osteophytes, JSN, degenerative cysts and subchondral sclerosis observed in both TF compartments^[98]. Psychometric testing was not reported.

Compartmental Grading scale for knee OA

The compartmental grading scale for knee OA (CG) was created in 1999 by Derek *et al.*^[100], who wished to create a scale that was correlated with changes in alignment and deformity caused by OA. The CG scores femoral osteophytes (out of three), JSN (out of three), tibial erosion (out of four) and subluxation (out of three) for

a total possible score of 13 (Figure 3). Only the most-affected TF compartment is scored. Tibial osteophytes are excluded in order to prevent over-weighting the scale with osteophytes and because tibial osteophytes frequently decrease in size as OA worsens and the knee subluxes. Tibial erosion is included because it is common and may contribute to joint instability as it progresses. Similarly subluxation, a feature unique to the CG, is incorporated because it also contributes to joint instability and disability. The CG is highly correlated to frontal-plane alignment (Pearson's correlation $r = 0.77$, $P < 0.001$). Sclerosis is not included because bone density is highly variable between people and is affected by obesity and variations in image quality. Equal weight is given to osteophytes, JSN and subluxation, and slightly more weight to tibial erosion. This approach was intended to reduce the emphasis of one feature (*i.e.*, osteophytes) over another and provide for a balanced opportunity for sensitivity to change in those with different presentations of OA.

Initial results showed an inter-rater reliability (Cohen's weighted kappa) of 0.92 using anteroposterior full-extension radiographs^[100]. The CG has been used for research^[103] and is a component of the Knee Surgery Triage tool, which incorporates disability evaluation and radiographic grading to guide clinicians in surgical decision-making^[104].

Individual OA Feature Grading scales

Apart from the KL scale, the most common method to assess knee OA severity is to assign grades to individual features of OA such as osteophytes, JSN and sclerosis^[26,82,105-110]. An atlas is used to guide interpretation of each feature. Even though each individual feature only describes one aspect of OA, individual feature scales are often used to monitor change over time. The most-often used individual OA feature scale was described by Altman *et al.*^[26].

OA Research Society International Atlas

The most commonly-used individual OA feature scale is the OA Research Society International (OARSI) atlas, which was created by Altman *et al.*^[26] (the San Francisco Conference Group) in 1987 (Figure 3). For the knee, five OA features were assessed [JSN, spur formation, loss of bone stock (attrition), subchondral bony sclerosis and frontal-plane alignment] and each scored from zero to three. Medial and lateral TF compartments were assessed separately (except for alignment), giving nine individual scores. A total score was not calculated. Initial intra-rater reliability scores (measured with ICCs) for each feature varied from 0.40 to 1.0, although it is important to note that only three radiographs were used for this analysis^[26]. Inter-rater reliability scores (measured with ICCs) were slightly lower, varying between 0.32 and 0.86, with JSN having the best reliability. In all cases medial compartment scores were more reliable than lateral compartment scores. JSN and bone spurs were

most sensitive to change over time.

In order to standardize the interpretation of radiographs, OARSI published another radiographic atlas in 1995 showing the spectrum of severity of three osteoarthritic features (JSN, marginal osteophytes and subchondral sclerosis), each scored from zero to three^[111]. An updated atlas, available electronically, was published in 2007, emphasizing OA changes of medial and lateral femoral and tibial plateau osteophytes, medial and lateral JSN, medial tibial attrition, medial tibial sclerosis and lateral femoral sclerosis^[112]. A modified version of the OARSI JSN scale was also created by Felson *et al.*^[13], whereby if JSN had increased over time, but not enough to warrant the next grade on the zero to three scale, a one-half grade was assigned. This modification enhanced sensitivity to change^[13].

Grades assessed using the OARSI atlas have moderate to good reliability, with JSN more reliable than osteophytes^[107]. Intra-rater reliability (Cohen's kappa 0.57 to 0.91 for osteophytes, 0.77 to 0.83 for sclerosis and 0.68 to 0.80 or ICC 0.79 to 0.95 for JSN) is somewhat higher than inter-rater reliability (Cohen's kappa 0.33 to 0.88 for osteophytes, 0.77 for sclerosis, and 0.48 to 0.70 or ICC 0.66 to 0.87 for JSN)^[39,78,84,107,113,114].

Comparison of the OARSI atlas to findings from arthroscopy has been performed^[115]. Osteophytes show moderate sensitivity (49% to 67%) compared to arthroscopy however the other OA features show fair to poor sensitivity (3% to 46%). Specificity of all features is good to excellent (73% to 100%) relative to arthroscopic findings.

Other Individual OA Feature Scales

Thomas *et al.*^[110] and Cooper *et al.*^[105] created ordinal scales for individual features of knee OA, similar to the OARSI scale. Thomas *et al.*^[110] scored osteophytes, JSN, sclerosis and cysts, each on a scale of zero to three. Cooper *et al.*^[105] scored these same four features, plus abnormality of the bony contour, each on a scale of zero to two. Neither scale has been used extensively. More extensive use was made of an atlas produced by Spector *et al.*^[30,34,109,116,117] which scored TF osteophytes, sclerosis, JSN and cortical collapse, each on a scale of zero to one or three. Intra-rater reliability (Cohen's kappa 0.41 to 0.96) and inter-rater reliability (Cohen's kappa 0.30 to 0.90) for osteophytes and JSN scored according to this scale ranged from fair to excellent^[40,118].

Scott *et al.*^[82] published an atlas similar to the OARSI atlas which scored eight individual features of knee OA (medial and lateral osteophytes, medial and lateral JSN, medial and lateral subchondral sclerosis, osteophytes of the tibial spines and chondrocalcinosis) each on a scale from zero to one or three. Both medial and lateral TF compartments were included. This atlas was created for the Baltimore Longitudinal Study of Aging and is now referred to as the Scott Feature Based Scoring System^[119]. It has been used in epidemiological studies and as an outcome measure^[120-122]. Intra-rater reliability

(ICC 0.80 to 0.89) and inter-rater reliability (ICC 0.40 to 0.87) have been tested for osteophytes, JSN and sclerosis scored with this system and ranged from fair to excellent^[82,85].

The nottingham logically derived line drawing atlas (LDLDA) consisted of line drawings rather than photographs of radiographs^[107]. JSN and osteophytes were scored on a scale of zero to three. The authors felt that line drawings could overcome some issues with the OARSI atlas^[26], such as differences in magnification between radiographs and more than one OA feature shown on a particular radiograph. The LDLDA has been used to describe the participant sample in epidemiological studies^[123], and as an outcome measure^[124]. Also tested were variations of the scoring system described in the LDLDA, using grading scores from minus one to three, four and five^[125], and from minus three to three, minus four to four, and minus five to five^[126]. The authors expected that sensitivity to change might be enhanced with some of these variations, but did not actually test this hypothesis^[125,126]. Finally, one of the modified scales was tested using an acetate overlay placed directly on the radiograph, to aid in determining the grades^[127]. Reliability for each of these modified scales was as good as or better than the original scale^[125-127].

Digital evaluations

Two scales used computer software to quantitatively assess knee radiographs for OA changes^[81,128]. The knee images digital analysis was an interactive software tool created for the cohort hip and cohort knee study^[128,129]. Joint space width, osteophyte area, subchondral bone density, joint angle and tibial eminence height were measured using continuous scales^[128,129]. While intra- and inter-rater reliability were excellent, only good-quality radiographs could be fully analyzed by the software, and careful participant positioning was particularly important^[129,130].

Knee OA computer-aided diagnosis was a fully automated diagnostic system that measured joint space area, minimum joint space width, osteophyte area and TF angle on continuous scales^[81]. It was created for the research on OA against disability (ROAD) study^[81,131,132]. The intra-rater reliability (ICC) for all parameters was 1.0^[81]. Sensitivity to change has not been investigated, but the authors claimed that quantitative radiograph analysis could be as sensitive as quantitative MRI.

Summary and recommendations

The accurate and reliable assessment of knee OA severity as seen on a radiograph is important for diagnosis and monitoring of disease progression. Since 1957, many global, composite and individual feature scales have been developed towards these goals. Global scales, while commonly used, may not be as valid or sensitive to change as other types of scales. Composite grading scales have the advantage that they can be responsive to different presentations of knee OA. Individual OA

feature scales are often used to monitor the progression of knee OA, but only respond to changes in a particular OA feature.

The consistent use of one scale is useful to enable comparison of participant groups in research studies and the identification of risk factors. The KL grading scale has been most-commonly used in epidemiological and outcomes research to group and describe participants; however the KL scale has not always been applied consistently, limiting comparison between studies. The OARSI JSN scale is also commonly used, especially to monitor change in JSN, which is used as a proxy for worsening knee OA. However, the selective use of individual feature scales does not allow a variety of presentations of knee OA to be described and monitored. To overcome the above shortcomings, the use of a composite scale is suggested. Several individual features of OA are included, but a single total score gives an indication of the overall severity of arthritic change in the joint.

Many of the existing scales have not had adequate psychometric testing. Reliability, validity (concurrent, content) and sensitivity to change (responsiveness) need to be documented for a scale to be used confidently. However, in recent work, the authors, in collaboration with investigators from the multicenter OA study, evaluated the psychometric properties of the KL, OARSI and CG scales using MRI as a gold standard^[133] (Unpublished observations). The findings indicate comparable reliability, validity and sensitivity to change. However the CG scale, which is not subject to the ceiling effects exhibited by the other two scales, suggested responsiveness to more severe joint changes. Further studies are required to establish this. Researchers using scales which do not have adequate testing should perform and report appropriate psychometric assessments as part of their study. In conclusion, the variation in grading scales indicates that a single method is not yet established that will meet the requirements of all needs. Careful consideration of the different grading scales is recommended before one is chosen for a clinical or research application.

The use of grading scales for clinical use is not widespread. Radiologists practicing in the clinical realm typically describe knee OA changes seen on radiographs and make a conclusion about the presence or absence and severity of disease, but do not use a specific grading scale. This practice can reduce the objectiveness of radiologists' observations and make it difficult to detect change over time and compare reports by different radiologists. We recommend that grading scales be used to ensure consistency in interpreting and reporting radiographic knee OA for clinical use.

REFERENCES

- 1 **Loeser RF**, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* 2012; **64**: 1697-1707 [PMID: 22392533 DOI: 10.1002/art.34453]
- 2 **Salaffi F**, De Angelis R, Grassi W. Prevalence of musculoskeletal

- conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. *Clin Exp Rheumatol* 2005; **23**: 819-828 [PMID: 16396700]
- 3 **Guillemin F**, Rat AC, Mazieres B, Pouchot J, Fautrel B, Euller-Ziegler L, Fardellone P, Morvan J, Roux CH, Verrouil E, Saraux A, Coste J. Prevalence of symptomatic hip and knee osteoarthritis: a two-phase population-based survey. *Osteoarthritis Cartilage* 2011; **19**: 1314-1322 [PMID: 21875676 DOI: 10.1016/j.joca.2011.08.004]
- 4 **Andrianakos AA**, Kontelis LK, Karamitsos DG, Aslanidis SI, Georgountzos AI, Kaziolas GO, Pantelidou KV, Vafiadou EV, Dantis PC. Prevalence of symptomatic knee, hand, and hip osteoarthritis in Greece. The ESORDIG study. *J Rheumatol* 2006; **33**: 2507-2513 [PMID: 17143985]
- 5 **Felson DT**, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1987; **30**: 914-918 [PMID: 3632732 DOI: 10.1002/art.1780300811]
- 6 **Jordan JM**, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, Fang F, Schwartz TA, Abbate LM, Callahan LF, Kalsbeek WD, Hochberg MC. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *J Rheumatol* 2007; **34**: 172-180 [PMID: 17216685]
- 7 **Jiang L**, Rong J, Zhang Q, Hu F, Zhang S, Li X, Zhao Y, Tao T. Prevalence and associated factors of knee osteoarthritis in a community-based population in Heilongjiang, Northeast China. *Rheumatol Int* 2012; **32**: 1189-1195 [PMID: 21253732 DOI: 10.1007/s00296-010-1773-y]
- 8 **Muraki S**, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, Saika A, Suzuki T, Yoshida H, Ishibashi H, Yamamoto S, Nakamura K, Kawaguchi H, Yoshimura N. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. *Osteoarthritis Cartilage* 2009; **17**: 1137-1143 [PMID: 19410032 DOI: 10.1016/j.joca.2009.04.005]
- 9 **Cho HJ**, Chang CB, Kim KW, Park JH, Yoo JH, Koh IJ, Kim TK. Gender and prevalence of knee osteoarthritis types in elderly Koreans. *J Arthroplasty* 2011; **26**: 994-999 [PMID: 21414750 DOI: 10.1016/j.arth.2011.01.007]
- 10 **Tufan A**, Meulenbelt I, Bijsterbosch J, Kroon HM, Bierma-Zeinstra SM, Nelissen RG, Kloppenburg M. Familial influence on tibiofemoral alignment. *Ann Rheum Dis* 2010; **69**: 542-545 [PMID: 19351626 DOI: 10.1136/ard.2008.097873]
- 11 **Sharma L**, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA* 2001; **286**: 188-195 [PMID: 11448282 DOI: 10.1001/jama.286.2.188]
- 12 **Sharma L**, Song J, Dunlop D, Felson D, Lewis CE, Segal N, Torner J, Cooke TD, Hietpas J, Lynch J, Nevitt M. Varus and valgus alignment and incident and progressive knee osteoarthritis. *Ann Rheum Dis* 2010; **69**: 1940-1945 [PMID: 20511608 DOI: 10.1136/ard.2010.129742]
- 13 **Felson DT**, Nevitt MC, Yang M, Clancy M, Niu J, Torner JC, Lewis CE, Aliabadi P, Sack B, McCulloch C, Zhang Y. A new approach yields high rates of radiographic progression in knee osteoarthritis. *J Rheumatol* 2008; **35**: 2047-2054 [PMID: 18793000]
- 14 **Cerejo R**, Dunlop DD, Cahue S, Channin D, Song J, Sharma L. The influence of alignment on risk of knee osteoarthritis progression according to baseline stage of disease. *Arthritis Rheum* 2002; **46**: 2632-2636 [PMID: 12384921 DOI: 10.1002/art.10530]
- 15 **Chapple CM**, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. *Arthritis Care Res (Hoboken)* 2011; **63**: 1115-1125 [PMID: 21560257 DOI: 10.1002/acr.20492]
- 16 **Felson DT**, Niu J, Gross KD, Englund M, Sharma L, Cooke TD, Guermazi A, Roemer FW, Segal N, Goggins JM, Lewis CE, Eaton C, Nevitt MC. Valgus malalignment is a risk factor for lateral knee osteoarthritis incidence and progression: findings from the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative.

- Arthritis Rheum* 2013; **65**: 355-362 [PMID: 23203672 DOI: 10.1002/art.37726]
- 17 **Brouwer GM**, van Tol AW, Bergink AP, Belo JN, Bernsen RM, Reijman M, Pols HA, Bierma-Zeinstra SM. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. *Arthritis Rheum* 2007; **56**: 1204-1211 [PMID: 17393449 DOI: 10.1002/art.22515]
- 18 **Cicuttini F**, Wluka A, Hankin J, Wang Y. Longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. *Rheumatology* (Oxford) 2004; **43**: 321-324 [PMID: 14963201 DOI: 10.1093/rheumatology/keh017]
- 19 **Nourbakhsh M**, Motififar M, Shemshaki H, Etemadifar Mr, Zarezaade A, Farajzadegan Z, Mazoochian F. Efficacy of tibial proximal osteotomy in correction of lower limb alignment indexes in patients with osteoarthritis in medial compartment of knee. *Med Arh* 2012; **66**: 58-60 [PMID: 22482346 DOI: 10.5455/medarh.2012.66.58-60]
- 20 **Werner FW**, Ayers DC, Maletsky LP, Rullkoetter PJ. The effect of valgus/varus malalignment on load distribution in total knee replacements. *J Biomech* 2005; **38**: 349-355 [PMID: 15598463 DOI: 10.1016/j.jbiomech.2004.02.024]
- 21 **Ritter MA**, Faris PM, Keating EM, Meding JB. Postoperative alignment of total knee replacement. Its effect on survival. *Clin Orthop Relat Res* 1994; **299**: 153-156 [PMID: 8119010]
- 22 **Koeck FX**, Beckmann J, Luring C, Rath B, Grifka J, Basad E. Evaluation of implant position and knee alignment after patient-specific unicompartmental knee arthroplasty. *Knee* 2011; **18**: 294-299 [PMID: 20688521 DOI: 10.1016/j.knee.2010.06.008]
- 23 **Zhang GQ**, Chen JY, Chai W, Liu M, Wang Y. Comparison between computer-assisted-navigation and conventional total knee arthroplasties in patients undergoing simultaneous bilateral procedures: a randomized clinical trial. *J Bone Joint Surg Am* 2011; **93**: 1190-1196 [PMID: 21776571 DOI: 10.2106/JBJS.I.01778]
- 24 NIH Consensus Statement on total knee replacement December 8-10, 2003. *J Bone Joint Surg Am* 2004; **86-A**: 1328-1335 [PMID: 15173310]
- 25 **Wong J**, Steklov N, Patil S, Flores-Hernandez C, Kester M, Colwell CW, D'Lima DD. Predicting the effect of tray malalignment on risk for bone damage and implant subsidence after total knee arthroplasty. *J Orthop Res* 2011; **29**: 347-353 [PMID: 20882595 DOI: 10.1002/jor.21221]
- 26 **Altman RD**, Fries JF, Bloch DA, Carstens J, Cooke TD, Genant H, Gofton P, Groth H, McShane DJ, Murphy WA. Radiographic assessment of progression in osteoarthritis. *Arthritis Rheum* 1987; **30**: 1214-1225 [PMID: 3689459 DOI: 10.1002/art.1780301103]
- 27 **Cicuttini FM**, Jones G, Forbes A, Wluka AE. Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study. *Ann Rheum Dis* 2004; **63**: 1124-1127 [PMID: 15115714 DOI: 10.1136/ard.2004.021253]
- 28 **Fransen M**, McConnell S. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2008; **4**: CD004376 [PMID: 18843657 DOI: 10.1002/14651858.CD004376.pub2]
- 29 **Guermazi A**, Hunter DJ, Roemer FW. Plain radiography and magnetic resonance imaging diagnostics in osteoarthritis: validated staging and scoring. *J Bone Joint Surg Am* 2009; **91** Suppl 1: 54-62 [PMID: 19182026 DOI: 10.2106/JBJS.H.01385]
- 30 **Spector TD**, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. *Ann Rheum Dis* 1994; **53**: 565-568 [PMID: 7979593 DOI: 10.1136/ard.53.9.565]
- 31 **Hashikawa T**, Osaki M, Ye Z, Tomita M, Abe Y, Honda S, Takamura N, Shindo H, Aoyagi K. Factors associated with radiographic osteoarthritis of the knee among community-dwelling Japanese women: the Hizen-Oshima Study. *J Orthop Sci* 2011; **16**: 51-55 [PMID: 21293895 DOI: 10.1007/s00776-010-0013-3]
- 32 **Hunter DJ**, Niu J, Felson DT, Harvey WF, Gross KD, McCree P, Aliabadi P, Sack B, Zhang Y. Knee alignment does not predict incident osteoarthritis: the Framingham osteoarthritis study. *Arthritis Rheum* 2007; **56**: 1212-1218 [PMID: 17393450 DOI: 10.1002/art.22508]
- 33 **Li RT**, Lorenz S, Xu Y, Harner CD, Fu FH, Irrgang JJ. Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. *Am J Sports Med* 2011; **39**: 2595-2603 [PMID: 22021585 DOI: 10.1177/0363546511424720]
- 34 **Spector TD**, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. *BMJ* 1996; **312**: 940-943 [PMID: 8616305 DOI: 10.1136/bmj.312.7036.940]
- 35 **Srikanth VK**, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* 2005; **13**: 769-781 [PMID: 15978850 DOI: 10.1016/j.joca.2005.04.014]
- 36 **Vrezas I**, Elsner G, Bolm-Audorff U, Abolmaali N, Seidler A. Case-control study of knee osteoarthritis and lifestyle factors considering their interaction with physical workload. *Int Arch Occup Environ Health* 2010; **83**: 291-300 [PMID: 19921240 DOI: 10.1007/s00420-009-0486-6]
- 37 **Abadie E**, Ethgen D, Avouac B, Bouvenot G, Branco J, Bruyere O, Calvo G, Devogelaer JP, Dreiser RL, Herrero-Beaumont G, Kahan A, Kreutz G, Laslop A, Lemmel EM, Nuki G, Van De Putte L, Vanhaelst L, Reginster JY. Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 2004; **12**: 263-268 [PMID: 15023377 DOI: 10.1016/j.joca.2004.01.006]
- 38 **Mazzuca SA**, Brandt KD. Is knee radiography useful for studying the efficacy of a disease-modifying osteoarthritis drug in humans? *Rheum Dis Clin North Am* 2003; **29**: 819-830 [PMID: 14603585 DOI: 10.1016/S0889-857X(03)00055-3]
- 39 **Gossec L**, Jordan JM, Mazzuca SA, Lam MA, Suarez-Almazor ME, Renner JB, Lopez-Olivo MA, Hawker G, Dougados M, Maillefer JF. Comparative evaluation of three semi-quantitative radiographic grading techniques for knee osteoarthritis in terms of validity and reproducibility in 1759 X-rays: report of the OARSI-OMERACT task force. *Osteoarthritis Cartilage* 2008; **16**: 742-748 [PMID: 18417373 DOI: 10.1016/j.joca.2008.02.021]
- 40 **Spector TD**, Hart DJ, Byrne J, Harris PA, Dacre JE, Doyle DV. Definition of osteoarthritis of the knee for epidemiological studies. *Ann Rheum Dis* 1993; **52**: 790-794 [PMID: 8250610 DOI: 10.1136/ard.52.11.790]
- 41 **Amin S**, LaValley MP, Guermazi A, Grigoryan M, Hunter DJ, Clancy M, Niu J, Gale DR, Felson DT. The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. *Arthritis Rheum* 2005; **52**: 3152-3159 [PMID: 16200595 DOI: 10.1002/art.21296]
- 42 **Emrani PS**, Katz JN, Kessler CL, Reichmann WM, Wright EA, McAlindon TE, Losina E. Joint space narrowing and Kellgren-Lawrence progression in knee osteoarthritis: an analytic literature synthesis. *Osteoarthritis Cartilage* 2008; **16**: 873-882 [PMID: 18280757 DOI: 10.1016/j.joca.2007.12.004]
- 43 **Dieppe PA**, Cushnaghan J, Shepstone L. The Bristol 'OA500' study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. *Osteoarthritis Cartilage* 1997; **5**: 87-97 [PMID: 9135820 DOI: 10.1016/S1063-4584(97)80002-7]
- 44 **Link TM**, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, Majumdar S. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* 2003; **226**: 373-381 [PMID: 12563128 DOI: 10.1148/radiol.2262012190]
- 45 **Sanghi D**, Avasthi S, Mishra A, Singh A, Agarwal S, Srivastava RN. Is radiology a determinant of pain, stiffness, and functional disability in knee osteoarthritis? A cross-sectional study. *J Orthop Sci* 2011; **16**: 719-725 [PMID: 21874334 DOI: 10.1007/s00776-011-0147-y]
- 46 **Cooke TD**, Sled EA. Optimizing limb position for measuring knee anatomical axis alignment from standing knee radiographs. *J Rheumatol* 2009; **36**: 472-477 [PMID: 19286859 DOI: 10.3899/jrheum.080732]
- 47 **Kraus VB**, Vail TP, Worrell T, McDaniel G. A comparative assessment of alignment angle of the knee by radiographic

- and physical examination methods. *Arthritis Rheum* 2005; **52**: 1730-1735 [PMID: 15934069 DOI: 10.1002/art.21100]
- 48 **Cooke TD**, Sled EA, Scudamore RA. Frontal plane knee alignment: a call for standardized measurement. *J Rheumatol* 2007; **34**: 1796-1801 [PMID: 17787049]
- 49 **Hsu RW**, Himeno S, Coventry MB, Chao EY. Normal axial alignment of the lower extremity and load-bearing distribution at the knee. *Clin Orthop Relat Res* 1990; **255**: 215-227 [PMID: 2347155]
- 50 **Cooke D**, Scudamore A, Li J, Wyss U, Bryant T, Costigan P. Axial lower-limb alignment: comparison of knee geometry in normal volunteers and osteoarthritis patients. *Osteoarthritis Cartilage* 1997; **5**: 39-47 [PMID: 9010877 DOI: 10.1016/S1063-4584(97)80030-1]
- 51 **Moreland JR**, Bassett LW, Harker GJ. Radiographic analysis of the axial alignment of the lower extremity. *J Bone Joint Surg Am* 1987; **69**: 745-749 [PMID: 3597474]
- 52 **Chang CB**, Choi JY, Koh IJ, Seo ES, Seong SC, Kim TK. What should be considered in using standard knee radiographs to estimate mechanical alignment of the knee? *Osteoarthritis Cartilage* 2010; **18**: 530-538 [PMID: 20060951 DOI: 10.1016/j.joca.2009.12.004]
- 53 **Felson DT**, Cooke TD, Niu J, Goggins J, Choi J, Yu J, Nevitt MC. Can anatomic alignment measured from a knee radiograph substitute for mechanical alignment from full limb films? *Osteoarthritis Cartilage* 2009; **17**: 1448-1452 [PMID: 19505430 DOI: 10.1016/j.joca.2009.05.012]
- 54 **Schmitt H**, Kappel H, Moser MT, Cardenas-Montemayor E, Engelleiter K, Kuni B, Clarius M. Determining knee joint alignment using digital photographs. *Knee Surg Sports Traumatol Arthrosc* 2008; **16**: 776-780 [PMID: 18551275 DOI: 10.1007/s00167-008-0570-6]
- 55 **Siu D**, Cooke TD, Broekhoven LD, Lam M, Fisher B, Saunders G, Challis TW. A standardized technique for lower limb radiography. Practice, applications, and error analysis. *Invest Radiol* 1991; **26**: 71-77 [PMID: 2022456 DOI: 10.1097/00004424-199101000-00013]
- 56 **Hunt MA**, Fowler PJ, Birmingham TB, Jenkyn TR, Giffin JR. Foot rotational effects on radiographic measures of lower limb alignment. *Can J Surg* 2006; **49**: 401-406 [PMID: 17234068]
- 57 **Moncrieff MJ**, Livingston LA. Reliability of a digital-photographic-goniometric method for coronal-plane lower limb measurements. *J Sport Rehabil* 2009; **18**: 296-315 [PMID: 19561371]
- 58 **Hinman RS**, May RL, Crossley KM. Is there an alternative to the full-leg radiograph for determining knee joint alignment in osteoarthritis? *Arthritis Rheum* 2006; **55**: 306-313 [PMID: 16583430 DOI: 10.1002/art.21836]
- 59 **McDaniel G**, Mitchell KL, Charles C, Kraus VB. A comparison of five approaches to measurement of anatomic knee alignment from radiographs. *Osteoarthritis Cartilage* 2010; **18**: 273-277 [PMID: 19897069 DOI: 10.1016/j.joca.2009.10.005]
- 60 **Sheehy L**, Felson D, Zhang Y, Niu J, Lam YM, Segal N, Lynch J, Cooke TD. Does measurement of the anatomic axis consistently predict hip-knee-ankle angle (HKA) for knee alignment studies in osteoarthritis? Analysis of long limb radiographs from the multicenter osteoarthritis (MOST) study. *Osteoarthritis Cartilage* 2011; **19**: 58-64 [PMID: 20950695 DOI: 10.1016/j.joca.2010.09.011]
- 61 **Issa SN**, Dunlop D, Chang A, Song J, Prasad PV, Guermazi A, Peterfy C, Cahue S, Marshall M, Kapoor D, Hayes K, Sharma L. Full-limb and knee radiography assessments of varus-valgus alignment and their relationship to osteoarthritis disease features by magnetic resonance imaging. *Arthritis Rheum* 2007; **57**: 398-406 [PMID: 17394225 DOI: 10.1002/art.22618]
- 62 **van Raaij TM**, Brouwer RW, Reijman M, Bierma-Zeinstra SM, Verhaar JA. Conventional knee films hamper accurate knee alignment determination in patients with varus osteoarthritis of the knee. *Knee* 2009; **16**: 109-111 [PMID: 19019686 DOI: 10.1016/j.jknee.2008.10.003]
- 63 **Cooke TD**. Static knee alignment and its association with radiographic knee osteoarthritis. *Osteoarthritis Cartilage* 2007; **15**: 844-845; author reply 844-845 [PMID: 17433882 DOI: 10.1016/j.joca.2007.02.017]
- 64 **Nguyen C**, Bryant JT, Cooke TDV, Chow D. Alignment and geometry of the normal knee in stance. *J Bone Joint Surg Brit* 1989; **71-B**: 346
- 65 **Ahlbäck S**. Osteoarthritis of the knee. A radiographic investigation. *Acta Radiol Diagn (Stockh)* 1968; **277**: Suppl 277: 7-27772 [PMID: 5706059]
- 66 **Brandt KD**, Fife RS, Braunstein EM, Katz B. Radiographic grading of the severity of knee osteoarthritis: relation of the Kellgren and Lawrence grade to a grade based on joint space narrowing, and correlation with arthroscopic evidence of articular cartilage degeneration. *Arthritis Rheum* 1991; **34**: 1381-1386 [PMID: 1953815 DOI: 10.1002/art.1780341106]
- 67 **Kellgren JH**, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957; **16**: 494-502 [PMID: 13498604 DOI: 10.1136/ard.16.4.494]
- 68 **Sundaram NA**, Hallett JP, Sullivan MF. Dome osteotomy of the tibia for osteoarthritis of the knee. *J Bone Joint Surg Br* 1986; **68**: 782-786 [PMID: 3782246]
- 69 **Kellgren J**, Jeffrey MR, Ball J. The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis. Oxford: Blackwell Scientific; 1963
- 70 The Atlas of Standard Radiographs of Arthritis. *Rheumatology* (Oxford) 2005; **44** Suppl 4: iv46-iv72 [PMID: 16306483]
- 71 **Lawrence J**. Rheumatism in populations. London: W.M. Heinemann Medical Books, 1977
- 72 **Croft P**. An introduction to the Atlas of Standard Radiographs of Arthritis. *Rheumatology* (Oxford) 2005; **44** Suppl 4: iv42 [PMID: 16306482 DOI: 10.1093/rheumatology/kei051]
- 73 **Bellamy N**, Bennett PH, Burch TA. New York symposium on population studies in rheumatic diseases: new diagnostic criteria. *Bulletin Rheum Dis* 1967; **17**: 453-458
- 74 **Felson DT**, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. *Ann Rheum Dis* 2011; **70**: 1884-1886 [PMID: 21908453 DOI: 10.1136/ard.2011.155119]
- 75 **Spector TD**, Cooper C. Radiographic assessment of osteoarthritis in population studies: whither Kellgren and Lawrence? *Osteoarthritis Cartilage* 1993; **1**: 203-206 [PMID: 15449506 DOI: 10.1016/S1063-4584(05)80325-5]
- 76 **Felson DT**, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, Levy D. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1995; **38**: 1500-1505 [PMID: 7575700 DOI: 10.1002/art.1780381017]
- 77 **Schiphof D**, Boers M, Bierma-Zeinstra SM. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. *Ann Rheum Dis* 2008; **67**: 1034-1036 [PMID: 18198197 DOI: 10.1136/ard.2007.079020]
- 78 **Dowsey MM**, Nikpour M, Dieppe P, Choong PF. Associations between pre-operative radiographic changes and outcomes after total knee joint replacement for osteoarthritis. *Osteoarthritis Cartilage* 2012; **20**: 1095-1102 [PMID: 22800770 DOI: 10.1016/j.joca.2012.05.015]
- 79 **Schiphof D**, de Klerk BM, Kerkhof HJ, Hofman A, Koes BW, Boers M, Bierma-Zeinstra SM. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. *Ann Rheum Dis* 2011; **70**: 1422-1427 [PMID: 21555325 DOI: 10.1136/ard.2010.147520]
- 80 **Kessler S**, Guenther KP, Puhl W. Scoring prevalence and severity in gonarthrosis: the suitability of the Kellgren & amp; Lawrence scale. *Clin Rheumatol* 1998; **17**: 205-209 [PMID: 9694053 DOI: 10.1007/BF01451048]
- 81 **Oka H**, Muraki S, Akune T, Mabuchi A, Suzuki T, Yoshida H, Yamamoto S, Nakamura K, Yoshimura N, Kawaguchi H. Fully automatic quantification of knee osteoarthritis severity on plain radiographs. *Osteoarthritis Cartilage* 2008; **16**: 1300-1306 [PMID: 18424107 DOI: 10.1016/j.joca.2008.03.011]
- 82 **Scott WW**, Lethbridge-Cejku M, Reichle R, Wigley FM, Tobin JD, Hochberg MC. Reliability of grading scales for individual

- radiographic features of osteoarthritis of the knee. The Baltimore longitudinal study of aging atlas of knee osteoarthritis. *Invest Radiol* 1993; **28**: 497-501 [PMID: 8320066]
- 83 **Spector TD**, Dacre JE, Harris PA, Huskisson EC. Radiological progression of osteoarthritis: an 11 year follow up study of the knee. *Ann Rheum Dis* 1992; **51**: 1107-1110 [PMID: 1444622 DOI: 10.1136/ard.51.10.1107]
- 84 **Szebenyi B**, Hollander AP, Dieppe P, Quilty B, Duddy J, Clarke S, Kirwan JR. Associations between pain, function, and radiographic features in osteoarthritis of the knee. *Arthritis Rheum* 2006; **54**: 230-235 [PMID: 16385522 DOI: 10.1002/art.21534]
- 85 **Günther KP**, Sun Y. Reliability of radiographic assessment in hip and knee osteoarthritis. *Osteoarthritis Cartilage* 1999; **7**: 239-246 [PMID: 10222223 DOI: 10.1053/joca.1998.0152]
- 86 **McAlindon TE**, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, Rush D, Wilson PW, Jacques P. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med* 1996; **125**: 353-359 [PMID: 8702085 DOI: 10.7326/0003-4819-125-5-199609010-00001]
- 87 **Shamir L**, Ling SM, Scott WW, Bos A, Orlov N, Macura TJ, Eckley DM, Ferrucci L, Goldberg IG. Knee x-ray image analysis method for automated detection of osteoarthritis. *IEEE Trans Biomed Eng* 2009; **56**: 407-415 [PMID: 19342330 DOI: 10.1109/TBME.2008.2006025]
- 88 **Harada Y**, Tokuda O, Fukuda K, Shiraishi G, Motomura T, Kimura M, Matsunaga N. Relationship between cartilage volume using MRI and Kellgren-Lawrence radiographic score in knee osteoarthritis with and without meniscal tears. *AJR Am J Roentgenol* 2011; **196**: W298-W304 [PMID: 21343478 DOI: 10.2214/AJR.09.3556]
- 89 **Kijowski R**, Blankenbaker D, Stanton P, Fine J, De Smet A. Arthroscopic validation of radiographic grading scales of osteoarthritis of the tibiofemoral joint. *AJR Am J Roentgenol* 2006; **187**: 794-799 [PMID: 16928947 DOI: 10.2214/AJR.05.1123]
- 90 **Wada M**, Baba H, Imura S, Morita A, Kusaka Y. Relationship between radiographic classification and arthroscopic findings of articular cartilage lesions in osteoarthritis of the knee. *Clin Exp Rheumatol* 1998; **16**: 15-20 [PMID: 9543556]
- 91 **Galli M**, De Santis V, Tafuro L. Reliability of the Ahlbäck classification of knee osteoarthritis. *Osteoarthritis Cartilage* 2003; **11**: 580-584 [PMID: 12880580 DOI: 10.1016/S1063-4584(03)00095-5]
- 92 **Ahlbäck S**, Rydberg J. [X-ray classification and examination techniques in gonarthrosis]. *Lakartidningen* 1980; **77**: 2091-2093, 2096 [PMID: 7401762]
- 93 **Weidow J**, Cederlund CG, Ranstam J, Kärrholm J. Ahlbäck grading of osteoarthritis of the knee: poor reproducibility and validity based on visual inspection of the joint. *Acta Orthop* 2006; **77**: 262-266 [PMID: 16752288 DOI: 10.1080/17453670610046000]
- 94 **Dieppe PA**, Reichenbach S, Williams S, Gregg P, Watt I, Jüni P. Assessing bone loss on radiographs of the knee in osteoarthritis: a cross-sectional study. *Arthritis Rheum* 2005; **52**: 3536-3541 [PMID: 16255025 DOI: 10.1002/art.21418]
- 95 **Choy WS**, Lee SK, Kim KJ, Kam BS, Yang DS, Bae KW. Two continuous femoral nerve block strategies after TKA. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 1901-1908 [PMID: 21484386 DOI: 10.1007/s00167-011-1510-4]
- 96 **Kannus P**, Järvinen M, Paakkala T. A radiological scoring scale for evaluation of post-traumatic osteoarthritis after knee ligament injuries. *Int Orthop* 1988; **12**: 291-297 [PMID: 3220621 DOI: 10.1007/BF00317827]
- 97 **Satku K**, Kumar VP, Ngoi SS. Anterior cruciate ligament injuries. To counsel or to operate? *J Bone Joint Surg Br* 1986; **68**: 458-461 [PMID: 3755441]
- 98 **Merchant TC**, Dietz FR. Long-term follow-up after fractures of the tibial and fibular shafts. *J Bone Joint Surg Am* 1989; **71**: 599-606 [PMID: 2703519]
- 99 **McAlindon TE**, Cooper C, Kirwan JR, Dieppe PA. Determinants of disability in osteoarthritis of the knee. *Ann Rheum Dis* 1993; **52**: 258-262 [PMID: 8484690 DOI: 10.1136/ard.52.4.258]
- 100 **Derek T**, Cooke TDV, Kelly BP, Harrison L, Mohamed G, Khan B. Radiographic grading for knee osteoarthritis. A revised scheme that relates to alignment and deformity. *J Rheumatol* 1999; **26**: 641-644 [PMID: 10090176]
- 101 **Felson DT**, McAlindon TE, Anderson JJ, Naimark A, Weissman BW, Aliabadi P, Evans S, Levy D, LaValley MP. Defining radiographic osteoarthritis for the whole knee. *Osteoarthritis Cartilage* 1997; **5**: 241-250 [PMID: 9404469 DOI: 10.1016/S1063-4584(97)80020-9]
- 102 **Michael JW**, Wurth A, Eysel P, König DP. Long-term results after operative treatment of osteochondritis dissecans of the knee joint-30 year results. *Int Orthop* 2008; **32**: 217-221 [PMID: 18350293 DOI: 10.1007/s00264-006-0292-7]
- 103 **Lynn SK**, Costigan PA. Effect of foot rotation on knee kinetics and hamstring activation in older adults with and without signs of knee osteoarthritis. *Clin Biomech* (Bristol, Avon) 2008; **23**: 779-786 [PMID: 18343001 DOI: 10.1016/j.clinbiomech.2008.01.012]
- 104 **Harrison M**, Hopman W, Hope J, Brean M. Development of a novel triage tool for knee surgery. *Osteoarthritis Cartilage* 2013; **21** (Suppl): S140
- 105 **Cooper C**, Cushnaghan J, Kirwan JR, Dieppe PA, Rogers J, McAlindon T, McCrae F. Radiographic assessment of the knee joint in osteoarthritis. *Ann Rheum Dis* 1992; **51**: 80-82 [PMID: 1540044 DOI: 10.1136/ard.51.1.80]
- 106 **Hellio Le Graverand MP**, Mazzuca S, Duryea J, Brett A. Radiographic grading and measurement of joint space width in osteoarthritis. *Rheum Dis Clin North Am* 2009; **35**: 485-502 [PMID: 19931800 DOI: 10.1016/j.rdc.2009.08.005]
- 107 **Nagaosa Y**, Mateus M, Hassan B, Lanyon P, Doherty M. Development of a logically devised line drawing atlas for grading of knee osteoarthritis. *Ann Rheum Dis* 2000; **59**: 587-595 [PMID: 10913052 DOI: 10.1136/ard.59.8.587]
- 108 **Neumann G**, Hunter D, Nevitt M, Chibnik LB, Kwoh K, Chen H, Harris T, Satterfield S, Duryea J. Location specific radiographic joint space width for osteoarthritis progression. *Osteoarthritis Cartilage* 2009; **17**: 761-765 [PMID: 19073368 DOI: 10.1016/j.joca.2008.11.001]
- 109 **Spector T**, Cooper C, Cushnaghan J, Hart DJ, Dieppe PA. A radiographic atlas of knee osteoarthritis. London: Springer Verlag, 1992
- 110 **Thomas RH**, Resnick D, Alazraki NP, Daniel D, Greenfield R. Compartmental evaluation of osteoarthritis of the knee. A comparative study of available diagnostic modalities. *Radiology* 1975; **116**: 585-594 [PMID: 1153764 DOI: 10.1148/116.3.585]
- 111 **Altman RD**, Hochberg M, Murphy WA, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage* 1995; **3** Suppl A: 3-70 [PMID: 8581752]
- 112 **Altman RD**, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007; **15** Suppl A: A1-56 [PMID: 17320422]
- 113 **Boegård T**, Rudling O, Petersson IF, Jonsson K. Correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the tibiofemoral joint. *Ann Rheum Dis* 1998; **57**: 401-407 [PMID: 9797566 DOI: 10.1136/ard.57.7.401]
- 114 **Lanyon P**, O'Reilly S, Jones A, Doherty M. Radiographic assessment of symptomatic knee osteoarthritis in the community: definitions and normal joint space. *Ann Rheum Dis* 1998; **57**: 595-601 [PMID: 9893570 DOI: 10.1136/ard.57.10.595]
- 115 **Kijowski R**, Blankenbaker DG, Stanton PT, Fine JP, De Smet AA. Radiographic findings of osteoarthritis versus arthroscopic findings of articular cartilage degeneration in the tibiofemoral joint. *Radiology* 2006; **239**: 818-824 [PMID: 16641340 DOI: 10.1148/radiol.2393050584]
- 116 **Braga L**, Renner JB, Schwartz TA, Woodard J, Helmick CG, Hochberg MC, Jordan JM. Differences in radiographic features of knee osteoarthritis in African-Americans and Caucasians: the Johnston county osteoarthritis project. *Osteoarthritis Cartilage* 2009; **17**: 1554-1561 [PMID: 19735758 DOI: 10.1016/j.joca.2009.07.011]
- 117 **O'Reilly SC**, Muir KR, Doherty M. Effectiveness of home exercise

- on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Ann Rheum Dis* 1999; **58**: 15-19 [PMID: 10343535 DOI: 10.1136/ard.58.1.15]
- 118 **Cicuttini FM**, Baker J, Hart DJ, Spector TD. Association of pain with radiological changes in different compartments and views of the knee joint. *Osteoarthritis Cartilage* 1996; **4**: 143-147 [PMID: 8806116 DOI: 10.1016/S1063-4584(05)80323-1]
 - 119 **Hurley ST**, Hatfield Murdock GL, Stanish WD, Hubley-Kozey CL. Is there a dose response for valgus unloader brace usage on knee pain, function, and muscle strength? *Arch Phys Med Rehabil* 2012; **93**: 496-502 [PMID: 22244248 DOI: 10.1016/j.apmr.2011.09.002]
 - 120 **Lynn SK**, Reid SM, Costigan PA. The influence of gait pattern on signs of knee osteoarthritis in older adults over a 5-11 year follow-up period: a case study analysis. *Knee* 2007; **14**: 22-28 [PMID: 17092727 DOI: 10.1016/j.knee.2006.09.002]
 - 121 **Lethbridge-Cejku M**, Scott WW, Reichle R, Ettinger WH, Zonderman A, Costa P, Plato CC, Tobin JD, Hochberg MC. Association of radiographic features of osteoarthritis of the knee with knee pain: data from the Baltimore Longitudinal Study of Aging. *Arthritis Care Res* 1995; **8**: 182-188 [PMID: 7654803 DOI: 10.1002/art.1790080311]
 - 122 **Hubley-Kozey CL**, Hatfield GL, Astephen Wilson JL, Dunbar MJ. Alterations in neuromuscular patterns between pre and one-year post-total knee arthroplasty. *Clin Biomech (Bristol, Avon)* 2010; **25**: 995-1002 [PMID: 20728970 DOI: 10.1016/j.clinbiomech.2010.07.008]
 - 123 **Kerna I**, Kisand K, Laitinen P, Tamm AE, Kumm J, Lintrop M, Tamm AO. Association of ADAM12-S protein with radiographic features of knee osteoarthritis and bone and cartilage markers. *Rheumatol Int* 2012; **32**: 519-523 [PMID: 21258805 DOI: 10.1007/s00296-010-1717-6]
 - 124 **Jenkinson CM**, Doherty M, Avery AJ, Read A, Taylor MA, Sach TH, Silcocks P, Muir KR. Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: randomised controlled trial. *BMJ* 2009; **339**: b3170 [PMID: 19690345 DOI: 10.1136/bmj.b3170]
 - 125 **Wilkinson CE**, Neame R, Prabu A, Carr AJ, Doherty M. Further development of a logically derived line drawing atlas (LDLDA) for grading knee osteoarthritis (OA). *Arthritis Rheum* 2001; **44**: S227
 - 126 **Wilkinson CE**, Carr AJ, Doherty M. Does increasing the grades of the knee osteoarthritis line drawing atlas alter its clinimetric properties? *Ann Rheum Dis* 2005; **64**: 1467-1473 [PMID: 15817656 DOI: 10.1136/ard.2004.033282]
 - 127 **Wilkinson CE**, Carr AJ, Doherty M. Does grading improve by overlaying an acetate line drawing atlas directly over a radiograph? *Rheumatology* 2004; **43** Suppl 2: 65
 - 128 **Marijnissen AC**, Vincken KL, Vos PA, Saris DB, Viergever MA, Bijlsma JW, Bartels LW, Lafeber FP. Knee Images Digital Analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail. *Osteoarthritis Cartilage* 2008; **16**: 234-243 [PMID: 17693099 DOI: 10.1016/j.joca.2007.06.009]
 - 129 **Kinds MB**, Marijnissen AC, Vincken KL, Viergever MA, Drossaers-Bakker KW, Bijlsma JW, Bierma-Zeinstra SM, Welsing PM, Lafeber FP. Evaluation of separate quantitative radiographic features adds to the prediction of incident radiographic osteoarthritis in individuals with recent onset of knee pain: 5-year follow-up in the CHECK cohort. *Osteoarthritis Cartilage* 2012; **20**: 548-556 [PMID: 22366685 DOI: 10.1016/j.joca.2012.02.009]
 - 130 **Kinds MB**, Vincken KL, Hoppinga TN, Bleys RL, Viergever MA, Marijnissen AC, Welsing PM, Lafeber FP. Influence of variation in semiflexed knee positioning during image acquisition on separate quantitative radiographic parameters of osteoarthritis, measured by Knee Images Digital Analysis. *Osteoarthritis Cartilage* 2012; **20**: 997-1003 [PMID: 22542633 DOI: 10.1016/j.joca.2012.04.016]
 - 131 **Muraki S**, Oka H, Akune T, En-yo Y, Yoshida M, Suzuki T, Yoshida H, Ishibashi H, Tokimura F, Yamamoto S, Nakamura K, Kawaguchi H, Yoshimura N. Independent association of joint space narrowing and osteophyte formation at the knee with health-related quality of life in Japan: a cross-sectional study. *Arthritis Rheum* 2011; **63**: 3859-3864 [PMID: 21898346 DOI: 10.1002/art.30641]
 - 132 **Muraki S**, Oka H, Akune T, En-yo Y, Yoshida M, Nakamura K, Kawaguchi H, Yoshimura N. Association of occupational activity with joint space narrowing and osteophytosis in the medial compartment of the knee: the ROAD study (OAC5914R2). *Osteoarthritis Cartilage* 2011; **19**: 840-846 [PMID: 21447396 DOI: 10.1016/j.joca.2011.03.008]
 - 133 **Sheehy L**, Cooke TDV, McLean L, Niu J, Lynch J, Segal NA, Singh J, Culham E. Reliability of the uni-compartmental scale for the radiographic evaluation of knee osteoarthritis: Data from the Multicenter Osteoarthritis Study. *Osteoarthritis Cartilage* 2013; **21** Suppl: S201 [DOI: 10.1016/j.joca.2013.02.420]

P- Reviewer: Garip Y, Singh A, Tawonsawatruk T

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Jiao XK



Safety of biologic therapies during pregnancy in women with rheumatic disease

Natalia Mena-Vazquez, Sara Manrique-Arija, Antonio Fernandez-Nebro

Natalia Mena-Vazquez, Sara Manrique-Arija, Antonio Fernandez-Nebro, Department of Rheumatology, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Regional Universitario de Málaga, Universidad de Málaga, 29009 Málaga, Spain

Author contributions: All the authors contributed to this paper.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Antonio Fernandez-Nebro, PhD, Department of Rheumatology, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Regional Universitario de Málaga, Universidad de Málaga, Plaza del Hospital Civil s/n Pabellón 7 – 2ª planta, 29009 Málaga, Spain. afernandezn@uma.es
 Telephone: +34-951-290360
 Fax: +34-951-290360

Received: August 2, 2014
 Peer-review started: August 3, 2014
 First decision: August 28, 2014
 Revised: March 8, 2015
 Accepted: April 1, 2015
 Article in press: April 7, 2015
 Published online: July 12, 2015

Abstract

Inflammatory rheumatic diseases frequently affect women of childbearing age. Biologic therapy during pregnancy is an important topic that is yet unresolved.

The majority of documented experiences are in case series, case reports, or registries. Tumor necrosis factor (TNF) inhibitors are now better known. Some evidence suggests that it is possible that differences between drugs regarding safety are associated with the structure and capacity to cross the placenta, but we are not aware of any study that supports unequivocally this statement. Most of the monoclonal antibodies are actively transferred to fetal circulation using the neonatal Fc receptor. Although this transfer does not appear to be associated with the risk of miscarriage, stillbirth, or congenital abnormality, the rate of premature births and lower birth weight may be increased. During fetal development, the neonatal period, and childhood, the immune system is constantly maturing. The ability to produce cytokines in response to infectious stimulus remains low for years, but is similar to that of an adult around the age of 3 years owing to the adaptive nature of the newborn's immune system as a result of exposure to microbes. Therefore, exposure to TNF inhibitors may have serious consequences on the newborn, such as severe infections or allergic reactions. Regarding the former, an anecdotal case report described a fatal case of disseminated bacillus Calmette-Guérin (BCG) infection in an infant born to a mother taking infliximab for Crohn's disease. Although the baby was born and progressed well initially, he died at 4.5 mo after he was vaccinated with BCG. Fortunately, serious infections do not appear to be frequent in newborns exposed to in utero biologic therapy. However, very limited short-term experiences are available regarding complications in an exposed fetus, and no data are available about long-term implications on the child's developing immune system. Therefore, we must be aware of potential complications in later years. Although the clinical data to date are promising, no firm conclusions can be drawn about the safety of biologic drugs during pregnancy, and, without further evidence, guidelines that suggest these drugs should be avoided at the time of conception cannot yet be changed.

Key words: Pregnancy; Biologic therapy; Monoclonal

antibodies; Rheumatic diseases; Safety

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Biologic therapy during pregnancy is an important topic that remains unresolved. Most of the monoclonal antibodies are actively transferred to fetal circulation using the neonatal Fc receptor. Some evidence suggests that differences may exist between drugs relating to safety associated with structure and the capacity to cross the placenta, but we are not aware of any study that supports this statement. Although the clinical data to date are promising, no firm conclusions can be drawn about the safety of biologic drugs during pregnancy, and, without further evidence, guidelines that suggest these drugs should be avoided at the time of conception cannot yet be changed.

Mena-Vazquez N, Manrique-Ariza S, Fernandez-Nebro A. Safety of biologic therapies during pregnancy in women with rheumatic disease. *World J Rheumatol* 2015; 5(2): 82-89 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i2/82.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i2.82>

INTRODUCTION

Inflammatory rheumatic diseases affect women of child-bearing age. Therapy for these diseases during pregnancy is an important topic that remains unresolved. Although there is considerable evidence for interaction of pregnancy and rheumatic diseases, little information is available about the safety of biologic drugs in pregnancy in humans. Most of the information is based on experimental studies with animals, but animal pregnancies differ considerably from human pregnancies in many aspects; as a result, the manufacturers of biological drugs advise that these agents be discontinued prior to a planned pregnancy for varying periods of time (Table 1). Despite this advice, numerous new pregnancies that occur during therapy with biological agents have been reported.

The reasons for exposure to biological agents during pregnancy are diverse. Many cases involve unintended pregnancies. However, in other cases, the pregnancy was planned, but the treatment is continued until the pregnancy is verified to avoid a flare-up of the condition. This behavior is reinforced owing to the unknown time to conception, and both patients and physicians fear that the disease may become active. Although the biological therapy is discontinued in the majority of cases when the pregnancy is confirmed, other cases are treated throughout pregnancy to avoid a flare-up of the disease and ensure a successful pregnancy outcome. Because this occurs in women with more severe disease during pregnancy in particular, most of the information regarding exposure to biologic drugs throughout pregnancy is based on patients with severe inflammatory bowel disease^[1].

Because these reports have generally been positive, there is growing interest among rheumatologists about the possibility of prolonging the biological treatment until the second trimester or later. Unfortunately, too many uncertainties remain about the potential long-term effects of treatment during pregnancy, as has happened with other drugs in the past^[2].

Because of an increasing use of biological agents, the aim of this paper was to examine some of the safety issues of biologic therapies during pregnancy, specifically in women with rheumatic diseases.

BIOLOGICAL AGENTS TARGETING CYTOKINES

Tumor necrosis factor inhibitors

Currently, there are 5 licensed tumor necrosis factor (TNF) inhibitors. Three of these - infliximab (IFX), adalimumab (ADA), and golimumab - are structurally complete IgG1 monoclonal antibodies, *i.e.*, they contain a fragment crystallizable (Fc) region that interacts with Fc receptors, including neonatal Fc receptor (RnFc). These receptors transfer IgG from mother to fetus through the placenta and from mother to infant in milk in addition to protecting IgG from degradation^[3].

In contrast, both etanercept (ETN) and certolizumab pegol (CZP) have structural peculiarities that may influence their fetal toxicity. The former is a fusion protein directed against the TNF receptor with a low affinity for RnFc^[4], while the latter is an incomplete antibody that contains only a pegylated Fab fragment against TNF. Because CZP does not have an Fc part, it cannot interact with RnFc.

The United States Food and Drug Administration (FDA) classifies all 5 biologic agents as pregnancy category B drugs, *i.e.*, animal reproduction studies have not shown any risk to the fetus, but adequate and well-controlled studies in pregnant women are lacking.

Potential risks to pregnant women: The risks of biologic therapy in pregnant rheumatic women should be at least equivalent to non-pregnant rheumatic patients. Therefore, the main risks with biologic therapy use should include infections, allergic reactions, infusion reactions, or local reactions. Although pregnancy implies a relative immunosuppression, studies do not exist that suggest the risk of infections associated with biologic drugs increase during pregnancy. However, there are also no studies that address this topic specifically. Only Casanova *et al.*^[5] retrospectively studied 66 pregnant women with inflammatory bowel disease who were exposed to anti-TNF drugs and compared their outcomes with patients exposed to thiopurines ($n = 187$) and non-exposed controls ($n = 318$). The infection rates were similar in all of the participants (3%, 1.5%, and 2.5% in those exposed to anti-TNF, those exposed to thiopurines, and the non-exposed, respectively).

Nevertheless, because these results are very limited,

Table 1 Current European Medicines Agency recommendations about licensed biologic therapies and pregnancy (from <http://www.ema.europa.eu/ema/>)

Biologic drug	Recommendations for women of childbearing potential	Recommendations for the infant exposed in utero
Infliximab ¹	Adequate contraception for at least 6 mo after the last infusion	Neither live vaccines administration nor breast-feeding is recommended while treated and for 6 mo following the mother's last infliximab infusion during pregnancy
Etanercept	To use appropriate contraception during therapy and for 3 wk after discontinuation of therapy	Neither live vaccines administration nor breast-feeding is recommended while treated and for 16 wk after the mother's last dose of Enbrel is generally not recommended
Adalimumab ²	Adequate contraception for at least 5 mo after the last injection	Neither live vaccines administration nor breast-feeding is recommended while treated and for 5 mo following the mother's last injection during pregnancy
Golimumab	Adequate contraception for at least 6 mo after the last injection	Neither live vaccines administration nor breast-feeding is recommended while treated and for 6 mo following the mother's last injection during pregnancy
Certolizumab	Adequate contraception for at least 5 mo after the last injection	Neither live vaccines administration nor breast-feeding is recommended while treated and for 5 mo following the mother's last injection during pregnancy
Anakinra	Not recommended during pregnancy and in women of childbearing potential not using contraception	No data
Tocilizumab	Adequate contraception for at least 3 mo after the last infusion	A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman Advice about live vaccine use in newborns is not given
Rituximab	Adequate contraception for at least 12 mo after the last infusion	No breast-feeding is recommended while treated and for 12 mo following the mother's last infusion during pregnancy Advice about live vaccine use in newborns is not given
Abatacept	Adequate contraception for at least 14 wk after the last dose	No breast-feeding is recommended while treated and for 14 wk following the mother's last infusion during pregnancy Advice about live vaccine use in newborns is not given

¹Remicade[®], Inflectra[®] and Remsima[®]; ²Humira[®] and Trudexa[®].

physicians should be aware of the infection risks in these patients. In this sense, it is worth remembering that anti-TNF increases the risk of infections such as *Listeria* or *Salmonella*^[6]. These infections may occur in pregnant women and their unborn fetuses, in whom life-threatening infections and fetal miscarriage can occur. Therefore, pregnant women who are in treatment or have been recently treated with biologic drugs should particularly follow the preventive measures to avoid food consumption of unpasteurized milk, raw eggs, or raw meat^[7].

On the other hand, both patients and rheumatologists should weight up the risks and benefits of continuing biologic therapy with planned pregnancies. One of the most important considerations is the diagnosis and level of control. The risks of flare-up may differ based on the disorder; for example, upto 60% of patients with rheumatoid arthritis improve during pregnancy, while the symptoms of ankylosing spondylitis do not improve^[8]. However, studies regarding the impact of biologic drug discontinuation are limited in patients with rheumatic disease owing to the incidental nature of the main exposure, and three-quarters of the cases with confirmed pregnancy in the first trimester discontinue biologic drugs^[4,9-43]. Only a minority of cases continue biologic therapy throughout their pregnancy, in agreement with their doctors. It is possible that these patients were treated to avoid the high risk of flare-ups.

Potential risks to pregnancy outcomes: In normal fetus, responsiveness to infection is low and associated

with spontaneous abortion^[44]. Therefore, an increased risk of miscarriage might be expected with infection related to TNF inhibitor exposure. However, intrauterine production of pro-inflammatory cytokines during the pregnancy is associated with intrauterine growth restriction and spontaneous abortion^[45]. Therefore, the use of TNF inhibitors during pregnancy may have be theoretically advantageous.

Only a few clinical studies have provided data regarding pregnancy outcomes in patients with inflammatory rheumatic disease undergoing anti-TNF therapy. The majority of this evidence is based on women with inflammatory bowel disease. A recent systematic review identified 472 cases with exposure to anti-TNF drugs during pregnancy^[46]. The rates of miscarriage, stillbirth, and congenital abnormalities were similar to previously reported rates in the general population; however, the rates of preterm/premature births (19.9% in anti-TNF-exposed vs 12.3% in the general population) and low birth weight/small for gestational age (6.1% in anti-TNF-exposed vs 8.2% in the general population) were not as expected for the general United States population. However, the authors indicated that sufficient evidence, particularly from controlled trials, was not available to guarantee absolute safety with the use of these drugs during pregnancy.

Clinical data from registries of rheumatic patients are consistent with some but not all of these results (Table 2). As a result, the Organization of Teratology Information Specialists autoimmune disease in pregnancy project did not find a specific pattern of defects in infants prenatally

Table 2 Tumor necrosis factor inhibitors use during pregnancy and the conception period

Ref./registry	No. of pregnancies	Disease	Biologic drugs	Pregnancy stage	Pregnancy outcome
Lichtenstein <i>et al</i> ^[61]	36	CD	IFX	Any exposure	11.1% miscarriage (NS), 8.3% neonatal complications (NS)
TREAT registry					
Katz <i>et al</i> ^[62]	96	CD, UC, RA	IFX	7 prior to conception, 53 conception, 30 T1, 6 unknown	67% live births, 15% miscarriages, and 19% elective termination. Results similar to those expected for the general United States population or pregnant women with CD not exposed to infliximab
Infliximab safety database					
Garcia <i>et al</i> ^[50]	14	RA, AS, PsA	IFX, ETN, ADA	First trimester	7 live births, 1 miscarriage, 3 therapeutic termination, 3 therapeutic termination, 2 on-going pregnancies, 0 malformations
BIOBADASER					
Strangfeld <i>et al</i> ^[10]	37		IFX, ETN, ADA, ANK	22 first-trimester (2 restarted biologic after week 20)	Similar miscarriage (4.5% <i>vs</i> 6.6%); 0 marformations
RABBIT					
Johnson <i>et al</i> ^[17]	175	RA, PsA, AS, CPs	ETN	15 prior to conception 139 first trimester 67 disease matched	Similar live births (93.5% <i>vs</i> 88.1%); more miscarriage (14% <i>vs</i> 5% <i>vs</i> 1.1%); malformations (9.4% <i>vs</i> 4.5%)
OTIS					
Verstappen <i>et al</i> ^[11]	140	RA, PsA, JIA, AS, SLE, AOSD	IFX, ETN, ADA	59 prior conception 71 at conception 10 controls never exposed	In post-conception exposures <i>vs</i> never exposed: less live births (59% <i>vs</i> 100%; <i>P</i> = 0.012), more miscarriages (27% <i>vs</i> 10%; <i>P</i> = 0.437), elective terminations (11% <i>vs</i> 10%; <i>P</i> = 0.587)
BSRBR					
Chambers <i>et al</i> ^[14]	239	RA, CD	ADA	94 first trimester 58 disease-matched controls 87 non-disease controls	Similar live births (85% <i>vs</i> 91.4% <i>vs</i> 89.7%), miscarriages (4.3% <i>vs</i> 9%); similar preterm deliveries (15% <i>vs</i> 17% <i>vs</i> 4%); malformations (9.6% <i>vs</i> 5.4% <i>vs</i> 5%)
OTIS					

Experience from national registries. CD: Crohn's disease; UC: Ulcerative colitis; RA: Rheumatoid arthritis; PsA: Psoriatic arthritis; JIA: Juvenile idiopathic arthritis; AS: Ankylosing spondylitis; SLE: Systemic lupus erythematosus; AOSD: Adult onset still disease; CPs: Cutaneous psoriasis; BSRBR: British society for rheumatology biologics register; NS: Non-significant; T1: First-trimester; IFX: Infliximab; ETN: Etanercept; ADA: Adalimumab.

exposed to ETN^[17] or ADA^[47]. Spontaneous abortions were higher in women exposed to ADA when compared to the controls who were never exposed, but had the disease, and non-diseased controls; however, the proportion was within the expected range of 10%-15% in clinically recognized pregnancies in the general population. The other pregnancy outcomes were similar to the comparison group and within the expected range for the general population.

The British Society for Rheumatology Biologics Register published a review of 130 pregnancies in patients who received anti-TNF before or during pregnancy^[11]. The spontaneous abortion rate was highest among patients exposed to anti-TNF at the time of conception. Comparatively, the rate of spontaneous abortions was 17% in those with prior exposure to anti-TNF and 10% in the control group. Although 20 of these patients became pregnant while receiving methotrexate or leflunomide, the authors did not believe that this was not related to the outcomes. The authors suggested that data are available to suggest that women with severe RA may have unfavorable pregnancy outcomes and those patients unable to discontinue anti-TNF therapies may be those with the most severe disease^[48,49].

The Spanish registry BIOBADASER identified 13 women (14 pregnancies) among a total of 3550 women treated with anti-TNF (4 with IFX, 8 with ETN, and 2 with ADA)^[50]. Although the number of observations was small, all pregnancy outcomes were within the expected range.

The German biologics register (RABBIT) identified, among 5244 patients, 37 pregnancies in 29 women

treated with anti-TNF (*n* = 27) and anakinra (ANK) (*n* = 2)^[10]. Two patients were exposed to biologics and methotrexate or leflunomide until confirmation of pregnancy, and 3 restarted treatment after week 20 and continued until delivery. The remaining patients discontinued the biologic treatment prior to conception. The authors did not find an increased risk for congenital malformations, miscarriages, or low birth weight.

Potential risks to newborns: During fetal development, the neonatal period, and childhood, the immune system is constantly maturing. The ability to produce cytokines in response to infectious stimulus remains low for years, but is similar to that of an adult around the age of 3 years owing to the adaptive nature of the newborn's immune system as a result of exposure to microbes. Therefore, the exposure to TNF inhibitors may have serious consequences on a newborn. An unfortunate example of this was presented by Cheent *et al*^[51]. They described a fatal case of disseminated *Bacillus de Calmette y Guérin* infection in an infant born to a mother taking IFX for Crohn's disease. Although the baby born and initially progressed well, he died at 4.5 mo, after he was vaccinated with *Bacillus de Calmette y Guérin*.

The majority of monoclonal antibodies actively cross the placenta, resulting in higher concentrations of these drugs in neonates than that in their mothers. Because of possible immunosuppression, live vaccines are contraindicated in newborns of mothers who have been treated with biologic therapy (Table 1).

Because the immune system is not yet completely

Table 3 Others biological agents use during pregnancy and the conception period

Ref./study	No. of pregnancies	Disease	Biologic drugs	Pregnancy stage	Pregnancy outcome
Berger <i>et al</i> ^[56]	3	AOSD	ANK	Through pregnancy	3 healthy live birth, full-term deliveries
Fischer-Betz <i>et al</i> ^[57] Case report					
Rubbert-Roth <i>et al</i> ^[58] Case series from clinical trials	33	RA	TCZ	Non-data	26/32 treated with TCZ + MTX, 6/32 TCZ monotherapy or concomitant with DMARD other than MTX 10/33 healthy live birth at term; 1/33 (1 infant died of ARDS 3 d after emergency cesarean section for intrapartum fetomaternal hemorrhage due to placenta previa; 13/33 elective terminations, 7/33 miscarriages 90 live births: 68 full-term deliveries; 22 preterm; 1 neonatal death at 6 wk; 2 malformations (clubfoot in one twin, and cardiac malformation in a singleton birth)
Chakravarty <i>et al</i> ^[59]	153	NHL, RA, SLE, Others ¹	RTX	132 prior to the conception	11 newborns had hematologic abnormalities (none with infections); 4 neonatal infections (fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis)
Biogen Idec/ Genentech/Roche rituximab global drug safety database				21 after the conception	
Ojeda-Urbe <i>et al</i> ^[22]	1	RA	ABT	First trimester	No complications. One healthy live birth

¹Idiopathic purpura thrombocytopenic, autoimmune haemolytic anaemia, multiple sclerosis, thrombotic thrombocytopenia. Purpura, Castleman disease, mixed connective tissue disease, and renal transplantation. AOSD: Adult onset still disease; RA: Rheumatoid arthritis; NHL: No Hodgkin lymphoma; SLE: Systemic lupus erythematosus; ANK: Anakinra; TCZ: Tocilizumab; RTX: Rituximab; ABT: Abatacept; ARDS: Acute respiratory distress syndrome.

developed in the newborn, the majority of antibodies are actively transferred from the mother to the offspring to confer short-term passive immunity. As mentioned earlier, the specific transport of IgG is conducted by the RnFc^[3]. IgG transfer from mother to fetus begins as early as 13 wk of gestation, and transport happens in a linear fashion as the pregnancy progresses. The fetus acquires the majority of IgG during the last 4 wk of pregnancy, and the concentrations usually exceed those of the mother by 20%-30% at full term^[52]. Therefore, the primary risk occurs after week 30.

Most monoclonal antibodies are of the IgG1 class and use the RnFc to actively cross the placenta. Because of this, newborns have a higher concentration than the mothers, and vaccinations containing live attenuated microorganisms are contraindicated. However, CZP has the lowest capacity to cross the placenta owing to the absence of the Fc fraction. Mohadevan *et al*^[53] studied 31 pregnant women with intestinal bowel disease receiving IFX, ADA, or CZP. Although IFX and ADA were detected in infants up to 6 mo after birth (up to 160% that of the mother), CZP had the lowest level of placental transfer (3.9%-22% that of the mother) of the drugs tested, based on the levels measured in the cord and infants at birth. Nevertheless, CZP was present to an extent; therefore, some passive placental transport may occur. It is possible that the small size and polyethylene glycol polymer chains attached to the Fab fragment may result in different qualities to cross the placenta.

On the other hand, ETN is also different to IFX and ADA because it has low affinity to the neonatal IgG transporter; this could also account for the limited placental transfer of this fusion protein^[54]. The concentration of ETN in cord blood can be 4%-7% of the concentration present in maternal blood^[55].

Although only limited short-term experiences are

available with regards to complications in an exposed fetus, there is no known data available regarding long-term effects on the child's developing immune system. Therefore, we must be aware in the years beyond the available data.

Others biological agents targeting cytokines

Published information about the pregnancy experience with ANK and tocilizumab (TCZ) is limited to case reports, but the preventive principles should be the same as that with TNF inhibitors. Table 3 summarizes the studies of other biological agents, including non-TNF inhibitors, during the conception period and pregnancy.

ANK: ANK is an interleukin (IL)-1 receptor antagonist, but it is currently possible to block IL-1 with monoclonal antibodies that are directly targeted at IL-1, such as canakinumab or rilonacept. ANK has been used throughout pregnancy in 3 pregnant patients with adult-onset Still's disease, and the children were born at term with no complications^[56,57]. However, measurements of ANK in the maternal or cord serum were not performed.

TCZ: TCZ is a humanized anti-human IL-6 receptor monoclonal antibody that inhibits IL-6. Experience with TCZ is limited to case series from the clinical trials reported at the ACR Annual Meeting in 2010^[58]. Thirty-three pregnancies were reported in 32 patients, despite a requirement for contraceptive use, among 4009 patients enrolled in several clinical trials. The small number of cases and high rate of therapeutic abortions, as well as concomitant medication use, limit the conclusions that can be drawn regarding the safety of TCZ during pregnancy. The authors reported that a pregnancy registry was being established to assess pregnancy outcomes in women exposed to TCZ during pregnancy.

BIOLOGICAL AGENTS TARGETING CELLS

Currently, there are 2 different licensed biological agents targeting B cells in rheumatology [rituximab (RTX) and belimumab] and 1 targeting T cells (abatacept). All of these drugs can cross the placenta; therefore, women should be advised to discontinue these drugs prior to a planned pregnancy (Table 1).

RTX

RTX is a chimeric monoclonal antibody against the antigen CD20 on the surface of B-cells. Because its B-cell depletion capacity has been shown useful for the treatment of lymphomas, leukemias, transplant rejections, and autoimmune disorders. In rheumatology, it is licensed to treat RA and ANCA-positive vasculitis and is also widely used off-label for systemic lupus erythematosus (SLE).

Like other monoclonal antibodies, RTX contains IgG1, which can cross the placenta using RnFc. RTX is classified as a pregnancy category C drug by the FDA (*i.e.*, animal reproduction studies have shown some risk to the fetus, but there adequate and well-controlled studies in pregnant women are lacking).

The majority of experiences with RTX in pregnant women are documented from the BiogenIdec/Genentech/Roche rituximab global drug safety database^[59]. This registry collects information about RTX from patients with diverse diseases, including mothers with lymphoma, autoimmune cytopenias, and other autoimmune diseases (Table 3). The majority of the mothers had RA ($n = 29$), non-Hodgkin lymphoma ($n = 24$), SLE ($n = 11$), or idiopathic thrombocytopenia ($n = 11$). This database identified 231 pregnancies (153 with known outcomes) associated with maternal RTX exposure (Table 3). Most cases were confounded by concomitant use of potentially teratogenic drugs and severe underlying diseases. Ninety resulted in live births, of which 22 were born prematurely. One neonatal death occurred at 6 wk. Eleven neonates had hematologic abnormalities: $n = 1$, low white blood cell count; $n = 4$, depleted B-cells; $n = 3$, thrombocytopenia; $n = 2$ neutropenia; and $n = 1$, lymphopenia. However, none of these neonates had infections. Four additional neonates had neonatal infections: fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis. Two congenital malformations were identified: clubfoot in one twin and cardiac malformation in a singleton birth. One maternal death from pre-existing autoimmune thrombocytopenia occurred. In all but 2 cases, RTX was administered during the second or third trimester of pregnancy.

Belimumab

Although belimumab and tofacitinib were also included in our search strategy, no report was found in humans. However, data from 83 unintended pregnancies with known outcomes in phase II and III studies indicated elective termination in 24%, spontaneous abortion in 27%, and live births in 42%^[60]. No increase in birth defects was observed.

Abatacept

ABT is a fusion recombinant molecule containing cytotoxic T lymphocyte-associated antigen 4 and the Fc fragment of IgG1 (CTLA4Ig) that blocks the CD80/CD86: CD28 co-stimulatory signal for T-cell activation.

The experience of ABT in humans is limited to one case report^[22]. The patient was a 33-year-old woman with RA treated with ABT plus MTX until gestation week 2.5. Delivery occurred at 40 wk of gestation. The newborn was healthy and was well after a 3.5-year follow-up.

CONCLUSION

Almost all of the experiences with the safety of biologic drugs during pregnancy in women with rheumatic diseases are documented in case series, case reports, or registries. TNF inhibitors are now better known. Some evidence suggests that differences in safety between drugs are associated with structure and the capacity to cross the placenta, but we are not aware of any study that supports this statement.

Although the clinical data to date are promising, no firm conclusions can be drawn regarding the safety of biologic drugs during pregnancy, and, without further evidence, guidelines that suggest these drugs should be avoided at the time of conception cannot yet be changed.

REFERENCES

- 1 Nielsen OH, Loftus EV, Jess T. Safety of TNF- α inhibitors during IBD pregnancy: a systematic review. *BMC Med* 2013; **11**: 174 [PMID: 23902720 DOI: 10.1186/1741-7015-11-174]
- 2 Swan SH. Intrauterine exposure to diethylstilbestrol: long-term effects in humans. *APMIS* 2000; **108**: 793-804 [PMID: 11252812]
- 3 Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol* 2007; **7**: 715-725 [PMID: 17703228 DOI: 10.1038/nri2155]
- 4 Murashima A, Watanabe N, Ozawa N, Saito H, Yamaguchi K. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. *Ann Rheum Dis* 2009; **68**: 1793-1794 [PMID: 19822717 DOI: 10.1136/ard.2008.105924]
- 5 Casanova MJ, Chaparro M, Domènech E, Barreiro-de Acosta M, Bermejo F, Iglesias E, Gomollón F, Rodrigo L, Calvet X, Esteve M, García-Planella E, García-López S, Taxonera C, Calvo M, López M, Ginard D, Gómez-García M, Garrido E, Pérez-Calle JL, Beltrán B, Piqueras M, Saro C, Botella B, Dueñas C, Ponferrada A, Mañosa M, García-Sánchez V, Maté J, Gisbert JP. Safety of thiopurines and anti-TNF- α drugs during pregnancy in patients with inflammatory bowel disease. *Am J Gastroenterol* 2013; **108**: 433-440 [PMID: 23318480 DOI: 10.1038/ajg.2012.430]
- 6 Davies R, Dixon WG, Watson KD, Lunt M, Symmons DP, Hyrich KL. Influence of anti-TNF patient warning regarding avoidance of high risk foods on rates of listeria and salmonella infections in the UK. *Ann Rheum Dis* 2013; **72**: 461-462 [PMID: 23076071]
- 7 Committee on Infectious Diseases, Committee on Nutrition, American Academy of Pediatrics. Consumption of raw or unpasteurized milk and milk products by pregnant women and children. *Pediatrics* 2014; **133**: 175-179 [PMID: 24344105 DOI: 10.1542/peds.2013-3502]
- 8 Jain V, Gordon C. Managing pregnancy in inflammatory rheumatological diseases. *Arthritis Res Ther* 2011; **13**: 206 [PMID: 21371350 DOI: 10.1186/ar3227]

- 9 **Pendergraft WF**, McGrath MM, Murphy AP, Murphy P, Laliberte KA, Greene MF, Niles JL. Fetal outcomes after rituximab exposure in women with autoimmune vasculitis. *Ann Rheum Dis* 2013; **72**: 2051-2053 [PMID: 23864238]
- 10 **Strangfeld A**, Listing J, Rau R, Schneider M, Hierse F, Krause A, Backhaus F, Zink A. Pregnancy Outcome after Exposure to Biologics: Results from the German Biologics Register RABBIT. *Arthritis Rheum* 2007; **9** (suppl): S311
- 11 **Verstappen SM**, King Y, Watson KD, Symmons DP, Hyrich KL. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011; **70**: 823-826 [PMID: 21362710 DOI: 10.1136/ard.2010.140822]
- 12 **Hyrich KL**, Symmons DP, Watson KD, Silman AJ. Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. *Arthritis Rheum* 2006; **54**: 2701-2702 [PMID: 16871549 DOI: 10.1002/art.22028]
- 13 **Kalari S**, Granath F, Guo CY, Harrison DD, Broms G, Geldhof A, Nissinen R, Sanders M, Gissler M, Pedersen L, Sorensen HT, Kieler H. Pregnancy outcomes in women with rheumatologic conditions exposed to infliximab. *Arthritis and Rheumatism* 2013; **65**: S871
- 14 **Chambers CD**, Johnson DL, Luo Y, Jimenez JL, Mirrasoul N, Salas E, Jones KL, Grp OR. Pregnancy outcome in women treated with adalimumab for the treatment of rheumatoid arthritis: The OTIS autoimmune diseases in pregnancy project. *Arthritis and Rheumatism* 2012; **64**: S1039
- 15 **Ishikawa H**, Kaneko A, Hattori Y, Takahashi N, Kida D, Sato T, Osawa Y. Pregnancy outcomes in rheumatoid arthritis patients treated with tocilizumab. *Ann Rheum Dis* 2014; **73**: 501-502 [DOI: 10.1136/annrheumdis-2014-eular.1417]
- 16 **Jarosova K**, Hejduk K, Uher M, Vencovsky J. Pregnancy outcome in adult juvenile idiopathic arthritis patients treated with biologic agents. *Ann Rheum Dis* 2014; **73**: 583 [DOI: 10.1136/annrheumdis-2014-eular.2913]
- 17 **Johnson DL**, Jones KL, Chambers C, Grp OCR. Pregnancy outcomes in women exposed to etanercept: The OTIS autoimmune diseases in pregnancy project. *Arthritis and Rheumatism* 2008; **58**: S682
- 18 **Ishikawa H**, Hirano Y, Kaneko A, Kida D, Sato T, Kojima T, Kanamono T, Ishiguro N. Pregnancy in patients with rheumatoid arthritis treated with biological agents: Results of the 8-year of Japanese the registry. *Ann Rheum Dis* 2012; **71**: 501 [DOI: 10.1136/annrheumdis-2012-eular.3040]
- 19 **Lau AG**, Clark M, Harrison DD, Geldhof A, Nissinen R, Sanders M. Pregnancy outcomes in women exposed to golimumab. *Arthritis and Rheumatism* 2013; **65**: S870-S871
- 20 **Østensen M**, Lockshin M, Doria A, Valesini G, Meroni P, Gordon C, Brucato A, Tincani A. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. *Rheumatology* (Oxford) 2008; **47** Suppl 3: iii28-iii31 [PMID: 18504282 DOI: 10.1093/rheumatology/ken168]
- 21 **Sangle SR**, Lutalo PM, Davies RJ, Khamashta MA, D'Cruz DP. B-cell depletion therapy and pregnancy outcome in severe, refractory systemic autoimmune diseases. *J Autoimmun* 2013; **43**: 55-59 [PMID: 23608146 DOI: 10.1016/j.jaut.2013.03.001]
- 22 **Ojeda-Urbe M**, Afif N, Dahan E, Sparsa L, Haby C, Sibilia J, Ternant D, Ardizzone M. Exposure to abatacept or rituximab in the first trimester of pregnancy in three women with autoimmune diseases. *Clin Rheumatol* 2013; **32**: 695-700 [PMID: 23292481 DOI: 10.1007/s10067-012-2156-4]
- 23 **Berthelot JM**, De Bandt M, Goupille P, Solau-Gervais E, Lioté F, Goeb V, Azaïs I, Martin A, Pallot-Prades B, Maugars Y, Mariette X. Exposition to anti-TNF drugs during pregnancy: outcome of 15 cases and review of the literature. *Joint Bone Spine* 2009; **76**: 28-34 [PMID: 19059799 DOI: 10.1016/j.jbspin.2008.04.016]
- 24 **Clowse MEB**, Wolf DC, Forger F, Cush JJ, Stach C, Kosutic G, Williams S, Maduka C, Mahadevan U. Retrospective analysis of certolizumab pegol use during pregnancy: Update of impact on birth outcomes. *Arthritis and Rheumatism* 2013; **65**: S187-S188
- 25 **Bazzani C**, Ramoni V, Scrivo R, Biggioggero M, Nuzzo M, Filippini M, Pontikaki I, Gerosa M, Mosca M, Gorla R, Caporali R, Cattaneo R, Meroni P, Valesini G, Montecucco C, Tincani C. Pregnancy outcomes in women exposed to biologic treatment and affected by chronic arthritis. *Ann Rheum Dis* 2010; **69**: 678
- 26 **Koksvik HS**, Magnussen AS, Skomsvoll JF. One year follow-up of etanercept exposed pregnancies. *Ann Rheum Dis* 2005; **64**: 449
- 27 **Umeda N**, Ito S, Hayashi T, Goto D, Matsumoto I, Sumida T. A patient with rheumatoid arthritis who had a normal delivery under etanercept treatment. *Intern Med* 2010; **49**: 187-189 [PMID: 20075588 DOI: 10.2169/internalmedicine.49.2439]
- 28 **Akinci A**, Ozçakar L. Infliximab use during pregnancy revisited. *Acta Reumatol Port* 2008; **33**: 374-375 [PMID: 18846021]
- 29 **Kinder AJ**, Edwards J, Samanta A, Nichol F. Pregnancy in a rheumatoid arthritis patient on infliximab and methotrexate. *Rheumatology* (Oxford) 2004; **43**: 1195-1196 [PMID: 15317958 DOI: 10.1093/rheumatology/keh264]
- 30 **Sinha A**, Patient C. Rheumatoid arthritis in pregnancy: successful outcome with anti-TNF agent (Etanercept). *J Obstet Gynaecol* 2006; **26**: 689-691 [PMID: 17071443 DOI: 10.1080/01443610600930647]
- 31 **Ton E**, Tekstra J, Hellmann PM, Nuver-Zwart IH, Bijlsma JW. Safety of rituximab therapy during twins' pregnancy. *Rheumatology* (Oxford) 2011; **50**: 806-808 [PMID: 21177333 DOI: 10.1093/rheumatology/keq403]
- 32 **Ng CT**, O'Neil M, Walsh D, Walsh T, Veale DJ. Successful pregnancy after rituximab in a women with recurrent in vitro fertilisation failures and anti-phospholipid antibody positive. *Ir J Med Sci* 2009; **178**: 531-533 [PMID: 19043774 DOI: 10.1007/s11845-008-0265-5]
- 33 **Carter JD**, Valeriano J, Vasey FB. Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. *J Rheumatol* 2006; **33**: 1014-1017 [PMID: 16652431]
- 34 **Sills ES**, Perloe M, Tucker MJ, Kaplan CR, Palermo GD. Successful ovulation induction, conception, and normal delivery after chronic therapy with etanercept: a recombinant fusion anti-cytokine treatment for rheumatoid arthritis. *Am J Reprod Immunol* 2001; **46**: 366-368 [PMID: 11712766 DOI: 10.1034/j.1600-0897.2001.d01-25.x]
- 35 **Rosner I**, Haddad A, Boulman N, Feld J, Avshovich N, Slobodin G, Rozenbaum M. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. *Rheumatology* (Oxford) 2007; **46**: 1508; author reply 1508-1509 [PMID: 17684027 DOI: 10.1093/rheumatology/kem068]
- 36 **Roux CH**, Brocq O, Breuil V, Albert C, Euler-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. *Rheumatology* (Oxford) 2007; **46**: 695-698 [PMID: 17158212 DOI: 10.1093/rheumatology/keh400]
- 37 **Feyertag J**, Dinhof G, Salzer H, Dunky A. Pregnancy in a rheumatoid arthritis patient treated with etanercept. *Ann Rheum Dis* 2004; **63**: 198
- 38 **Mainini G**, Di Donna MC, Esposito E, Ercolano S, Correa R, Stradella L, Della Gala A, De Francis P. Pregnancy management in Behçet's disease treated with uninterrupted infliximab. Report of a case with fetal growth restriction and mini-review of the literature. *Clin Exp Obstet Gynecol* 2014; **41**: 205-207 [PMID: 24779253]
- 39 **Antoni C**, Dechant C, Hanns-Martin Lorenz PD, Wendler J, Ogilvie A, Lueftl M, Kalden-Nemeth D, Kalden JR, Manger B. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. *Arthritis Rheum* 2002; **47**: 506-512 [PMID: 12382299 DOI: 10.1002/art.10671]
- 40 **Scioscia C**, Scioscia M, Anelli MG, Praino E, Bettocchi S, Lapadula G. Intentional etanercept use during pregnancy for maintenance of remission in rheumatoid arthritis. *Clin Exp Rheumatol* 2011; **29**: 93-95 [PMID: 21269575]
- 41 **Kraemer B**, Abele H, Hahn M, Rajab T, Kraemer E, Wallweiner D, Becker S. A successful pregnancy in a patient with Takayasu's arteritis. *Hypertens Pregnancy* 2008; **27**: 247-252 [PMID: 18696353 DOI: 10.1080/10641950801955741]
- 42 **Østensen M**, Raio L. A woman with rheumatoid arthritis whose

- condition did not improve during pregnancy. *Nat Clin Pract Rheumatol* 2005; **1**: 111-114; quiz 1 p. following 114 [PMID: 16932640 DOI: 10.1038/ncprheum0044]
- 43 **Chakravarty EF**, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. *J Rheumatol* 2003; **30**: 241-246 [PMID: 12563675]
 - 44 **Ygberg S**, Nilsson A. The developing immune system - from foetus to toddler. *Acta Paediatr* 2012; **101**: 120-127 [PMID: 22003882 DOI: 10.1111/j.1651-2227.2011.02494.x]
 - 45 **Levy O**. Innate immunity of the newborn: basic mechanisms and clinical correlates. *Nat Rev Immunol* 2007; **7**: 379-390 [PMID: 17457344 DOI: 10.1038/nri2075]
 - 46 **Marchioni RM**, Lichtenstein GR. Tumor necrosis factor- α inhibitor therapy and fetal risk: a systematic literature review. *World J Gastroenterol* 2013; **19**: 2591-2602 [PMID: 23674866 DOI: 10.3748/wjg.v19.i17.2591]
 - 47 **Johnson DL**, Jones KL, Chambers CD, Salas E. Pregnancy outcomes in women exposed to adalimumab: The OTIS autoimmune diseases in pregnancy project. *Gastroenterology* 2009; **136**: A27
 - 48 **de Man YA**, Hazes JM, van der Heide H, Willemssen SP, de Groot CJ, Steegers EA, Dolhain RJ. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009; **60**: 3196-3206 [PMID: 19877045 DOI: 10.1002/art.24914]
 - 49 **Skomsvoll JF**, Ostensen M, Irgens LM, Baste V. Pregnancy complications and delivery practice in women with connective tissue disease and inflammatory rheumatic disease in Norway. *Acta Obstet Gynecol Scand* 2000; **79**: 490-495 [PMID: 10857874]
 - 50 **Garcia J**, Joven B, Ruiz T, Moreno E, Cebrian L, Valero M, Perez C, Martinez F, Hernandez B, Morcillo M, Carmona L, Mateo I. Pregnancy in women receiving anti-TNF- α therapy. Experience in Spain. *Ann Rheum Dis* 2006; **65**: 317-317
 - 51 **Cheent K**, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 2010; **4**: 603-605 [PMID: 21122568 DOI: 10.1016/j.crohns.2010.05.001]
 - 52 **Palmeira P**, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol* 2012; **2012**: 985646 [PMID: 22235228 DOI: 10.1155/2012/985646]
 - 53 **Mahadevan U**, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, Ullman T, Glover S, Valentine JF, Rubin DT, Miller J, Abreu MT. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 286-292; quiz e24 [PMID: 23200982 DOI: 10.1016/j.cgh.2012.11.011]
 - 54 **Suzuki T**, Ishii-Watabe A, Tada M, Kobayashi T, Kanayasu-Toyoda T, Kawanishi T, Yamaguchi T. Importance of neonatal FcR in regulating the serum half-life of therapeutic proteins containing the Fc domain of human IgG1: a comparative study of the affinity of monoclonal antibodies and Fc-fusion proteins to human neonatal FcR. *J Immunol* 2010; **184**: 1968-1976 [PMID: 20083659 DOI: 10.4049/jimmunol.0903296]
 - 55 **Berthelsen BG**, Fjeldsøe-Nielsen H, Nielsen CT, Hellmuth E. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. *Rheumatology (Oxford)* 2010; **49**: 2225-2227 [PMID: 20581374 DOI: 10.1093/rheumatology/keq185]
 - 56 **Berger CT**, Recher M, Steiner U, Hauser TM. A patient's wish: anakinra in pregnancy. *Ann Rheum Dis* 2009; **68**: 1794-1795 [PMID: 19822718 DOI: 10.1136/ard.2008.105833]
 - 57 **Fischer-Betz R**, Specker C, Schneider M. Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra). *Clin Exp Rheumatol* 2011; **29**: 1021-1023 [PMID: 22153586]
 - 58 **Rubbert-Roth A**, Goupille PM, Moosavi S, Hou A. First experiences with pregnancies in RA patients (Pts) receiving tocilizumab (TCZ) therapy. [abstract]. *Arthritis Rheum* 2010; **62** Suppl 10: 384
 - 59 **Chakravarty EF**, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. *Blood* 2011; **117**: 1499-1506 [PMID: 21098742 DOI: 10.1182/blood-2010-07-295444]
 - 60 **Ostensen M**. Safety issues of biologics in pregnant patients with rheumatic diseases. *Ann N Y Acad Sci* 2014; **1317**: 32-38 [PMID: 24840548 DOI: 10.1111/nyas.12456]
 - 61 **Lichtenstein GR**, Cohen RD, Feagan BG, Sandborn WJ, Salzberg BA, Chen BM, Diamond RH. Safety of infliximab in Crohn's disease: Data from the 5000-patient TREAT registry. *Gastroenterology* 2004; **126**: A54
 - 62 **Katz JA**, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am J Gastroenterol* 2004; **99**: 2385-2392 [PMID: 15571587 DOI: 10.1111/j.1572-0241.2004.30186.x]

P- Reviewer: Chui YL S- Editor: Gong XM

L- Editor: A E- Editor: Jiao XK



Current review of trapeziometacarpal osteoarthritis (rhizarthrosis)

Onur Bilge, Nazim Karalezli

Onur Bilge, Nazim Karalezli, Department of Orthopaedics and Traumatology, Meram Faculty of Medicine, Konya Necmettin Erbakan University, 42000 Konya, Turkey

Onur Bilge, Nazim Karalezli, Department of Sports Medicine, Meram Faculty of Medicine, Konya Necmettin Erbakan University, 42000 Konya, Turkey

Author contributions: Bilge O and Karalezli N designed research, performed research, contributed new reagents or analytic tools, analyzed data and wrote the paper.

Conflict-of-interest statement: The authors have no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Onur Bilge, MD, FEBOT, Assistant Professor, Department of Orthopaedics and Traumatology, Meram Faculty of Medicine, Konya Necmettin Erbakan University, Yunus Emre, Mah, Beysehir Cevre Yolu Cad. Meram, 42000 Konya, Turkey. onurbilgemd@gmail.com
Telephone: +90-332-2237220
Fax: +90-332-2236182

Received: June 28, 2014
Peer-review started: June 29, 2014
First decision: November 27, 2014
Revised: December 5, 2014
Accepted: March 16, 2015
Article in press: March 18, 2015
Published online: July 12, 2015

Abstract

Trapeziometacarpal (TMC) joint is the secondly affected

joint for osteoarthritis in the hand. TMC joint arthritis affects most commonly postmenopausal women after the fifth decade of life, due to hormonal and structural factors. Rhizarthrosis may lead to a clinical spectrum from subtle symptoms to advanced symptoms such as; severe pain, limitation of range of motion, muscular weakness, bony deformities, and end up ultimately with disability. Regardless of the etiopathogenesis; a variety of non-surgical and surgical methods have been used for the treatment of rhizarthrosis, depending on the age of the patient, symptomatology and the stage of the disease. The main goals of the treatments are as follows; relief of pain, conservation or restoration the stability and mobility of the TMC joint with the optimal preservation of the strength of surrounding musculature. In this article, the current methods, which have been used for the treatment of TMC joint osteoarthritis, will be mainly reviewed, together with concise up-to-date information on both its diagnosis and the anatomy of the TMC joint.

Key words: Osteoarthritis; Thumb; Trapeziometacarpal joint; Rhizarthrosis

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The trapeziometacarpal joint is a common region in the body, where osteoarthritis is encountered, especially in the postmenopausal women. Although the exact etiology is not still certain, ligamentous laxity is a common finding in most of the cases. Regarding to the existing literature, the most commonly used treatment methods are conservative measures and trapeziectomy with ligament reconstruction tendon interposition. Moreover newer treatment methods have emerged in the recent years. In conclusion, if long-term prospective, randomized, comparative studies are performed, there will be an appropriate answer to choose the optimal treatment methods for each stage of rhizarthrosis.

Bilge O, Karalezli N. Current review of trapeziometacarpal osteoarthritis (rhizarthrosis). *World J Rheumatol* 2015; 5(2): 90-95 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i2/90.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i2.90>

INTRODUCTION

Trapeziometacarpal (TMC) joint is the secondly affected joint for osteoarthritis (OA) in the hand^[1]. TMC OA or rhizarthrosis affects most commonly postmenopausal women after the fifth decade of life, due to hormonal and structural factors^[2-4]. Rhizarthrosis may lead to a clinical spectrum from subtle symptoms to advanced symptoms such as; severe pain, limitation of range of motion, muscular weakness, bony deformities, and end up ultimately with disability.

Although the exact etiology of rhizarthrosis has not been clearly evidenced yet, most postulated theories related this entity with the surrounding ligamentous laxity or weakness of this joint, leading to the disturbed congruency between the trapezium and the basis of first metacarpus^[5-9]. The incongruence and increased contact stresses end up eventually with rhizarthrosis.

Regardless of the etiopathogenesis; a variety of non-surgical and surgical methods have been used for the treatment of rhizarthrosis, depending on the age of the patient, symptomatology and the stage of the disease. The main goals of the treatments are as follows; relief of pain, conservation or restoration the stability and mobility of the TMC joint with the optimal preservation of the strength of surrounding musculature.

In this article, the current methods, which have been used for the treatment of rhizarthrosis, will be mainly reviewed, together with concise up-to-date information on both its diagnosis and the anatomy of the TMC joint.

LIGAMENTOUS ANATOMY OF THE TMC JOINT

The TMC joint of the thumb has a vital function nearly for all functions of the thumb, mainly by opposition. It is a combination of "saddle" and "universal" types of joint with confronting biconcave-convex shapes of trapezium and the basis of the first metacarpal bone. Its stability mostly depends on the ligaments, which support this joint mostly around the dorsal and volar regions. The understanding of this complex ligamentous anatomy is highly important for the stability of this joint, and its osteoarthritic process. This joint and its supporting ligamentous structures have been studied extensively in terms of anatomy, histopathology or biomechanics^[5,9-18].

In general, 6 main ligaments of the TMC joint were consistently identified in the literature. These are as follows: dorsoradial ligament (DRL), anterior oblique ligaments (AOL, superficial and deep), intermetacarpal ligament, ulnar collateral ligament and posterior oblique ligament. The functions of these stabilizing ligaments are

summarized in Table 1^[19].

Among these ligaments, AOL was shown to be the primary stabilizer of the TMC joint by Eaton, Littler and Pellegrini^[7,8,20]. But, this information has been challenged by many recent studies, in such a way that the DRL is the primary stabilizer against dorsal translation of the TMC joint^[9,15,18,21-25]. It seems that this controversial debate on the main stabilizing ligaments of the TMC joint will continue over the coming years by ending up with an ultimate prospective conclusion.

DIAGNOSIS

In general, patients with rhizarthrosis have a spectrum of symptomatology. On one hand a patient may be asymptomatic or may have subtle symptoms despite pantrapezial arthritis, on the other hand another patient may have severe symptoms despite a lower radiological stage. Although this disease interferes with recreational and professional activities and performances, most patients live by adapting themselves to this situation with the avoidance of some thumb movements, such as abduction and key pinch. So, the symptomatology may not correlate with the radiology in most of the times^[26].

Symptomatic patients usually present with a pain located at the base of the thumb, which may radiate to the thenar region or metacarpophalangeal joint. It is usually worsened by some unique movements of the thumb (pinch or grip during turning a key, sewing, writing, opening a jar, etc.). As the disease progresses, the position of the thumb shifts from an adducted but lax position to a more ankylosed position, and the previously lax joint becomes stiffer. The final position of the deformity is defined as "pollux adductus" (adducted metacarpal shaft with metacarpophalangeal hyperextension).

In physical examination, tenderness and some provocative tests help to the establishment of the diagnosis. The tenderness is usually at the radiopalmar surface of the TMC joint, especially coexisting with inflammation at earlier stages. The provocative tests, which include the grind test and Glickel test, aim to reproduce pain at the TMC joint level^[27,28].

In practice, radiography should at least include; posteroanterior (PA) neutral, PA clenched fist, lateral, and oblique views. The most popular and the most commonly used radiological classification of rhizarthrosis is the Eaton-Littler Classification, which uses a true lateral view of the thumb centered over the trapezium and sesamoids superimposed (Table 2)^[13]. Later, a fifth stage was described as pan-trapezial arthritis, as TMC joint arthritis was observed rarely as an isolated entity^[29].

The most common pathology co-existing with rhizarthrosis was reported to be the carpal tunnel syndrome^[30]. Differential diagnosis of rhizarthrosis includes De Quervain's disease, trigger thumb, scaphoid fracture (distal pole), flexor carpi radialis (FCR) tenosynovitis, scaphotrapezial arthritis, wrist arthritis and subsesamoid

Table 1 Main ligaments of the trapeziometacarpal joint

Ligament		Description of the function
Dorsoradial (Figure 1)		Shortest and thickest ligament (Recently possible) Primary stabilizer against dorsal translation of the joint Opposes anterior oblique ligaments Basis for Eaton-Littler procedure
Anterior oblique (Figure 1)	Superficial	Stabilization against volar joint subluxation
	Deep	Known as beak ligament Act as a pivot point Primary joint stabilizer against dorsal translation
Posterior oblique Intermetacarpal		Stabilization of rotation Stabilization during radiovolar translation
Ulnar collateral		Stabilization of the thumb against collapse especially after trapeziectomy Helps to stabilization against volar joint subluxation

arthritis^[19]. But careful and proper clinical and radiological evaluations will differentiate rhizarthrosis from the aforementioned clinical entities.

TREATMENT

The treatment of rhizarthrosis has evolved in the last decade, especially in terms of surgical methods. In general, the treatment mainly aims to relieve pain, to regain stability, mobility of the joint, to reestablish the strength of surrounding structures and to increase the comfort and function of the patient clinically. Treatment methods will be summarized concisely in this section.

Non-surgical treatment

In general, non-surgical methods are preferred at the initial stages by most of the clinicians, as the initial method of management. The choices include: non-steroidal inflammatory drugs, splinting with thumb spica cast, physical therapy and injections (steroid and hyaluronic acid)^[3,31-36]. It should be kept in mind that continuous and repeated steroid injections have been shown to weaken the joint capsule^[37]. They may complicate further surgeries. Therefore they should be used specially at inflammatory flare-up periods, but should not be applied repeatedly. Another important point is that; although most studies on conservative methods report good-excellent results on pain and functional scores, the methodological quality of these studies was recently found to be poor to fair^[38].

Surgical treatment

Surgical treatment is most commonly reserved for symptomatic patients who are unresponsive to conservative methods or who are at advanced stages of the disease. Although several surgical treatment methods have been introduced since last 50 years, none of them has achieved to be the single most efficient treatment of rhizarthrosis. As the detail of the surgical techniques of all described procedures is not the aim of this review, a concise explanation of these methods will be discussed together with clinical results of relevant studies.

Trapeziectomy with or without tendon interposition or ligament reconstruction

The total excision of the trapezium was described firstly in 1949^[39]. It was also called as "hematoma arthroplasty"^[40]. Although symptomatology was not believed to correlate with its late problems, trapeziectomy alone does carry the risk of shortening of trapezial height and scaphoid impingement. That is why when trapeziectomy is performed alone; fixation with a K-wire is advised to prevent the height loss to some extent^[41]. Based on mostly short-term follow-up studies, trapeziectomy alone yielded good clinical results^[41,42]. In a Level III study by Ritchie *et al.*^[43], it was shown that anterior approach yielded better clinical results than posterior approach.

There are two main methods, which can be added to total trapeziectomy; tendon interposition (TI) or ligament reconstruction (LR). The main aim of the LRTI is the reconstruction of AOL by using the half of flexor carpi radialis tendon or abductor pollicis longus tendon. TI arthroplasty by using the half of FCR tendon was firstly described in 1973^[7]. The first description of LRTI arthroplasty was first described in 1986^[37]. Although the strength and stability may not be restored fully with these procedures, it is possible to obtain a painless joint, as their main advantage^[44]. Other than tendons, interposition with fascia lata, chondral tissue, Gelfoam, Gore-Tex, Marlex, Artelon implants, *etc.*, were also reported^[45-48]. Due to increased complications with non-autologous tissue, autologous tissue interposition should be preferred^[45].

In a recent survey study among the active members of the American Academy for Surgery of the Hand, it was concluded that, trapeziectomy + LRTI was the treatment of choice by most surgeons and that the process of choosing treatment strategies was a question of future^[49]. Longer follow-up clinical results also support the use of LRTI arthroplasty^[50].

According to the current literature, three important results are obvious^[42,51-54]. Firstly the addition of LR or TI to trapeziectomy has no clinical superiority over trapeziectomy alone. Secondly, trapeziectomy with LRTI was found to have more complications than trapeziectomy

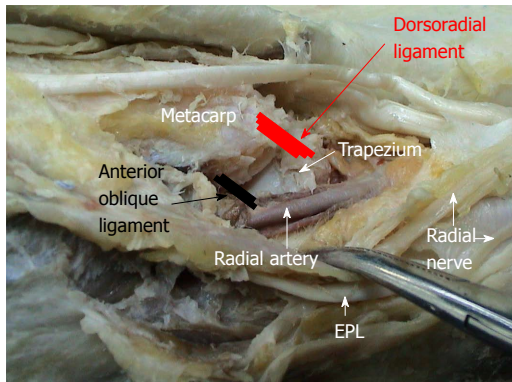


Figure 1 Anatomic dissection of the trapeziometacarpal joint, demonstrating dorsoradial ligament (red) and anterior oblique ligament (black). EPL: Extensor pollicis longus.

Table 2 Eaton-Littler classification of rhizarthrosis

Stage	Definition
I	Normal articular surface Possible widening of TMC joint indicating synovitis
II	Joint space narrowing Osteophytes < 2 mm Normal ST joint
III	Severe TMC destruction with subchondral sclerosis Osteophytes > 2 mm and presence of loose bodies Normal ST joint
IV	TMC and ST joints are both affected

TMC: Trapeziometacarpal; ST: Scaphotrapezial.

alone. At last, trapeziectomy alone or with LRTI have no evidence-based clinical superiority over other techniques.

TMC joint arthrodesis: Another alternative technique for the treatment of rhizarthrosis is the arthrodesis of this joint. The optimal position of the arthrodesis was defined classically as 45 degrees of abduction and antepulsion, slight pronation of the thumb^[53]. Since the first report on its results^[54], high-level randomized studies are still lacking. One problem related with arthrodesis is the relatively high rates of delayed union and non-union (8%-21%), especially when K-wire is used^[55-58]. Although complication and reoperation rates are higher than that of trapeziectomy or trapeziectomy + LRTI, this was not found to be significant clinically^[59]. In a recent prospective, randomized study by Vermuelen *et al.*^[60] arthrodesis was not recommended in the treatment of women who are forty years or older with stage II or III rhizarthrosis.

In conclusion, high-level randomized studies are still needed for definite conclusions of the clinical efficacy of TMC joint arthrodesis. So it should not be used as a first-line treatment especially in young patients.

TMC joint replacement: The first prosthetic replacement of TMC joint following trapeziectomy was performed by Swanson at late 1960s^[61]. In this technique, trapezial Silicastic implants were used. In the two main review

studies in the literature by Martou *et al.*^[53] and Wajon *et al.*^[54], it was pointed out that silicastic implants had high complication rates with only short term clinical satisfaction and that silicone arthroplasty had no additional benefits but comparable adverse effects when compared with trapeziectomy and LRTI, respectively. It was also revealed from these studies that these implants have more long-term complications such as subluxation, fractures and silicone synovitis^[62].

Total TMC joint arthroplasty has evolved over time since its first development at early 1970s^[63]. Currently, this option is advisable for stages II and III, with its reported mostly better outcomes and lesser implant failures^[53,64-67]. The amelioration of the outcomes and decrements of failures may be attributable to the gradual improvement of the quality of the implants. Prospective randomized studies with long-term follow-up are required in order to make concrete conclusion on various arthroplasty options and on their cost-effectiveness.

Thumb metacarpal osteotomy: The closing wedge abduction osteotomy at the level of proximal metacarpus of the thumb was firstly introduced in 1973^[68]. Although the studies lack both sufficient sample size and higher level of scientific evidence, it was advised to prefer this technique at earlier stages -at most stage I or II^[69].

Other treatment methods of denervation of TMC joint, reconstruction of the volar beak ligament, suture button suspensionplasty and role of arthroscopy: Besides the core treatment options mentioned before, there are other methods described in the literature for Rhizarthrosis, such as: denervation of the TMC joint, reconstruction of the volar beak ligament, suture button suspensionplasty and TMC joint arthroscopy^[70-72]. The common point for all of these procedures is that prospective, randomized, comparative studies are required in order to determine for using which method for which group of patients.

CONCLUSION

The TMC joint is a common region in the body, where OA is encountered, especially in the postmenopausal women. Although the exact etiology is not still certain, ligamentous laxity is a common finding in most of the cases. Regarding to the existing literature, the most commonly used treatment methods are conservative measures and trapeziectomy with LRTI. Moreover newer treatment methods have emerged in the recent years. In conclusion, if long-term prospective, randomized, comparative studies are performed, there will be an appropriate answer to choose the optimal treatment methods for each stage of rhizarthrosis.

REFERENCES

1. Peyron JG. Osteoarthritis. The epidemiologic viewpoint. *Clin Orthop Relat Res* 1986; (213): 13-19 [PMID: 3536247]

- 2 **Armstrong AL**, Hunter JB, Davis TR. The prevalence of degenerative arthritis of the base of the thumb in post-menopausal women. *J Hand Surg Br* 1994; **19**: 340-341 [PMID: 8077824 DOI: 10.1016/0266-7681(94)90085-X]
- 3 **Swigart CR**, Eaton RG, Glickel SZ, Johnson C. Splinting in the treatment of arthritis of the first carpometacarpal joint. *J Hand Surg Am* 1999; **24**: 86-91 [PMID: 10048521 DOI: 10.1053/jhsu.1999.jhsu24a0086]
- 4 **Clifton KB**, Rodner C, Wolf JM. Detection of relaxin receptor in the dorsoradial ligament, synovium, and articular cartilage of the trapeziometacarpal joint. *J Orthop Res* 2014; **32**: 1061-1067 [PMID: 24797570 DOI: 10.1002/jor.22640]
- 5 **Eaton RG**, Littler JW. A study of the basal joint of the thumb. Treatment of its disabilities by fusion. *J Bone Joint Surg Am* 1969; **51**: 661-668 [PMID: 5783846]
- 6 **Cho KO**. Translocation of the abductor pollicis longus tendon. A treatment for chronic subluxation of the thumb carpometacarpal joint. *J Bone Joint Surg Am* 1970; **52**: 1166-1170 [PMID: 5455344]
- 7 **Eaton RG**, Littler JW. Ligament reconstruction for the painful thumb carpometacarpal joint. *J Bone Joint Surg Am* 1973; **55**: 1655-1666 [PMID: 4804988]
- 8 **Pellegrini VD**, Olcott CW, Hollenberg G. Contact patterns in the trapeziometacarpal joint: the role of the palmar beak ligament. *J Hand Surg Am* 1993; **18**: 238-244 [PMID: 8463587 DOI: 10.1016/0363-5023(93)90354-6]
- 9 **Lin JD**, Karl JW, Strauch RJ. Trapeziometacarpal joint stability: the evolving importance of the dorsal ligaments. *Clin Orthop Relat Res* 2014; **472**: 1138-1145 [PMID: 23456188 DOI: 10.1007/s11999-013-2879-9]
- 10 **Haines RW**. The mechanism of rotation at the first carpometacarpal joint. *J Anat* 1944; **78**: 44-46 [PMID: 17104939]
- 11 **Napier JR**. The form and function of the carpo-metacarpal joint of the thumb. *J Anat* 1955; **89**: 362-369 [PMID: 13251966]
- 12 **Bojsen-Moller F**. Osteoligamentous guidance of the movements of the human thumb. *Am J Anat* 1976; **147**: 71-80 [PMID: 970347 DOI: 10.1002/aja.1001470106]
- 13 **Eaton RG**, Lane LB, Littler JW, Keyser JJ. Ligament reconstruction for the painful thumb carpometacarpal joint: a long-term assessment. *J Hand Surg Am* 1984; **9**: 692-699 [PMID: 6491213 DOI: 10.1016/S0363-5023(84)80015-5]
- 14 **Drewniany JJ**, Palmer AK, Flatt AE. The scaphotrapezial ligament complex: an anatomic and biomechanical study. *J Hand Surg Am* 1985; **10**: 492-498 [PMID: 4020059 DOI: 10.1016/S0363-5023(85)80070-8]
- 15 **Bettinger PC**, Linscheid RL, Berger RA, Cooney WP, An KN. An anatomic study of the stabilizing ligaments of the trapezium and trapeziometacarpal joint. *J Hand Surg Am* 1999; **24**: 786-798 [PMID: 10447171 DOI: 10.1053/jhsu.1999.0786]
- 16 **Bettinger PC**, Berger RA. Functional ligamentous anatomy of the trapezium and trapeziometacarpal joint (gross and arthroscopic). *Hand Clin* 2001; **17**: 151-168, vii [PMID: 11478038]
- 17 **Edmunds JO**. Current concepts of the anatomy of the thumb trapeziometacarpal joint. *J Hand Surg Am* 2011; **36**: 170-182 [PMID: 21193137 DOI: 10.1016/j.jhsa.2010.10.029]
- 18 **D'Agostino P**, Kerkhof FD, Shahabpour M, Moermans JP, Stockmans F, Vereecke EE. Comparison of the anatomical dimensions and mechanical properties of the dorsoradial and anterior oblique ligaments of the trapeziometacarpal joint. *J Hand Surg Am* 2014; **39**: 1098-1107 [PMID: 24810939 DOI: 10.1016/j.jhsa.2014.02.025]
- 19 **Ghavami A**, Oishi SN. Thumb trapeziometacarpal arthritis: treatment with ligament reconstruction tendon interposition arthroplasty. *Plast Reconstr Surg* 2006; **117**: 116e-128e [PMID: 16651933 DOI: 10.1097/01.prs.0000214652.31293.23]
- 20 **Pellegrini VD**. Osteoarthritis of the trapeziometacarpal joint: the pathophysiology of articular cartilage degeneration. I. Anatomy and pathology of the aging joint. *J Hand Surg Am* 1991; **16**: 967-974 [PMID: 1748767 DOI: 10.1016/S0363-5023(10)80054-1]
- 21 **Strauch RJ**, Behrman MJ, Rosenwasser MP. Acute dislocation of the carpometacarpal joint of the thumb: an anatomic and cadaver study. *J Hand Surg Am* 1994; **19**: 93-98 [PMID: 8169374 DOI: 10.1016/0363-5023(94)90229-1]
- 22 **Najima H**, Oberlin C, Alnot JY, Cadot B. Anatomical and biomechanical studies of the pathogenesis of trapeziometacarpal degenerative arthritis. *J Hand Surg Br* 1997; **22**: 183-188 [PMID: 9149983 DOI: 10.1016/S0266-7681(97)80058-7]
- 23 **Van Brenk B**, Richards RR, Mackay MB, Boynton EL. A biomechanical assessment of ligaments preventing dorsoradial subluxation of the trapeziometacarpal joint. *J Hand Surg Am* 1998; **23**: 607-611 [PMID: 9708373 DOI: 10.1016/S0363-5023(98)80045-2]
- 24 **Colman M**, Mass DP, Draganich LF. Effects of the deep anterior oblique and dorsoradial ligaments on trapeziometacarpal joint stability. *J Hand Surg Am* 2007; **32**: 310-317 [PMID: 17336836 DOI: 10.1016/j.jhsa.2006.12.002]
- 25 **Ladd AL**, Lee J, Hagert E. Macroscopic and microscopic analysis of the thumb carpometacarpal ligaments: a cadaveric study of ligament anatomy and histology. *J Bone Joint Surg Am* 2012; **94**: 1468-1477 [PMID: 22992815 DOI: 10.2106/JBJS.K.00329]
- 26 **Glickel SZ**, Kornstein AN, Eaton RG. Long-term follow-up of trapeziometacarpal arthroplasty with coexisting scaphotrapezial disease. *J Hand Surg Am* 1992; **17**: 612-620 [PMID: 1629539 DOI: 10.1016/0363-5023(92)90303-7]
- 27 **Eaton RG**, Floyd WE. Thumb metacarpophalangeal capsulodesis: an adjunct procedure to basal joint arthroplasty for collapse deformity of the first ray. *J Hand Surg Am* 1988; **13**: 449-453 [PMID: 3379288 DOI: 10.1016/S0363-5023(88)80029-7]
- 28 **Glickel SZ**. Clinical assessment of the thumb trapeziometacarpal joint. *Hand Clin* 2001; **17**: 185-195 [PMID: 11478041]
- 29 **Swanson AB**, deGoot Swanson G, Watermeier JJ. Trapezium implant arthroplasty. Long-term evaluation of 150 cases. *J Hand Surg Am* 1981; **6**: 125-141 [PMID: 7229288 DOI: 10.1016/S0363-5023(81)80165-7]
- 30 **Florack TM**, Miller RJ, Pellegrini VD, Burton RI, Dunn MG. The prevalence of carpal tunnel syndrome in patients with basal joint arthritis of the thumb. *J Hand Surg Am* 1992; **17**: 624-630 [PMID: 1629540 DOI: 10.1016/0363-5023(92)90305-9]
- 31 **Day CS**, Gelberman R, Patel AA, Vogt MT, Ditsios K, Boyer MI. Basal joint osteoarthritis of the thumb: a prospective trial of steroid injection and splinting. *J Hand Surg Am* 2004; **29**: 247-251 [PMID: 15043897 DOI: 10.1016/j.jhsa.2003.12.002]
- 32 **Karalezli N**, Ogun TC, Kartal S, Saracgil SN, Yel M, Tuncay I. The pain associated with intraarticular hyaluronic acid injections for trapeziometacarpal osteoarthritis. *Clin Rheumatol* 2007; **26**: 569-571 [PMID: 16799752 DOI: 10.1007/s10067-006-0354-7]
- 33 **Moran SL**, Duymaz A, Karabekmez FE. The efficacy of hyaluronic acid in the treatment of osteoarthritis of the trapeziometacarpal joint. *J Hand Surg Am* 2009; **34**: 942-944 [PMID: 19411002 DOI: 10.1016/j.jhsa.2009.03.009]
- 34 **Swindells MG**, Logan AJ, Armstrong DJ, Chan P, Burke FD, Lindau TR. The benefit of radiologically-guided steroid injections for trapeziometacarpal osteoarthritis. *Ann R Coll Surg Engl* 2010; **92**: 680-684 [PMID: 20659360 DOI: 10.1308/003588410X12699663905078]
- 35 **Becker SJ**, Bot AG, Curley SE, Jupiter JB, Ring D. A prospective randomized comparison of neoprene vs thermoplast hand-based thumb spica splinting for trapeziometacarpal arthrosis. *Osteoarthritis Cartilage* 2013; **21**: 668-675 [PMID: 23458785 DOI: 10.1016/j.joca.2013.02.006]
- 36 **Maddali-Bongi S**, Del Rosso A, Galluccio F, Sigismondi F, Matucci-Cerenic M. Is an intervention with a custom-made splint and an educational program useful on pain in patients with trapeziometacarpal joint osteoarthritis in a daily clinical setting? *Int J Rheum Dis* 2014 Mar 6; Epub ahead of print [PMID: 24597788 DOI: 10.1111/1756-185X]
- 37 **Burton RI**, Pellegrini VD. Surgical management of basal joint arthritis of the thumb. Part II. Ligament reconstruction with tendon interposition arthroplasty. *J Hand Surg Am* 1986; **11**: 324-332 [PMID: 3711604]
- 38 **Marks M**, Schoones JW, Kolling C, Herren DB, Goldhahn J, Vliet Vlieland TP. Outcome measures and their measurement properties for trapeziometacarpal osteoarthritis: a systematic literature review. *J Hand Surg Eur Vol* 2013; **38**: 822-838 [PMID: 23649014 DOI: 10.1177/1753193413488301]

- 39 **Gervis WH.** Excision of the trapezium for osteoarthritis of the trapezio-metacarpal joint. *J Bone Joint Surg Br* 1949; **31B**: 537-559, illust [PMID: 15397137]
- 40 **Jones NF, Maser BM.** Treatment of arthritis of the trapezio-metacarpal joint with trapeziectomy and hematoma arthroplasty. *Hand Clin* 2001; **17**: 237-243 [PMID: 11478045]
- 41 **Varley GW, Calvey J, Hunter JB, Barton NJ, Davis TR.** Excision of the trapezium for osteoarthritis at the base of the thumb. *J Bone Joint Surg Br* 1994; **76**: 964-968 [PMID: 7983129]
- 42 **Davis TR, Brady O, Dias JJ.** Excision of the trapezium for osteoarthritis of the trapeziometacarpal joint: a study of the benefit of ligament reconstruction or tendon interposition. *J Hand Surg Am* 2004; **29**: 1069-1077 [PMID: 15576217 DOI: 10.1016/j.jhsa.2004.06.017]
- 43 **Ritchie JF, Belcher HJ.** A comparison of trapeziectomy via anterior and posterior approaches. *J Hand Surg Eur Vol* 2008; **33**: 137-143 [PMID: 18443051 DOI: 10.1177/1753193407087571]
- 44 **Pellegrini VD, Burton RI.** Surgical management of basal joint arthritis of the thumb. Part I. Long-term results of silicone implant arthroplasty. *J Hand Surg Am* 1986; **11**: 309-324 [PMID: 3711603]
- 45 **Muermans S, Coenen L.** Interpositional arthroplasty with Gore-Tex, Marlex or tendon for osteoarthritis of the trapeziometacarpal joint. A retrospective comparative study. *J Hand Surg Br* 1998; **23**: 64-68 [PMID: 9571484 DOI: 10.1016/S0266-7681(98)80222-2]
- 46 **Park MJ, Lichtman G, Christian JB, Weintraub J, Chang J, Hentz VR, Ladd AL, Yao J.** Surgical treatment of thumb carpometacarpal joint arthritis: a single institution experience from 1995-2005. *Hand (N Y)* 2008; **3**: 304-310 [PMID: 18780018 DOI: 10.1007/s11552-008-9109-z]
- 47 **Jörheim M, Isaxon I, Flondell M, Kalén P, Atroshi I.** Short-term outcomes of trapeziometacarpal arthroplasty compared with tendon suspension interposition arthroplasty for osteoarthritis: a matched cohort study. *J Hand Surg Am* 2009; **34**: 1381-1387 [PMID: 19683881 DOI: 10.1016/j.jhsa.2009.04.016]
- 48 **Pritchett JW, Habryl LS.** A promising thumb Basal joint hemiarthroplasty for treatment of trapeziometacarpal osteoarthritis. *Clin Orthop Relat Res* 2012; **470**: 2756-2763 [PMID: 22585348 DOI: 10.1007/s11999-012-2367-7]
- 49 **Wolf JM, Delaronde S.** Current trends in nonoperative and operative treatment of trapeziometacarpal osteoarthritis: a survey of US hand surgeons. *J Hand Surg Am* 2012; **37**: 77-82 [PMID: 22119601 DOI: 10.1016/j.jhsa.2011.10.010]
- 50 **Tomaino MM, Pellegrini VD, Burton RI.** Arthroplasty of the basal joint of the thumb. Long-term follow-up after ligament reconstruction with tendon interposition. *J Bone Joint Surg Am* 1995; **77**: 346-355 [PMID: 7890782]
- 51 **Belcher HJ, Nicholl JE.** A comparison of trapeziectomy with and without ligament reconstruction and tendon interposition. *J Hand Surg Br* 2000; **25**: 350-356 [PMID: 11058002 DOI: 10.1054/jhsb.2000.0431]
- 52 **Davis TR, Pace A.** Trapeziectomy for trapeziometacarpal joint osteoarthritis: is ligament reconstruction and temporary stabilisation of the pseudarthrosis with a Kirschner wire important? *J Hand Surg Eur Vol* 2009; **34**: 312-321 [PMID: 19321528 DOI: 10.1177/1753193408098483]
- 53 **Martou G, Veltri K, Thoma A.** Surgical treatment of osteoarthritis of the carpometacarpal joint of the thumb: a systematic review. *Plast Reconstr Surg* 2004; **114**: 421-432 [PMID: 15277809 DOI: 10.1097/01.PRS.0000131989.86319.B1]
- 54 **Wajon A, Carr E, Edmunds I, Ada L.** Surgery for thumb (trapeziometacarpal joint) osteoarthritis. *Cochrane Database Syst Rev* 2009; **(4)**: CD004631 [PMID: 19821330 DOI: 10.1002/14651858.CD004631.pub3]
- 55 **Muller GM.** Arthrodesis of the trapezio-metacarpal joint for osteoarthritis. *J Bone Joint Surg Br* 1949; **31B**: 540-552, illust [PMID: 15397138]
- 56 **Taylor EJ, Desari K, D'Arcy JC, Bonnici AV.** A comparison of fusion, trapeziectomy and silastic replacement for the treatment of osteoarthritis of the trapeziometacarpal joint. *J Hand Surg Br* 2005; **30**: 45-49 [PMID: 15620491 DOI: 10.1016/j.jhsb.2004.08.006]
- 57 **Raven EE, Kerkhoffs GM, Rutten S, Marsman AJ, Marti RK, Albers GH.** Long term results of surgical intervention for osteoarthritis of the trapeziometacarpal joint: comparison of resection arthroplasty, trapeziectomy with tendon interposition and trapezio-metacarpal arthrodesis. *Int Orthop* 2007; **31**: 547-554 [PMID: 17021835 DOI: 10.1007/s00264-006-0217-5]
- 58 **Singh HP, Hoare C, Beresford-Cleary N, Anakwe R, Hayton M.** Nonunion after trapeziometacarpal arthrodesis: comparison between K-wire and internal fixation. *J Hand Surg Eur Vol* 2015; **40**: 351-355 [PMID: 24916633]
- 59 **Forseth MJ, Stern PJ.** Complications of trapeziometacarpal arthrodesis using plate and screw fixation. *J Hand Surg Am* 2003; **28**: 342-345 [PMID: 12671869 DOI: 10.1053/jhsu.2003.50042]
- 60 **Vermeulen GM, Brink SM, Slijper H, Feitz R, Moojen TM, Hovius SE, Selles RW.** Trapeziometacarpal arthrodesis or trapeziectomy with ligament reconstruction in primary trapeziometacarpal osteoarthritis: a randomized controlled trial. *J Bone Joint Surg Am* 2014; **96**: 726-733 [PMID: 24806009 DOI: 10.2106/JBJS.L.01344]
- 61 **Swanson AB.** Silicone rubber implants for replacement of arthritis or destroyed joints in the hand. *Surg Clin North Am* 1968; **48**: 1113-1127 [PMID: 4879121]
- 62 **Vermeulen GM, Slijper H, Feitz R, Hovius SE, Moojen TM, Selles RW.** Surgical management of primary thumb carpometacarpal osteoarthritis: a systematic review. *J Hand Surg Am* 2011; **36**: 157-169 [PMID: 21193136 DOI: 10.1016/j.jhsa.2010.10.028]
- 63 **de la Caffiniere JY, Aucouturier P.** Trapezio-metacarpal arthroplasty by total prosthesis. *Hand* 1979; **11**: 41-46 [PMID: 488776]
- 64 **Amadio PC, De Silva SP.** Comparison of the results of trapezio-metacarpal arthrodesis and arthroplasty in men with osteoarthritis of the trapeziometacarpal joint. *Ann Chir Main Memb Super* 1990; **9**: 358-363 [PMID: 1705132 DOI: 10.1016/S0753-9053(05)80509-5]
- 65 **Alnot JY, Muller GP.** A retrospective review of 115 cases of surgically-treated trapeziometacarpal osteoarthritis. *Rev Rhum Engl Ed* 1998; **65**: 95-108 [PMID: 9540118]
- 66 **Ulrich-Vinther M, Puggaard H, Lange B.** Prospective 1-year follow-up study comparing joint prosthesis with tendon interposition arthroplasty in treatment of trapeziometacarpal osteoarthritis. *J Hand Surg Am* 2008; **33**: 1369-1377 [PMID: 18929203 DOI: 10.1016/j.jhsa.2008.04.028]
- 67 **Lluch AL, Garcia-Elias M, Lluch AB.** Arthroplasty of the scaphoid-trapezium-trapezoid and carpometacarpal joints. *Hand Clin* 2013; **29**: 57-68 [PMID: 23168028 DOI: 10.1016/j.hcl.2012.08.021]
- 68 **Wilson JN.** Basal osteotomy of the first metacarpal in the treatment of arthritis of the carpometacarpal joint of the thumb. *Br J Surg* 1973; **60**: 854-858 [PMID: 4752729]
- 69 **Atroshi I, Axelsson G, Nilsson EL.** Osteotomy versus tendon arthroplasty in trapeziometacarpal arthrosis: 17 patients followed for 1 year. *Acta Orthop Scand* 1998; **69**: 287-290 [PMID: 9703405 DOI: 10.3109/17453679809000932]
- 70 **Hartigan BJ, Stern PJ, Kieffhaber TR.** Thumb carpometacarpal osteoarthritis: arthrodesis compared with ligament reconstruction and tendon interposition. *J Bone Joint Surg Am* 2001; **83-A**: 1470-1478 [PMID: 11679595]
- 71 **Anley C, Ikram A, Y Elghawail, Wells M.** Using a mini-TightRope (Arthrex) alone, to suspend the thumb metacarpal after a trapeziectomy: Is this a viable option? 1-year and 2 year results. *J Hand Surg Eur* 2014; **39E** Suppl: 92
- 72 **Slutsky DJ.** The role of arthroscopy in trapeziometacarpal arthritis. *Clin Orthop Relat Res* 2014; **472**: 1173-1183 [PMID: 23129468 DOI: 10.1007/s11999-012-2673-0]

P- Reviewer: Zhai G S- Editor: Tian YL
L- Editor: A E- Editor: Jiao XK



Ins and outs of *Helicobacter pylori* association with autoimmune rheumatic diseases

Jibran Sualeh Muhammad, Syed Faisal Zaidi, Muhammad Ishaq

Jibran Sualeh Muhammad, Department of Gastroenterology and Hematology, Faculty of Medicine, University of Toyama, Toyama 930-0914, Japan

Syed Faisal Zaidi, Department of Basic Medical Sciences, College of Medicine, King Saud bin Abdulaziz University of Health Sciences, Jeddah 21423, Saudi Arabia

Muhammad Ishaq, Department of Internal Medicine, Jinnah Medical College Hospital, Korangi, Karachi 74000, Pakistan

Author contributions: Muhammad JS designed research, performed research; wrote the paper; Zaidi SF and Ishaq M critically reviewed and corrected the manuscript; all authors have approved the final manuscript.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Jibran Sualeh Muhammad, Department of Gastroenterology and Hematology, Faculty of Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. dr.jibran@live.com
Telephone: +81-80-42501703
Fax: +81-76-4345027

Received: November 6, 2014
Peer-review started: November 10, 2014
First decision: December 26, 2014
Revised: January 28, 2015
Accepted: March 30, 2015
Article in press: April 4, 2015
Published online: July 12, 2015

Abstract

Helicobacter pylori (*H. pylori*) infection is widely prevalent throughout worldwide. *H. pylori* manage a long-term survival in hostile environment of human stomach leading to peptic ulcer diseases and gastric cancer. But mostly infected person remains asymptomatic. Its chronic interaction with immune system makes *H. pylori* as an attractive candidate for the researchers to study its association with autoimmune diseases. This article presents a review of the literature on the association of *H. pylori* infection in selective autoimmune rheumatic diseases (RD). The authors used MeSH terms "*Helicobacter pylori*" with "rheumatoid arthritis," "systemic lupus erythematosus," or "fibromyalgia" to search PubMed database. All relevant studies identified were included. Despite extensive medical advancement many questions on role of *H. pylori* infection in autoimmune RD still remain unanswered. Further studies are therefore needed to address the role of *H. pylori* in pathogenesis of RD.

Key words: Autoimmunity; Systemic lupus erythematosus; Rheumatoid arthritis; Fibromyalgia; *Helicobacter pylori*

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: *Helicobacter pylori* (*H. pylori*) infection is widely prevalent throughout worldwide. Its chronic interaction with immune system makes *H. pylori* is an attractive candidate for the researchers to study its association with autoimmune disorders. This study presents a review of the literature on the *H. pylori* association with selective autoimmune rheumatic disorders. Despite extensive medical advancement many questions on the association of *H. pylori* infection with autoimmune rheumatic disorders still remain unanswered. More studies are therefore required to address the role of *H. pylori* infection in

pathogenesis of rheumatic diseases.

Muhammad JS, Zaidi SF, Ishaq M. Ins and outs of *Helicobacter pylori* association with autoimmune rheumatic diseases. *World J Rheumatol* 2015; 5(2): 96-100 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i2/96.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i2.96>

INTRODUCTION

Rheumatic diseases (RD) include disorders related to joints and connective tissue. Generally these disorders have an autoimmune origin that is associated with progressive disability, systemic complications and early death. Involvement of musculoskeletal system, central and peripheral nervous systems, and other organs such as blood vessels, bone marrow, eye, heart, kidneys, lungs, skin and salivary glands may occurs in more than 40% of patients with RD over a lifetime of disease^[1-3].

Typically initial *Helicobacter pylori* (*H. pylori*) infection is acquired by oral ingestion during the early childhood and *H. pylori* will persist for life in untreated cases^[4]. Frequency of *H. pylori* infection is approximately 80% in underdeveloped countries compared to 50% in developed parts of the world, correlating the disease prevalence with poor socioeconomic status^[5]. Clinically *H. pylori* infection leads to gastric diseases such as gastric ulcer, mucosa-associated lymphoid tissue lymphoma and gastric cancer^[6]. *H. pylori* infection can induce a chronic immune response in the host cells (Figure 1), suggesting a possible role of *H. pylori* in the development of autoimmune disorders^[7].

Autoimmune RD are thought to depend upon host genetic susceptibility interaction with environmental factors^[8]. Amongst various environmental factors, infections agents plays significant role and have been studied extensively^[9]. Infectious agents include bacteria, viruses and parasites. Out of all bacterial species implicated in non-organ specific autoimmune disorders, *H. pylori* have received much attention by researchers^[10]. The purpose of this study was to summarize the recent literature on selected RD with autoimmune pathophysiologic mechanisms, which shows positive or negative evidence in relation to *H. pylori*-associated autoimmune rheumatic disorders.

H. PYLORI -INDUCED IMMUNOLOGIC RESPONSE

H. pylori have evolved various survival mechanisms to combat harsh acidic gastric environment and to suppress host immune response. Urease is a key virulence factor of *H. pylori* which is required for bacterial colonization to gastric mucosa; also it is a potent immunogen that elicits a strong immune response^[11]. Urease also serves to promote bacterial motility by decreasing gastric mucous

viscosity^[12]. In order to evade host innate immune response, the bacterium is also capable of altering its own cell wall antigens rendering antigens to relatively non-antigenic^[13].

H. pylori Infection induces a number of immune responses in the host cell by bacterial adhesion to cells and leading to chronic inflammation (Figure 1)^[11]. Pathogen can bind to class II major histocompatibility complex present on the cell membrane of gastric epithelial cells leading to apoptosis^[14]. CagA translocate inside the gastric epithelial cells to induce high levels of inflammatory cytokines such as IL-6, IL-8, IL-10 and TNF- α ^[15]. The VacA protein interacts with lymphocytes resulting in blockage of IL-2-mediated T-lymphocyte proliferation^[16].

A study by Jackson *et al*^[17] shows elevated C-reactive protein in chronic *H. pylori* infected patients. Few other reports have demonstrated that chronic *H. pylori* infection leads to activation and survival of B lymphocytes to produce rheumatoid factor (IgM), antisingle-stranded DNA (anti-ssDNA) and anti-double-stranded DNA (anti-dsDNA) antibody and antiphosphatidylcholine antibody^[18,19]. Instead of clearing *H. pylori*, these antibodies result in the synthesis of anti-H⁺/K⁺-ATPase antibodies^[20]. These auto-reactive autoantibodies have been involved in the progress of atrophic gastritis. Complex and persistent interaction between host immune system and pathogen might cause immune dysregulation and consequent development of autoimmune RD in susceptible patients.

H. PYLORI-ASSOCIATED RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disorder primarily of unknown origin. The arthritis in RA is symmetrical destructive polyarthritis affecting almost all joints of the body^[21]. Various environmental and genetic factors may contribute to disease onset and severity^[22]. Search for the role of microbial association with RA dates back to 19th century^[23], and several viral and bacterial pathogens such as hepatitis C virus, parvovirus B19, Epstein-Barr virus (EBV), *Proteus mirabilis*, and *Mycobacterium tuberculosis* may have a role in its pathogenesis^[24]. However the role of *H. pylori* infection in the pathogenesis of RA is controversial.

A cohort study on RA patients showed 80.4% to be seropositive for *H. pylori*. However, this was not significantly different from the control group^[25]. A study from Japan by Tanaka *et al*^[26] reported 49.3% of RA patients to have *H. pylori* antibodies, which was lesser compared with the healthy population. Another Japanese study reported a much higher prevalence (61.4%) of *H. pylori* infection in RA patients^[27]. A study by Zentilin *et al*^[28] showed severity of RA in *H. pylori* seropositive patients and suggested improvement in clinical symptoms after *H. pylori* eradication.

A direct role of *H. pylori* infection in RA pathogenesis seems controversial. Besides studies given above, few *in vitro* studies also suggest association of *H. pylori*

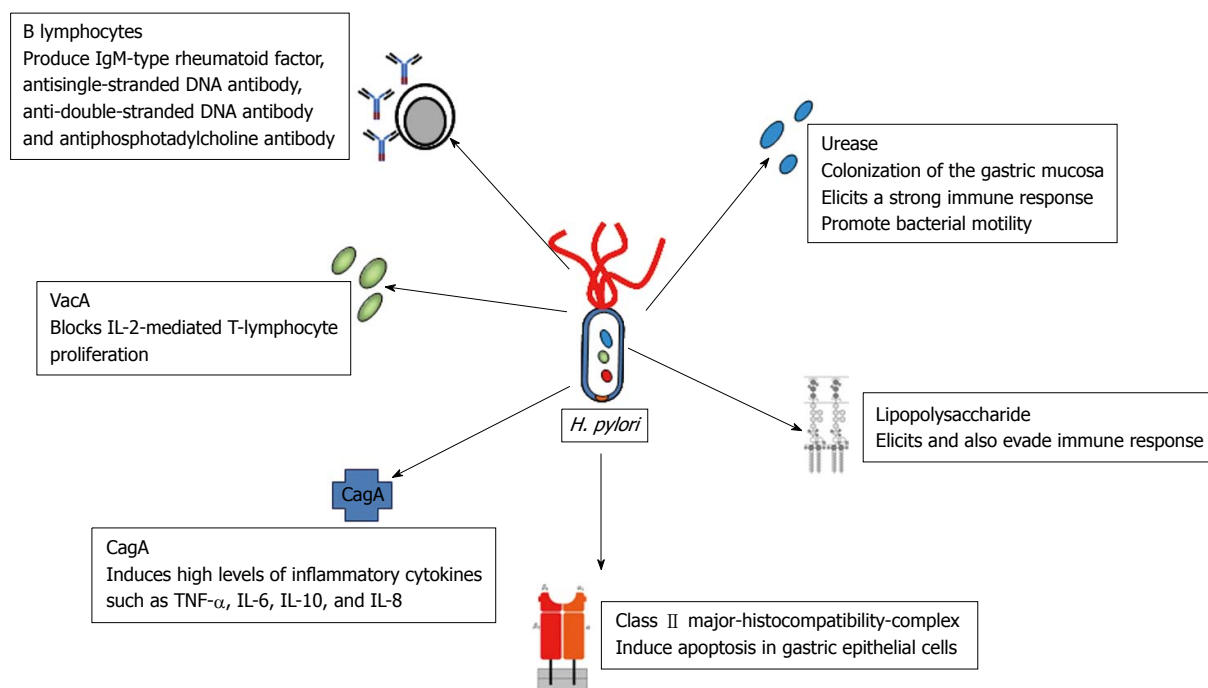


Figure 1 *Helicobacter pylori* mediated immunologic responses. IL: Interleukin; TNF: Tumor necrosis factor; *H. pylori*: *Helicobacter pylori*; DNA: Deoxyribonucleic acid.

in development of autoimmunity in RA patients. Like Yamanishi *et al.*^[18] found chronic stimulation of B cells due to urease produced by *H. pylori*. This ultimately leads to the generation of rheumatoid factor. But, on the other hand, the clinical evidence for association between RA and *H. pylori* infection is less substantial and inconclusive. Although RA patients have a high risk of developing peptic ulcer disease (PUD), but the abundant use of non-steroidal anti-inflammatory drugs in the RA patient may also contribute to the risk for PUD development^[26]. Furthermore, studies have shown that not only RA patients but also other connective tissue disease patients have a prevalence of *H. pylori* infection nearly similar to that of control group^[25,26]. Hence, the overall data regarding the association of *H. pylori* infection with RA pathogenesis remains controversial. Further specific *in vitro* and large scale clinical trials are required to provide clear understanding of this relationship.

H. PYLORI-ASSOCIATED SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune chronic inflammatory disease affecting multi-system. Immunologic abnormalities include the production of a number of autoantibodies, such as anti-dsDNA and anti-nuclear antibodies^[29]. A number of microorganisms such as parvovirus B19, EBV and cytomegalovirus are associated in the disease pathogenesis^[24].

H. pylori prevalence has been studied in SLE patients, but unlike other infectious agents, results vary significantly in published literature. A study by Kalabay *et*

al.^[30] demonstrated similar frequency of *H. pylori* infection in SLE patients and control group. Also a study by Showji *et al.*^[31] demonstrated that patients with SLE have lesser anti-*H. pylori* antibodies in contrast to patients with some other connective tissue diseases. However, Yamanashi *et al.*^[18] have shown *in-vivo* induction of anti-single stranded DNA antibodies by *H. pylori* urease. In contrast to this evidence of SLE related antibody induction by *H. pylori*, fewer studies have shown protective role of *H. pylori*-infection in patients with SLE. Such as, Sawalha *et al.*^[32] have compared 466 SLE patients to matched control showing lower anti-*H. pylori* sero-positivity in SLE patients (36.5%:42.9%). Furthermore, in this study African American old age sero-positive females developed SLE more frequently compared to sero-negative females. Hence suggesting that *H. pylori*-infection have a protective role in the development of SLE is specific to this population group.

H. PYLORI-ASSOCIATED FIBROMYALGIA

Fibromyalgia (FMG), a chronic pain disorder, is associated with widespread musculoskeletal pain, stiffness, fatigue, anxiety, cognitive dysfunction, sleep difficulties and depression. Etiology and pathogenesis of FMG remains unknown^[33]. Studies have evaluated association of FMG with bacterial and viral infection, however literature regarding specific role of *H. pylori*-infection in FMG development is inadequate. Microorganisms might contribute to the development of FMG by activation of inflammatory cytokines leading towards neuroendocrine abnormalities^[34].

A study by Malt *et al.*^[35] shows that about 33% of the subjects were *H. pylori* positive in both FMG and control

group, therefore they concluded that *H. pylori*-infection was not associated with psychological changes in both diseased and control subjects. A recent study by Akkaya *et al.*^[36] demonstrated an association of *H. pylori*-infection with FMG patients and compared to similar gender control group. The FMG patients demonstrated higher frequency of an anti-*H. pylori* antibody (IgG) was seen in when compared to the control group, (30.8% and 17.1% respectively. Further, amongst FMG patients' depression and anxiety levels were not different between *H. pylori*-infected FMG patients or un-infected FMG patients.

CONCLUSION

The unique ability of *H. pylori* to chronically infect human gastric mucosa to activate inflammation and host immunological response suggests its role in autoimmune diseases. Associations with few autoimmune diseases are strong^[7], whereas association of *H. pylori* infection with autoimmune RD remains controversial. To develop better understanding of *H. pylori*-association with RD further molecular and clinical research studies with larger sample sizes are warranted.

REFERENCES

- Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. *Arthritis Rheum* 1996; **39**: 1-8 [PMID: 8546717 DOI: 10.1002/art.1780390102]
- McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011; **365**: 2205-2219 [PMID: 22150039 DOI: 10.1056/NEJMra1004965]
- Myasoedova E, Crowson CS, Turesson C, Gabriel SE, Matteson EL. Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995-2007 versus 1985-1994: a population-based study. *J Rheumatol* 2011; **38**: 983-989 [PMID: 21459933 DOI: 10.3899/jrheum.101133]
- Everhart JE. Recent developments in the epidemiology of Helicobacter pylori. *Gastroenterol Clin North Am* 2000; **29**: 559-578 [PMID: 11030073 DOI: 10.1016/S0889-8553(05)70130-8]
- Muhammad JS, Zaidi SF, Sugiyama T. Epidemiological ins and outs of helicobacter pylori: a review. *J Pak Med Assoc* 2012; **62**: 955-959 [PMID: 23139983]
- Muhammad JS, Sugiyama T, Zaidi SF. Gastric pathophysiological ins and outs of helicobacter pylori: a review. *J Pak Med Assoc* 2013; **63**: 1528-1533 [PMID: 24397100]
- Smyk DS, Koutsoumpas AL, Mytilinaiou MG, Rigopoulou EI, Sakkas LI, Bogdanos DP. Helicobacter pylori and autoimmune disease: cause or bystander. *World J Gastroenterol* 2014; **20**: 613-629 [PMID: 24574735 DOI: 10.3748/wjg.v20.i3.613]
- Smyk D, Rigopoulou EI, Baum H, Burroughs AK, Vergani D, Bogdanos DP. Autoimmunity and environment: am I at risk? *Clin Rev Allergy Immunol* 2012; **42**: 199-212 [PMID: 21337133 DOI: 10.1007/s12016-011-8259-x]
- Bogdanos DP, Smyk DS, Invernizzi P, Rigopoulou EI, Blank M, Pouria S, Shoenfeld Y. Infectome: a platform to trace infectious triggers of autoimmunity. *Autoimmun Rev* 2013; **12**: 726-740 [PMID: 23266520 DOI: 10.1016/j.autrev.2012.12.005]
- Ram M, Barzilai O, Shapira Y, Anaya JM, Tincani A, Stojanovich L, Bombardieri S, Bizzaro N, Kivity S, Agmon Levin N, Shoenfeld Y. Helicobacter pylori serology in autoimmune diseases - fact or fiction? *Clin Chem Lab Med* 2013; **51**: 1075-1082 [PMID: 23079514 DOI: 10.1515/cclm-2012-0477]
- Suerbaum S, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]
- McGee DJ, Mobley HL. Mechanisms of Helicobacter pylori infection: bacterial factors. *Curr Top Microbiol Immunol* 1999; **241**: 155-180 [PMID: 10087661 DOI: 10.1007/978-3-642-60013-5_9]
- Peek RM, Fiske C, Wilson KT. Role of innate immunity in Helicobacter pylori-induced gastric malignancy. *Physiol Rev* 2010; **90**: 831-858 [PMID: 20664074 DOI: 10.1152/physrev.00039.2009]
- Fan X, Gunasena H, Cheng Z, Espejo R, Crowe SE, Ernst PB, Reyes VE. Helicobacter pylori urease binds to class II MHC on gastric epithelial cells and induces their apoptosis. *J Immunol* 2000; **165**: 1918-1924 [PMID: 10925273 DOI: 10.4049/jimmunol.165.4.1918]
- Kim SY, Lee YC, Kim HK, Blaser MJ. Helicobacter pylori CagA transfection of gastric epithelial cells induces interleukin-8. *Cell Microbiol* 2006; **8**: 97-106 [PMID: 16367869 DOI: 10.1111/j.1462-5822.2005.00603.x]
- Sundrud MS, Torres VJ, Unutmaz D, Cover TL. Inhibition of primary human T cell proliferation by Helicobacter pylori vacuolating toxin (VacA) is independent of VacA effects on IL-2 secretion. *Proc Natl Acad Sci USA* 2004; **101**: 7727-7732 [PMID: 15128946 DOI: 10.1073/pnas.0401528101]
- Jackson L, Britton J, Lewis SA, McKeever TM, Atherton J, Fullerton D, Fogarty AW. A population-based epidemiologic study of Helicobacter pylori infection and its association with systemic inflammation. *Helicobacter* 2009; **14**: 108-113 [PMID: 19751435]
- Yamanishi S, Iizumi T, Watanabe E, Shimizu M, Kamiya S, Nagata K, Kumagai Y, Fukunaga Y, Takahashi H. Implications for induction of autoimmunity via activation of B-1 cells by Helicobacter pylori urease. *Infect Immun* 2006; **74**: 248-256 [PMID: 16368978 DOI: 10.1128/IAI.74.1.248-256.2006]
- Kobayashi F, Watanabe E, Nakagawa Y, Yamanishi S, Norose Y, Fukunaga Y, Takahashi H. Production of autoantibodies by murine B-1a cells stimulated with Helicobacter pylori urease through toll-like receptor 2 signaling. *Infect Immun* 2011; **79**: 4791-4801 [PMID: 21947775 DOI: 10.1128/IAI.05808-11]
- Amedei A, Bergman MP, Appelmelk BJ, Azzurri A, Benagiano M, Tamburini C, van der Zee R, Telford JL, Vandenbroucke-Grauls CM, D'Elios MM, Del Prete G. Molecular mimicry between Helicobacter pylori antigens and H+, K+ --adenosine triphosphatase in human gastric autoimmunity. *J Exp Med* 2003; **198**: 1147-1156 [PMID: 14568977 DOI: 10.1084/jem.20030530]
- Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet* 2001; **358**: 903-911 [PMID: 11567728 DOI: 10.1016/S0140-6736(01)06075-5]
- Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010; **376**: 1094-1108 [PMID: 20870100 DOI: 10.1016/S0140-6736(10)60826-4]
- Benedek TG. The history of bacteriologic concepts of rheumatic fever and rheumatoid arthritis. *Semin Arthritis Rheum* 2006; **36**: 109-123 [PMID: 16884972 DOI: 10.1016/j.semarthrit.2006.05.001]
- Pordeus V, Szyper-Kravitz M, Levy RA, Vaz NM, Shoenfeld Y. Infections and autoimmunity: a panorama. *Clin Rev Allergy Immunol* 2008; **34**: 283-299 [PMID: 18231878 DOI: 10.1007/s12016-007-8048-8]
- Meron MK, Amital H, Shepshelovich D, Barzilai O, Ram M, Anaya JM, Gerli R, Bizzaro N, Shoenfeld Y. Infectious aspects and the etiopathogenesis of rheumatoid arthritis. *Clin Rev Allergy Immunol* 2010; **38**: 287-291 [PMID: 19575154 DOI: 10.1007/s12016-009-8158-6]
- Tanaka E, Singh G, Saito A, Syouji A, Yamada T, Urano W, Nakajima A, Taniguchi A, Tomatsu T, Hara M, Saito T, Kamatani N, Yamanaka H. Prevalence of Helicobacter pylori infection and risk of upper gastrointestinal ulcer in patients with rheumatoid arthritis in Japan. *Mod Rheumatol* 2005; **15**: 340-345 [PMID: 17029090 DOI: 10.3109/s10165-005-0419-5]
- Ishikawa N, Fuchigami T, Matsumoto T, Kobayashi H, Sakai Y, Tabata H, Takubo N, Yamamoto S, Nakanishi M, Tomioka K, Fujishima M. Helicobacter pylori infection in rheumatoid arthritis: effect of drugs on prevalence and correlation with gastroduodenal

- lesions. *Rheumatology* (Oxford) 2002; **41**: 72-77 [PMID: 11792883 DOI: 10.1093/rheumatology/41.1.72]
- 28 **Zentilin P**, Serio B, Dulbecco P, Caratto E, Iiritano E, Fasciolo D, Bilardi C, Mansi C, Testa E, Savarino V. Eradication of *Helicobacter pylori* may reduce disease severity in rheumatoid arthritis. *Aliment Pharmacol Ther* 2002; **16**: 1291-1299 [PMID: 12144579 DOI: 10.1046/j.1365-2036.2002.01284.x]
 - 29 **Lisnevskaja L**, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet* 2014; **384**: 1878-1888 [PMID: 24881804 DOI: 10.1016/S0140-6736(14)60128-8]
 - 30 **Kalabay L**, Fekete B, Cziráj L, Horváth L, Doha MR, Veres A, Fonyad G, Horváth A, Viczian A, Singh M, Hoffer I, Füst G, Romics L, Prohászka Z. *Helicobacter pylori* infection in connective tissue disorders is associated with high levels of antibodies to mycobacterial hsp65 but not to human hsp60. *Helicobacter* 2002; **7**: 250-256 [PMID: 12165033 DOI: 10.1046/j.1523-5378.2002.00092.x]
 - 31 **Showji Y**, Nozawa R, Sato K, Suzuki H. Seroprevalence of *Helicobacter pylori* infection in patients with connective tissue diseases. *Microbiol Immunol* 1996; **40**: 499-503 [PMID: 8865155 DOI: 10.1111/j.1348-0421.1996.tb01100.x]
 - 32 **Sawalha AH**, Schmid WR, Binder SR, Bacino DK, Harley JB. Association between systemic lupus erythematosus and *Helicobacter pylori* seronegativity. *J Rheumatol* 2004; **31**: 1546-1550 [PMID: 15290733]
 - 33 **Goldenberg DL**. Diagnosis and differential diagnosis of fibromyalgia. *Am J Med* 2009; **122**: S14-S21 [PMID: 19962492 DOI: 10.1016/j.amjmed.2009.09.007]
 - 34 **Goldenberg DL**. Do infections trigger fibromyalgia? *Arthritis Rheum* 1993; **36**: 1489-1492 [PMID: 8240426]
 - 35 **Malt EA**, Olafsson S, Ursin H. Fibromyalgia a manifestation of *Helicobacter pylori* infection? *Scand J Rheum* 2004; **33**: 131 [DOI: 10.1080/03009740410006826-1468]
 - 36 **Akkaya N**, Akkaya S, Polat Y, Turk M, Turk T, Turhal E, Sahin F. *Helicobacter pylori* seropositivity in fibromyalgia syndrome. *Clin Rheumatol* 2011; **30**: 43-49 [PMID: 21120564 DOI: 10.1007/s10067-010-1618-9]

P- Reviewer: Agarwal V, Cavallasca JA, Enlander D, Martinez-Lostao L, Rothschild BM **S- Editor:** Tian YL
L- Editor: A **E- Editor:** Jiao XK



Pyoderma gangrenosum: An important dermatologic condition occasionally associated with rheumatic diseases

Toshiyuki Yamamoto

Toshiyuki Yamamoto, Department of Dermatology, Fukushima Medical University, Fukushima 960-1295, Japan

Author contributions: Yamamoto T solely contributed to this work.

Conflict-of-interest statement: None declared.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Toshiyuki Yamamoto, MD, PhD, Department of Dermatology, Fukushima Medical University, Hikarigaoka 1, Fukushima 960-1295, Japan. toyamade@fmu.ac.jp
Telephone: +81-24-5471307
Fax: +81-24-5471307

Received: November 26, 2014
Peer-review started: November 26, 2014
First decision: January 20, 2015
Revised: March 13, 2015
Accepted: April 27, 2015
Article in press: April 29, 2015
Published online: July 12, 2015

Abstract

Pyoderma gangrenosum (PG) presents with refractory, sterile, deep ulcers most often on the lower legs. Clinically, PG exhibits four types, *i.e.*, ulcerative, bullous, pustular, and vegetative types. PG may be triggered by surgical operation or even by minor iatrogenic procedures such as needle prick or catheter insertion, which is well-

known as pathergy. PG is sometimes seen in association with several systemic diseases including rheumatoid arthritis (RA), inflammatory bowel disease, hematologic malignancy, and Takayasu's arteritis. In particular, various cutaneous manifestations are induced in association with RA by virtue of the activation of inflammatory cells (neutrophils, lymphocytes, macrophages), vasculopathy, vasculitis, drugs, and so on. Clinical appearances of ulcerative PG mimic rheumatoid vasculitis or leg ulcers due to impaired circulation in patients with RA. In addition, patients with PG sometimes develop joint manifestations as well. Therefore, it is necessary for not only dermatologists but also rheumatologists to understand PG.

Key words: Neutrophilic dermatosis; Pathergy; Köebner phenomenon; Autoinflammatory disorder

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Pyoderma gangrenosum (PG) is occasionally seen in patients with systemic diseases such as rheumatoid arthritis (RA), inflammatory bowel disease, hematologic malignancy, and Takayasu's arteritis. PG is sometimes precipitated by minor trauma or triggered by surgical operation or even by iatrogenic procedures such as needle prick or catheter insertion, which play a role as pathergy. Clinical appearances of ulcerative pyoderma gangrenosum mimic rheumatoid vasculitis or leg ulcers caused by impaired circulation in patients with RA. It is necessary for rheumatologists as well to understand pyoderma gangrenosum.

Yamamoto T. Pyoderma gangrenosum: An important dermatologic condition occasionally associated with rheumatic diseases. *World J Rheumatol* 2015; 5(2): 101-107 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i2/101.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i2.101>

INTRODUCTION

Pyoderma gangrenosum (PG) is a refractory disease characterized by deep ulcers, predominantly in the lower extremities^[1-4]. PG usually occurs in young to middle-aged, but sometimes involves elderly patients, with a slight predilection for females. The general incidence has been estimated to be 3 to 10 per million per year^[5]. More recent studies have shown that the overall incidence was 6.3 (95%CI: 5.7-7.1) per million person-years in the United Kingdom^[6]. PG is often triggered by iatrogenic or surgical procedures such as injection, needle prick, and catheter insertion, in patients with rheumatoid arthritis (RA), inflammatory bowel disease (IBD), acute myeloid leukemia, and Takayasu's arteritis (TA) through the therapies for primary diseases. RA presents with various cutaneous conditions, either specific or non-specific findings^[7]. Among them, PG is the representative neutrophilic condition caused by activated neutrophil infiltration into the dermis. It is important for rheumatologists to know PG, because PG is sometimes misdiagnosed as rheumatoid vasculitis or leg ulcers due to impaired circulation, based on similar clinical appearances. This review provides current updates of the pathophysiology to better understand PG for especially rheumatologists.

CLINICAL FEATURES

PG is clinically classified into 4 types, *i.e.*, ulcerative, bullous, pustular and vegetative types. Ulcerative type PG is most common, which rapidly enlarges with central deep ulceration and undermined borders. The ulcerations are surrounded by raised edematous borders on the pretibial areas (Figure 1A). Initially, a small sterile follicular pustule arises, and rapidly forms abscess, ulcerated and spread outwards. The surface is covered with necrotic tissues.

Bullous PG is relatively rare, and more than 30 cases of bullous PG have been so far reported^[8]. This type is characterized by rapid development of vesicles and enlarging bullae with central necrosis and shallow erosions (Figure 1B). Previous reports indicate that extremities are the most frequently involved, and hematological malignancies, *i.e.*, preleukemic conditions and leukemia, are mostly associated. In the majority of cases, development of bullous PG was related with the activity of gastrointestinal or hematological conditions.

Pustular PG is a rare type, and occasionally appears in association with other types. According to the frequent involvement of the lower extremities, pustules are often seen along with ulcerative lesion (Figure 1C). Additionally, pustules can be seen on the back, or scalp, as well.

Vegetative PG is a superficial, non-aggressive form with verrucous appearance (Figure 1D). Although several different clinical and histological features are proposed between PG and superficial granuloma pyoderma^[9], vegetative type PG is nowadays considered to be the same as superficial granulomatous pyoderma^[2]. Malignant

pyoderma is a rare pyodermatous condition, which rapidly progresses and ulcerates, predominantly affecting the head and neck in young patients without associated systemic disorders^[10]. Some of the reported cases present with similar clinical features to PG, whereas others not.

The most frequently involved site of PG is the lower legs, however, any other sites such as the face, trunk, and genital regions can also be involved. Genital PG is relatively few, with a male predominance^[11]. It is important not to misdiagnose as decubitus. Rarely, PG occurs on the face, and also involves peripheral sites such as digits, ears and scalp^[12] (Figure 2). Those cases may be considered to be peripheral PG. Periauricular PG is also rare, and several cases of auricular PG have been reported^[13-15]. Peripheral PG involving fingers/toes, ears, and genital areas, should be widely recognized.

Other than the skin, several symptoms are occasionally seen associated with PG. Arthritis is the most common^[16], followed by eye lesion and multiple organ involvement. Aseptic neutrophilic abscess is occasionally seen in the lung, kidney, liver, heart, central nervous system, and musculo-skeletal system, which disappear along with systemic steroid therapy.

ATYPICAL SUBSETS

Peristomal PG

Peristomal PG (PPG) is sometimes seen, mainly in patients with Crohn's disease. PPG begins with painful tender or pustular lesions which form fistulous tracts or ulcerations spreading outward, occasionally without involvement of the mucocutaneous junction. Continual irritation, infection, increased pressure of stoma, or allergic reaction, as well as predisposition of parastomal skin of patients are suggested to induce PPG^[17].

Superficial granulomatous PG

Superficial granulomatous pyoderma is a mild subtype of PG, which is slowly progressive and presents with superficial ulcers. Histologically, superficial granulomatous pyoderma shows a three-layered granuloma, such as inner neutrophils and necrosis surrounded by histiocytes and giant cells, with an outer layer of inflammatory cells. Apart from PG, superficial PG does not accompany other systemic disorders. Although superficial ulcers may respond to topical agents, some cases need systemic corticosteroids or disease modifying anti-rheumatic drugs. Those refractory cases are sometimes called superficial granulomatous PG. This condition is considered to be similar to vegetative PG and also malignant pyoderma^[2].

Drug-induced PG

PG is rarely induced by drugs, *i.e.*, iodide, bromide, isotretinoin, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor. A few cases of propylthiouracil-induced PG have been reported in patients with positive ANCA^[18-20]. By contrast, PR3-ANCA is extremely rare.

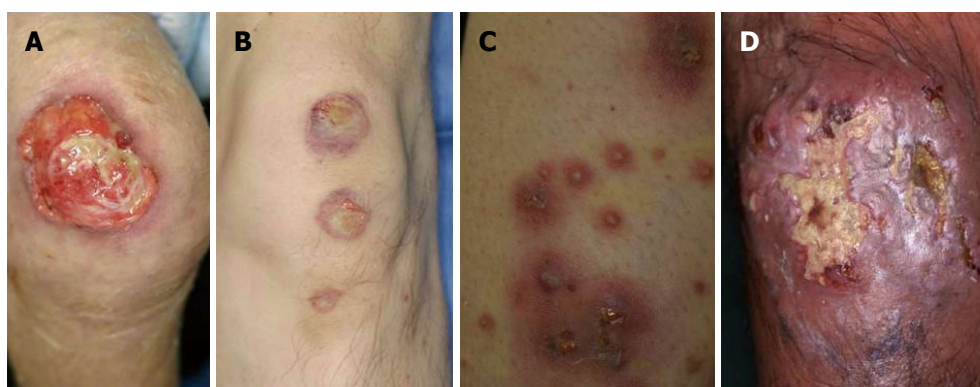


Figure 1 Clinical features of pyoderma gangrenosum involving lower legs. Ulcerative type (A), bullous type (B), pustular type (C), and vegetative type (D).



Figure 2 Pyoderma gangrenosum arising on rare sites, such as the toes (A), scalp (B) and glans (C).

Pyodermatitis-pyostomatitis vegetans

Pyodermatitis-pyostomatitis vegetans involves the oral cavity and skin, especially in patients with UC. This form may be a variant of pustular PG.

ASSOCIATED DISEASES

PG is sometimes associated with systemic diseases such as IBD, RA, TA, and hematologic disorders. Between rheumatic disease-associated and non-rheumatic disease-associated PG, there are no differences in the aspects of clinical features, pathogenesis, and response to therapy. Because PG is a relatively rare disease, case reports are the main and there are so far very few reports analyzing a significant number of cases. Neutrophils play an important role in the onset and perpetuation of RA, and activated neutrophils are recruited to the skin and induce various neutrophilic dermatosis such as PG, Sweet's disease and erythema elevatum diutinum. PG is occasionally seen in relation with the severity and activity of RA. Very recently, a cohort study has been published which analyzed a large database of IBD^[21]. The ratio of PG was 1.9% among patients with IBD, and more than half of the patients had active bowel disease in relation with the episodes of PG. TA is characterized by stenosis or occlusion affecting mainly the aorta and its branches in young women. Several kinds of cutaneous manifestations

are occasionally seen in association with TA, with representative lesions such as erythema nodosum and PG. To date, the association of PG and TA has not been frequently reported^[22]. PG occurring in patients with TA usually involves the upper limbs, followed by the scalp, face, neck, trunk, buttocks, and pubic region, in addition to the lower limbs^[23]. Inflammatory cytokines, such as tumor necrosis factor - α (TNF- α), are considered to play an important role in the pathogenesis of TA. Recent studies have shown that TNF- α targeted therapies are effective for both TA^[24] and PG^[25], suggesting possible pathogenic similarities between these disorders. In addition, hematologic malignancies such as malignant lymphoma and leukemia, systemic lupus erythematosus, chronic hepatitis, and primary biliary cirrhosis are associated.

AUTOINFLAMMATORY DISEASES

Autoinflammatory disease is characterized by hyperactivation of the innate immune system, some of which show skin, joint, and eye manifestations. PG may be included in idiopathic febrile syndromes of autoinflammatory diseases, along with fever, systemic symptoms (*i.e.*, anemia, aseptic arthritis, liver dysfunction, lymphadenopathy), and increased levels of acute-phase protein. Not all of the cases of PG mean autoi-

inflammatory diseases, however, cases accompanied with other symptoms may be considered to represent autoinflammatory disorders. pyoderma gangrenosum, acne, pyogenic arthritis syndrome is caused by mutations in the *PSTPIP1* gene on chromosome 15. pyoderma gangrenosum, acne, suppurative hidradenitis syndrome lacks pyogenic arthritis, and genetic analysis revealed frequent CCTG repeat in the *PSTPIP1* promoter^[26]. Very recently, pyoderma gangrenosum, acne conglobate, suppurative hidradenitis, axial spondylarthritis syndrome and pyoderma gangrenosum, acne, psoriasis, arthritis, suppurative hidradenitis (PAPASH) syndrome have been proposed^[27,28].

ASSOCIATION WITH OTHER NEUTROPHILIC DISORDERS

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is caused by follicular occlusion by infundibular hyperkeratinization and dilatation. HS is occasionally associated with IBD and more recently developed as one of the major skin manifestations of autoinflammatory syndrome. Recent advances in the pathogenesis of HS suggest the significant role of IL-23/Th17 signaling pathway, reduced innate defense antimicrobial peptides, and elevated levels of TNF- α ^[29,30].

Psoriasis

Psoriasis is immunologically mediated by aberrant, skin-directed T cells belonging to Th1/Th17 subset. In a large review of more than 100 patients with PG, 11 (11%) patients had psoriasis^[31]. Fewer number of cases of PG associated with psoriatic arthritis have also been reported^[32,33].

Palmoplantar pustulosis

Palmoplantar pustulosis (PPP) presents with sterile pustules on the palms and soles, with a predilection for females. PPP is a disease close to psoriasis, and the IL-23/IL-17 inflammatory pathway has recently been suggested to be important also in PPP. IL-23 expression is enhanced in the lesional skin^[34], and IL-17 is detected close to or in the acrosyringium^[35]. IL-8 has been considered to play a key role in the neutrophil accumulation in the epidermis, but recent findings suggest that IL-17 may also play an important role, because IL-17 promotes neutrophil migration *via* the release of CXC chemokines^[36]. IL-17 and IL-22 are increased in the peripheral blood of patients with PPP^[37]. Although the simultaneous co-existence of PPP and PG in a single patient is rare, several cases have been reported^[38], which suggest an etiological link between those disorders.

HISTOPATHOLOGY

Histological features are not pathognomonic, and dense neutrophil and lymphocyte infiltration is seen in the whole

dermis. In the upper edematous dermis, a number of neutrophils and lymphocytes infiltrate, and neutrophilic abscess was located in the mid- to lower dermis with the basophilic collagen bundles accompanied by histiocytes as well as plasma cells. There are no features of vasculitis. Histological features of bullous PG show subepidermal edema with numerous neutrophil infiltration. Histological features of pustular type shows dense neutrophil infiltration in the upper to mid-dermis. Because the diagnosis of PG is made clinically, exclusion of other disorders presenting ulcers is necessary.

PATHOGENESIS

Although PG is a neutrophilic disorder, not only neutrophils but also a number of CD3-positive T cells infiltrate in the lesional skin^[39], which suggests that T cells play an important role in the induction of PG, *via* T cell-derived cytokines and chemokines. Histological features of PG have shown that neutrophil recruitment was predominant in the ulcerative wound bed, whereas in the wound edge, activated T cells and macrophages were abundant and play a role as effector cells to ulcer formation^[40]. IL-8 has been implicated to play an important role in neutrophil recruitment in the lesional skin. TNF- α induces IL-8 production by peripheral mononuclear cells^[41]. Also, therapies targeting TNF- α result in beneficial effects on refractory PG^[42,43], suggesting a crucial role of TNF- α in the pathogenesis of PG. TNF- α enhances vascular permeability in endothelial cells^[44] as well as endothelial barrier dysfunction, which may be relevant to bullous formation of PG. TNF- α plays an important role in IBD, whereas role of TNF- α in hematological malignancy is unclear. The etiology of bullous PG in hematological conditions needs further studies.

In addition, Th17 cells promote neutrophil-mediated inflammation. IL-17 activates the endothelium to lead to neutrophil infiltration in a p38 mitogen-activated protein kinase-dependent manner^[45]. In addition, IL-17 and TNF- α enhance endothelial expression of neutrophil chemokines, *i.e.*, CXCL1, CXCL2 and CXCL5, leading to leukocyte migration^[46]. Recently, increased expression of IL-23 was found in the lesional skin of PG, and targeting therapy of IL-12/IL-23 p40 was effective^[47], suggesting that IL-23 may play a pathogenic role in PG.

PATHERGY

It is well-known that surgical operation and minor trauma precipitate PG. There are many reports of PG occurring at percutaneous surgical sites, such as breast surgery, pacemaker implantation, splenectomy, hysterectomy, endoscopic tube insertion, cholecystectomy, and cesarean delivery^[22,48]. Similar cases have been reported which were triggered even by less invasive iatrogenic procedures such as injection, needle prick, and catheter insertion, in patients with underlying systemic diseases. Such phenomena are called pathergy, which means

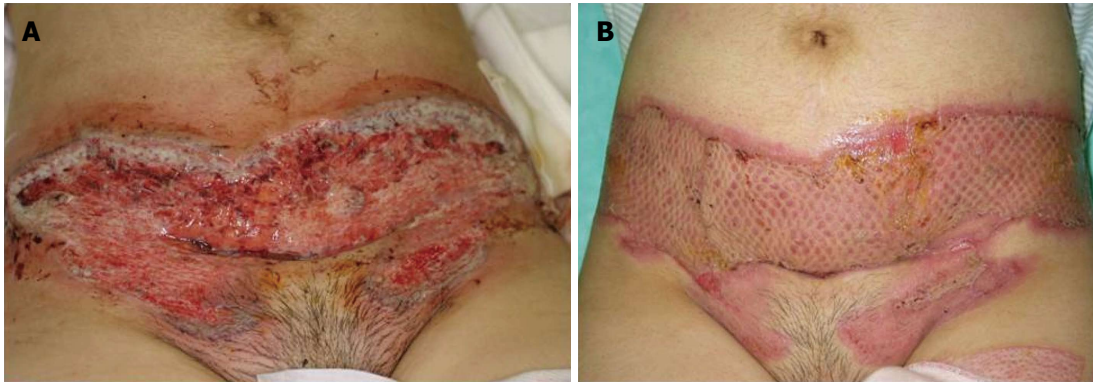


Figure 3 Pyoderma gangrenosum triggered by caesarean operation (A), which was surgically treated by mesh grafting with oral prednisolone (B).

hyper-reactivity of the skin in response to even minor trauma. Because the majority of patients with PG have systemic disorders, PG should be correctly and widely recognized, not misdiagnosed as infectious conditions, by the doctors belonging to other departments than dermatology. These results suggest that pathergy reaction is implicated as a triggering role in PG in susceptible patients, even without systemic diseases. Pathergy can be seen in about 20% of cases of PG^[2]. The etiology of pathergy is still unknown, however, activated neutrophils recruited to the injured skin, via an aberrant immune response to minor trauma, defective cell-mediated immunity, aberrant integrin oscillations on neutrophils and abnormal neutrophil tracking, have been speculated.

DIFFERENTIAL DIAGNOSIS

Skin diseases exhibiting refractory ulcers, due to infection, vascular insufficiency, vasculitis, and malignancy should be differentiated. Especially in cases affecting patients with RA, rheumatoid vasculitis or leg ulcers due to impaired circulation should be carefully differentiated.

Cutaneous manifestations of granulomatosis with polyangiitis (Wegener's granulomatosis) present with purpura, ulcer, hemorrhagic bullae, livedo reticularis, and subcutaneous nodules. Histologically, specific skin lesions show granulomatous vasculitis. Sometimes, PG-like ulcerative lesions occur in patients with granulomatosis with polyangiitis^[49-51], which are sometimes reported as malignant pyoderma.

Cutaneous cryptococcosis presents with various features such as papules, pustules, nodules, granulomas, abscesses, subcutaneous swelling, cellulitis-like erythema, erysipelas, and ulcers. A few cases with clinical features mimicking PG have been reported^[52,53].

THERAPY

Occasionally, PG is improved only by topical immunotherapies, such as corticosteroids, tacrolimus, and pimecrolimus^[47,54], however, the first line for the therapy of PG is systemic corticosteroids. For steroid-resistant

cases, other immunosuppressive and immunomodulatory drugs, such as cyclosporine, thalidomide, tacrolimus, azathioprine, mycophenolate mofetil, and recently biologics are also used^[25,55]. In particular, anti-TNF- α therapies result in beneficial effects on refractory PG. A randomized, double-blind, placebo-controlled trial have demonstrated a superior effect of infliximab for PG^[56]. Also, a number of case reports have demonstrated that biologics targeting TNF- α and IL-12/23 p40 are effective for PG^[47,57-59]. Surgical therapy is also adopted at the last step, with the aid of prednisolone use (Figure 3). In contrast to dramatic effect of biologics, PG is paradoxically induced by biologics, in rare cases^[60-62].

CONCLUSION

To diagnose PG properly, it is important to lay stress on clinical features and to exclude other disorders exhibiting ulcers, because the histologic features are not diagnostic. At present, there are no diagnostic criteria. However, several proposals have recently been shown^[4,63], which are expected to be of great help for correct diagnosis. Furthermore, although there are many single case reports, very few cohort studies or comparative studies among underlying systemic diseases have been done. To perform those studies, collaboration of different departments is necessary in the future project.

REFERENCES

- 1 Crowson AN, Mihm MC, Magro C. Pyoderma gangrenosum: a review. *J Cutan Pathol* 2003; **30**: 97-107 [PMID: 12641787 DOI: 10.1034/j.1600-0560.2003.00024.x]
- 2 Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: an updated review. *J Eur Acad Dermatol Venereol* 2009; **23**: 1008-1017 [PMID: 19470075 DOI: 10.1111/j.1468-3083.2009.03199.x]
- 3 Wollina U. Pyoderma gangrenosum--a review. *Orphanet J Rare Dis* 2007; **2**: 19 [PMID: 17433111 DOI: 10.1186/1750-1172-2-19]
- 4 Jackson JM, Callen JP. Pyoderma gangrenosum: an expert commentary. *Exp Rev Dermatol* 2006; **1**: 391-400 [DOI: 10.1586/17469872.1.3.391]
- 5 Powell FC, Schroeter AL, Su WP, Perry HO. Pyoderma gangrenosum: a review of 86 patients. *Q J Med* 1985; **55**: 173-186 [PMID: 3889978]
- 6 Langan SM, Groves RW, Card TR, Gulliford MC. Incidence,

- mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: a retrospective cohort study. *J Invest Dermatol* 2012; **132**: 2166-2170 [PMID: 22534879 DOI: 10.1038/jid.2012.130]
- 7 **Yamamoto T**. Cutaneous manifestations associated with rheumatoid arthritis. *Rheumatol Int* 2009; **29**: 979-988 [PMID: 19242695 DOI: 10.1007/s00296-009-0881-z]
- 8 **Takenoshita H**, Yamamoto T. Bullous pyoderma gangrenosum in patients with ulcerative colitis and multiple myeloma. *Our Dermatol Online* 2014; **5**: 310-311 [DOI: 10.7241/ourd.20143.82]
- 9 **Thami GP**, Kaur S, Punia RS, Kanwart AJ. Superficial granulomatous pyoderma: an idiopathic granulomatous cutaneous ulceration. *J Eur Acad Dermatol Venereol* 2002; **16**: 159-161 [PMID: 12046823 DOI: 10.1046/j.1468-3083.2002.00425.x]
- 10 **Cardinali C**, Giomi B, Caproni M, Fabbri P. Guess what! Malignant pyoderma responding to cyclosporine. *Eur J Dermatol* 2001; **11**: 595-596 [PMID: 11701420]
- 11 **Satoh M**, Yamamoto T. Genital pyoderma gangrenosum: report of two cases and published work review of Japanese cases. *J Dermatol* 2013; **40**: 840-843 [PMID: 24033392 DOI: 10.1111/1346-8138.12252]
- 12 **Ohashi T**, Miura T, Yamamoto T. Auricular pyoderma gangrenosum with penetration in a patient with rheumatoid arthritis. *Int J Rheum Dis* 2014 Jun 10; Epub ahead of print [PMID: 24916772 DOI: 10.1111/1756-185X.12411]
- 13 **Iijima S**, Ogawa T, Nanno Y, Tsunoda T, Kudoh K. Pyoderma gangrenosum first presenting as a recalcitrant ulcer of the ear lobe. *Eur J Dermatol* 2003; **13**: 606-609 [PMID: 14721788]
- 14 **Sarma N**, Bandyopadhyay SK, Boler AK, Barman M. Progressive and extensive ulcerations in a girl since 4 months of age: the difficulty in diagnosis of pyoderma gangrenosum. *Indian J Dermatol* 2012; **57**: 48-49 [PMID: 22470210 DOI: 10.4103/0019-5154.92678]
- 15 **Ben Chaabane N**, Hellara O, Ben Mansour W, Ben Mansour I, Melki W, Loughmeri H, Safer L, Bdioui F, Saffar H. Auricular pyoderma gangrenosum associated with Crohn's disease. *Tunis Med* 2012; **90**: 414-415 [PMID: 22585655]
- 16 **Al Ghazal P**, Herberger K, Schaller J, Strölin A, Hoff NP, Goerge T, Roth H, Rabe E, Karrer S, Renner R, Maschke J, Horn T, Hepp J, Eming S, Wollina U, Zutt M, Sick I, Splieth B, Dill D, Klode J, Dissemond J. Associated factors and comorbidities in patients with pyoderma gangrenosum in Germany: a retrospective multicentric analysis in 259 patients. *Orphanet J Rare Dis* 2013; **8**: 136 [PMID: 24010984 DOI: 10.1186/1750-1172-8-136]
- 17 **Lyon CC**, Smith AJ, Griffiths CE, Beck MH. Peristomal dermatoses: a novel indication for topical steroid lotions. *J Am Acad Dermatol* 2000; **43**: 679-682 [PMID: 11004626 DOI: 10.1067/mjd.2000.106237]
- 18 **Darben T**, Savage J, Prentice R, Paspaliaris B, Chick J. Pyoderma gangrenosum with secondary pyarthrosis following propylthiouracil. *Australas J Dermatol* 1999; **40**: 144-146 [PMID: 10439526 DOI: 10.1046/j.1440-0960.1999.00346.x]
- 19 **Hong SB**, Lee MH. A case of propylthiouracil-induced pyoderma gangrenosum associated with antineutrophil cytoplasmic antibody. *Dermatology* 2004; **208**: 339-341 [PMID: 15178918 DOI: 10.1159/000077844]
- 20 **Seo JW**, Son HH, Choi JH, Lee SK. A Case of p-ANCA-Positive Propylthiouracil-Induced Pyoderma Gangrenosum. *Ann Dermatol* 2010; **22**: 48-50 [PMID: 20548880 DOI: 10.5021/ad.2010.22.1.48]
- 21 **Weizman AV**, Huang B, Targan S, Dubinsky M, Fleshner P, Kaur M, Ippoliti A, Panikath D, Vasiliaskas E, Shih D, McGovern DP, Melmed GY. Pyoderma Gangrenosum among Patients with Inflammatory Bowel Disease: A Descriptive Cohort Study. *J Cutan Med Surg* 2015; **19**: 125-131 [PMID: 25775631 DOI: 10.2310/7750.2014.14053]
- 22 **Hiraiwa T**, Furukawa H, Yamamoto T. Pyoderma gangrenosum triggered by surgical procedures in patients with underlying systemic diseases. *Our Dermatol Online* 2014; **5**: 432-433 [DOI: 10.7241/ourd.20144.111]
- 23 **Ujiie H**, Sawamura D, Yokota K, Nishie W, Shichinohe R, Shimizu H. Pyoderma gangrenosum associated with Takayasu's arteritis. *Clin Exp Dermatol* 2004; **29**: 357-359 [PMID: 15245528 DOI: 10.1111/j.1365-2230.2004.01514.x]
- 24 **Comarmond C**, Plaisier E, Dahan K, Mirault T, Emmerich J, Amoura Z, Cacoub P, Saadoun D. Anti TNF- α in refractory Takayasu's arteritis: cases series and review of the literature. *Autoimmun Rev* 2012; **11**: 678-684 [PMID: 22155781 DOI: 10.1016/j.autrev.2011.11.025]
- 25 **Ahronowitz I**, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. *Am J Clin Dermatol* 2012; **13**: 191-211 [PMID: 22356259 DOI: 10.2165/11595240-000000000-00000]
- 26 **Braun-Falco M**, Kovnerystyy O, Lohse P, Ruzicka T. Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)--a new autoinflammatory syndrome distinct from PAPA syndrome. *J Am Acad Dermatol* 2012; **66**: 409-415 [PMID: 21745697 DOI: 10.1016/j.jaad.2010.12.025]
- 27 **Bruzzese V**. Pyoderma gangrenosum, acne conglobata, suppurative hidradenitis, and axial spondyloarthritis: efficacy of anti-tumor necrosis factor α therapy. *J Clin Rheumatol* 2012; **18**: 413-415 [PMID: 23188209 DOI: 10.1097/RHU.0b013e318278b84c]
- 28 **Garzorz N**, Papanagiotou V, Atenhan A, Andres C, Eyerich S, Eyerich K, Ring J, Brockow K. Pyoderma gangrenosum, acne, psoriasis, arthritis and suppurative hidradenitis (PAPASH)-syndrome: a new entity within the spectrum of autoinflammatory syndromes? *J Eur Acad Dermatol Venereol* 2014 Jul 28; Epub ahead of print [PMID: 25070077 DOI: 10.1111/jdv.12631]
- 29 **Schlapbach C**, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol* 2011; **65**: 790-798 [PMID: 21641076 DOI: 10.1016/j.jaad.2010.07.010]
- 30 **Wolk K**, Warszawska K, Hoeflich C, Witte E, Schneider-Burrus S, Witte K, Kunz S, Buss A, Roewert HJ, Krause M, Lukowsky A, Volk HD, Sterry W, Sabat R. Deficiency of IL-22 contributes to a chronic inflammatory disease: pathogenetic mechanisms in acne inversa. *J Immunol* 2011; **186**: 1228-1239 [PMID: 21148041 DOI: 10.4049/jimmunol.0903907]
- 31 **Binus AM**, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br J Dermatol* 2011; **165**: 1244-1250 [PMID: 21824126 DOI: 10.1111/j.1365-2133.2011.10565.x]
- 32 **Smith DL**, White CR. Pyoderma gangrenosum in association with psoriatic arthritis. *Arthritis Rheum* 1994; **37**: 1258-1260 [PMID: 8053964 DOI: 10.1002/art.1780370823]
- 33 **Spangler JG**. Pyoderma gangrenosum in a patient with psoriatic arthritis. *J Am Board Fam Pract* 2001; **14**: 466-469 [PMID: 11757891]
- 34 **Lillis JV**, Guo CS, Lee JJ, Blauvelt A. Increased IL-23 expression in palmoplantar psoriasis and hyperkeratotic hand dermatitis. *Arch Dermatol* 2010; **146**: 918-919 [PMID: 20713832 DOI: 10.1001/archdermatol.2010.168]
- 35 **Hagforsen E**, Hedstrand H, Nyberg F, Michaëlsson G. Novel findings of Langerhans cells and interleukin-17 expression in relation to the acro-syringium and pustule in palmoplantar pustulosis. *Br J Dermatol* 2010; **163**: 572-579 [PMID: 20426778 DOI: 10.1111/j.1365-2133.2010.09819.x]
- 36 **Laan M**, Cui ZH, Hoshino H, Lötval J, Sjöstrand M, Gruenert DC, Skoogh BE, Lindén A. Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways. *J Immunol* 1999; **162**: 2347-2352 [PMID: 9973514]
- 37 **Murakami M**, Hagforsen E, Morhenn V, Ishida-Yamamoto A, Iizuka H. Patients with palmoplantar pustulosis have increased IL-17 and IL-22 levels both in the lesion and serum. *Exp Dermatol* 2011; **20**: 845-847 [PMID: 21732985 DOI: 10.1111/j.1600-0625.2011.01325.x]
- 38 **Ohtsuka M**, Yamamoto T. Rare association of pyoderma gangrenosum and palmoplantar pustulosis: a case report and review of the previous works. *J Dermatol* 2014; **41**: 732-735 [PMID: 24986043 DOI: 10.1111/1346-8138.12543]
- 39 **Brooklyn TN**, Williams AM, Dunnill MG, Probert CS. T-cell

- receptor repertoire in pyoderma gangrenosum: evidence for clonal expansions and trafficking. *Br J Dermatol* 2007; **157**: 960-966 [PMID: 17935516 DOI: 10.1111/j.1365-2133.2007.08211.x]
- 40 **Marzano AV**, Cugno M, Trevisan V, Fanoni D, Venegoni L, Berti E, Crosti C. Role of inflammatory cells, cytokines and matrix metalloproteinases in neutrophil-mediated skin diseases. *Clin Exp Immunol* 2010; **162**: 100-107 [PMID: 20636397 DOI: 10.1111/j.1365-2249.2010.04201.x]
 - 41 **Andoh A**, Ogawa A, Kitamura K, Inatomi O, Fujino S, Tsujikawa T, Sasaki M, Mitsuyama K, Fujiyama Y. Suppression of interleukin-1 β - and tumor necrosis factor- α -induced inflammatory responses by leukocytapheresis therapy in patients with ulcerative colitis. *J Gastroenterol* 2004; **39**: 1150-1157 [PMID: 15622478 DOI: 10.1007/s00535-004-1464-0]
 - 42 **Stichweh DS**, Punaro M, Pascual V. Dramatic improvement of pyoderma gangrenosum with infliximab in a patient with PAPA syndrome. *Pediatr Dermatol* 2005; **22**: 262-265 [PMID: 15916580 DOI: 10.1111/j.1525-1470.2005.22320.x]
 - 43 **Fonder MA**, Cummins DL, Ehst BD, Anhalt GJ, Meyerle JH. Adalimumab therapy for recalcitrant pyoderma gangrenosum. *J Burns Wounds* 2006; **5**: e8 [PMID: 17149453]
 - 44 **Brett J**, Gerlach H, Nawroth P, Steinberg S, Godman G, Stern D. Tumor necrosis factor/cachectin increases permeability of endothelial cell monolayers by a mechanism involving regulatory G proteins. *J Exp Med* 1989; **169**: 1977-1991 [PMID: 2499653 DOI: 10.1084/jem.169.6.1977]
 - 45 **Roussel L**, Houle F, Chan C, Yao Y, Bérubé J, Olivenstein R, Martin JG, Huot J, Hamid Q, Ferri L, Rousseau S. IL-17 promotes p38 MAPK-dependent endothelial activation enhancing neutrophil recruitment to sites of inflammation. *J Immunol* 2010; **184**: 4531-4537 [PMID: 20228195 DOI: 10.4049/jimmunol.0903162]
 - 46 **Griffin GK**, Newton G, Tarrio ML, Bu DX, Maganto-Garcia E, Azcutia V, Alcaide P, Grabie N, Luscinskas FW, Croce KJ, Lichtman AH. IL-17 and TNF- α sustain neutrophil recruitment during inflammation through synergistic effects on endothelial activation. *J Immunol* 2012; **188**: 6287-6299 [PMID: 22566565 DOI: 10.4049/jimmunol.1200385]
 - 47 **Guenova E**, Teske A, Fehrenbacher B, Hoerber S, Adamczyk A, Schaller M, Hoetzenecker W, Biedermann T. Interleukin 23 expression in pyoderma gangrenosum and targeted therapy with ustekinumab. *Arch Dermatol* 2011; **147**: 1203-1205 [PMID: 21680759 DOI: 10.1001/archdermatol.2011.168]
 - 48 **Kikuchi N**, Hanami Y, Miura T, Kawakami Y, Satoh M, Ohtsuka M, Yamamoto T. Pyoderma gangrenosum following surgical procedures. *Int J Dermatol* 2010; **49**: 346-348 [PMID: 20465683 DOI: 10.1111/j.1365-4632.2009.04201.x]
 - 49 **Jacob SE**, Martin LK, Kerdel FA. Cutaneous Wegener's granulomatosis (malignant pyoderma) in a patient with Crohn's disease. *Int J Dermatol* 2003; **42**: 896-898 [PMID: 14636208 DOI: 10.1046/j.1365-4362.2003.01919.x]
 - 50 **Szöcs HI**, Torma K, Petrovicz E, Hársing J, Fekete G, Kárpáti S, Horváth A. Wegener's granulomatosis presenting as pyoderma gangrenosum. *Int J Dermatol* 2003; **42**: 898-902 [PMID: 14636209 DOI: 10.1046/j.1365-4362.2003.01924.x]
 - 51 **Kouba DJ**, Mimouni D, Ha CT, Nousari CH. Limited Wegener's granulomatosis manifesting as malignant pyoderma with corneal melt. *Int J Dermatol* 2003; **42**: 902-904 [PMID: 14636210 DOI: 10.1046/j.1365-4362.2003.01915.x]
 - 52 **Massa MC**, Doyle JA. Cutaneous cryptococcosis simulating pyoderma gangrenosum. *J Am Acad Dermatol* 1981; **5**: 32-36 [PMID: 7276272 DOI: 10.1016/S0190-9622(81)70074-4]
 - 53 **Jasch KC**, Hermes B, Scheller U, Harth W. Pyoderma gangrenosum-like primary cutaneous cryptococcosis. *Acta Derm Venereol* 2008; **88**: 76-77 [PMID: 18176763 DOI: 10.2340/00015555-0328]
 - 54 **Kontos AP**, Kerr HA, Fivenson DP, Remishofsky C, Jacobsen G. An open-label study of topical tacrolimus ointment 0.1% under occlusion for the treatment of pyoderma gangrenosum. *Int J Dermatol* 2006; **45**: 1383-1385 [PMID: 17076739 DOI: 10.1111/j.1365-4632.2006.03133.x]
 - 55 **Miller J**, Yentzer BA, Clark A, Jorizzo JL, Feldman SR. Pyoderma gangrenosum: a review and update on new therapies. *J Am Acad Dermatol* 2010; **62**: 646-654 [PMID: 20227580 DOI: 10.1016/j.jaad.2009.05.030]
 - 56 **Brooklyn TN**, Dunnill MG, Shetty A, Bowden JJ, Williams JD, Griffiths CE, Forbes A, Greenwood R, Probert CS. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut* 2006; **55**: 505-509 [PMID: 16188920 DOI: 10.1136/gut.2005.074815]
 - 57 **Juillerat P**, Christen-Zäch S, Troillet FX, Gallot-Lavallée S, Pannizzon RG, Michetti P. Infliximab for the treatment of disseminated pyoderma gangrenosum associated with ulcerative colitis. Case report and literature review. *Dermatology* 2007; **215**: 245-251 [PMID: 17823524 DOI: 10.1159/000106584]
 - 58 **Mooij JE**, van Rappard DC, Mekkes JR. Six patients with pyoderma gangrenosum successfully treated with infliximab. *Int J Dermatol* 2013; **52**: 1418-1420 [PMID: 22512250 DOI: 10.1111/j.1365-4632.2011.05201.x]
 - 59 **Heffernan MP**, Anadkat MJ, Smith DI. Adalimumab treatment for pyoderma gangrenosum. *Arch Dermatol* 2007; **143**: 306-308 [PMID: 17372094 DOI: 10.1001/archderm.143.3.306]
 - 60 **Le Cleach L**, Moguelet P, Perrin P, Chosidow O. Is topical monotherapy effective for localized pyoderma gangrenosum? *Arch Dermatol* 2011; **147**: 101-103 [PMID: 21242400 DOI: 10.1001/archdermatol.2010.393]
 - 61 **Kikuchi N**, Hiraiwa T, Ohashi T, Hanami Y, Satoh M, Takenoshita H, Yamamoto T. Pyoderma gangrenosum possibly triggered by adalimumab. *Eur J Dermatol* 2012; **22**: 804-805 [PMID: 23107608]
 - 62 **Brunasso AM**, Laimer M, Massone C. Paradoxical reactions to targeted biological treatments: A way to treat and trigger? *Acta Derm Venereol* 2010; **90**: 183-185 [PMID: 20169304 DOI: 10.2340/00015555-0777]
 - 63 **Hadi A**, Lebwohl M. Clinical features of pyoderma gangrenosum and current diagnostic trends. *J Am Acad Dermatol* 2011; **64**: 950-954 [PMID: 21292348 DOI: 10.1016/j.jaad.2010.01.049]

P-Reviewer: Agarwal V, Cavallasca JA, Rothschild BM
S-Editor: Tian YL **L-Editor:** Wang TQ **E-Editor:** Jiao XK



What is the best biological treatment for rheumatoid arthritis? A systematic review of effectiveness

Jéssica Barreto dos Santos, Juliana de Oliveira Costa, Haliton Alves de Oliveira Junior, Livia Lovato Pires Lemos, Vânia Eloisa de Araújo, Marina Amaral de Ávila Machado, Alessandra Maciel Almeida, Francisco de Assis Acurcio, Juliana Alvares

Jéssica Barreto dos Santos, Haliton Alves de Oliveira Junior, Postgraduate Programme in Medicines and Pharmaceutical Assistance, College of Pharmacy, Federal University of Minas Gerais, Av. Presidente Antônio Carlos, 6627 Campus Pampulha, Belo Horizonte, Minas Gerais 31270-901, Brazil

Juliana de Oliveira Costa, Vânia Eloisa de Araújo, Francisco de Assis Acurcio, Juliana Alvares, College of Pharmacy, Federal University of Minas Gerais, Av. Presidente Antônio Carlos, 6627 Campus Pampulha, Belo Horizonte, Minas Gerais 31270-901, Brazil

Livia Lovato Pires Lemos, Department of Social Pharmacy, College of Pharmacy, SUS Collaborating Centre-CCATES, Federal University of Minas Gerais, Av. Presidente Antônio Carlos, 6627 Campus Pampulha, Belo Horizonte, Minas Gerais 31270-901, Brazil

Marina Amaral de Ávila Machado, Alessandra Maciel Almeida, College of Medicine, Federal University of Minas Gerais, Av. Prof. Alfredo Balena, 190, Belo Horizonte, Minas Gerais 30130-100, Brazil

Author contributions: dos Santos JB and Costa JO designed the study, analyzed the data and wrote the manuscript; Oliveira Junior HA and Lemos LLP designed the study and analyzed the data; Araújo VE designed the study, analyzed the data and edited the manuscript; Machado MAA contributed with the discussion; Almeida AM, Acurcio FA and Alvares J designed the study, contributed with the discussion and edited the manuscript.

Supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

[licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/)

Correspondence to: Jéssica Barreto dos Santos, Master Student of Post-Graduation, Postgraduate Programme in Medicines and Pharmaceutical Assistance, College of Pharmacy, Federal University of Minas Gerais, Av. Presidente Antônio Carlos, 6627 Campus Pampulha, bloco 2, 1o andar, sala 1023, Belo Horizonte, Minas Gerais 31270-901, Brazil. jessica_oterrab@hotmail.com
 Telephone: +55-31-99944477
 Fax: +55-31-99944477

Received: June 27, 2014
Peer-review started: June 29, 2014
First decision: September 27, 2014
Revised: October 24, 2014
Accepted: October 31, 2014
Article in press: November 3, 2014
Published online: July 12, 2015

Abstract

AIM: To evaluate the effectiveness of the biological disease-modifying antirheumatic drugs (bDMARD) in the treatment of rheumatoid arthritis through a systematic review of observational studies.

METHODS: The studies were searched in the PubMed, EMBASE, Cochrane Controlled Trials Register and LILACS databases (until August 2014), in the grey literature and conducted a manual search. The assessed criteria of effectiveness included the EULAR, the disease activity score (DAS), the Clinical Disease Activity Index, the Simplified Disease Activity Index, the American College of Rheumatology and the Health Assessment Questionnaire. The meta-analysis was performed with Review Manager® 5.2 software using a random effects model. A total of 35 studies were included in this review.

RESULTS: The participants anti-tumor necrosis factor inhibitors (TNF) naïve, who used adalimumab ($P = 0.0002$) and etanercept ($P = 0.0006$) exhibited greater good EULAR response compared to the participants who used infliximab. No difference was detected between adalimumab and etanercept ($P = 0.05$). The participants who used etanercept exhibited greater remission according to DAS28 compared to the participants who used infliximab ($P = 0.01$). No differences were detected between adalimumab and infliximab ($P = 0.12$) or etanercept ($P = 0.79$). Better results were obtained with bDMARD associated with methotrexate than with bDMARD alone. The good EULAR response and DAS 28 was better for combination with methotrexate than bDMARD monotherapy ($P = 0.03$ e $P < 0.00001$). In cases of therapeutic failure, the participants who used rituximab exhibited greater DAS28 reduction compared to those who used anti-TNF agents ($P = 0.0002$). The participants who used etanercept achieved greater good EULAR response compared to those who did not use that drug ($P = 0.007$). Studies that assessed reduction of the CDAI score indicated the superiority of abatacept over rituximab (12.4 *vs* +1.7) and anti-TNF agents (7.6 *vs* 8.3). The present systematic review with meta-analysis found that relative to anti-TNF treatment-naïve patients, adalimumab and etanercept were more effective when combined with methotrexate than when used alone. Furthermore, in case of therapeutic failure with anti-TNF agents; rituximab and abatacept (non anti-TNF) and etanercept (as second anti-TNF) were more effective. However, more studies of effectiveness were found for the rituximab.

CONCLUSION: The best treatment for treatment-naïve patients is adalimumab or etanercept combined with methotrexate. For anti-TNF therapeutic failure, the best choice is rituximab, abatacept or etanercept.

Key words: Systematic review; Meta-analysis; Effectiveness; Biological disease-modifying antirheumatic drugs; Rheumatoid arthritis

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Rheumatoid arthritis is a chronic, progressive, systemic inflammatory disease that preferentially affects the synovial membranes of joints, eventually leading to bone and cartilage destruction. Its worldwide prevalence is estimated to be 0.3% to 1%. Observational studies could provide relevant information for deciding the choice of treatments, the elaboration of clinical protocols, and the formulation of health policies. The present systematic review of biological disease-modifying antirheumatic drugs included cohort observational studies that reported treatment results applied in real-life conditions; thus, these studies are able to fill in gaps in knowledge left by clinical trials.

VE, Machado MAA, Almeida AM, Acurcio FA, Alvares J. What is the best biological treatment for rheumatoid arthritis? A systematic review of effectiveness. *World J Rheumatol* 2015; 5(2): 108-126 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i2/108.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i2.108>

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory disease that preferentially affects the synovial membranes of joints, eventually resulting in destruction of bone and cartilage^[1]. Its worldwide prevalence is estimated to be 0.3% to 1%^[2].

Treatment of RA includes non-steroidal anti-inflammatory drugs, corticoids and synthetic (sDMARD) and biological [biological disease-modifying antirheumatic drugs (bDMARD)] disease-modifying antirheumatic drugs. bDMARD are indicated for individuals with persistent disease activity despite the use of sDMARD^[3-5]. Tumor necrosis factor inhibitors (anti-TNF) are inhibitors of tumor necrosis factor alpha, rituximab is depleting B lymphocyte, abatacept is blocking of costimulation of T lymphocyte and tocilizumab is a blocking interleukin-6 receptor. Among the bDMARD, anti-TNF represent the first choice after failure of regimens that included sDMARD, and there is more evidence of the post-marketing efficacy and safety for anti-TNF agents^[4,5]. Nevertheless, anti-TNF could eventually exhibit therapeutic failure, in which case another anti-TNF drug or another class of bDMARD might be used^[6,7].

Appropriate knowledge of the effectiveness profiles of all of these strategies is relevant for choosing the best option for each patient. In this regard, observational studies are particularly interesting, as they seek to understand treatments in the actual practice setting. Thus, this type of study could contribute to decide the choice of treatments, the elaboration of clinical protocols, and the formulation of health policies. The present systematic review selected cohort observational studies. These types of studies more accurately represent real-life conditions (actual practice setting) and are able to provide complementary data to the results of randomized clinical studies conducted in controlled conditions^[8].

The aim of the present study was to assess the effectiveness of the anti-TNFs adalimumab, etanercept, infliximab, golimumab and certolizumab pegol and of the non anti-TNF rituximab, tocilizumab and abatacept, in the treatment of active RA by means of a systematic review with meta-analysis.

MATERIALS AND METHODS

This systematic review followed the recommendations in the Cochrane Collaboration Handbook and was elaborated using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)^[9,10].

Table 1 Search strategies**PubMed**

((Arthritis, Rheumatoid[Text Word] or "Arthritis, Rheumatoid"[Mesh]) and (((((((((((rituximab[Text Word] or Mabthera[Text Word]) or Rituxan[Text Word]) or IDEC-C2B8 antibody[Text Word]) or "rituximab"[Supplementary Concept]) or ((((((TNFR-Fc fusion protein[Text Word] or TNR 001[Text Word]) or TNR-001[Text Word]) or TNF receptor type II-IgG fusion protein[Text Word]) or recombinant human dimeric TNF receptor type II-IgG fusion protein[Text Word]) or Enbrel[Text Word]) or etanercept[Text Word]) or "TNFR-Fc fusion protein"[Supplementary Concept])) or (((infiximab[Text Word] or monoclonal antibody cA2[Text Word]) or MAb cA2[Text Word]) or Remicade[Text Word]) or "infiximab"[Supplementary Concept])) or ((adalimumab[Text Word] or Humira[Text Word]) or "adalimumab"[Supplementary Concept])) or (((certolizumab[Text Word] or CDP870[Text Word]) or CDP 870[Text Word]) or Cimzia[Text Word]) or certolizumab pegol[Text Word]) or "certolizumab pegol"[Supplementary Concept])) or (((((((((((abatacept[Text Word] or BMS 188667[Text Word]) or BMS-188667[Text Word]) or nulojix[Text Word]) or CTLA-4-Ig[Text Word]) or cytotoxic T lymphocyte-associated antigen 4-immunoglobulin[Text Word]) or CTLA4-Fc[Text Word]) or CTLA4-Ig[Text Word]) or LEA29Y[Text Word]) or Orenia[Text Word]) or BELATACEPT[Text Word]) or BMS-224818[Text Word]) or "abatacept"[Supplementary Concept])) or ((tocilizumab[Text Word] or atlizumab[Text Word]) or Actemra[Text Word]) or "tocilizumab"[Supplementary Concept])) or ("golimumab"[Supplementary Concept] or Simponi[Text Word] or golimumab[Text Word])))) and ("Cohort Studies"[Mesh]) or ((cohort*[Text Word] or controlled clinical trial[Publication Type]) or epidemiologic methods))

EMBASE

"golimumab"/exp and [embase]/lim or ("cnto\$148" and [embase]/lim) or ("simponi" and [embase]/lim) or ("tocilizumab"/exp and [embase]/lim) or ("actemra" and [embase]/lim) or ("actemra 200" and [embase]/lim) or ("atlizumab" and [embase]/lim) or ("r\$1569" and [embase]/lim) or ("roactemra" and [embase]/lim) or ("abatacept"/exp and [embase]/lim) or ("bms\$188667" and [embase]/lim) or ("ctla4\$ig" and [embase]/lim) or ("ctla4 immunoglobulin" and [embase]/lim) or ("ctla4 immunoglobulin g" and [embase]/lim) or ("orencia" and [embase]/lim) or ("certolizumab pegol"/exp and [embase]/lim) or ("cdp\$870" and [embase]/lim) or ("cimzia" and [embase]/lim) or ("pha\$738144" and [embase]/lim) or ("adalimumab"/exp and [embase]/lim) or ("humira"/exp and [embase]/lim) or ("monoclonal antibody d2e7" and [embase]/lim) or ("trudexa" and [embase]/lim) or ("infiximab"/exp and [embase]/lim) or ("avakine" and [embase]/lim) or ("inflectra" and [embase]/lim) or ("remicade" and [embase]/lim) or ("remsima" and [embase]/lim) or ("revellex" and [embase]/lim) or ("etanercept"/exp and [embase]/lim) or ("embrel" and [embase]/lim) or ("enbrel" and [embase]/lim) or ("recombinant tumor necrosis factor receptor fc fusion protein" and [embase]/lim) or ("tnr\$001" and [embase]/lim) or ("tumor necrosis factor receptor fc fusion protein" and [embase]/lim) or ("rituximab"/exp and [embase]/lim) or ("idec c2b8" and [embase]/lim) or ("mabthera" and [embase]/lim) or ("monoclonal antibody idec c2b8" and [embase]/lim) or ("reditux" and [embase]/lim) or ("rituxan" and [embase]/lim) or ("rituxin" and [embase]/lim) or ("rheumatoid arthritis"/exp and [embase]/lim) or ("arthritis, rheumatoid" and [embase]/lim) and ("cohort analysis"/exp and [embase]/lim or ("longitudinal study"/exp and [embase]/lim) or ("prospective study"/exp and [embase]/lim) or ("follow up"/exp and [embase]/lim) or ("cohort\$" and [embase]/lim))

Cochrane Controlled Trials Register

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees

#2 Rheumatoid Arthritis in Trials

#3 golimumab in Trials

#4 tocilizumab in Trials

#5 abatacept in Trials

#6 certolizumab pegol in Trials

#7 adalimumab in Trials

#8 infiximab in Trials

#9 etanercept in Trials

#10 rituximab in Trials

#11 #1 or #2 in Trials

#12 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 in Trials

#13 #11 and #12

LILACS

(tw:((mh:(arthritis, rheumatoid)) or (tw:(artrite reumatoide)) or (tw:(arthritis reumatoide))) and (tw:((tw:(adalimumab)) or (tw:(etanercept)) or (tw:(infiximab)) or (tw:(rituximab)) or (tw:(golimumab)) or (tw:(tocilizumab)) or (tw:(abatacept)) or (tw:(certolizumab pegol))))

Eligibility criteria

We included prospective and retrospective cohort studies and database records of patients with RA whose diagnoses were confirmed based on the ACR 1987 and the more recent ACR/EULAR 2010 criteria. Studies that accessed the effectiveness of adalimumab, etanercept, infiximab, golimumab, certolizumab pegol, rituximab, tocilizumab and abatacept between themselves, in monotherapy or combined with sDMARD were evaluated for inclusion.

Study search

We performed an electronic search of relevant articles published before August 2014 in the PubMed, EMBASE, Cochrane Controlled Trials Register and LILACS databases. Several combinations of terms corresponding

to the disease, interventions and type of study were used in the search strategy (Table 1).

In addition, we conducted a manual search in the 2012 and 2013 editions of four rheumatology journals (Journal Rheumatology, Rheumatology, Rheumatology International and the Brazilian Journal of Rheumatology) and in the abstracts of the ACR and the EULAR meetings. Also, we searched for grey literature in the Digital Library of Theses and Dissertations of University of São Paulo, and ProQuest Dissertation and Theses Database.

Study selection and data collection processes

We performed the study selection in duplicate by four independent examiners (JBS, JOC, HAOJ, LLPL). The steps included analysis of titles, abstracts, and analysis of the full-texts of articles. Divergences were analyzed by

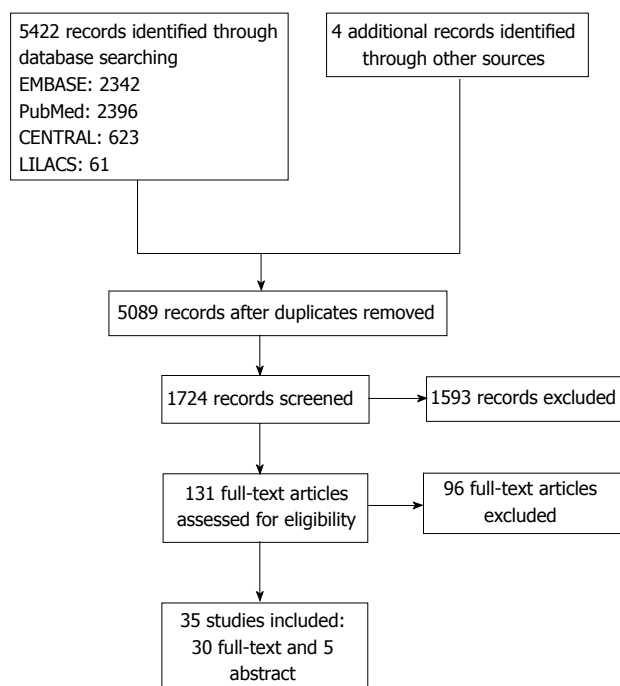


Figure 1 Study flow diagram.

another reviewer (VEA). Data collection was performed by four investigators (JBS, JOC, HAOJ, LLPL). The authors were contacted for additional information whenever needed. We assessed effectiveness as indicated by the rate of response to bDMARD according to the criteria of ACR and EULAR. We also analysed the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS28) and the Health Assessment Questionnaire (HAQ).

Assessment of methodological quality

The methodological quality of each study was assessed by four examiners (JBS, JOC, HAOJ, LLPL); divergences were solved by consensus. For that purpose, we used the Newcastle-Ottawa scale, as recommended by the Cochrane Collaboration in the case of observational studies^[11]. This scale assesses studies in three major domains: selection of the study groups, comparability of groups, and ascertainment of exposure and of results of interest. The maximum total score is nine stars, and scores above six stars are indicative of high methodological quality.

Funding sources were identified to establish potential sources of bias. Publication bias was assessed by funnel plot analysis of the results of EULAR responses and DAS28.

Statistical analysis

We used the Software Review Manager® 5.2 to perform the meta-analyses. The results are expressed as relative risks (dichotomous variables) or means differences (continuous variables) with the corresponding 95% CIs. Values of $I^2 > 40\%$ and $P < 0.10$ on the χ^2 test were considered as indicative of significant heterogeneity. The

causes of heterogeneity were investigated by excluding one study at a time and checking the changes in I^2 and P values.

RESULTS

Study inclusion

A total of 5422 articles were found in the investigated electronic databases, and a further four after manual search. Following the exclusion of duplicates, 5089 articles were selected for title analysis, from which 1724 were selected for abstract analysis, and finally 131 for full-text reading. Following full-text reading, 35 studies were included in the review, corresponding to 30 full-text articles^[12-42] and five abstracts^[43-47] (Figure 1). No observational study assessed the medicines golimumab or certolizumab pegol.

Characteristics of the studies

Among the 35 observational studies included, 16 were registry studies and 19 were cohort studies; eight were retrospective, and 27 were prospective. The study duration varied from 15 to 80 mo, though this information was not provided by some authors. The participants were followed from three to 48 mo. Five studies were funded by pharmaceutical companies, two studies were not funded by the pharmaceutical industry, and 16 had mixed funding; in the remainder articles the authors did not disclose the funding source. Nine studies assessed anti-TNF naïve participants, and 11 studies assessed cases of therapeutic failure with at least one anti-TNF agent; the remainder of the studies did not inform whether therapeutic failure had occurred or did not separate patients into subgroups (Table 2). Disease duration varied from 6 to 20 years. Approximately 50% of the participants used glucocorticoids and the use of sDMARD varied from 31% to 100%. In most of the studies, the DAS28 score was > 5.1 , which indicates high disease activity. The HAQ score varied from 0.4 to 2.2 (Figure 2).

Methodological quality

From the 35 analyzed studies, two achieved the highest score on the Newcastle-Ottawa scale, nine stars; 14, eight stars; seven, seven stars; 10, six stars; and two, five stars (Table 3). The funnel plot did not exhibit asymmetry relative to outcomes in the DAS 28 and EULAR response, which indicated the absence of publication bias, and thus of overestimation of the intervention effects calculated in the meta-analysis (data not shown).

Data synthesis

A total of 22 studies assessed the drugs adalimumab, etanercept and infliximab; nine studies assessed anti-TNF naïve patients only and seven anti-TNF naïve participants and cases of therapeutic failure; six studies did not inform whether therapeutic failure had occurred. Nineteen of those studies were included in the meta-analyses of EULAR responses, DAS28, remission

Table 2 Characteristics of included studies

N study	Ref.	Type of study	Time horizon	Patient	Intervention	Country conducting the study	Funding Sources	Duration of the study (mo)	Follow-up (mo)
1	Geborek <i>et al</i> ^[12]	Cohort	Prospective	Naive	ETA vs IFX vs LEF	Sweden	NR	24	12
2	Van Vollenhoven <i>et al</i> ^[13]	Registry	Prospective	NR	ETA vs ETA + MTX	Sweden	Mixed	NR	12
3	Cohen <i>et al</i> ^[14]	Cohort	Retrospective	Therapeutic failure	IFX vs ETA	France	NR	48	3
4	Finckh <i>et al</i> ^[15]	Registry	Prospective	Mixed	ADA vs ETA vs IFX	Switzerland	Mixed	80	12
5	Heiberg <i>et al</i> ^[16]	Cohort	Prospective	Mixed	ADA	Norway	Mixed	NR	12
6	Hyrich <i>et al</i> ^[17,18]	Registry	Prospective	NR	monotherapy vs ADA + MTX ETA monotherapy vs ETA + MTX vs ETA + DMARD and ADA monotherapy vs ADA + MTX vs ADA + DMARD	England	Pharmaceutical industry	NR	6
7	Kristensen <i>et al</i> ^[19]	Cohort	Prospective	Naive	ETA vs IFX	Sweden	Mixed	55	36
8	Bernal Rivera <i>et al</i> ^[20]	Cohort	Prospective	Naive	ADA vs ETA vs IFX	Spain	NR	24	12
9	Kristensen <i>et al</i> ^[19]	Cohort	Prospective	Naive	ETA vs IFX	Spain	NR	72	6
10	Radstake <i>et al</i> ^[23]	Cohort	Prospective	NR	IFX vs ADA	The Netherlands	Mixed	NR	6
12	Bazzani <i>et al</i> ^[24]	Registry	Prospective	Mixed	ADA vs ETA vs IFX	Italy	Pharmaceutical industry	25.29	36
13	Greenwood <i>et al</i> ^[47]	Cohort	Retrospective	NR	ADA vs ETA vs IFX	England	NR	NR	12
14	Laas <i>et al</i> ^[25]	Cohort	Prospective	Naive	ETA vs ADA	Finland	No pharmaceutical industry	36	3
15	Arenere Mendoza <i>et al</i> ^[26]	Cohort	Retrospective	Mixed	ADA vs ETA vs IFX	Spain	NR	80	12
16	Buch <i>et al</i> ^[46]	Cohort	Prospective	Therapeutic failure	RTX vs anti-TNF	England	NR	NR	6
17	Canhão <i>et al</i> ^[27]	Registry	Prospective	Naive	ADA vs ETA vs IFX	Portugal	Mixed	NR	12
18	Hetland <i>et al</i> ^[28]	Registry	Prospective	Naive	ADA vs ETA vs IFX	Denmark	Mixed	86	12
19	Blom <i>et al</i> ^[29]	Registry	Prospective	Therapeutic failure	RTX vs anti-TNF	The Netherlands	Mixed	NR	12
20	Chatzidionysiou <i>et al</i> ^[30]	Registry	Prospective	Mixed	RTX monotherapy vs RTX + MTX vs RTX + LEF	Europe	Pharmaceutical industry	NR	12
21	Gotenberg <i>et al</i> ^[45]	Registry	Prospective	Mixed	RTX vs ABAT	France	NR	NR	6
22	Iannone <i>et al</i> ^[32]	Registry	Prospective	NR	ADA vs ETA vs IFX	Italy	NR	NR	48
23	Leffers <i>et al</i> ^[33]	Registry	Prospective	Mixed	ABAT vs TOCI	Denmark	Mixed	NR	48
24	Martinez-Pérez <i>et al</i> ^[44]	Cohort	Retrospective	Mixed	RTX vs IFX	Spain	NR	NR	12
25	Wakabayashi <i>et al</i> ^[34]	Cohort	Retrospective	Therapeutic failure	TOCI vs ETA	Japan	No pharmaceutical industry	60	12
26	Finckh <i>et al</i> ^[36]	Cohort	Prospective	Therapeutic failure	RTX vs anti-TNF	Switzerland	Mixed	NR	24
27	Gomez-Reino <i>et al</i> ^[35]	Cohort	Prospective	Therapeutic failure	RTX vs anti-TNF	Spain	Pharmaceutical industry	36	12
28	Greenberg <i>et al</i> ^[37]	Registry	Prospective	Naive	ADA vs ETA vs IFX	United States	Mixed	74	24
29	Kekow <i>et al</i> ^[38]	Cohort	Retrospective	Therapeutic failure	RTX vs anti-TNF	Germany	Pharmaceutical industry	NR	6
30	Schabert <i>et al</i> ^[39]	Cohort	Retrospective	NR	ADA vs ETA vs IFX	United States	Mixed	15	12

31	Chatzidionysiou <i>et al</i> ^[40]	Registry	Prospective	Therapeutic failure	Anti-TNF <i>vs</i> ETA <i>vs</i> ADA	Stockholm	NR	NR	6
32	Keystone <i>et al</i> ^[43]	Cohort	Retrospective	Therapeutic failure	ABAT <i>vs</i> TOCI	Canada	NR	NR	12
33	Emery <i>et al</i> ^[41]	Cohort	Prospective	Therapeutic failure	RTX <i>vs</i> anti-TNF	Multicentre	Mixed	NR	12
34	Flouri <i>et al</i> ^[42]	Registry	Prospective	Mixed	ADA <i>vs</i> ETA <i>vs</i> IFX	Greece	Mixed	60	12
35	Harrold <i>et al</i> ^[31]	Registry	Prospective	Therapeutic failure	ABAT <i>vs</i> TOCI	United States	Mixed	NR	12

ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; RTX: Rituximab; ABAT: Abatacept; TOCI: Tocilizumab; LEF: Leflunomid; MTX: Methotrexate; sDMARD: Synthetic disease-modifying antirheumatic drugs; NR: Not reported.

according to DAS28, CDAI, SDAI, ACR20, 50 and 70, and HAQ (Table 4).

The good EULAR response for the participants who used etanercept was no different as that for the participants who used infliximab ($P = 0.08$) (Figure 3). However, the meta-analysis exhibited high heterogeneity. Following exclusion of the studies by Kristensen *et al*^[19] (2006) and Hyrich *et al*^[17] (2006), the heterogeneity was lowered, and the results became favorable to etanercept ($P < 0.0001$). No difference was found between adalimumab and etanercept ($P = 0.80$) (Figure 4). That meta-analysis also exhibited high heterogeneity; and after the exclusion of the study by Iannone *et al*^[32] (2011), no heterogeneity was detected ($P = 0.05$). The participants who used adalimumab presented higher good EULAR response compared to those who used infliximab ($P = 0.009$) (Figure 5). However, that meta-analysis exhibited high heterogeneity. Following exclusion of the study by Iannone *et al*^[32] (2011), the heterogeneity was lowered ($P < 0.00001$). Comparison of etanercept *vs* infliximab, adalimumab *vs* etanercept, and adalimumab *vs* infliximab found similar results relative to moderate EULAR response ($P > 0.05$). Regarding the EULAR no response, the results were favorable to infliximab compared to etanercept ($P = 0.01$), while no difference was detected between adalimumab and infliximab ($P = 0.09$) or etanercept ($P = 0.60$). The study by Gotteberg *et al*^[45] (2011), which was not included in the meta-analysis due to the lack of studies comparing abatacept and rituximab, did not detect a difference in the EULAR responses between the two drugs ($P > 0.05$). Additionally, the study by Leffers *et al*^[33] could not be included in the meta-analysis for the same reason and did not detect a difference in the EULAR responses between abatacept and tocilizumab ($P > 0.05$).

The participants who used etanercept exhibited greater remission according to DAS28 compared to the participants who used infliximab ($P < 0.0001$). Comparison of adalimumab and infliximab did not reveal a significant difference ($P = 0.23$). However, that meta-analysis exhibited moderate heterogeneity. Following exclusion of the study by Iannone *et al*^[32], the heterogeneity was lowered, and the result became favorable to adalimumab ($P = 0.001$). No significant difference was detected between adalimumab and etanercept ($P = 0.63$). However, the meta-analysis

exhibited high heterogeneity. Following exclusion of the study by Iannone *et al*^[32], heterogeneity was lowered ($P = 0.21$). The participants who used etanercept exhibited greater reduction in the DAS28 score compared to the participants who used infliximab ($P = 0.03$). Significant differences were not detected between adalimumab and etanercept ($P = 0.36$) or infliximab ($P = 0.52$). Comparison of etanercept *vs* infliximab or adalimumab did not reveal any statistically significant differences relative to DAS28 ($P > 0.05$). The study by Arenere Mendoza *et al*^[26] (2010), which was not included in the meta-analysis due to the lack of studies that analyzed the DAS28 outcome, did not report differences between adalimumab and infliximab ($P > 0.05$). The study by Greenwood *et al*^[47] (2009), which was not included in the meta-analysis due to lack of data, did not report significant differences in the DAS28 response when comparing adalimumab *vs* etanercept, infliximab *vs* adalimumab, and infliximab *vs* etanercept ($P > 0.05$). The study by Gotteberg *et al*^[45] (2011), which was also not included in meta-analysis, did not report a difference relative to DAS28 outcome between abatacept and rituximab ($P > 0.05$). The study by Leffers *et al*^[33] (2011) also did not report a difference between abatacept and tocilizumab relative to DAS28 remission ($P > 0.05$).

In regard to the ACR20 outcome, the comparison of etanercept *vs* adalimumab or infliximab presented similar results ($P > 0.05$). Comparisons of etanercept *vs* infliximab, etanercept *vs* adalimumab, and infliximab *vs* adalimumab did not reveal differences relative to the outcomes of CDAI and SDAI remission, ACR50 and ACR70 ($P > 0.05$).

The HAQ scores of the participants who used adalimumab ($P = 0.0009$) and etanercept ($P = 0.04$) were better compared to the participants who used infliximab. Adalimumab and etanercept were not different in regard to that outcome ($P = 0.23$). Adalimumab and etanercept were also not different in terms of the HAQ reduction outcome ($P = 0.16$). The study by Martinez-Pérez *et al*^[44] (2011), which was not included in the meta-analysis due to the lack of studies comparing infliximab and rituximab, did not report a difference with respect to HAQ ($P > 0.05$). The study by Leffers *et al*^[33] (2011), which was also not included in the meta-analysis, did not report a significant difference in HAQ between abatacept and tocilizumab ($P > 0.05$).

N study	Author, Year, Study, Intervention	n	Age (yr)	Male sex (%)	Disease duration, years	Previous anti-TNF (% ou DP)	Previous sDMARD (% ou DP)	Concomitant sDMARD (% ou DP)	Concomitant MTX (% ou DP)	Concomitant steroids (% ou DP)	DAS 28 (DP)	HAQ (DP)
1	Geborek <i>et al</i> ^[12]											
	ETA	166	54.0	22	14.9	NR	4.5	0.7	NR	NR	5.8	1.55
	IFX	135	55.4	21	14.1	NR	4.0	1.0	NR	NR	5.6	1.47
	Value p ETA vs IFX	NA	NS	NS	NS	NR	NS	< 0.001	NR	NR	NS	NS
2	Van Vollenhoven <i>et al</i> ^[13]											
	ETA monotherapy	40	53.3 (2.0)	30	12.7 (1.5)	NR	NR	NR	NR	NR	NR	1.62 (0.08)
	ETA + MTX	57	51.1 (1.7)	9	14.5 (1.3)	NR	NR	NR	NR	NR	NR	1.86 (0.09)
	Value P	NA	NS	< 0.02	NS	NR	NR	NR	NR	NR	NR	NS
3	Cohen <i>et al</i> ^[14]											
	IFX to ETA	24	53.6 (11.3)	12.5	12.2 (9.6)	NR	4.1 (1.8)	NR	NR	NR	5.6 (1.1)	NR
	ETA to IFX	14	55.8 (12.8)	28.6	15.7 (8.9)	NR	4.6 (1.8)	NR	NR	NR	5.9 (1.2)	NR
	Value P	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
4	Finckh <i>et al</i> ^[15]											
	ADA	317	53.0 (51.4-54.7)	26	10.1 (5.6-17.5)	39	NR	53	NR	41	4.19 (4.02-4.36)	1.25 (1.18-1.33)
	IFX	362	53.1 (51.7-54.5)	25	10.2 (5.0-16.5)	12	NR	93	NR	56	4.54 (4.38-4.7)	1.37 (1.29-1.44)
	ETA	519	54.4 (53.2-55.6)	26	10.3 (5.7-15.9)	7	NR	64	NR	60	4.72 (4.59-4.85)	1.37 (1.31-1.43)
	Value P		0.24	0.89	0.97	< 0.001	NR	NR	NR	< 0.001	< 0.001	0.04
5	Heiberg <i>et al</i> ^[16]											
	ADA	84	56.1 (12.9)	21.4	13.5 (9.7)	46	4.9 (2.5)	NR	NR	5.4 (4.7)	5.5 (1.2)	1.89 (0.57)
	ADA+MTX	99	52.4 (14.4)	21.2	11.8 (9.7)	42	3.8 (3.2)	NR	NR	3.4 (4.1)	5.4 (1.2)	1.84 (0.45)
	Value P	NA	0.07	0.97	0.26	0.29	0.01	NR	NR	< 0.01	0.60	0.52
6	Hyrich <i>et al</i> ^[17]											
	ETA monotherapy	763	58 (12)	20	16 (10)	NR	5.0 (2)	NR	NR	54	6.8 (1.0)	2.2 (0.5)
	ETA + MTX	250	54 (12)	24	13 (8)	NR	4.0 (2)	NR	NR	44	6.6 (0.9)	2.1 (0.5)
	ETA + sDMARD	245	55 (12)	21	15 (9)	NR	5.0 (2)	NR	NR	51	6.6 (0.9)	2.1 (0.5)
	IFX monotherapy	128	59 (12)	21	16 (11)	NR	5.0 (2)	NR	NR	69	6.8 (1.1)	2.2 (0.5)
	IFX + MTX	1204	55 (12)	23	14 (9)	NR	4.0 (2)	NR	NR	48	6.7 (0.9)	2.1 (0.5)
	IFX + sDMARD	121	58 (12)	26	14 (9)	NR	5.0 (2)	NR	NR	59	6.8 (1.1)	2.2 (0.6)
	Value P ETA	NA	< 0.001	0.27	0.005	NR	< 0.001	NR	NR	0.01	< 0.001	< 0.001
	Value P IFX	NA	< 0.001	0.65	0.11	NR	< 0.001	NR	NR	< 0.001	0.50	0.03
	Hyrich <i>et al</i> ^[18]											
	ETA	1413	56 (12)	22	15 (9)	NR	4.5 (1.7)	46	27	50	6.7 (1.0)	2.1 (0.5)
	IFX	1810	55 (12)	23	14 (9)	NR	4.2 (1.7)	93	85	50	6.7 (1.0)	2.1 (0.5)
	Value P	NA	NS	NS	NS	NR	NS	< 0.05	< 0.05	NS	NS	NS
7	Kristensen <i>et al</i> ^[19]											
	ETA	309	55.1 (13.0)	18	14.7 (10.1)	NR	4.2 (2.05)	NR	31	NR	5.9 (1.06)	1.6 (0.64)
	IFX	640	56.2 (14.0)	25	12.7 (10.0)	NR	3.6 (1.98)	NR	73	NR	5.6 (1.20)	1.4 (0.62)
	Value P	NA	NR	0.021	< 0.001	NR	< 0.001	NR	< 0.001	NR	< 0.001	0.002
8	Bernal Rivera <i>et al</i> ^[20]											
	ETA total	49	45.3 (5.3)	37	9.9 (2.0)	NR	3.2 (0.26)	NR	65	43	6.3 (0.4)	NR
	ETA + MTX	32	NR	NR	NR	NR	NR	NR	NR	NR	6.2 (0.4)	NR
	ETA monotherapy	10	NR	NR	NR	NR	NR	NR	NR	NR	5.7 (0.9)	NR
	ADA total	50	51.5 (3.7)	42	12.4 (1.9)	NR	3.1 (0.4)	NR	42	52	6.7 (0.3)	NR
	ADA + MTX	21	NR	NR	NR	NR	NR	NR	NR	NR	6.7 (0.5)	NR
	ADA monotherapy	15	NR	NR	NR	NR	NR	NR	NR	NR	6.5 (0.7)	NR
	Value P	NA	NS	NS	NS	NR	NS	NS	NS	NS	NS	NR
9	Fernández-Nebro <i>et al</i> ^[21]											
	IFX	60	54 (11.6)	12	9.6 (7.9)	NR	3.8 (1.5)	NR	83	65	6.2 (1.3)	1.78 (0.56)
	ETA	79	54 (12.4)	24	9.9 (7.9)	NR	3.6 ± 1.3	NR	52	67	5.9 (1.4)	1.71 (0.65)
	ADA	22	54 (10.4)	18	9.5 (8.3)	NR	3.8 ± 1.5	NR	50	48	6.2 (0.9)	1.74 (0.71)
	Value P	NA	NS	NS	NS	NR	NS	NR	< 0.05	NS	NS	NS
10	Radstake <i>et al</i> ^[23]											
	IFX	35	57 (10)	14	NR	NR	NR	NR	100	NR	5.6 (1.2)	NR
	ADA	34	56 (10)	21	NR	NR	NR	NR	41	NR	5.7 (1.0)	NR
	Value P	NA	NS	NS	NR	NR	NR	NR	NS	NR	NS	NR
11	Kievit <i>et al</i> ^[22]											
	ADA	267	55.1 (12.6)	30	7.7 (2.7-13.6)	NR	3.0 (2-4)	NR	NR	NR	5.3 (1.3)	1.3 (0.7)
	ETA	289	54.6 (14.2)	31.1	6 (2.1-13.4)	NR	3.0 (2-4.75)	NR	NR	NR	5.5 (1.2)	1.4 (0.7)
	IFX	151	57.8 (13.4)	29.8	7.7 (2.7-14.1)	NR	3.0 (2-5)	NR	NR	NR	5.2 (1.3)	1.4 (0.7)
	Value P	NA	0.05	0.939	0.356	NR	0.385	NR	NR	NR	0.059	0.176

12	Bazzani <i>et al</i> ^[24]											
	IFX	498	NR	NR	NR	NR	NR	NR	NR	NR	6.01	1.5
	ETA	229	NR	NR	NR	NR	NR	NR	NR	NR	6.05	1.23
	ADA	283	NR	NR	NR	NR	NR	NR	NR	NR	5.76	1.2
13	Value P	NA	NS	NR	NS	NR	NS	NR	NR	NR	< 0.05	< 0.05
	Greenwood <i>et al</i> ^[47]											
	IFX	74	55	28	14	NR	NR	NR	NR	NR	6.86	NR
	ETA	108	57	28	14	NR	NR	NR	NR	NR	6.59	NR
14	ADA	27	55	30	12	NR	NR	NR	NR	NR	6.44	NR
	Value P	NA	NS	NS	NS	NR	NR	NR	NR	NR	NS	NR
	Laas <i>et al</i> ^[25]											
	ETA	58	50 (14)	26	16 (1-47)	NR	NR	NR	53	NR	NR	1.22 (0.68)
15	ADA	39	55 (11)	24	17 (1-37)	NR	NR	NR	54	NR	NR	1.14 (0.72)
	Value P	NA	NS	NS	NS	NR	NR	NR	NS	NR	NR	NR
	Arenere Mendoza <i>et al</i> ^[26]											
	IFX	38	53.4 (14.0)	23.7	9.3 (8.0)	NR	NR	NR	NR	NR	5.60 (1.10)	1.6 (0.7)
16	ETA	44	50.5 (15.0)	15.9	11.9 (9.5)	NR	NR	NR	NR	NR	5.54 (1.27)	1.2 (0.7)
	ADA	37	52.3 (12.8)	16.2	8.1 (6.2)	NR	NR	NR	NR	NR	5.60 (0.88)	1.1 (0.5)
	Value P	NA	0.695	0.606	0.121	NR	NR	NR	NR	NR	0.836	0.051
	Buch <i>et al</i> ^[46]											
17	RTX	101	NR	NR	NR	1.93 (0.77)	NR	NR	NR	NR	6.30 (1.84)	NR
	Anti-TNF	101	NR	NR	NR	1.17 (0.38)	NR	NR	NR	NR	6.29 (1.07)	NR
	Value P	NA	NR	NR	NR	NS	NR	NR	NR	NR	NS	NR
	Canhão <i>et al</i> ^[27]											
18	IFX	206	54.1 (11.9)	15.1	11.2 (9.4)	NR	NR	95.1	NR	73.8	5.9 (1.1)	1.53 (0.62)
	ETA	250	52.4 (12.1)	9.2	10.4 (8.6)	NR	NR	82.4	NR	74.4	5.8 (1.2)	1.55 (0.57)
	ADA	161	50.9 (12.0)	11.8	9.5 (7.6)	NR	NR	86.3	NR	62.1	5.5 (1.1)	1.3 (0.6)
	Value P	NA	0.04	0.16	0.21	NR	NR	0.0001	NR	0.02	0.02	0.008
	Value p IFX vs ETA	NA	NS	NS	NS	NR	NR	NS	NR	NS	NS	NS
	Value p IFX vs ADA	NA	0.01	NS	NS	NR	NR	NS	NR	NS	0.007	0.01
	Value p ETA vs ADA	NA	NS	NS	NS	NR	NR	NS	NR	NS	NS	0.003
	Hetland <i>et al</i> ^[28]											
19	ADA	544	56 (15-85)	25	9 (0-51)	NR	3.0 (0-8)	NR	70	40	5.3 (3.3-8.3)	NR
	ETA	425	58 (19-89)	28	8 (0-47)	NR	3.0 (0-8)	NR	61	43	5.4 (3.3-8.4)	NR
	IFX	908	57 (17-85)	27	9 (0-68)	NR	3.0 (0-9)	NR	87	50	5.4 (3.3-8.3)	NR
	Value p	NA	0.30	0.58	0.24	NR	0.0044	NR	< 0.0001	< 0.0001	0.035	NR
20	Blom <i>et al</i> ^[29]											
	Terceiro anti-TNF	64	53.3 (12.9)	28	8.9 (9.2)	100	4.0 (2.0)	NR	53	38	5.1 (1.30)	1.51 (0.64)
	RTX	90	56.6 (12.2)	27	10.9 (13.7)	100	4.0 (2.3)	NR	49	44	5.32 (1.25)	1.52 (0.78)
	Value P	NA	NS	NS	NS	NS	NS	NR	NS	NS	NS	NS
21	Chatzidionysiou <i>et al</i> ^[30]											
	RTX	505	55.2 (12.9)	18.9	13.2 (10.1)	1.0 (0.8)	2.8 (1.8)	NR	NR	56.6	5.7 (1.3)	1.7 (0.7)
	RTX + MTX	1195	51.9 (13.1)	18.7	11.7 (8.8)	0.9 (0.8)	2.6 (1.5)	NR	NR	59.9	5.9 (1.3)	1.6 (0.7)
	RTX + LEF	177	52.3 (12.1)	16.9	11.4 (7.9)	0.6 (0.8)	2.5 (1.4)	NR	NR	53.2	5.9 (1.2)	1.6 (0.7)
	Value p RTX vs RTX + MTX	NA	< 0.0001	NS	0.003	0.01	0.003	NR	NR	NS	0.02	NS
	Value p RTX vs RTX + LEF	NA	0.001	NS	0.04	< 0.0001	0.05	NR	NR	NS	NS	NS
22	Value p RTX + MTX vs RTX + LEF	NA	NS	NS	NS	0.001	NS	NR	NR	NS	NS	NS
	Gotenberg <i>et al</i> ^[45]											
	RTX	1732	NR	NR	NR	78.8	3.1 (1.4)	NR	NR	NR	5.6 (1.2)	NR
	ABAT	508	NR	NR	NR	89.3	2.8 (1.4)	NR	NR	NR	5.3 (1.3)	NR
23	Value P	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Iannone <i>et al</i> ^[32]											
	ADA	324	54.5 (12)	17.7	11.5 (8.8)	NR	97	25	NR	29	5.37 (1.5)	1.28 (0.5)
	ETA	311	53.5 (14)	13.8	10.7 (8.6)	NR	99	31	NR	44	5.71 (1.5)	1.6 (0.7)
24	IFX	218	51.9 (13)	21.1	9.9 (7.7)	NR	96	44	NR	30	5.6 (1.4)	1.5 (0.6)
	Value p	NA	0.06	NR	0.17	NR	0.19	0.01	NR	0.06	0.04	0.03
	Leffers <i>et al</i> ^[33]											
	ABAT	104	54 (23-82)	22	8 (1-38)	97	3.0 (0-8)	NR	NR	45	5.3 (2.6-7.5)	NR
25	TOCI	97	56 (20-81)	26	7 (1-45)	98	3.0 (1-8)	NR	NR	38	5.4 (1.6-7.8)	NR
	Value p	NA	NS	NS	NS	NS	NS	NR	NR	NS	NS	NR
	Martínez-Pérez <i>et al</i> ^[44]											
	IFX	23	NR	28.6	NR	4.8	NR	NR	NR	NR	NR	1.996 (0.764)
26	RTX	19	NR		NR	100	NR	NR	NR	NR	NR	1.680 (0.763)
	Value P	NA	NR	NA	NR	NR	NR	NR	NR	NR	NR	NR

25	Wakabayashi <i>et al</i> ^[34]											
	ETA	16	57.0 (14.1)	25	10.8 (9.5)	100	NR	NR	NR	100	5.4 (1.3)	NR
	TOCI	23	54.6 (14.6)	13	6.8 (6.4)	100	NR	NR	NR	95.6	4.9 (1.7)	NR
	Value P	NA	0.5389	0.4151	0.2377	NS	NR	NR	NR	1,000	0.3246	NR
26	Finckh <i>et al</i> ^[36]											
	Anti-TNF	163	56 (44-64)	19	11 (0.5)	100	NR	74	NR	48	4.2 (0.08)	1.13 (0.04)
	RTX	155	58 (47-66)	25	12 (0.8)	100	NR	79	NR	56	4.7 (0.14)	1.27 (0.07)
	Value P		0.15	0.18	0.13	NS	NR	0.30	NR	0.16	0.003	0.07
27	Gomez-Reino <i>et al</i> ^[35]						> 2 DMARD					
	RTX	575	55.3 (12.8)	18	NR	100	92.7	NR	NR	NR	5.5 (1.20)	NR
	anti-TNF	513	54.5 (13.5)	19.5	NR	100	86.6	NR	NR	NR	5.0 (1.30)	NR
	Value P	NA	0.364	0.400	NR	NS	0.0028	NR	NR	NR	< 0.0001	NR
28	Greenberg <i>et al</i> ^[37]											
	ADA	460	55 (12)	22	8.9 (9.5)	NR	0.7 (1.0)	NR	NR	35	4.49 (1.6)	0.5 (0.5)
	ETA	480	54 (13)	24	8.8 (9.2)	NR	0.7 (1.0)	NR	NR	33	4.48 (1.4)	0.5 (0.5)
	IFX	535	61 (13)	28	9.6 (9.9)	NR	0.7 (1.0)	NR	NR	33	4.53 (1.4)	0.4 (0.5)
	Value P	NA	< 0.001	0.06	< 0.001	NR	0.73	NR	NR	0.80	0.91	0.11
29	Kekow <i>et al</i> ^[38]											
	RTX	90	57 (27-79)	26.7	7.3 (0.9-30.6)	100	80	83.3	NR	NR	5.6 (0.1)	1.8 (0.1)
	anti-TNF	106	58 (21-83)	18.9	8.4 (0.2-38.3)	100	86.7	82.1	NR	NR	5.4 (0.1)	1.6 (0.2)
	Value P	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
30	Schabert <i>et al</i> ^[39]											
	ETA	218	55.1 (11.6)	15.6	18.52 (10.88)	NR	NR	NR	62.8	61	NR	1.20 (0.73)
	IFX	93	60.2 (12.8)	16.1	19.66 (11.36)	NR	NR	NR	66.7	50.5	NR	1.24 (0.72)
	ADA	40	56.6 (13.0)	30	19.16 (10.9)	NR	NR	NR	62.5	52.5	NR	0.92 (0.76)
	Value p IFX vs ETA	NA	< 0.001	NS	NS	NR	NR	NR	NS	NS	NR	NS
	Value p IFX vs ADA	NA	NS	< 0.05	NS	NR	NR	NR	NS	NS	NR	< 0.05
	Value p ETA vs ADA	NA	NS	< 0.05	NS	NR	NR	NR	NS	NS	NR	< 0.05
31	Chatzidionysiou <i>et al</i> ^[40]											
	Anti-TNF (ADA ou IFX)	161	55.8 (13.8)	21.1	6 (3-15)	100	NR	68.9	NR	45.3	4.87 (1.27)	1.14 (0.65)
	ETA	98	52.7 (14.4)	12.2	7 (2-15)	100	NR	71.4	NR	54.1	4.86 (1.21)	1.14 (0.62)
	RTX	69	60.3 (14.0)	15.9	9 (3-16)	100	NR	59.4	NR	58.0	5.30 (1.29)	1.43 (0.57)
	Value P	NA	< 0.05	NS	NS	NS	NR	NS	NR	NS	NS	< 0.05
32	Keystone <i>et al</i> ^[43]											
	ABAT	24	NR	NR	NR	11 (45.8)	NR	NR	NR	NR	NR	NR
	RTX	37	NR	NR	NR	9 (33.3)	NR	NR	NR	NR	NR	NR
	Value P	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
33	Emery <i>et al</i> ^[41]											
	RTX	405	56.5 (12.6)	23	9.1 (7.7)	NR	2.2 (1.1)	NR	NR	293 (72.3)	5.2 (1.2)	1.5 (0.8)
	Anti-TNF	323	54.7 (13.3)	20	7.8 (6.8)	NR	2.3 (1.3)	NR	NR	229 (70.9)	4.8 (1.3)	1.3 (0.8)
	Value p	NA	0.0611	0.2376	0.1044	NR	0.3853	NR	NR	0.6666	<0.0001	0.0945
34	Flouri <i>et al</i> ^[42]											
	IFX	560	58 (17)	26	8.5 (12.7)	7.0	2.0 (1)	93	NR	59	5.4 (1.5)	1.0 (0.9)
	ADA	435	59 (18)	19	7.8 (12.8)	29.7	2.0 (1)	88	NR	55	5.6 (1.6)	1.0 (0.9)
	ETA	302	57 (19)	20	7.4 (10.6)	33.4	2.0 (1)	87	NR	53	5.7 (1.6)	1.0 (0.9)
	Value P	NA	0.995	0.995	0.354	< 0.001	0.229	0.017	NR	0.259	0.331	0.634
	Value p IFX vs ETA	NA	NS	NS	NS	< 0.05	NS	< 0.05	NR	NS	NS	NS
	Value p IFX vs ADA	NA	NS	< 0.05	NS	< 0.05	NS	< 0.05	NR	NS	NS	NS
	Value p ETA vs ADA	NA	NS	NS	NS	NS	NS	NS	NR	NS	NS	NS
35	Harrold <i>et al</i> ^[31]											
	ABAT	431	57.6 (12.4)	17.6	13.3 (10.0)	NR	NR	NR	55.2	39.4	NR	0.7 (0.5)
	Anti-TNF	746	57.2 (11.7)	20.9	12.1 (9.8)	NR	NR	NR	55.5	33.0	NR	0.6 (0.5)
	Value P	NA	0.578	0.196	0.045	NR	NR	NR	0.951	0.027	NR	0.047

Figure 2 Patient characteristics of included articles. ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; RTX: Rituximab; ABAT: Abatacept; TOCI: Tocilizumab; MTX: Methotrexate; sDMARD: Synthetic disease-modifying antirheumatic drugs; NR: Not reported; NS: Not significant; NA: Not applicable.

Table 3 Quality assessment of articles for Newcastle Ottawa scale

N study	Ref.	Selection				Comparability	Results			Total
		Representativeness of the cases	Selection of controls	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	
1	Geborek <i>et al</i> ^[12]	1	1	1	1	2	0	1 (12 mo)	1	8
2	Van Vollenhoven <i>et al</i> ^[13]	0	1	1	1	2	0	1 (24 mo)	0	6
3	Cohen <i>et al</i> ^[14]	1	1	1	1	1	0	1 (3 mo)	0	6
4	Finckh <i>et al</i> ^[15]	1	1	1	0	1	1	1 (12 mo)	1	7
5	Heiberg <i>et al</i> ^[16]	1	1	1	1	2	0	1 (6 mo)	1	8
6	Hyrich <i>et al</i> ^[17,18]	1	1	1	1	2	0	1 (6 mo)	1	8
7	Kristensen <i>et al</i> ^[19]	1	1	1	0	2	0	1 (36 mo)	0	6
8	Bernal Rivera <i>et al</i> ^[20]	1	1	1	0	2	0	1 (12 mo)	1	7
9	Fernández-Nebro <i>et al</i> ^[21]	1	1	1	1	2	0	1 (6 mo)	1	8
10	Radstake <i>et al</i> ^[23]	0	1	1	1	2	0	1 (6 mo)	0	6
11	Kievit <i>et al</i> ^[22]	1	1	1	1	2	0	1 (6 mo)	0	7
12	Bazzani <i>et al</i> ^[24]	1	1	1	0	2	1	1 (6 mo)	1	8
13	Greenwood <i>et al</i> ^[47]	0	1	1	1	2	0	1 (12 mo)	0	6
14	Laas <i>et al</i> ^[25]	1	1	1	1	2	1	1 (3 mo)	1	9
15	Arenere Mendoza <i>et al</i> ^[26]	1	1	1	1	2	0	1 (12 mo)	0	7
16	Buch <i>et al</i> ^[46]	1	1	1	0	2	0	1 (6 mo)	0	6
17	Canhão <i>et al</i> ^[27]	1	1	1	0	2	0	1 (12 mo)	1	7
18	Hetland <i>et al</i> ^[28]	1	1	1	1	2	0	1 (12 mo)	1	8
19	Blom <i>et al</i> ^[29]	1	1	1	1	2	1	1 (12 mo)	1	9
20	Chatzidionysiou <i>et al</i> ^[30]	1	1	1	1	2	0	1 (12 mo)	0	7
21	Gotenberg <i>et al</i> ^[45]	1	1	1	1	2	0	1 (6 mo)	1	8
22	Iannone <i>et al</i> ^[32]	1	1	1	0	2	0	1 (48 mo)	0	6
23	Leffers <i>et al</i> ^[33]	1	1	1	1	2	0	1 (12 mo)	0	7
24	Martínez-Pérez <i>et al</i> ^[44]	0	1	0	1	2	0	1 (12 mo)	0	5
25	Wakabayashi <i>et al</i> ^[34]	0	1	1	1	2	1	1 (12 mo)	1	8
26	Finckh <i>et al</i> ^[36]	1	1	1	1	1	1	1 (24 mo)	1	8
27	Gomez-Reino <i>et al</i> ^[35]	1	1	1	0	2	1	1 (12 mo)	1	8
28	Greenberg <i>et al</i> ^[37]	1	1	1	1	2	0	1 (24 mo)	1	8
29	Kekow <i>et al</i> ^[38]	1	1	1	1	2	0	1 (6 mo)	1	8
30	Schabert <i>et al</i> ^[39]	1	1	1	1	1	1	1 (12 mo)	1	8
31	Chatzidionysiou <i>et al</i> ^[40]	1	1	1	0	2	0	1 (6 mo)	0	6
32	Keystone <i>et al</i> ^[43]	0	1	1	0	2	0	1 (12 mo)	0	5
33	Emery <i>et al</i> ^[41]	1	1	1	0	2	0	1 (12 mo)	0	6
34	Flouri <i>et al</i> ^[42]	1	1	1	1	2	0	1 (12 mo)	1	8
35	Harrold <i>et al</i> ^[31]	1	1	1	0	2	0	1 (12 mo)	0	6

Anti-TNF naïve patients: Nine studies assessed anti-TNF-naïve individuals only, from which seven were included in the meta-analysis that assessed the outcomes of EULAR, remission according to DAS28 and CDAI, and ACR20, 50, 70 (Table 5).

The good EULAR response for the participants who used etanercept were the same as those of the participants who used infliximab ($P = 0.17$). However, that meta-analysis exhibited high heterogeneity. Following exclusion of the study by Kristensen *et al*^[19] (2006), the heterogeneity was low, and the results became favorable to etanercept ($P = 0.0006$). No difference was detected between adalimumab and etanercept ($P = 0.05$). The participants who used adalimumab exhibited greater good EULAR response compared to the participants who used infliximab ($P = 0.0002$). The results relative to the moderate EULAR response outcome were similar in the comparisons of etanercept vs infliximab, adalimumab vs etanercept, and adalimumab vs infliximab ($P > 0.05$). With regard to the EULAR no response, the results were favorable to infliximab compared to etanercept ($P =$

0.004) or adalimumab ($P < 0.00001$) and to etanercept compared to adalimumab ($P = 0.004$).

The participants who used etanercept exhibited greater remission according to DAS28 compared to the participants who used infliximab ($P = 0.01$). No differences were detected between adalimumab and infliximab ($P = 0.12$) or etanercept ($P = 0.79$).

With regard to the ACR20 outcome, the results of etanercept vs adalimumab or infliximab were not different ($P > 0.05$). No differences were detected for the outcomes of ACR50 and 70 and the remission according to CDAI between etanercept and infliximab, etanercept and adalimumab, and infliximab and adalimumab ($P > 0.05$). Only the study by Greenberg *et al*^[37] (2012) compared the ACR20 outcome between adalimumab and infliximab ($P > 0.05$). The study by Geborek *et al*^[12] (2002), which was not included in the meta-analysis because it reported graphical data without numerical values; showed that the ACR 20 response was better with etanercept compared to infliximab ($P < 0.05$), while no differences were detected relative to ACR50 and 70.

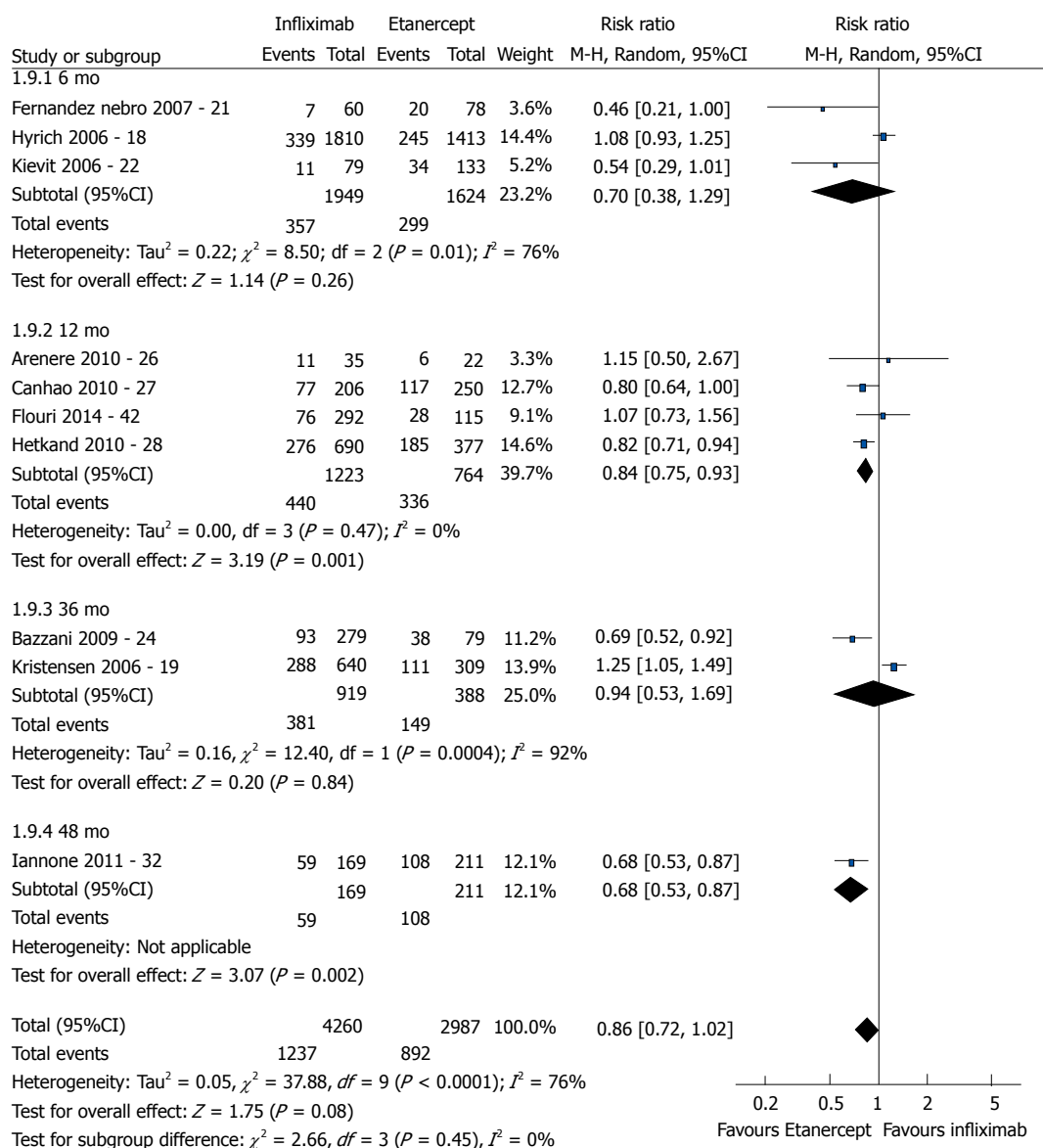


Figure 3 EULAR good response - Etanercept vs Infliximab.

The study by Kievit *et al.*^[22] (2008) assessed the HAQ reduction outcome and found that the results were better with adalimumab compared to infliximab ($P < 0.05$). Kievit *et al.*^[22] (2008) and Laas *et al.*^[25] (2009) did not detect a difference between adalimumab and etanercept ($P = 0.16$).

Patients with anti-TNF therapeutic failure: Eleven studies assessed anti-TNF therapeutic failure only, from which nine were included in the meta-analyses that assessed the outcomes of EULAR response and DAS28 reduction (Table 6).

The participants who used rituximab exhibited greater DAS28 reduction compared to those who used anti-TNF agents ($P = 0.0002$); however, the EULAR responses did not differ between these groups ($P > 0.05$). In addition, all of the corresponding meta-analyses exhibited high statistical heterogeneity. The study by Blom *et al.*^[29] (2011), which was not included in the meta-analysis

because it did not report the DAS28 absolute scores, also detected lower scores for the participants who used rituximab compared to those who used anti-TNF ($P = 0.004$). Among four studies that assessed HAQ, only the Finckh *et al.*^[36] study (2012) found that the participants who used rituximab exhibited greater score reductions compared to those who used anti-TNF, which did not represent a clinically significant improvement (e.g., a reduction of 0.22 points in the HAQ score).

The participants who used etanercept achieved greater good EULAR response compared to those who did not use that drug ($P = 0.007$); that difference resulted from one study that compared etanercept vs rituximab^[37]. With regard to the DAS28 score reduction, no differences were reported between the groups ($P = 0.71$).

The abstracts of studies that assessed reduction of the CDAI score indicated the superiority of abatacept over rituximab (12.4 vs +1.7) and anti-TNF agents (7.6

Table 4 Meta-analysis of the outcomes for patients with treatment-naïve and therapeutic failure

Intervention	Outcomes	Studies (references)	Partici-pants	Relative risk (95%CI) or other mesure	I ² (%)	P value
IFX <i>vs</i> ETA	EULAR good response	10 (18,19,21,22,24, 26,27, 28, 32,42)	7247	0.86 [0.72-1.02]	76	< 0.0001
	EULAR moderate response	9 (18,19,21,22,24, 26, 28, 32,42)	6791	0.98 [0.84-1.15]	78	< 0.0001
	EULAR no response	9 (18,19,21,22,24, 26, 28, 32,42)	6791	1.20 [1.05-1.38]	46	0.06
	DAS 28 remission	7 (21,26,27,28,32,37,42)	2868	0.70 [0.59-0.84]	0	0.51
	DAS 28	2 (21,26)	196	0.40 [-0.27- 1.07]	59	0.12
	DAS 28 reduction	2 (15,22)	1321	0.40 [0.04-0.77]	77	0.04
	CDAI remission	4 (27,28,37,42)	2293	0.90 [0.74-1.09]	0	0.89
	SDAI remission	2 (27,42)	840	0.87 [0.61-1.26]	0	0.9
	HAQ	3 (21,26,39)	495	0.14 [0.00-0.27]	0	0.51
	ACR 20	2 (19,37)	1309	0.95 [0.86-1.06]	0	0.47
	ACR50	3 (19,28,37)	2315	0.92 [0.81-1.03]	10	0.33
	ACR70	3 (19,28,37)	2315	0.88 [0.57-1.36]	79	0.009
ADA <i>vs</i> ETA	EULAR good response	8 (20,22,24,26,27,28,32,42)	2492	0.97 [0.79-1.20]	73	0.0005
	EULAR moderate response	7 (20,22,24,26,28,32,42)	2080	1.00 [0.89-1.12]	0	0.48
	EULAR no response	7 (20,22,24,26,28,32,42)	2080	0.90 [0.62-1.32]	76	0.0003
	DAS 28 remission	6 (26,27,28,32,37,42)	2412	0.93 [0.68-1.26]	80	0.0001
	DAS 28	2 (20,26)	180	-0.09 [-0.25-0.06]	0	0.73
	DAS 28 reduction	2 (15,22)	1392	0.17 [-0.19-0.52]	68	0.08
	CDAI remission	4 (27,28,37,42)	1883	1.16 [0.77-1.74]	70	0.02
	SDAI remission	2 (27,42)	641	1.40 [0.76-2.59]	55	0.13
	HAQ	2 (26,39)	339	-0.15 [-0.39-0.10]	49	0.16
	HAQ reduction	2 (22,25)	653	-0.07 [-0.16-0.03]	0	0.92
	ACR 20	2 (20,37)	445	0.89 [0.71-1.12]	0	0.68
	ACR 50	3 (20,28,37)	1217	1.09 [0.91-1.31]	18	0.3
	ACR 70	3 (20,28,37)	1436	1.15 [0.92-1.43]	0	0.82
IFX <i>vs</i> ADA	EULAR good response	8 (22,23,24,26,27,28,32,42)	3025	1.25 [1.06-1.47]	57	0.02
	EULAR moderate response	7 (22,23,24,26,28,32,42)	2657	0.91 [0.79-1.04]	31	0.19
	EULAR no response	7 (22,23,24,26,28,32,42)	2657	0.77 [0.56-1.05]	75	0.0006
	DAS 28 remission	6 (26,27,28,32,37,42)	2760	1.15 [0.91-1.46]	63	0.02
	DAS 28 reduction	2 (15,22)	1097	-0.24 [-0.96-0.48]	91	0.001
	CDAI remission	4 (27,28,37,42)	2332	1.30 [0.90-1.88]	68	0.02
	SDAI remission	2 (27,42)	765	1.66 [0.94-2.93]	61	0.11
	HAQ	2 (26,39)	182	-0.33 [-0.53-0.13]	0	0.92
	ACR 50	2 (28,37)	1458	1.14 [0.71-1.84]	79	0.03
	ACR 70	2 (28,37)	1458	1.41 [0.81-2.44]	72	0.06

A value of $I^2 > 40\%$ indicates statistical heterogeneity between the studies. A value of $P < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies. CI: Confidence interval; ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; EULAR: European League Against Rheumatism; DAS 28: Disease activity score; SDAI: Simplified disease activity index; CDAI: Clinical disease activity; HAQ: Health Assessment Questionnaire; ACR: American College Rheumatology.

vs 8.3); those results could not be assessed in the meta-analysis due to the lack of data^[28,41]. Harrold *et al.*^[31] (2014) also assessed ACR20 and 50 outcomes and did not detect any differences between the groups treated with abatacept or anti-TNF agents [0.87 (0.59; 1.29) and 0.86 (0.58; 1.27), respectively].

Patients who used bDMARD in monotherapy or in combination with methotrexate: Four studies assessed individuals treated with bDMARD monotherapy or in combination with methotrexate, and three were included in the meta-analysis that assessed EULAR response, DAS28 and HAQ outcomes (Table 7).

Regarding the good EULAR response, combination with methotrexate was better than bDMARD monotherapy ($P = 0.03$) (Figure 6). No difference was found relative to DAS28 between bDMARD monotherapy and combination with methotrexate ($P = 0.07$). However, this meta-analysis exhibited high heterogeneity. Following exclusion of the study by Chatzidionysiou *et al.*^[30] (2012)^[30], no heterogeneity was detected, and the results

became favorable to the combination with methotrexate ($P < 0.00001$). The study by van Vollenhoven *et al.*^[13] (2003), which was not included in the meta-analysis because it reported graphical data without numerical values, reported a difference in DAS28 favorable to combination with methotrexate compared to bDMARD monotherapy ($P < 0.05$). The study by Heiberg *et al.*^[16] (2006), which was not included in the meta-analysis due to the lack of studies that assessed the DAS28 reduction outcome, reported a difference favorable to bDMARD in combination with methotrexate ($P < 0.05$). With regard to the HAQ score outcome, the best results were exhibited by bDMARD in combination with methotrexate ($P = 0.009$).

DISCUSSION

Patients who used adalimumab and etanercept presented similar results among them and better outcomes compared to patients under infliximab therapy. The analysis of subgroup of anti-TNF naïve participants

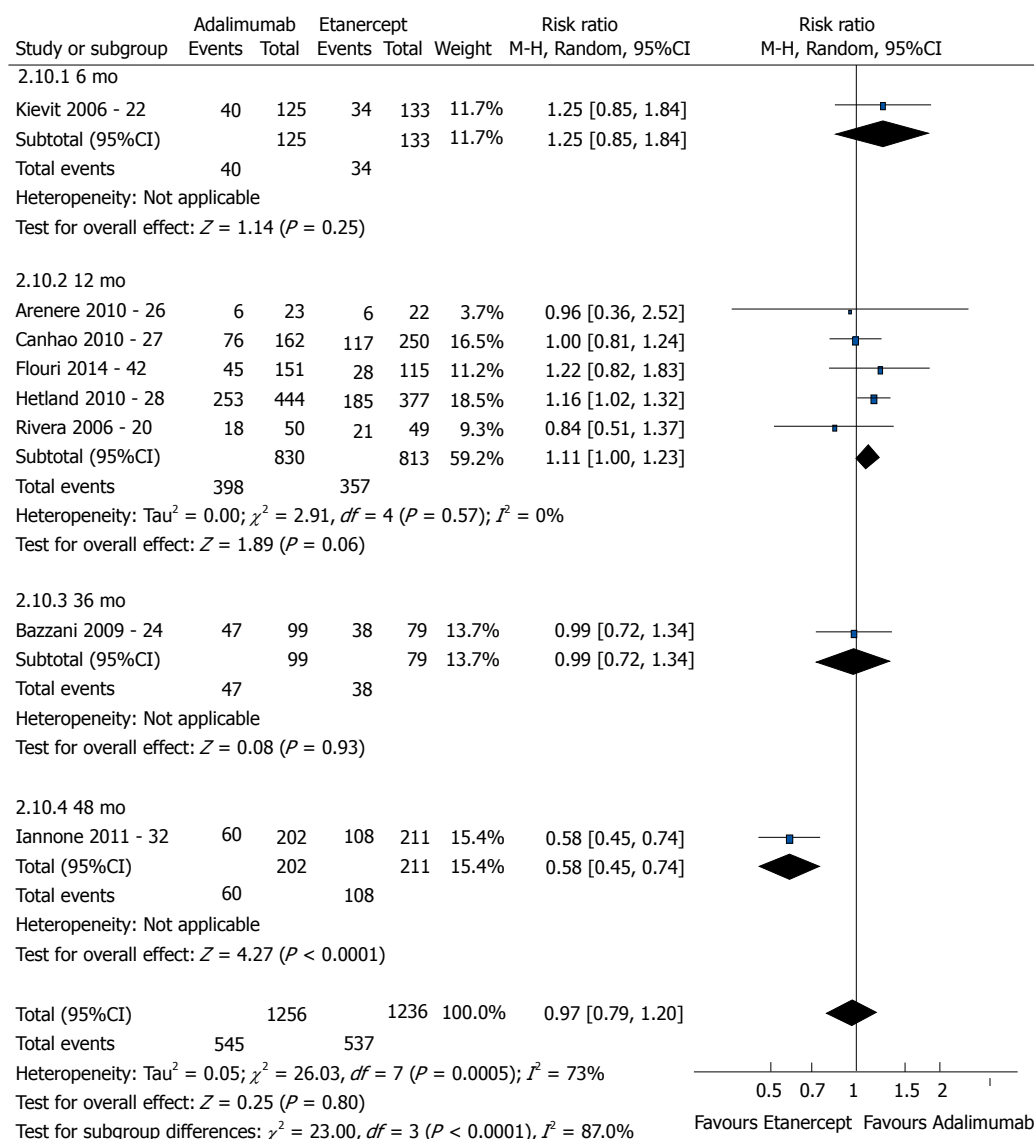


Figure 4 EULAR good response - Etanercept vs Adalimumab.

showed better results for adalimumab and etanercept compared to infliximab. The results were similar to the group with all patients (anti-TNF naïve and/or therapeutic failure), probably because most of the participants under treatment were anti-TNF naïve. The use of bDMARD in combination with methotrexate exhibited greater results than bDMARD monotherapy. Rituximab, etanercept and abatacept proved to be effective therapeutic options following therapeutic failure with anti-TNF agents. However, most of the studies on therapeutic failure assessed rituximab; thus, more studies comparing other drugs are needed to contribute to the choice of third-line agents in actual clinical practice.

Systematic reviews that performed indirect comparison meta-analyses of randomized clinical trials that assessed the efficacy of the anti-TNFs adalimumab, etanercept and infliximab reported similar results^[48-50]. One meta-analysis found that the efficacy of etanercept was lower compared to that of infliximab and adalimumab; however, the patients selection for the

study was different: the study divided patients by those on etanercept (methotrexate-naïve individuals) and other drugs (patients resistant to methotrexate), which makes the comparison of the results between the medicines difficult^[51]. The difference of these studies relative to ours might be most likely due to the characteristics of the participants and the low dose of infliximab (3 mg/kg). Some studies reported that patients using infliximab required dose escalation more often compared to those who used etanercept and adalimumab^[52,53]. Dose escalation might increase the cost of treatment with infliximab^[52] and might thus result in moderate effectiveness^[54]. In addition, Pascual-Salcedo *et al.*^[55] observed that the production of anti-infliximab antibodies is associated with loss of clinical response^[55].

The superiority of the combination of bDMARD and sDMARD compared to bDMARD monotherapy was also reported in other recent meta-analyses^[51,56]. In particular, the same pattern was reported for etanercept in combination with methotrexate in a randomized clinical

Table 5 Meta-analysis of the outcomes for anti-tumor necrosis factor naïve patients

Intervention	Outcomes	Studies (references)	<i>n</i>	RR (95%CI) or other mesure	<i>I</i> ² (%)	<i>P</i> value
IFX <i>vs</i> ETA	EULAR good response	5 (19, 21, 22, 27, 28)	2822	0.82 [0.62-1.09]	82	0.0001
	EULAR moderate response	4 (19, 21, 22, 28)	2366	0.90 [0.61-1.33]	90	< 0.00001
	EULAR no response	4 (19, 21, 22, 28)	2366	1.29 [1.09-1.53]	27	0.25
	DAS 28 remission	4 (21, 27, 28, 37)	1804	0.82 [0.70-0.95]	0	0.4
	ACR 20	2 (19, 37)	1309	0.95 [0.86-1.06]	0	0.47
	ACR50	3 (19, 28, 37)	2315	0.92 [0.81-1.03]	10	0.33
	ACR70	3 (19, 28, 37)	2315	0.88 [0.57-1.36]	79	0.009
	CDAI remission	3 (27, 28, 37)	1876	0.88 [0.72-1.08]	0	0.93
ADA <i>vs</i> ETA	EULAR good response	4 (20, 22, 27, 28)	1590	1.11 [1.00-1.23]	0	0.4
	EULAR moderate response	3 (20, 22, 28)	1178	1.01 [0.83-1.24]	19	0.29
	EULAR no response	3 (20, 22, 28)	1178	0.69 [0.53-0.89]	11	0.32
	DAS 28 remission	3 (27, 28, 37)	1380	1.03 [0.82-1.29]	37	0.21
	ACR 20	2 (20, 37)	445	0.89 [0.71-1.12]	0	0.68
	ACR 50	3 (20, 28, 37)	1217	1.09 [0.91-1.31]	18	0.3
	ACR 70	3 (20, 28, 37)	1436	1.15 [0.92-1.43]	0	0.82
	HAQ reduction	2 (22, 25)	653	-0.07 [-0.16-0.03]	0	0.92
IFX <i>vs</i> ADA	CDAI remission	3 (27, 28, 37)	1601	1.02 [0.67-1.56]	72	0.03
	EULAR good response	3 (22, 27, 28)	1706	1.42 [1.18-1.72]	42	0.18
	EULAR moderate response	2 (22, 28)	1338	0.96 [0.58-1.59]	80	0.03
	EULAR no response	2 (22, 28)	1338	0.56 [0.45-0.69]	0	0.88
	DAS 28 remission	3 (27, 28)	1648	1.23 [0.95-1.59]	48	0.15
	ACR 50	2 (28, 37)	1458	1.14 [0.71-1.84]	79	0.03
	ACR 70	2 (28, 37)	1458	1.41 [0.81-2.44]	72	0.06
	CDAI remission	3 (27, 28, 37)	1875	1.17 [0.75-1.82]	75	0.02

A value of $I^2 > 40\%$ indicates statistical heterogeneity between the studies. A value of $P < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies. CI: Confidence interval; ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; EULAR: European League Against Rheumatism; DAS 28: Disease activity score; CDAI: Clinical disease activity; HAQ: Health assessment questionnaire; ACR: American College Rheumatology.

Table 6 Meta-analysis of the outcomes for patients with anti-tumor necrosis factor therapeutic failure

Intervention	Outcomes	Studies (references)	<i>n</i>	Relative risk (95%CI) or other mesure	<i>I</i> ² (%)	<i>P</i> value
RTX <i>vs</i> anti-TNF	EULAR good response	4 (35, 38, 40, 46)	1608	0.96 [0.60-1.54]	74	0.009
	EULAR moderate response	5 (29, 35, 38, 40, 46)	1706	1.02 [0.79-1.32]	66	0.02
	EULAR no response	3 (35, 38, 40)	1406	1.00 [0.53-1.89]	85	0.001
	DAS 28 reduction	6 (35, 36, 38, 40, 41, 46)	1584	0.42 [-0.65--0.20]	62	0.02
ETA <i>vs</i> control	EULAR good response	2 (14, 40)	173	2.11 [1.23-3.62]	0	0.48
	IFX		38	1.60 [0.63-4.09]		
	RTX		135	2.42 [1.25-4.68]		
	DAS 28 reduction	2 (34, 40)	152	0.15 [-0.65-0.95]	77	0.04
	RTX		113	-0.22 [-0.64-0.20]		
	TOCI		39	0.60 [-0.05-1.25]		

A value of $I^2 > 40\%$ indicates statistical heterogeneity between the studies. A value of $P < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies. CI: Confidence interval; RTX: Rituximab; ETA: Etanercept; IFX: Infliximab; TOCI: Tocilizumab; EULAR: European League Against Rheumatism; DAS 28: Disease activity score.

trial^[57,58]. The fact that infliximab should be administered in combination with methotrexate is well established^[59].

Despite the publication of recent studies on the subject, the definition of the best strategy for patients who exhibit therapeutic failure to at least one anti-TNF agent still poses a challenge^[60]. Some studies assessed subgroups in an attempt to identify profiles of patients who will benefit from treatment with rituximab. Thus, whereas testing positive for rheumatoid factor did not induce significant changes in the results^[61], rituximab proved to be more effective in individuals who tested positive for rheumatoid factor and for anti-cyclic citrullinated peptide antibody^[39].

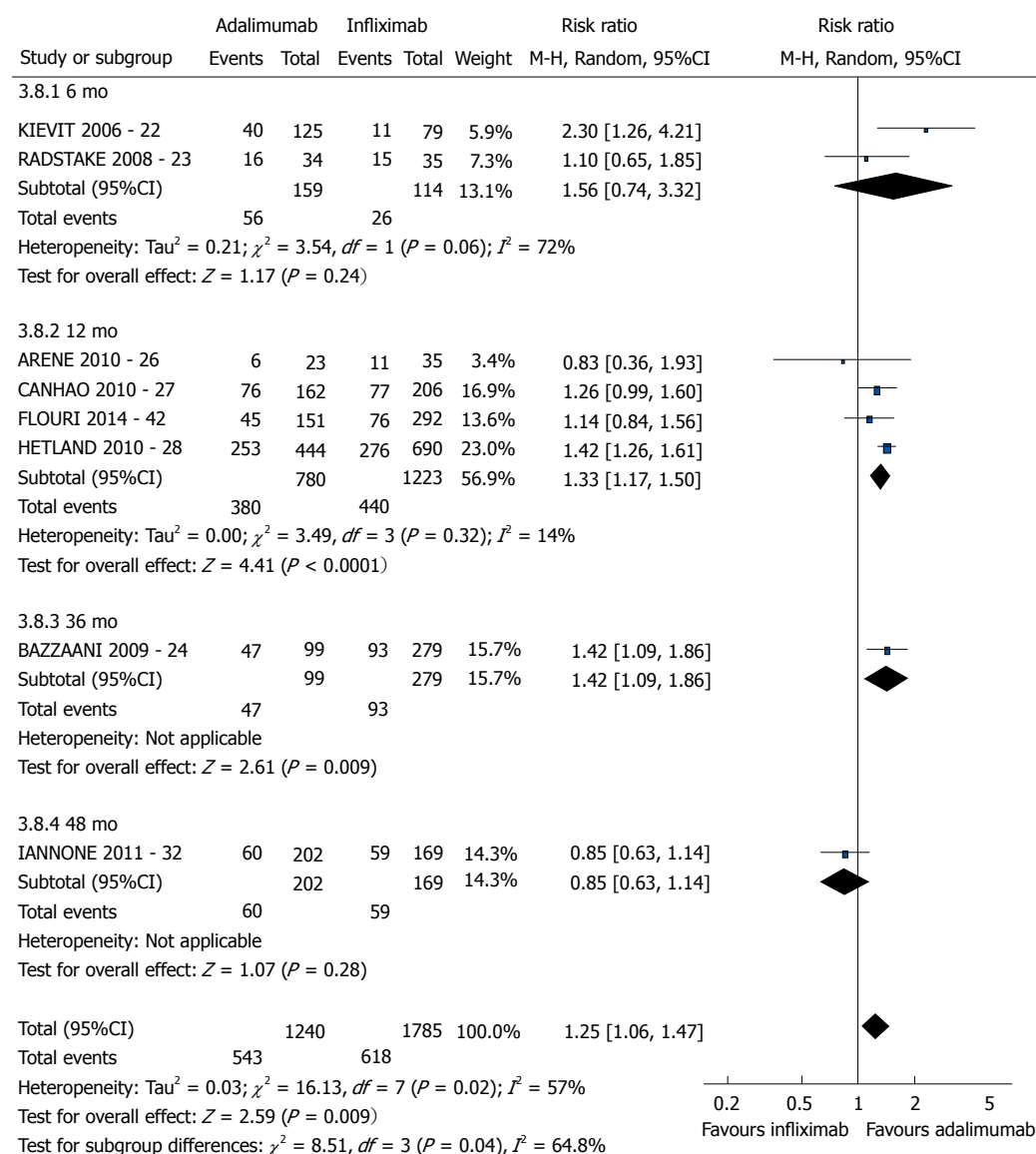
One of the limitations of systematic reviews with meta-analysis of cohort studies concerns selection bias, which is intrinsic to the design of such studies, as the participants are not randomized but might be allocated to a given treatment based on their patient and physician preferences. A consequence of that limitation was the difference noted among the groups at the onset of treatment that, as a whole, manifested as poorer prognosis in the participants from the rituximab group relative to the numbers of anti-TNF and sDMARD previously used, older age, and greater DAS28 and HAQ scores at baseline^[22,36,41].

One further limitation is related to the fact that

Table 7 Meta-analysis of the outcomes for patients in treatment with biological monotherapy *vs* biological in combination with methotrexate

Intervention	Outcomes	Studies (references)	Participants	Relative risk (95%CI) or other measure	I^2 (%)	P value
bDMARD	EULAR good response	3 (16,17, 30)	3000	0.57 [0.34-0.95]	82	0.0008
monotherapy <i>vs</i>	DAS 28	3 (17, 20, 30)	2913	0.25 [-0.02-0.52]	69	0.01
bDMARD + MTX	HAQ	2 (165, 30)	655	0.13 [0.03-0.22]	0	0.43

A value of $I^2 > 40\%$ indicates statistical heterogeneity between the studies. A value of $P < 0.10$ from the χ^2 test indicates statistical heterogeneity between the studies. CI: Confidence interval; bDMARD: Biological disease-modifying antirheumatic drugs; MTX: Methotrexate; EULAR: European League Against Rheumatism; DAS 28: Disease activity score; HAQ: Health Assessment Questionnaire.

**Figure 5** EULAR good response - Infliximab vs Adalimumab.

observational studies are conducted under real-life non-controlled conditions. For that reason, differences were detected in the number of participants among the groups, in the disease activity, and in the lack of dose standardization, especially in the case of infliximab. Moreover, observational studies have the advantage of recruiting large numbers of participants. These types of

studies more accurately represent real-life conditions and are able to provide complementary data to the results of randomized clinical studies. Some studies reported that the participants in randomized controlled clinical trials exhibited greater disease activity and fewer associated comorbidities compared to those patients treated in the actual practice setting. The practice of prescribing

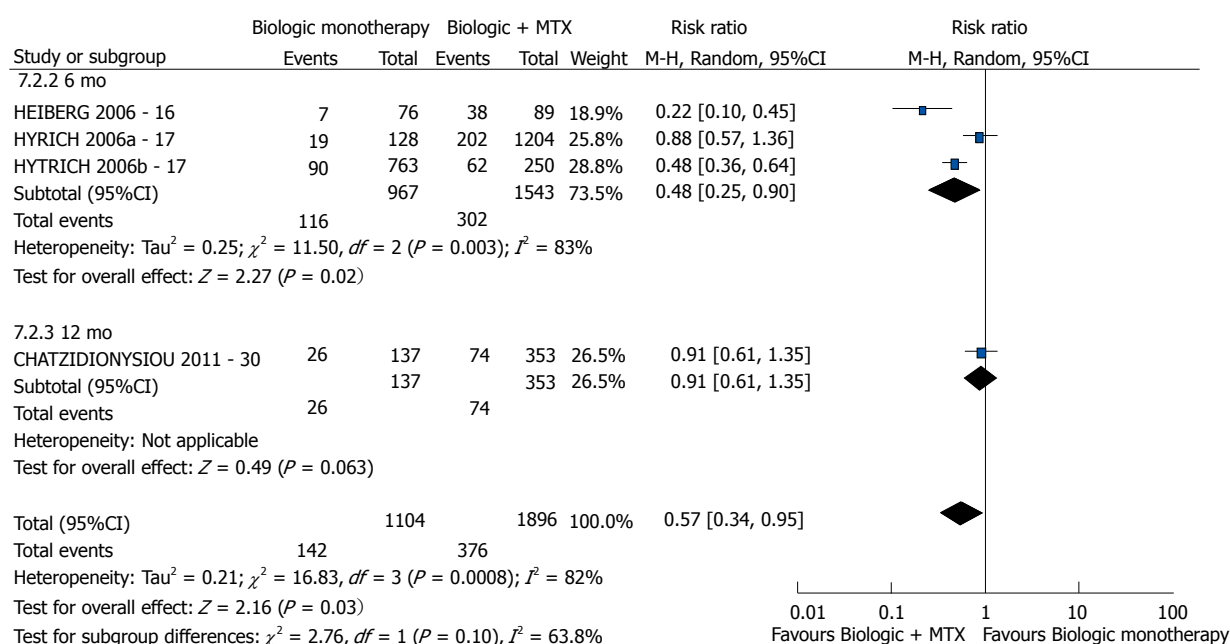


Figure 6 EULAR good response - Biologic monotherapy vs Biologic + MTX.

has been modified over time in real-life. bDMARDs (specially in clinical trials) were prescribed only when patients presented high activity of disease and, now, the medicines are prescribed when the activity is moderate or high^[62-64]. Kievit *et al.*^[65] (2007) called attention to the reduction of the external validity of randomized clinical trials^[65], while another study found similar rates of response in both randomized clinical trials and clinical practice^[62].

Nevertheless, all of the assessed therapies were effective to reduce the disease activity and might be considered as therapeutic alternatives as they are proven to exhibit benefits such as greater comfort, less adverse effects and lower cost.

The results of the observational studies included in this review, which reflect the "real-life" use of bDMARD. The best choice for bDMARD treatment-naïve individuals are adalimumab or etanercept in combination with methotrexate. In cases of therapeutic failure with anti-TNF agents rituximab or abatacept (non anti-TNF) or etanercept (as second anti-TNF) might be used; however, more studies of effectiveness were found for rituximab.

COMMENTS

Background

Observational studies could provide relevant information for deciding the choice of treatments, the elaboration of clinical protocols, and the formulation of health policies. The present systematic review of biological disease-modifying antirheumatic drugs included cohort observational studies that reported treatment results applied in real-life conditions; thus, these studies are able to fill in gaps in knowledge left by clinical trials.

Research frontiers

This study evaluate, by systematic review and metanalysis, the effectiveness of biological disease-modifying antirheumatic drugs (bDMARD) for treatment of rheumatoid arthritis for naïve and therapeutic failure patients.

Innovations and breakthroughs

The innovations of this study is that do not exist others studies evaluating the direct comparison between bDMARD adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, rituximab, tocilizumab and abatacept in the real-world. Furthermore, the study assess naïve and therapeutic failure patients groups.

Applications

That study is able to fill in gaps in knowledge left by clinical trials with bDMARD adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, rituximab, tocilizumab and abatacept. Furthermore, do not exist others studies evaluating the direct comparison. Then provide relevant information for deciding the choice of treatments.

Terminology

The Disease Activity Score (DAS) is a clinical index of rheumatoid arthritis (RA) disease activity that combines information from swollen joints, tender joints, the acute phase response and general health. The EULAR response criteria is a classified response criteria which classifies the patients individual as non, moderate or good responders dependent on the change and the level of the DAS and DAS28. The ACR score represents a percentage. An ACR20 score means that a person's RA has improved by 20%, an ACR50 score means it has improved by 50%, and an ACR70 score means it has improved by 70%. The CDAl is a clinical index of RA disease activity that combines information from swollen joints, tender joints and general health. The HAQ is one of the first self-report functional status (disability) measures.

Peer-review

The authors present an extensive revision about the effectiveness of the biological treatment for rheumatoid arthritis. The paper is well written. It explores the best treatment options for patients with DMARDs failure and provides useful and practical information for clinicians involved in the care of patients with this disease.

REFERENCES

- 1 Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet* 2001; **358**: 903-911 [PMID: 11567728]
- 2 World Health Organization (WHO). Chronic rheumatic conditions. Available from: URL: <http://www.who.int/chp/topics/rheumatic/en/>
- 3 da Mota LM, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, de Freitas MV, da Silva NA, Louzada-Júnior P, Giorgi RD, Lima RA, da Rocha Castelar Pinheiro G. 2012 Brazilian Society of Rheumatology Consensus for the treatment of rheumatoid arthritis. *Rev Bras Reumatol* 2012; **52**: 152-174 [PMID: 22811111]

- 22460407]
- 4 **Smolen JS**, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, Gorter S, Knevel R, Nam J, Schoels M, Aletaha D, Buch M, Gossec L, Huizinga T, Bijlsma JW, Burmester G, Combe B, Cutolo M, Gabay C, Gomez-Reino J, Kouloumas M, Kvien TK, Martin-Mola E, McInnes I, Pavelka K, van Riel P, Scholte M, Scott DL, Sokka T, Valesini G, van Vollenhoven R, Winthrop KL, Wong J, Zink A, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; **69**: 964-975 [PMID: 20444750 DOI: 10.1136/ard.2009.126532]
 - 5 **Singh JA**, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012; **64**: 625-639 [PMID: 22473917 DOI: 10.1002/acr.21641]
 - 6 **Salliot C**, Finckh A, Katchamart W, Lu Y, Sun Y, Bombardier C, Keystone E. Indirect comparisons of the efficacy of biological antirheumatic agents in rheumatoid arthritis in patients with an inadequate response to conventional disease-modifying antirheumatic drugs or to an anti-tumour necrosis factor agent: a meta-analysis. *Ann Rheum Dis* 2011; **70**: 266-271 [PMID: 21097801 DOI: 10.1136/ard.2010.132134]
 - 7 **Malottki K**, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, Connock M, Jobanputra P, Moore D, Fry-Smith A, Chen YF. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. *Health Technol Assess* 2011; **15**: 1-278 [PMID: 21439251 DOI: 10.3310/hta15140]
 - 8 **Black N**. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996; **312**: 1215-1218 [PMID: 8634569]
 - 9 **Higgins JPT**, Altman DG, Sterne JAC. Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated 2011 March]. The Cochrane Collaboration, 2011. Available from: URL: <http://www.cochrane-handbook.org>
 - 10 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis PA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [DOI: 10.1136/bmj.b2700]
 - 11 **Hartling L**, Hamm M, Milne A, Vandermeer B, Santaguida PL, Ansari M, Tsertsvadze A, Hempel S, Shekelle P, Dryden DM. Validity and interrater reliability testing of quality assessment instruments [Internet]. Appendix E, decision rules for application of the Newcastle-Ottawa Scale., Rockville, MD: Agency for Healthcare Research and Quality, 2012. Available from: URL: <http://www.ncbi.nlm.nih.gov/books/NBK92291/>
 - 12 **Geborek P**, Crnkic M, Petersson IF, Saxne T. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann Rheum Dis* 2002; **61**: 793-798 [PMID: 12176803]
 - 13 **van Vollenhoven RF**, Ernestam S, Harju A, Bratt J, Klareskog L. Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically more efficacious. *Arthritis Res Ther* 2003; **5**: R347-R351 [PMID: 14680509]
 - 14 **Cohen G**, Courvoisier N, Cohen JD, Zaltini S, Sany J, Combe B. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005; **23**: 795-800 [PMID: 16396697]
 - 15 **Finckh A**, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. *Ann Rheum Dis* 2006; **65**: 746-752 [PMID: 16339288]
 - 16 **Heiberg MS**, Rødevand E, Mikkelsen K, Kaufmann C, Didriksen A, Mowinckel P, Kvien TK. Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study. *Ann Rheum Dis* 2006; **65**: 1379-1383 [PMID: 16679432]
 - 17 **Hyrich KL**, Symmons DP, Watson KD, Silman AJ. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006; **54**: 1786-1794 [PMID: 16736520]
 - 18 **Hyrich KL**, Watson KD, Silman AJ, Symmons DP. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)* 2006; **45**: 1558-1565 [PMID: 16705046]
 - 19 **Kristensen LE**, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. *Arthritis Rheum* 2006; **54**: 600-606 [PMID: 16447237]
 - 20 **Bernal Rivera L**, Guerrero Aznar MD, Monzó Moreno A, Beltrán García M, Hernández Cruz B, Colmenero MA. Effectiveness and safety of adalimumab and etanercept for rheumatoid arthritis in a third-level hospital. *Farm Hosp* 2006; **30**: 223-229 [PMID: 17022715]
 - 21 **Fernández-Nebro A**, Irigoyen MV, Ureña I, Belmonte-López MA, Coret V, Jiménez-Núñez FG, Díaz-Cordovés G, López-Lasanta MA, Ponce A, Rodríguez-Pérez M, Calero E, González-Santos P. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naïve rheumatoid arthritis. *J Rheumatol* 2007; **34**: 2334-2342 [PMID: 17985409]
 - 22 **Kievit W**, Adang EM, Fransen J, Kuper HH, van de Laar MA, Jansen TL, De Gendt CM, De Rooij DJ, Brus HL, Van Oijen PC, Van Riel PC. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. *Ann Rheum Dis* 2008; **67**: 1229-1234 [PMID: 18174220 DOI: 10.1136/ard.2007.083675]
 - 23 **Radstake TR**, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL, Bendtsen K. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. *Ann Rheum Dis* 2009; **68**: 1739-1745 [PMID: 19019895 DOI: 10.1136/ard.2008.092833]
 - 24 **Bazzani C**, Filippini M, Caporali R, Bobbio-Pallavicini F, Favalli EG, Marchesoni A, Atzeni F, Sarzi-Puttini P, Gorla R. Anti-TNFalpha therapy in a cohort of rheumatoid arthritis patients: clinical outcomes. *Autoimmun Rev* 2009; **8**: 260-265 [PMID: 19027090 DOI: 10.1016/j.autrev.2008.11.001]
 - 25 **Laas K**, Peltomaa R, Puolakka K, Kautiainen H, Leirisalo-Repo M. Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice. *Clin Exp Rheumatol* 2009; **27**: 315-320 [PMID: 19473574]
 - 26 **Arenere Mendoza M**, Manero Ruiz FJ, Carrera Lasfuentes P, Navarro Aznárez H, Pecondón Español A, Rabanaque Hernández MJ. [Tumour necrosis factor alpha antagonists in established rheumatoid arthritis: effectiveness comparative study]. *Med Clin (Barc)* 2010; **134**: 665-670 [PMID: 20363004 DOI: 10.1016/j.medcli.2009.09.050]
 - 27 **Canhão H**, Rodrigues AM, Mourão AF, Martins F, Santos MJ, Canas-Silva J, Polido-Pereira J, Pereira Silva JA, Costa JA, Araújo D, Silva C, Santos H, Duarte C, da Silva JA, Pimentel-Santos FM, Branco JC, Karlson EW, Fonseca JE, Solomon DH. Comparative effectiveness and predictors of response to tumour necrosis

- factor inhibitor therapies in rheumatoid arthritis. *Rheumatology* (Oxford) 2012; **51**: 2020-2026 [PMID: 22843791 DOI: 10.1093/rheumatology/kes184]
- 28 **Hetland ML**, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, Kollerup G, Linde L, Lindegaard HM, Poulsen UE, Schlemmer A, Jensen DV, Jensen S, Hostenkamp G, Østergaard M. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum* 2010; **62**: 22-32 [PMID: 20039405 DOI: 10.1002/art.27227]
 - 29 **Blom M**, Kievit W, Donders AR, den Broeder AA, Straten VH, Kuper I, Visser H, Jansen TL, Brus HL, Branten AJ, van de Laar MA, van Riel PL. Effectiveness of a third tumor necrosis factor- α -blocking agent compared with rituximab after failure of 2 TNF-blocking agents in rheumatoid arthritis. *J Rheumatol* 2011; **38**: 2355-2361 [PMID: 21885487 DOI: 10.3899/jrheum.101324]
 - 30 **Chatzidionysiou K**, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U, van Riel PL, Nordström DC, Gomez-Reino J, Pavelka K, Tomsic M, Kvien TK, van Vollenhoven RF, Gabay C. Effectiveness of disease-modifying antirheumatic drug co-therapy with methotrexate and leflunomide in rituximab-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. *Ann Rheum Dis* 2012; **71**: 374-377 [PMID: 21972242 DOI: 10.1136/annrheumdis-2011-200003]
 - 31 **Harrold LR**, Reed GW, Kremer JM, Curtis JR, Solomon DH, Hochberg MC, Greenberg JD. The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti-tumour necrosis factor. *Ann Rheum Dis* 2015; **74**: 430-436 [PMID: 24297378 DOI: 10.1136/annrheumdis-2013-203936]
 - 32 **Iannone F**, Gremese E, Atzeni F, Biasi D, Botsios C, Cipriani P, Ferri C, Foschi V, Galeazzi M, Gerli R, Giardina A, Marchesoni A, Salaffi F, Ziglioli T, Lapadula G. Longterm retention of tumor necrosis factor- α inhibitor therapy in a large italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. *J Rheumatol* 2012; **39**: 1179-1184 [PMID: 22467933 DOI: 10.3899/jrheum.111125]
 - 33 **Leffers HC**, Østergaard M, Glinthorp B, Krogh NS, Foged H, Tarp U, Lorenzen T, Hansen A, Hansen MS, Jacobsen MS, Dreyer L, Hetland ML. Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. *Ann Rheum Dis* 2011; **70**: 1216-1222 [PMID: 21551512 DOI: 10.1136/ard.2010.140129]
 - 34 **Wakabayashi H**, Hasegawa M, Nishioka Y, Sudo A, Nishioka K. Which subgroup of rheumatoid arthritis patients benefits from switching to tocilizumab versus etanercept after previous infliximab failure? A retrospective study. *Mod Rheumatol* 2012; **22**: 116-121 [PMID: 21710357 DOI: 10.1007/s10165-011-0485-9]
 - 35 **Gomez-Reino JJ**, Maneiro JR, Ruiz J, Roselló R, Sanmarti R, Romero AB. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study. *Ann Rheum Dis* 2012; **71**: 1861-1864 [PMID: 22736086 DOI: 10.1136/annrheumdis-2012-201324]
 - 36 **Finckh A**, Möller B, Dudler J, Walker UA, Kyburz D, Gabay C. Evolution of radiographic joint damage in rituximab-treated versus TNF-treated rheumatoid arthritis cases with inadequate response to TNF antagonists. *Ann Rheum Dis* 2012; **71**: 1680-1685 [PMID: 22419773]
 - 37 **Greenberg JD**, Reed G, Decktor D, Harrold L, Furst D, Gibofsky A, Dehoratius R, Kishimoto M, Kremer JM. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Ann Rheum Dis* 2012; **71**: 1134-1142 [PMID: 22294625 DOI: 10.1136/annrheumdis-2011-150573]
 - 38 **Kekow J**, Mueller-Ladner U, Schulze-Koops H. Rituximab is more effective than second anti-TNF therapy in rheumatoid arthritis patients and previous TNF α blocker failure. *Biologics* 2012; **6**: 191-199 [PMID: 22848150 DOI: 10.2147/BTT.S32244]
 - 39 **Schabert VF**, Bruce B, Ferrufino CF, Globe DR, Harrison DJ, Lingala B, Fries JF. Disability outcomes and dose escalation with etanercept, adalimumab, and infliximab in rheumatoid arthritis patients: a US-based retrospective comparative effectiveness study. *Curr Med Res Opin* 2012; **28**: 569-580 [PMID: 22236091 DOI: 10.1185/03007995.2012.656844]
 - 40 **Chatzidionysiou K**, van Vollenhoven RF. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. *Scand J Rheumatol* 2013; **42**: 190-195 [PMID: 23286833 DOI: 10.3109/03009742.2012.729607]
 - 41 **Emery P**, Gottenberg JE, Rubbert-Roth A, Sarzi-Puttini P, Choquette D, Martínez Taboada VM, Barile-Fabris L, Moots RJ, Ostor A, Andrianakos A, Gemmen E, Mpofu C, Chung C, Gylvin LH, Finckh A. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. *Ann Rheum Dis* 2014 Jan 29; Epub ahead of print [PMID: 24442884 DOI: 10.1136/annrheumdis-2013-203993]
 - 42 **Flouri I**, Markatseli TE, Voulgari PV, Boki KA, Papadopoulos I, Settas L, Zisopoulos D, Skopouli FN, Iliopoulos A, Bertsis GK, Geborek P, Drosos AA, Boumpas DT, Sidiropoulos P. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival. *Semin Arthritis Rheum* 2014; **43**: 447-457 [PMID: 24012040 DOI: 10.1016/j.semarthrit.2013.07.011]
 - 43 **Keystone E**, Weber D, Xiong J, et al. Rituximab versus abatacept in rheumatoid arthritis patients with an inadequate response to prior biologic therapy: a retrospective, single-center study (EULAR Abstracts 2013; FRI0226). Available from: URL: http://www.newevidence.com/rheumatology/entries/Rituximab_versus_abatacept_in_RA_patients_with/
 - 44 **Martínez-Pérez R**, Rodríguez-Montero S, Muñoz A, León M, Gallo F, Velloso ML, Marengo JL. Impact of two biological treatments in the functional capacity of a cohort of patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; **70**: A1-A94 [DOI: 10.1136/ard.2010.149021.18]
 - 45 **Gottenberg J**, Ravaud P, Bardin T, Cacoub P, Cantagrel AG, Combe BG, Dougados M. Comparative Effectiveness Of Rituximab And Abatacept In 1192 Patients With Rheumatoid Arthritis Included In The French Society Of Rheumatology AIR And ORA Registries. *Arthritis Rheum* 2011; **63** Suppl 10: 438. Available from: URL: <http://www.blackwellpublishing.com/acrmeeeting/abstract.asp?MeetingID=781&id=95188>
 - 46 **Buch M**, Vital EM, Dass S, Das S, Brayer D, Emery P. Switching to rituximab and an alternative TNF inhibitor in patients with rheumatoid arthritis that have failed previous TNF inhibitor(s) are both effective treatment options with good maintenance rates. *Ann Rheum Dis* 2010; **69** Suppl 3: 379
 - 47 **Greenwood MC**, Donnelly SP, Rooney MM, Hakim AJ, Tahir H. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Rheumatology* (Oxford) 2009; **48** Suppl 1: i58 - i71
 - 48 **Gartlehner G**, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. *J Rheumatol* 2006; **33**: 2398-2408 [PMID: 17225293]
 - 49 **Hochberg MC**, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2003; **62** Suppl 2: ii13-ii16 [PMID: 14532140]
 - 50 **Donahue KE**, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, Hansen RA, Morgan LC, Lohr KN. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med* 2008; **148**: 124-134 [PMID:

- 18025440]
- 51 **Lee YH**, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. *Rheumatol Int* 2008; **28**: 553-559 [PMID: 17943257]
- 52 **Ariza-Ariza R**, Navarro-Sarabia F, Hernández-Cruz B, Rodríguez-Arbolea L, Navarro-Compán V, Toyos J. Dose escalation of the anti-TNF-alpha agents in patients with rheumatoid arthritis. A systematic review. *Rheumatology* (Oxford) 2007; **46**: 529-532 [PMID: 17012439]
- 53 **Ollendorf DA**, Klingman D, Hazard E, Ray S. Differences in annual medication costs and rates of dosage increase between tumor necrosis factor-antagonist therapies for rheumatoid arthritis in a managed care population. *Clin Ther* 2009; **31**: 825-835 [PMID: 19446156 DOI: 10.1016/j.clinthera.2009.04.002]
- 54 **Harley CR**, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. *Am J Manag Care* 2003; **9**: S136-S143 [PMID: 14577718]
- 55 **Pascual-Salcedo D**, Plasencia C, Ramiro S, Nuño L, Bonilla G, Nagore D, Ruiz Del Agua A, Martínez A, Aarden L, Martín-Mola E, Balsa A. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology* (Oxford) 2011; **50**: 1445-1452 [PMID: 21427177 DOI: 10.1093/rheumatology/ker124]
- 56 **Machado MA**, Maciel AA, de Lemos LL, Costa JO, Kakehasi AM, Andrade EI, Cherchiglia ML, Acurcio Fde A, Sampaio-Barros PD. Adalimumab in rheumatoid arthritis treatment: a systematic review and meta-analysis of randomized clinical trials. *Rev Bras Reumatol* 2013; **53**: 419-430 [PMID: 24316899]
- 57 **Maini SR**. Infliximab treatment of rheumatoid arthritis. *Rheum Dis Clin North Am* 2004; **30**: 329-347, vii [PMID: 15172044]
- 58 **van der Heijde D**, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C, Pedersen R, Freundlich B, Fatenejad S. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis* 2006; **65**: 328-334 [PMID: 16079172]
- 59 **Klareskog L**, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martín Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363**: 675-681 [PMID: 15001324]
- 60 **Moots RJ**, Naisbett-Groet B. The efficacy of biologic agents in patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor inhibitors: a systematic review. *Rheumatology* (Oxford) 2012; **51**: 2252-2261 [PMID: 22942404 DOI: 10.1093/rheumatology/kes217]
- 61 **Finckh A**, Ciurea A, Brulhart L, Kyburz D, Möller B, Dehler S, Revaz S, Dudler J, Gabay C. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. *Arthritis Rheum* 2007; **56**: 1417-1423 [PMID: 17469098]
- 62 **Hetland ML**, Lindegaard HM, Hansen A, Pødenphant J, Unkerskov J, Ringsdal VS, Østergaard M, Tarp U. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. *Ann Rheum Dis* 2008; **67**: 1023-1026 [PMID: 18272669 DOI: 10.1136/ard.2007.087262]
- 63 **Zink A**, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, Wassenberg S, Kapelle A, Listing J. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. *Arthritis Rheum* 2006; **54**: 3399-3407 [PMID: 17075823]
- 64 **Hjardem E**, Hetland ML, Østergaard M, Krogh NS, Kvien TK. Prescription practice of biological drugs in rheumatoid arthritis during the first 3 years of post-marketing use in Denmark and Norway: criteria are becoming less stringent. *Ann Rheum Dis* 2005; **64**: 1220-1223 [PMID: 15640272]
- 65 **Kievit W**, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, De Gendt CM, Ronday KH, Jansen TL, van Oijen PC, Brus HL, Adang EM, van Riel PL. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. *Ann Rheum Dis* 2007; **66**: 1473-1478 [PMID: 17426065]

P- Reviewer: Cavallasca JA, La Montagna G, Sakkas L, Turiel M

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

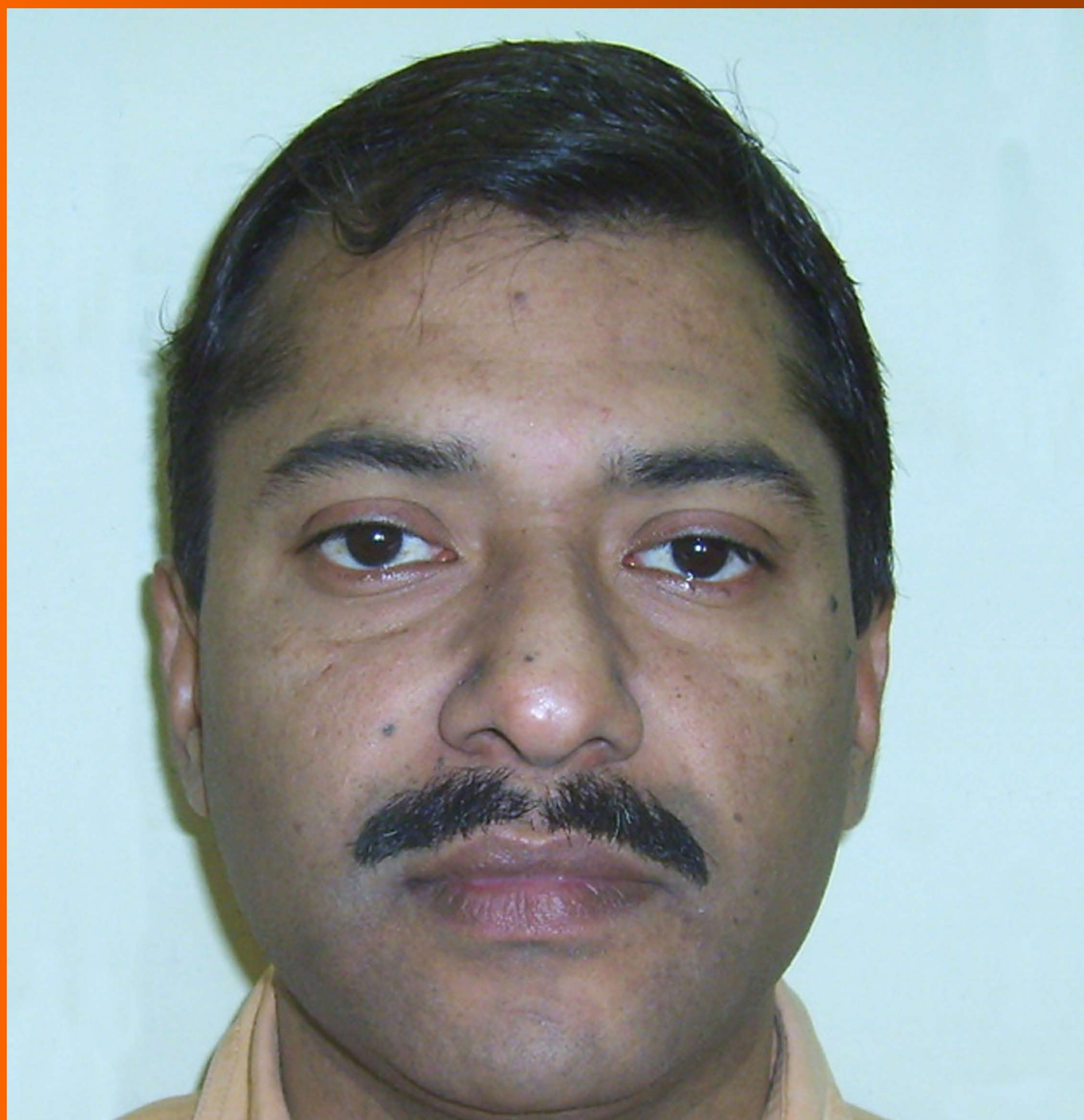
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Rheumatology*

World J Rheumatol 2015 November 12; 5(3): 127-147





Editorial Board

2011-2015

The *World Journal of Rheumatology* Editorial Board consists of 191 members, representing a team of worldwide experts in rheumatology. They are from 38 countries, including Argentina (2), Australia (4), Belgium (3), Brazil (3), Canada (2), Chile (1), China (16), Egypt (1), Finland (2), France (9), Germany (5), Greece (6), Hungary (2), India (3), Iran (2), Israel (6), Italy (11), Japan (2), Kuwait (1), Mexico (4), Morocco (2), Netherlands (3), Peru (1), Poland (1), Portugal (2), Qatar (1), Saudi Arabia (2), Slovakia (1), South Korea (4), Spain (7), Sweden (2), Switzerland (2), Thailand (1), Tunisia (1), Turkey (14), United Arab Emirates (1), United Kingdom (13), and United States (48).

EDITOR-IN-CHIEF

Jörg HW Distler, *Erlangen*

GUEST EDITORIAL BOARD MEMBERS

Yih-Hsin Chang, *Taichung*
Jing-Long Huang, *Taoyuan*
Pi-Chang Lee, *Taipei*
Chin-San Liu, *Changhua*
Ko-Hsiu Lu, *Taichung*
Fuu-Jen Tsai, *Taichung*
Chih-Shung Wong, *Taipei*
Jeng-Hsien Yen, *Kaohsiung*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Javier Alberto Cavallasca, *Santa Fe*
Enrique Roberto Soriano, *Buenos Aires*



Australia

Chang-Hai Ding, *Melbourne*
Davinder Singh-Grewal, *Sydney*
Gethin Thomas, *Brisbane*
Yin Xiao, *Brisbane*



Belgium

Olivier Bruyère, *Liège*
Nijs Jo, *Brussels*
Jean-Yves Reginster, *Liège*



Brazil

Simone Appenzeller, *Cidade Universitaria*
Mittermayer Santiago, *Nazaré Salvador*
Samuel K Shinjo, *São paulo*



Canada

Hong-Yu Luo, *Montreal*
Guang-Ju Zhai, *St John's*



Chile

Iván Palomo, *Maule*



China

Jun-Min Chen, *Fuzhou*
Sheng-Ming Dai, *Shanghai*
Ai-Ping Lu, *Beijing*
Chi Chiu Mok, *Hong Kong*
Ling Qin, *Hong Kong*
Han-Shi Xu, *Guangzhou*
Qing-Yu Zeng, *Shantou*
Peng Zhang, *Shenzhen*



Egypt

Yasser Emad, *Cairo*



Finland

Yrjö T Konttinen, *Helsinki*

Rahman Shiri, *Helsinki*



France

Didier Attaix, *Theix*
Francis Berenbaum, *Paris*
Michel Jacques de Bandt, *Aulnay sous Bois*
Pascal Laugier, *Paris*
Pierre Miossec, *Lyon*
M Djavad Mossalayi, *Bordeaux*
Luc Mouthon, *Paris*
Aleth Perdriger, *Rennes*
Alain Saraux, *Brest*



Germany

Magali Cucchiari, *Homburg*
Thomas Jax, *Neuss*
Friedrich Paul Paulsen, *Erlangen*
Med H H Peter, *Freiburg*



Greece

Andrew P Andonopoulos, *Rion*
Dimitrios Daoussis, *Patras*
Kosmas I Paraskevas, *Athens*
Grigorios Sakellariou, *Thessaloniki*
Lazaros I Sakkas, *Larissa*
Michael Voulgarelis, *Athens*



Hungary

Laszlo Czirkak, *Pecs*
András Komócsi, *Pecs*

**India**

Vikas Agarwal, *Lucknow*
Srikantiah Chandrashekara, *Bangalore*
Rajesh Vijayvergiya, *Chandigarh*

**Iran**

Nima Rezaei, *Tehran*
Zahra Rezaeiyazdi, *Mashhad*

**Israel**

Boaz Amichai, *Ramat Gan*
George S Habib, *Nazareth Illit*
Leonid Kalichman, *Beer Sheva*
Igal Leibovitch, *Tel-Aviv*
Ami Schattner, *Rehovot*
Elias Toubi, *Haifa*

**Italy**

Silvano Adami, *Verona*
Giuseppe Barbaro, *Rome*
Mauro Cellini, *Bologna*
Nicola Giordano, *Siena*
Estrella Garcia Gonzalez, *Siena*
Giovanni La Montagna, *Napoli*
Claudio Lunardi, *Verona*
Francesco Oliva, *Rome*
Donato Rigante, *Rome*
Dario Roccatello, *Turin*
Maurizio Turiel, *Milano*

**Japan**

Yoshiya Tanaka, *Kitakyushu*
Takashi Usui, *Kyoto*

**Kuwait**

Adel M A Alawadhi, *Kuwait*

**Mexico**

Carlos Abud-Mendoza, *San Luis Potosi*
Monica Vazquez-Del Mercado, *Guadalajara*
José F Muñoz-Valle, *Zapopan*
José Alvarez Nemegeyi, *Mérida*

**Morocco**

Zoubida Tazi Mezalek, *Rabat*
Faissal Tarrass, *Larache*

**Netherlands**

Esmeralda Blaney Davidson, *Nijmegen*
Timothy Ruben Radstake, *Nijmegen*

Nico M Wulffraat, *Utrecht*

**Peru**

Claudia Selene Mora-Trujillo, *Lima*

**Poland**

Przemyslaw Kotyla, *Katowice*

**Portugal**

Elizabeth Benito-Garcia, *Oeiras*
Alexandrina Ferreira Mendes, *Coimbra*

**Qatar**

Mohammed Hammoudeh, *Doha*

**Saudi Arabia**

Almoallim Hani Mohammad, *Jeddah*
Mohammed Tikly, *Johannesburg*

**Slovakia**

Ivica Lazúrová, *Košice*

**South Korea**

Dae-Hyun Hahm, *Seoul*
Young Mo Kang, *Daegu*
Myeong Soo Lee, *Daejeon*
Chang-Hee Suh, *Suwon*

**Spain**

Pedro Carpintero Benítez, *Cordoba*
Francisco J Blanco, *Coruña*
Vicente Giner Galvañ, *Alcoy*
Segundo Gonzalez, *Oviedo*
Narcis Gusi, *Caceres*
Luis Martinez-Lostao, *Zaragoza*
Gusi Narcis, *Caceres*

**Sweden**

Aladdin Mohammad, *Lund*
Ronald van Vollenhoven, *Stockholm*

**Switzerland**

Daniel Aeberli, *Bern*
Hossein Hemmatazad, *Zurich*

**Thailand**

Prachya Kongtawelert, *Chiang Mai*

**Tunisia**

Ghazi Chabchoub, *Sfax*

**Turkey**

Aynur Akay, *İzmir*
Deniz Evcik, *Ankara*
Sibel Eyigor, *Izmir*
Ozgur Kasapcopur, *Istanbul*
Suleyman Serdar Koca, *Elazig*
Ugur Musabak, *Ankara*
Demet Oflluoglu, *Istanbul*
Salih Ozgocmen, *Kayseri*
Cagatay Ozturk, *Istanbul*
Mehmet Akif Ozturk, *Ankara*
Ismail Sari, *Izmir*
Mehmet Soy, *Bolu*
Yavuz Yakut, *Ankara*
Serap Yalin, *Mersin*

**United Arab Emirates**

Ashok Kumar, *Dubai*

**United Kingdom**

Ade O Adebajo, *Sheffield*
Khalid Binyamin, *Mersyside*
Dimitrios P Bogdanos, *London*
David D'Cruz, *London*
Magdalena Dziadzio, *London*
Edzard Ernst, *Exeter*
Elena A Jones, *Leeds*
Joseph G McVeigh, *Belfast*
Sanjay Mehta, *London*
Jonathan Rees, *London*
Anita Williams, *Salford*
Hazem M Youssef, *Aberdeen*
Wei-Ya Zhang, *Nottingham*

**United States**

Cynthia Aranow, *Manhasset*
Joseph R Berger, *Lexington*
Vance Berger, *Rockville*
Daniel Bikle, *San Francisco*
Marc R Blackman, *Washington*
Galina S Bogatkevich, *Charleston*
Charles R Brown, *Columbia*
Leigh F Callahan, *Chapel Hill*
Hamid Chalian, *Chicago*
Majid Chalian, *Baltimore*
Sean Patrick Curtis, *Rahway*
Barbara A Eberhard, *New Hyde Park*
Luis R Espinoza, *New Orleans*
Shu -Man Fu, *Charlottesville*
Daniel E Furst, *Los Angeles*
Reda Ebeid Girgis, *Baltimore*
Alexei A Grom, *Cincinnati*
Simon Helfgott, *Boston*
Howard J Hillstrom, *New York*
Gary S Hoffman, *Cleveland*
Seung Jae Hong, *Chicago*

Meenakshi Jolly, *Chicago*
M Firoze Khan, *Galveston*
Irving Kushner, *Shaker Heights*
Antonio La Cava, *Los Angeles*
Yi Li, *Gainesville*
Chuan-Ju Liu, *New York*
Charles J Malemud, *Cleveland*
Mahnaz Momeni, *Washington*
Swapan K Nath, *Oklahoma*

Ewa Olech, *Oklahoma*
Alicia Rodríguez Pla, *Dallas*
Chaim Putterman, *Bronx*
Robert James Quinet, *New Orleans*
Allison B Reiss, *Mineola*
Lisa Georgianne Rider, *Bethesda*
Bruce M Rothschild, *Lawrence*
Hee-Jeong Im Sampen, *Chicago*
Naomi Schlesinger, *New Brunswick*

H Ralph Schumacher, *Philadelphia*
Jasvinder A Singh, *Birmingham*
Jianxun (Jim) Song, *Hershey*
Yu-Bo Sun, *Charlotte*
Thomas H Taylor, *Norwich*
George C Tsokos, *Boston*
Yu-Cheng Yao, *Los Angeles*
Ping Zhang, *Indianapolis*
Xiao-Dong Zhou, *Houston*

**EDITORIAL**

- 127 Epigenetic targets of rheumatoid arthritis
Chabchoub G

REVIEW

- 131 Scleroderma: Not an orphan disease any more
Misra DP, Chowdhury AC, Phatak S, Agarwal V

MINIREVIEWS

- 142 Complementary medicine use in rheumatology: A review
Wong WH, Litwic AE, Dennison EM

Contents

World Journal of Rheumatology
Volume 5 Number 3 November 12, 2015

ABOUT COVER

Editorial Board Member of *World Journal of Rheumatology*, Vikas Agarwal, MD, Associate Professor, Department of Immunology, SGPIMS, Lucknow 226014, India

AIM AND SCOPE

World Journal of Rheumatology (*World J Rheumatol*, *WJR*, online ISSN 2220-3214, DOI: 10.5499) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJR covers topics concerning osteoarthritis, metabolic bone disease, connective tissue diseases, antiphospholipid antibody-associated diseases, spondyloarthropathies, acute inflammatory arthritis, fibromyalgia, polymyalgia rheumatica, vasculitis syndromes, periarticular rheumatic disease, pediatric rheumatic disease, miscellaneous rheumatic diseases, and rheumatology-related therapy, pain management, rehabilitation.

We encourage authors to submit their manuscripts to *WJR*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ ABSTRACTING

World Journal of Rheumatology is now indexed in Digital Object Identifier.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Xiao-Kang Jiao*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Jin-Xin Kong*
Proofing Editorial Office Director: *Xin-Xia Song*

NAME OF JOURNAL

World Journal of Rheumatology

ISSN

ISSN 2220-3214 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Four-monthly

EDITOR-IN-CHIEF

Jörg HW Distler, MD, Department of Internal Medicine 3, University of Erlangen-Nuremberg, Universitätsstr. 29, 91054 Erlangen, Germany

EDITORIAL OFFICE

Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Rheumatology

Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLICATION DATE

November 12, 2015

COPYRIGHT

© 2015 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/2220-3214/g_info_20100722180909.htm

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Epigenetic targets of rheumatoid arthritis

Ghazi Chabchoub

Ghazi Chabchoub, Laboratoire de Génétique Moléculaire Humaine, Faculté de Médecine de Sfax, 3000 Sfax, Tunisia

Ghazi Chabchoub, Caisse National d'assurance Maladie, 3021 Sakiet Ezzit, Tunisia

Author contributions: Chabchoub G solely contributed to this paper.

Conflict-of-interest statement: No conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Ghazi Chabchoub, MD, PhD, Médecin Inspecteur, Caisse National d'assurance Maladie, Rue Mongi Slim Sakiet Ezzit, 3021 Sakiet Ezzit, Tunisia. ghazi.chabchoub@laposte.net
 Telephone: +216-98-291120

Received: February 5, 2015

Peer-review started: February 7, 2015

First decision: April 10, 2015

Revised: August 24, 2015

Accepted: September 7, 2015

Article in press: September 8, 2015

Published online: November 12, 2015

Abstract

Rheumatoid arthritis (RA) is a systemic, inflammatory and autoimmune disorder, characterized by chronic arthritis with progressive joint destruction. It has a multifactorial aetiology involving both genetic and environmental factors. Epigenetics can be defined as modifications of DNA that result in altered gene expression. The two main epigenetic mechanisms are post translational modifications to

histone tails and DNA methylation. Recent evidence has suggested that epigenetic mechanisms may be an important contributor to RA susceptibility. The aim of this editorial is to present evidence for the role of epigenetic mechanisms in the pathogenesis of RA and the potential to therapeutic target. Several studies targeting histone modification and DNA methylation in animal models of inflammatory arthritis will be reviewed and alterations in the epigenetic signature of genes of key RA related pathways such as pro-inflammatory cytokines, proteases and regulators of cellular proliferation.

Key words: Rheumatoid arthritis; Epigenetic; DNA methylation; Histone modification

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This paper has highlighted the numerous processes involved in the pathogenesis of rheumatoid arthritis (RA) that are modulated by epigenetic mechanisms. This is important hypotheses to explore a novel therapeutic target in RA.

Chabchoub G. Epigenetic targets of rheumatoid arthritis. *World J Rheumatol* 2015; 5(3): 127-130 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i3/127.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i3.127>

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, inflammatory and autoimmune disorder, characterized by chronic arthritis with progressive joint destruction^[1]. A typical feature is the over-production of pro-inflammatory cytokines including tumor necrosis factor (TNF) and interleukin-1 (IL-1), which lead to up-regulation of other pro-inflammatory molecules and proteases^[2].

RA is a complex disease, and its etiology involves an interaction of both genetic and environmental factors. Genome scans have identified multiple regions

linked to disease^[3-5]. Although interesting associations have been reported^[6,7], only alleles at the HLA-DRB1 locus have consistently demonstrated both linkage and association^[8].

Treatment of RA for most patients involves the administration of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide and sulphasalazine. If DMARDs treatment fails a new drug targets need to be identified to provide therapy for these patients who do not respond to either conventional treatment. Epigenetic mechanisms, which have been implicated in RA, systemic lupus erythematosus and systemic sclerosis^[9,10], offers both new targets for therapy but also may help predict the successful outcome of drug treatments in patients.

EPIGENETICS MECHANISMS

Epigenetics can be defined as modifications of DNA or associated proteins without a change in the DNA sequence itself that result in altered gene expression. The two main epigenetic mechanisms are post translational modifications to histone tails and methylation of DNA, which determine the chromatin state and there by access of transcription factors to gene promoter regions. In cells, DNA is packaged by being wound around nucleosome octomers containing two each of histone H2A, H2B, H3 and H4. These histone proteins have N-terminal tails that are susceptible to a number of post-translational alterations including acetylation, methylation, phosphorylation, sumolation, isomerisation of proline and ubiquitination^[11,12].

The most widely studied histone modification is the addition of acetyl groups to the lysine residues of the N-terminal tails of histones H3 and H4. Histone acetyltransferases add the acetyl groups to lysine residues within the histone tails from the donor acetyl coenzyme A. In turn the acetylation can be reversed by histone deacetylases (HDAC).

DNA methylation results from the addition of a methyl group to the 5-carbon position ring of cytosine. The methylation blocks binding of transcription factors and other co-activators to the DNA and recruits transcriptional repressors to the promoter^[13]. Three active DNA methyltransferases (DNMT) have been identified. De novo methylation is performed by DNMT3A and DNMT3B, whereas methylation is maintained following cell division by DNMT1^[14].

EPIGENETIC REGULATION OF IMMUNE CELLS AND PRO-INFLAMMATORY MOLECULES

Both DNA methylation and histone modifications contribute to the expression of a number of T-cell associated cytokines, including interferon gamma (IFN- γ), IL-2 and IL-7R α ^[15-21]. At the IFN- γ promoter differential methylation is seen in naïve, effector and memory T-cells

being highest in naïve cells. There is rapid loss of methylation upon re-stimulation in memory T-cells that is associated with these cells rapid ability to produce IFN- γ in response to reinfection by a virus^[17]. Interestingly, STAT4, which is involved in the stimulation of IFN- γ expression, is also regulated by DNA methylation suggesting that if methylation levels change at both these promoters together there could be a multiplicative effect on the quantity of IFN- γ produced^[18]. Protein kinase C activators and phosphatase inhibitors attenuate DNA methylation levels, possibly by altering the activity of DNMT1, correlating with the induction of IFN- γ providing one possible mechanism for changing methylation levels^[22]. IL-7 is involved in chronic inflammation in RA, not only does it increase osteoclast formation and thereby enhances bone loss but it is also important in maintaining T-cell homeostasis^[23]. Expression of the IL-7 receptor, IL-7R α , on T-cells is regulated by DNA methylation with T-cells showing only low surface IL-7R α having higher methylation at the gene promoter^[21].

TNF is a major player in the pathology of RA confirmed by the efficacy of anti-TNF treatment in many patients. There is increasing evidence that epigenetic mechanisms play a role in regulating TNF expression. Phosphorylation of Serine (S)¹⁰ of histone H3 and demethylation of Lysine (K)⁷ has been observed at the TNF promoter in THP-1 cells, following LPS stimulation^[24]. These changes to the histone code occur in conjunction with loss of heterochromatin binding protein 1 α (HP1 α) from the TNF promoter^[12]. The role of histone acetylation in the regulation of TNF production remains unclear. In animal models of arthritis it appears that HDAC inhibitors attenuate the expression of TNF whereas treatment of monocyte or macrophages with various inhibitors including sodium butyrate, Chlamydocin and HC-toxin generally increased TNF production with sodium butyrate increasing expression levels by 22 fold in THP-1 cells^[24].

Epigenetic regulation has been implicated in the modulation of both IL-1 α and IL-1 β . Methylation of the proximal promoter regulates the expression of IL-1 α and this methylation is responsible for the allele specific expression of this cytokine in CD4⁺ T cells^[25,26]. Histone modifications appear the major epigenetic mechanism regulating IL-1 β . Inhibiting HDAC activity with fibroblasts trichostatin A (TSA) caused an increase in LPS-induced IL-1 β expression in choriodecidual explants^[27]. Interestingly DNA methylation appears to have a role in regulating IL-6 gene expression^[2].

IL-6 is another important pro-inflammatory cytokine involved in the hepatic acute phase of RA and with its role confirmed by the success of the IL-6 receptor antibody, tocilizumab, in reducing disease activity and bone erosions^[2]. Interestingly DNA methylation appears to have a role in regulating IL-6 gene expression. In RA patients reduced DNA methylation at a single CpG site within the promoter (-1099) in comparison to healthy for controls has been identified^[28]. Reduced

methylation at this site was associated with increased IL-6 mRNA production in response to LPS. In addition to the role of epigenetics in regulating expression of pro-inflammatory cytokines, these molecules once produced may also have a role in epigenetic regulation. IL-6 has been shown to modulate the expression and activity of DNMTs leading to increased DNA methylation at the tumour suppressor gene p53 and Foxp3^[29,30]. Methylation induced by IL-6 at the p53 promoter could be playing a role in silencing pro-apoptotic genes in the rheumatoid synovium^[29].

Numerous HDAC inhibitors have been developed mainly to target histone acetylation in RA models. Various studies using topical application of suberoylanilide hydroxamic acid (SAHA), MS-275 and FK228 established their potential to decrease serum IL-6, IL-1 β and TNF levels suggesting an important role for HDAC in regulating production of pro-inflammatory cytokines^[31,32].

EPIGENETIC MECHANISMS AND REGULATION OF THE HOMEOSTASIS IN THE SYNOVIAL JOINT

Increasing evidence suggests that histone tail modifications have an important role in regulating synovial hyperplasia in the RA joint. HDAC inhibitors have been tested in several models of RA in both rats and mice. These studies demonstrated the efficacy of TSA, phenylbutyrate FK228, SAHA and MS275 in ameliorating joint swelling and inflammation associated with inflammatory arthritis^[31-34]. Treatment of RA synovial fibroblasts (RASf) with phenylbutyrate, TSA and FK228 causes histone hyperacetylation at p16^{INK4} and p21^{CIP1} promoters associated with expression of these two proteins which involved in the reduction of RASf numbers^[35]. Interestingly, treatment with TSA and phenyl butyrate established the potential of HDAC inhibitors to reduce paw swelling in an adjuvant arthritis model in rats. It was reported that treatment had to start early for the inhibitors to prevent pannus formation and associated joint damage. In addition, TSA was found to have a greater ability to suppress synovial hyperplasia than phenylbutyrate^[31].

Methylation of DNA may also play a role in regulating cartilage integrity. Demethylation of specific loci within the MMP-3, MMP-9, MMP-13 and ADAMTS-4 promoters is present in cartilage from patients with osteoarthritis compared to controls which, is seen in conjunction with other expression of these enzymes in osteoarthritis cartilage^[36]. Osteogenic protein-1 (OP-1) is a potent anabolic growth factor for articular chondrocytes, an aging-related increase in OP-1 promoter methylation that leads to decreased expression may contribute to cartilage loss seen with aging and in particular with the progression of osteoarthritis in older adults^[37]. In addition, when comparing DNA methylation patterns in chondrocytes and mesenchymal stem cells undergoing

chondrogenesis, loss of methylation at two CpG sites within the promoter of type X collagen is associated with the production of this collagen in the latter cell type^[38]. These findings demonstrate the importance of DNA methylation in regulating the homeostasis cartilage.

CONCLUSION

This editorial has highlighted the numerous processes involved in the pathogenesis of RA that are modulated by epigenetic mechanisms. Key aspects of the production of pro-inflammatory molecules, inappropriate immune cell responses, and abnormalities in the synovium and cartilage degradation have all been shown to be modulated by histone modifications and DNA methylation. However, the complete picture of how epigenetic mechanisms modulate cellular differentiation and response to activation remains unclear. The success of HDAC inhibitors in ameliorating the symptoms of inflammatory arthritis in animal models is an exciting new development for the treatment of RA. Further development in HDAC inhibitors especially as more complete clinical trials, will lead to further knowledge generation on their mechanisms, targets and ability to treat RA.

REFERENCES

- 1 **McInnes IB**, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011; **365**: 2205-2219 [PMID: 22150039 DOI: 10.1056/NEJMra1004965]
- 2 **Brennan FM**, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. *J Clin Invest* 2008; **118**: 3537-3545 [PMID: 18982160 DOI: 10.1172/JCI36389]
- 3 **Okada Y**, Wu D, Trynka G, Raj T, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, Yoshida S, Graham RR, Manoharan A, Ortmann W, Bhangale T, Denny JC, Carroll RJ, Eyler AE, Greenberg JD, Kremer JM, Pappas DA, Jiang L, Yin J, Ye L, Su DF, Yang J, Xie G, Keystone E, Westra HJ, Esko T, Metspalu A, Zhou X, Gupta N, Mirel D, Stahl EA, Diogo D, Cui J, Liao K, Guo MH, Myouzen K, Kawaguchi T, Coenen MJ, van Riel PL, van de Laar MA, Guchelaar HJ, Huizinga TW, Dieudé P, Mariette X, Bridges SL, Zhernakova A, Toes RE, Tak PP, Miceli-Richard C, Bang SY, Lee HS, Martin J, Gonzalez-Gay MA, Rodriguez-Rodriguez L, Rantapää-Dahlqvist S, Arlestig L, Choi HK, Kamatani Y, Galan P, Lathrop M, Eyre S, Bowes J, Barton A, de Vries N, Moreland LW, Criswell LA, Karlson EW, Taniguchi A, Yamada R, Kubo M, Liu JS, Bae SC, Worthington J, Padyukov L, Klareskog L, Gregersen PK, Raychaudhuri S, Stranger BE, De Jager PL, Franke L, Visscher PM, Brown MA, Yamanaka H, Mimori T, Takahashi A, Xu H, Behrens TW, Siminovitch KA, Momohara S, Matsuda F, Yamamoto K, Plenge RM. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 2014; **506**: 376-381 [PMID: 24390342]
- 4 **Zhang MM**, Jiang YS, Lv HC, Mu HB, Li J, Shang ZW, Zhang RJ. Pathway-based association analysis of two genome-wide screening data identifies rheumatoid arthritis-related pathways. *Genes Immun* 2014; **15**: 487-494 [PMID: 25101796]
- 5 **Neidhart M**, Karouzakis E. Genetics: a new interpretation of genetic studies in RA. *Nat Rev Rheumatol* 2014; **10**: 199-200 [PMID: 24567061]
- 6 **Zhang C**, Chen L, Gu Y. Polymorphisms of MMP-1 and MMP-3 and susceptibility to rheumatoid arthritis. A meta-analysis. *Z Rheumatol* 2015; **74**: 258-262 [PMID: 25854159 DOI: 10.1007/s00393-014-1537-2]
- 7 **Abd-Allah SH**, el-Shal AS, Shalaby SM, Pasha HF, Abou el-Saoud

- AM, el-Najjar AR, el-Shahawy EE. PADI4 polymorphisms and related haplotype in rheumatoid arthritis patients. *Joint Bone Spine* 2012; **79**: 124-128 [PMID: 21981985]
- 8 **Reynolds RJ**, Ahmed AF, Danila MI, Hughes LB, Gregersen PK, Raychaudhuri S, Plenge RM, Bridges SL. HLA-DRB1-associated rheumatoid arthritis risk at multiple levels in African Americans: hierarchical classification systems, amino acid positions, and residues. *Arthritis Rheumatol* 2014; **66**: 3274-3282 [PMID: 25524867]
 - 9 **Glant TT**, Mikecz K, Rauch TA. Epigenetics in the pathogenesis of rheumatoid arthritis. *BMC Med* 2014; **12**: 35 [PMID: 24568138]
 - 10 **Sánchez-Pernaute O**, Ospelt C, Neidhart M, Gay S. Epigenetic clues to rheumatoid arthritis. *J Autoimmun* 2014; **30**: 12-20 [PMID: 18155418 DOI: 10.1016/j.jaut.2007.11.006]
 - 11 **An W**. Histone acetylation and methylation: combinatorial players for transcriptional regulation. *Subcell Biochem* 2007; **41**: 351-369 [PMID: 17484136 DOI: 10.1007/1-4020-5466-1_16]
 - 12 **Berger SL**. The complex language of chromatin regulation during transcription. *Nature* 2007; **447**: 407-412 [PMID: 17522673 DOI: 10.1038/nature05915]
 - 13 **Meng H**, Cao Y, Qin J, Song X, Zhang Q, Shi Y, Cao L. DNA methylation, its mediators and genome integrity. *Int J Biol Sci* 2015; **11**: 604-617 [PMID: 25892967 DOI: 10.7150/ijbs.11218]
 - 14 **Baubec T**, Colombo DF, Wirbelauer C, Schmidt J, Burger L, Krebs AR, Akalin A, Schübeler D. Genomic profiling of DNA methyltransferases reveals a role for DNMT3B in genic methylation. *Nature* 2015; **520**: 243-247 [PMID: 25607372]
 - 15 **Berkley AM**, Hendricks DW, Simmons KB, Fink PJ. Recent thymic emigrants and mature naive T cells exhibit differential DNA methylation at key cytokine loci. *J Immunol* 2013; **190**: 6180-6186 [PMID: 23686491]
 - 16 **Komori HK**, Hart T, LaMere SA, Chew PV, Salomon DR. Defining CD4 T cell memory by the epigenetic landscape of CpG DNA methylation. *J Immunol* 2015; **194**: 1565-1579 [PMID: 25576597]
 - 17 **Gray SM**, Kaech SM, Staron MM. The interface between transcriptional and epigenetic control of effector and memory CD8+ T-cell differentiation. *Immunol Rev* 2014; **261**: 157-168 [PMID: 25123283]
 - 18 **Williams CL**, Schilling MM, Cho SH, Lee K, Wei M, Aditi M. STAT4 and T-bet are required for the plasticity of IFN- γ expression across Th2 ontogeny and influence changes in Ifng promoter DNA methylation. *J Immunol* 2013; **191**: 678-687 [PMID: 23761633]
 - 19 **Dong J**, Chang HD, Ivascu C, Qian Y, Rezai S, Okhrimenko A, Cosmi L, Maggi L, Eckhardt F, Wu P, Sieper J, Alexander T, Annunziato F, Gossen M, Li J, Radbruch A, Thiel A. Loss of methylation at the IFNG promoter and CNS-1 is associated with the development of functional IFN- γ memory in human CD4(+) T lymphocytes. *Eur J Immunol* 2013; **43**: 793-804 [PMID: 23255246 DOI: 10.1002/eji.201242858]
 - 20 **Northrop JK**, Thomas RM, Wells AD, Shen H. Epigenetic remodeling of the IL-2 and IFN-gamma loci in memory CD8 T cells is influenced by CD4 T cells. *J Immunol* 2006; **177**: 1062-1069 [PMID: 16818762 DOI: 10.4049/jimmunol.177.2.1062]
 - 21 **Kim HR**, Hwang KA, Kim KC, Kang I. Down-regulation of IL-7R α expression in human T cells via DNA methylation. *J Immunol* 2007; **178**: 5473-5479 [PMID: 17442928 DOI: 10.4049/jimmunol.178.9.5473]
 - 22 **Bonilla-Henao V**, Martínez R, Sobrino F, Pintado E. Different signaling pathways inhibit DNA methylation activity and up-regulate IFN-gamma in human lymphocytes. *J Leukoc Biol* 2005; **78**: 1339-1346 [PMID: 16204617 DOI: 10.1189/jlb.1004604]
 - 23 **Churchman SM**, El-Jawhari JJ, Burska AN, Parmar R, Goëb V, Conaghan PG, Emery P, Ponchel F. Modulation of peripheral T-cell function by interleukin-7 in rheumatoid arthritis. *Arthritis Res Ther* 2014; **16**: 511 [PMID: 25533722]
 - 24 **Falvo JV**, Jasenosky LD, Kruidenier L, Goldfeld AE. Epigenetic control of cytokine gene expression: regulation of the TNF/LT locus and T helper cell differentiation. *Adv Immunol* 2013; **118**: 37-128 [PMID: 23683942]
 - 25 **van Rietschoten JG**, Gal-Yam EN, Jeong S, Cortez CC, Verweij CL, Jones PA. Epigenetic regulation and nucleosome positioning in the human TATA-less IL-1 α promoter. *Genes Immun* 2008; **9**: 582-590 [PMID: 18615092]
 - 26 **van Rietschoten JG**, Verzijlbergen KF, Gringhuis SI, van der Pouw Kraan TC, Bayley JP, Wierenga EA, Jones PA, Kooter JM, Verweij CL. Differentially methylated alleles in a distinct region of the human interleukin-1 α promoter are associated with allele-specific expression of IL-1 α in CD4+ T cells. *Blood* 2006; **108**: 2143-2149 [PMID: 16788102 DOI: 10.1182/blood-2006-01-021147]
 - 27 **Sato TA**, Mitchell MD. Molecular inhibition of histone deacetylation results in major enhancement of the production of IL-1 β in response to LPS. *Am J Physiol Endocrinol Metab* 2006; **290**: E490-E493 [PMID: 16234266 DOI: 10.1152/ajpendo.00406.2005]
 - 28 **Ishida K**, Kobayashi T, Ito S, Komatsu Y, Yokoyama T, Okada M, Abe A, Murasawa A, Yoshie H. Interleukin-6 gene promoter methylation in rheumatoid arthritis and chronic periodontitis. *J Periodontol* 2012; **83**: 917-925 [PMID: 22122521]
 - 29 **Hodge DR**, Peng B, Cherry JC, Hurt EM, Fox SD, Kelley JA, Munroe DJ, Farrar WL. Interleukin 6 supports the maintenance of p53 tumor suppressor gene promoter methylation. *Cancer Res* 2005; **65**: 4673-4682 [PMID: 15930285 DOI: 10.1158/0008-5472.CAN-04-3589]
 - 30 **Lal G**, Zhang N, van der Touw W, Ding Y, Ju W, Bottinger EP, Reid SP, Levy DE, Bromberg JS. Epigenetic regulation of Foxp3 expression in regulatory T cells by DNA methylation. *J Immunol* 2009; **182**: 259-273 [PMID: 19109157 DOI: 10.4049/jimmunol.182.1.259]
 - 31 **Nishida K**, Komiyama T, Miyazawa S, Shen ZN, Furumatsu T, Doi H, Yoshida A, Yamana J, Yamamura M, Ninomiya Y, Inoue H, Asahara H. Histone deacetylase inhibitor suppression of autoantibody-mediated arthritis in mice via regulation of p16INK4a and p21(WAF1/Cip1) expression. *Arthritis Rheum* 2004; **50**: 3365-3376 [PMID: 15476220 DOI: 10.1002/art.20709]
 - 32 **Lin HS**, Hu CY, Chan HY, Liew YY, Huang HP, Lepescheux L, Bastianelli E, Baron R, Rawadi G, Clément-Lacroix P. Anti-rheumatic activities of histone deacetylase (HDAC) inhibitors in vivo in collagen-induced arthritis in rodents. *Br J Pharmacol* 2007; **150**: 862-872 [PMID: 17325656 DOI: 10.1038/sj.bjp.0707165]
 - 33 **Ocker M**, Schneider-Stock R. Histone deacetylase inhibitors: signalling towards p21cip1/waf1. *Int J Biochem Cell Biol* 2007; **39**: 1367-1374 [PMID: 17412634]
 - 34 **Zhou X**, Hua X, Ding X, Bian Y, Wang X. Trichostatin differentially regulates Th1 and Th2 responses and alleviates rheumatoid arthritis in mice. *J Clin Immunol* 2011; **31**: 395-405 [PMID: 21305388]
 - 35 **Morinobu A**, Wang B, Liu J, Yoshiya S, Kurosaka M, Kumagai S. Trichostatin A cooperates with Fas-mediated signal to induce apoptosis in rheumatoid arthritis synovial fibroblasts. *J Rheumatol* 2006; **33**: 1052-1060 [PMID: 16755652]
 - 36 **Cheung KS**, Hashimoto K, Yamada N, Roach HI. Expression of ADAMTS-4 by chondrocytes in the surface zone of human osteoarthritic cartilage is regulated by epigenetic DNA de-methylation. *Rheumatol Int* 2009; **29**: 525-534 [PMID: 18941754]
 - 37 **Loeser RF**, Im HJ, Richardson B, Lu Q, Chubinskaya S. Methylation of the OP-1 promoter: potential role in the age-related decline in OP-1 expression in cartilage. *Osteoarthritis Cartilage* 2009; **17**: 513-517 [PMID: 18829350]
 - 38 **Zimmermann P**, Boeuf S, Dickhut A, Boehmer S, Olek S, Richter W. Correlation of COL10A1 induction during chondrogenesis of mesenchymal stem cells with demethylation of two CpG sites in the COL10A1 promoter. *Arthritis Rheum* 2008; **58**: 2743-2753 [PMID: 18759285 DOI: 10.1002/art.23736]

P- Reviewer: Hammoudeh M, La Montagna G, Turiel M
S- Editor: Ji FF L- Editor: A E- Editor: Jiao XK



Scleroderma: Not an orphan disease any more

Durga Prasanna Misra, Abhra Chandra Chowdhury, Sanat Phatak, Vikas Agarwal

Durga Prasanna Misra, Abhra Chandra Chowdhury, Sanat Phatak, Vikas Agarwal, Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India

Author contributions: Misra DP, Chowdhury AC, Phatak S and Agarwal V contributed to the conception and design, acquisition of the data, analysis and interpretation of the data, and final approval of the version to be published; Misra DP, Chowdhury AC and Phatak S drafted the article; Agarwal V critically revised the article for important intellectual content.

Conflict-of-interest statement: Authors do not declare any conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Vikas Agarwal, Additional Professor, Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow 226014, India. vikasagr@yahoo.com
Telephone: +91-52-22494318
Fax: 91-52-22668812

Received: March 30, 2015
Peer-review started: March 31, 2015
First decision: April 27, 2015
Revised: June 26, 2015
Accepted: July 11, 2015
Article in press: July 14, 2015
Published online: November 12, 2015

Abstract

Scleroderma (or systemic sclerosis) is a rare disease associated with significant morbidity and mortality. Although previously thought to have a uniformly poor

prognosis, the outlook has changed in recent years. We review recent insights into the pathogenesis, clinical features, assessment and management of scleroderma.

Key words: Pulmonary hypertension; Scleroderma; Interstitial lung disease; Raynauds phenomenon; Fibrosis

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Scleroderma is a rare disease associated with significant morbidity and mortality. Better understanding regarding its pathogenesis has led to exploration of various newer therapeutic targets. Anti B cell therapy, endothelin receptor antagonists, phosphodiesterase-5 (PDE-5) inhibitors and autologous stem cell transplant holds promise in the management of systemic sclerosis. PDE-5 inhibitors in particular have potential to be disease modifying agents as they not only improve Raynaud's phenomenon, but also heal digital ulcers, improve pulmonary hypertension and in addition by virtue of antifibrotic properties may have beneficial effect on skin and lung fibrosis.

Misra DP, Chowdhury AC, Phatak S, Agarwal V. Scleroderma: Not an orphan disease any more. *World J Rheumatol* 2015; 5(3): 131-141 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i3/131.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i3.131>

INTRODUCTION

Scleroderma, also known as systemic sclerosis (SSc), is a disease characterized by fibrosis in skin and internal organs, most notably lungs, gastrointestinal tract (GIT), heart, kidneys and muscles. Until a couple of decades back, this rare disorder was associated with a poor clinical outcome, with mortality of up to 70% at 3 years, mostly from respiratory or renal involvement. Advances in understanding of pathogenesis, evolving criteria for early diagnosis and newer therapeutic modalities

provide a new ray of hope in this disease. Herein, we have reviewed recent advances in this field.

PATHOLOGY AND PATHOGENESIS

Scleroderma is characterized by excessive collagen deposition in skin, lungs, esophagus, intestines, heart (muscle and conduction system) and in and around small blood vessels (obliterative intimal proliferation and fibrosis with bland vasculopathy)^[1]. Biopsies of skin show atrophy of the epidermis with increased collagen deposition in the epidermis and dermis. Affected dermal capillaries show obliterative intimal proliferation and fibrosis with bland vasculopathy. Biopsies from lungs of affected individuals show increased alveolar septal thickening with infiltrates of lymphocytes, eosinophils, macrophages and mast cells in the interstitium^[1].

Two factors work in tandem - an inflammatory component with activation of innate and adaptive immunity and autoantibody production, with an additional component of endothelial dysfunction. The inciting event in pathogenesis is not known^[2]. A genetic component is considered likely in view of increased risk of developing SSc (13-19 fold) in siblings and first degree relatives of individuals with SSc. However, lack of significant concordance in monozygotic twins suggests that environmental influences play a significant role in predisposing to SSc^[2]. Candidate gene studies identified polymorphisms involved in T cell signaling (STAT4, TNFSF4, TBX21, NLRP1) and B cell signaling (FAM167A-BLK, BANK and IRAK1) as risk factors for SSc^[2]. Genome wide association studies (GWAS) further confirmed associations with HLA DPB1, DPB2, IRF5 and STAT4, whilst identifying newer genes (CD247 - a co-receptor in B cell signaling; PRORS1C1 - previously identified in psoriasis GWAS studies; rhoB)^[2]. Immunochip studies further implicated genes involved in DNA degradation (DNASE1L3), RNA degradation (TREX-DDX6) and autophagy (ATG5)^[2]. In view of the significant environmental influence on SSc susceptibility, epigenetic modification is proposed to play a major role in SSc pathogenesis^[2]. Global DNA hypomethylation in T lymphocytes and fibroblasts and increased FOXP3 methylation have been shown in SSc^[2]. Decreased histone3 lysine 27 methylation has been demonstrated^[2]. Use of histone deacetylase inhibitor trichostatin resulted in decreased fibrosis in fibroblast cultures by decreasing COL1A1 synthesis, restoring expression of negative regulator of fibrosis FLI1 and inhibiting TGF- β signaling through blockade of Smad3 and 4^[2]. Recently, downregulation of miRNA 30b has been demonstrated in sera of patients with SSc, inversely correlating with skin scores measured using the modified Rodnan skin score (mRSS), possibly acting *via* modulation of PDGF receptor β ^[2]. Increased miRNA 21 (with consequent upregulation of fibrosis related genes COL1A1, COL1A2 and FN1) and decreased antifibrotic miRNAs (miR29a, miR 150, miR 196a, let7a) have been found in patients with SSc^[3-8]. The circulating

profile of free microRNAs in sera of patients with SSc has been found to differ from the sera derived from both healthy controls as well as patients with systemic lupus erythematosus^[9]. Gene profiling in skin biopsies from patients with scleroderma confirmed increased expression of genes in the TGF- β and Wnt pathways, as well those involved in extracellular matrix synthesis and CCN family of proteins (encoding connective tissue growth factor - CTGF). These were expressed to a lesser extent in fibroblasts derived from these skin biopsy specimens, suggesting involvement of other cell types as well^[10]. Hyaluronan levels have been found to be elevated in sera of patients with SSc compared with healthy controls, and these correlated with levels of anti-topoisomerase-I antibodies. This may possibly be of relevance considering that hyaluron acts a ligand for TLR 2 and TLR 4, thereby driving Type I interferon production and autoantibody production in scleroderma^[11].

Environmental factors like exposure to organic solvents, silica, rapeseed oil and L-tryptophan have been implicated in causing skin thickening akin to scleroderma^[1]. Drugs such as bleomycin and pentazocine also cause a similar phenotype. Gadolinium administration in patients with renal dysfunction causes the rare complication of nephrogenic fibrosing sclerosis. Role of viruses (cytomegalovirus, parvovirus B19) has also been postulated^[1].

The inciting event in pathogenesis is endothelial injury, mediated by as yet poorly-characterized environmental influences. This leads on to a leaky endothelium with fluid extravasation (corresponding to the edematous phase of early scleroderma)^[1]. Anti-endothelial cell antibodies have been identified in almost 50% patients with scleroderma, and may drive the endothelial injury. Enhanced release of vasoconstrictors like endothelin 1 and impaired release of prostacyclins causes the endothelial dysfunction, resulting in an exaggerated vasospastic response to cold manifesting as Raynaud's phenomenon (RP)^[12]. There occurs apoptosis of endothelial cells and pericytes, with increased expression of integrins. Chemokines like CCL2 attract inflammatory cells (innate cells like macrophages, secreting type I interferons, and adaptive immune cells - T and B lymphocytes). Nucleic acid from damaged cells is taken up by macrophages and other antigen presenting cells, and presented to T cells by means of B cells, causing their activation to a Th2 phenotype (secreting interleukin-4, -5, -13) and Th17 cells^[1,12]. Simultaneously, B cells also differentiate to form plasma cells, and further form autoantibodies. Autoantibodies to centromeric proteins (specifically centromeric protein B - CENB), topoisomerase I and RNA polymerase III are identified in almost two-thirds of patients with SSc, and are mutually exclusive^[1]. The reparative process induced by this tissue damage is dysregulated, and involves excessive fibroblast activation. These fibroblasts may be derived from endothelial or epithelial cells (epithelial or endothelial to mesenchymal transformation), resident tissue fibroblasts or circulating pericytes. Th2 cytokines

Table 1 American College of Rheumatology 1980 criteria for systemic sclerosis

Major criterion	Minor criterion
Scleroderma like skin change proximal to MCP or MTP joints	Sclerodactyly Digital pitting scars of fingertips or loss of distal finger pad Bibasilar Pulmonary fibrosis

(IL-4, IL-13), chemokines like CCL2, excessive platelet derived growth factor (PDGF) receptor, stimulating agonist antibodies to PDGF receptor, increased thrombin, endothelin 1 and TGF- β levels in the milieu ultimately lead to increased signaling *via* the TGF- β receptor^[1,12]. Oxidative stress resulting from release of reactive oxygen species further drives augmented profibrotic signaling *via* Ras and ERK1/2, *via* a self-reinforcing loop. These culminate in increased collagen and alpha-smooth muscle actin (α -SMA) synthesis as well as production of connective tissue growth factor (CTGF and surface receptors for PDGF and TGF- β ^[1,12]. Hypoxia resulting from vasculopathy drives excessive production of angiogenic factors (PDGF, CTGF, VEGF) and the resulting neoangiogenesis is disordered^[1,12].

Animal models of SSc help further our understanding of these pathogenic processes *in vitro*^[13]. The four key components of SSc pathology are vasculopathy, fibrosis, inflammation and autoimmunity, and these are captured in different animal models. Induced models involve immunization of mice with bleomycin and topoisomerase I (lack vasculopathy), angiotensin II (lack autoimmunity), collagen V and models of graft-vs-host disease involving immunization of RAG knockout mice with splenocytes from B10.D2 mice (encompass all features of SSc)^[13]. Spontaneous models include the Tsk 1 mice (spontaneous mutation in fibrillin 1) and Tsk 2 mice (which have all the features except vasculopathy), constitutively active TGF- β receptor I and II (all features except autoimmunity) and UCD 200/206 model in chicken (encompassing all features of human scleroderma)^[13].

CLASSIFICATION CRITERIA

In 1980, the American College of Rheumatology (ACR) had proposed the preliminary classification criterion for diagnosis of SSc (Table 1)^[14].

Either 1 major or 2 or more of the minor criterion had to be fulfilled for a patient to be classified as SSc. This criterion had 98% specificity but it lacks sensitivity as it was developed using patients who had long standing SSc. Later on with the advent of nailfold capillaroscopy and scleroderma specific antibodies it was found that this criterion is unable to detect a subset of patients with early disease and those who lacks skin changes. In 1988, LeRoy *et al*^[15] proposed new criteria that included clinical features, autoantibodies, and capillaroscopy results, highlighting the differences

between the 2 main SSc subsets. In 2001 revision of the classification criteria was proposed by LeRoy and Medsger^[16] for the early diagnosis of SSc using nailfold capillary pattern and SSc-related autoantibodies. However neither the 1980 ACR criterion nor the LeRoy criterion was sensitive enough to diagnose very early/early phase of SSc. Internal organ involvement may be present from the earliest stages of SSc even before skin involvement- this necessitates that the diagnosis of SSc be made in the very early or at least early phase so that therapeutic options may be considered early^[17,18]. In 2008-2009 experts from 85 EUSTAR (EULAR Scleroderma Trial And Research) centers participated in a Delphi exercise to develop criterion for the Very Early Diagnosis Of Systemic Sclerosis (VEDOSS)^[19]. Three domains containing seven items were identified as follows: skin domain (puffy fingers/puffy swollen digits turning into sclerodactyly); vascular domain (RP, abnormal capillaroscopy with scleroderma pattern) and laboratory domain (antinuclear, anticentromere, and antitopoisomerase-I antibodies). In 2013 following consideration of the definition of early SSc, the ACR and European League Against Rheumatism (EULAR) jointly proposed a new criteria for the diagnosis of SSc (Table 2)^[20].

The criterion was tested in a validation cohort -sensitivity and specificity were 0.91 and 0.92 for the new classification criteria and 0.75 and 0.72 for the 1980 ACR classification criteria. The 2013 ACR criterion was tested in another cohort of 724 patients by the Canadian Scleroderma Research Group (CSRG) -sensitivity was consistent in subgroups of patients with lcSSc (98.8% vs 85.6%), anti-centromere antibodies (98.9% vs 79.8%), disease duration \leq 3 years (98.7% vs 84.7%) or no skin involvement proximal to the metacarpophalangeal joints (97% vs 60%)^[21]. The recent ACR classification criteria enable earlier diagnosis of patients, when the disease course may be potentially more amenable to modification with therapy.

AUTOANTIBODIES

Anti-Topoisomerase I /Scl-70 antibody (ATA), anti-centromere antibody (ACA) and anti-RNA polymerase III (anti-RNAP III) are the three major autoantibodies in SSc, mutually exclusive and present in about 70% patients with SSc. Each of these are associated with distinct clinical phenotype^[22]. ATA are associated with diffuse cutaneous involvement (although 30% patients can have limited cutaneous disease) and increased risk of interstitial lung disease (ILD) and mortality^[22]. Anti-RNAP III antibodies are also associated with diffuse skin involvement and higher risk of scleroderma renal crisis (SRC), but lesser risk of ILD^[22]. ACA are associated with limited skin involvement, oesophageal dysmotility, calcinosis and pulmonary hypertension^[22]. The presence of ACA in a patient with primary Raynaud's predicts future development of limited cutaneous SSc (LCSSc). Lesser prevalent antibodies include antibodies to Th/To

Table 2 American College of Rheumatology/European League Against Rheumatism criteria for diagnosis of systemic sclerosis (2013) (Reproduced with permission)

Item	Sub-item(s)	Weight/score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the higher score)	Puffy Fingers	2
	Sclerodactyly of the fingers (distal to the 4 metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nail fold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon		3
SSc-related autoantibodies [anticentromere, anti-topoisomerase I (anti-Scl-70), anti-RNA polymerase III] (maximum score is 3)	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

(limited skin involvement with severe ILD, SRC and poorer survival), anti-fibrillarin antibodies (severe Raynaud's and pulmonary hypertension) and anti-U11/U12 RNP antibodies (severe ILD)^[22].

CLINICAL FEATURES

Skin tightening in SSc characteristically is proximal to the metacarpophalangeal or metatarsophalangeal joints. Rarely, SSc can occur without skin tightening (only having Raynaud's, digital ulcers, ILD or gastrointestinal manifestations in conjunction with autoantibodies), when it is called as SSc sine scleroderma^[23]. When it is limited to areas distal to the elbow, knees or only involves the face and neck, the disease is characterized as limited cutaneous systemic sclerosis (lcSSc). More distal involvement of the extremities or skin tightening over the chest and trunk is defined as diffuse cutaneous systemic sclerosis (dcSSc). It is important to know these subsets due to characteristic differences in presentation and prognosis, as subsequently discussed^[24]. Skin tightening is quantified clinically using the mRSS, wherein 17 areas are assessed (bilateral arms, forearms, hands, fingers, thighs, legs and feet; face, chest and abdomen anteriorly) and graded between 0 to 3 (0 if skin is normal and 3 if there is hide-bound skin)^[24]. A greater mRSS portends a worse prognosis^[25]. Skin tightening tends to resolve with time, and patients with advanced disease may have atrophic skin with lack of subcutaneous fat. Hence patients with dcSSc, when seen late at a time when most of the skin tightening has resolved, may be mistakenly classified as lcSSc^[24].

The most characteristic feature of SSc is RP, which is defined as an exaggerated vasospastic response of the extremities to cold exposure^[26]. It typically involves the fingers and toes, which during a classical attack of Raynaud's progress through phases of pallor, cyanosis and reactive erythema (triphasic or complete Raynaud's). More commonly, the patient describes any two of these

three color changes (incomplete Raynaud's)^[26]. RP is a major cause of morbidity in patients with SSc. Raynaud's can be primary, usually affecting young females, with negative autoantibodies and younger age of onset, or secondary, when it occurs in conjunction with connective tissue diseases like scleroderma or mixed connective tissue diseases^[26]. Secondary Raynaud's is usually associated with antinuclear antibody positivity, nailfold capillary changes of dilated capillary loops (in the early phase) and capillary dropouts (in the later stages) and is often severe enough to cause digital ulcerations, digital pulp loss, resorption of distal portion of phalanges and digital gangrene. It is a manifestation of endothelial dysfunction in SSc^[26]. Patients with lcSSc usually have onset of RP a few years prior to onset of skin tightening, whereas those with dcSSc have onset either concurrent with or just preceding skin tightening^[26]. Abnormal angiogenesis is clinically manifest as telangiectasias in the skin, and stomach (gastric antral vascular ectasias or watermelon stomach); can result in severe upper gastrointestinal bleeding^[1].

The most common cause of morbidity and long term mortality in SSc is pulmonary involvement. Usually, this is in the form of pulmonary fibrosis, in a non-specific interstitial pneumonia pattern, affecting up to two-thirds of patients with dcSSc and a third of lcSSc patients^[12]. Clinically, patients present with insidious onset of exertional dyspnea, fatigue and dry cough. A good screening test is reduction in forced vital capacity (FVC) below 70%, which further mandates a high resolution computerized tomogram (HRCT) of the thorax to document the extent of pulmonary involvement. Early changes include ground-glass appearance of the lung fields, followed progressively by fibrosis, traction bronchiectasis and honeycombing^[27-30]. Pulmonary hypertension (PH) can result consequent to hypoxia resulting from ILD or it can occur *de novo*, more commonly in long-standing lcSSc (up to a fourth of patients at 10 years)^[27-30]. Recently emerging

biomarkers of ILD include lysyl oxidase, tenascin-C, thrombospondin 5, CXCL-5 in serum, and CXCL2, CXCL4, S100A8/9 in bronchoalveolar lavage. Positivity for ATA or anti-Th/To antibodies has been linked to development of ILD in SSc^[27-30].

As described above, pulmonary hypertension can occur *de novo* (usually in lcSSc) or consequent to ILD. Pulmonary function testing may show a disproportionate reduction in TLCO (diffusion capacity for carbon monoxide) compared to FVC, and a ratio of percentage predicted FVC to percentage predicted TLCO of greater than 1.6 has been proposed as a screening tool for further evaluation regarding PH^[31]. Transthoracic Doppler echocardiography shows elevated right sided pressures, with a right ventricular systolic pressure (RVSP) of greater than 40 mmHg proposed to diagnose pulmonary hypertension^[31]. Notably, resting pressures may be normal and right sided pressures may only be elevated during exercise, when the patient becomes short of breath. An elevation of RVSP should be confirmed with a right heart catheterization to document pulmonary arterial pressures, as well as to assess responsiveness of right sided pressures to calcium channel blockers^[31]. Apart from PH, SSc can affect the heart due to fibrosis involving the conduction system (manifesting as conduction blocks, paroxysmal atrial tachycardia or rarely ventricular arrhythmias), myocardium (diastolic dysfunction, myocarditis) or pericardium^[31]. Usually pericardial effusions are mild; moderate to severe symptomatic effusions portend a grave prognosis with increased mortality at 1 year. Cardiac involvement accounts for a third of deaths associated with SSc^[31].

SSc involves much of the gastrointestinal system from the mouth to the anal canal. Luminal effects of the disease process are usually more common and symptomatic than effects on the hepatobiliary system and pancreas. The gastrointestinal manifestations add considerably to disease related morbidity^[32]. About half the patients affected are symptomatic, while a vast majority has asymptomatic disease^[32].

The clinical features and principles of management revolve upon the pathogenesis and site of disease. Like the skin, the GI tract also faces dysfunction of the small blood vessels producing ischemia and fibroblast proliferation producing collagen deposition. However, as a general rule throughout the lumen, smooth muscle dysfunction is the mechanism more relevant to production of symptoms^[32]. Smooth muscle pathology in SSc goes through "stages": An early stage of neural dysfunction which produces smooth muscle "paresis" and dysmotility. The reason of the neural dysfunction is under debate but has been postulated to be an autoimmune process^[33]. In this stage, the smooth muscle itself is not weak and therefore may be amenable to prokinetic medications. The later stage constitutes one of smooth muscle atrophy, which does not respond much to drugs. The absorptive surface - the villi- are usually unaffected^[33].

Involvement of the esophagus is usually the most clinically evident GI manifestation. The lower esophagus is more affected than the upper^[34]. Symptoms of acid reflux are common when the lower esophageal sphincter is incompetent as a result of smooth muscle dysfunction. On the other hand, dysphagia may be seen in patients with diffuse esophageal spasm. In a patient with prominent regurgitation, disappearance of heartburn and a new onset dysphagia may herald a stricture forming in the area chronically exposed to acid^[34]. Lower esophageal manometry is a sensitive investigation and has a role in diagnostic dilemmas^[34]. Management involves Proton pump inhibitors in reflux disease; calcium channel blockers are best avoided. Strictures are usually amenable to endoscopic dilatation. An unusual manifestation in the esophagus is "esophageal Raynaud's" which refers to cold- induced vessel vasospasm producing pain^[34].

Gastric involvement is rarely symptomatic. Patients may have ectasia of the vessels (GAVE) which can cause blood loss and anemia. The patient may present with functional worsening of respiratory status. Small intestinal disease is mainly because of abnormal electrical activity in the smooth muscles. Patients present with abdominal pain which occurs due to stasis and intestinal dilatation due to ineffective peristalsis^[35]. A smaller number of patients present with symptoms suggestive of malabsorption- steatorrhea, diarrhea and weight loss. This is seen mainly in patients with bacterial overgrowth in dilated segments, possibly due to bacterial interference in micelle formation^[36]. While radiography with luminal contrast demonstrates dilated intestinal loops, a positive glucose H₂ breath test in a patient with chronic diarrhea suffices to make a diagnosis of SIBO^[37]. Treatment entails rotational antibiotics- commonly used regimens include trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin-clavulanate. Liver disease is relatively rare and represents an overlap phenomenon; usually with primary biliary cirrhosis. However, the prognosis is better than PBC and rarely progresses to end-stage liver disease^[38]. Often, simple modes of treatment provide considerable symptomatic relief such as facial exercise in tight mouth and dietary modifications in amount and timings of meals^[38].

Renal involvement is life threatening in SSc, and goes by the eponym of SRC. Typically, SRC occurs on a background of diffuse cutaneous disease^[39,40]. Presence of antibodies to RNA Polymerase III or treatment with steroids (greater than 15 mg prednisolone equivalent daily) increases the risk of developing SRC. The pathogenesis involves endothelial injury in the renal microvasculature, resulting in platelet aggregation and thrombotic microangiopathy with concomitant obliterative vasculopathy^[39,40]. Reduction in renal blood flow causes hyperreninemic hyperaldosteronism, resulting in hypertension, creatinine elevation and acute kidney injury. A rise of blood pressure greater than 20% above the baseline should ring the warning bells in patients with SSc, although in up to 20%, SRC can be

normotensive^[39,40]. Urinalysis shows proteinuria with or without hematuria and casts. Peripheral smear shows thrombocytopenia with fragmented red cells resulting from microangiopathy. A few decades back, SRC was associated with a mortality of greater than 80% at 1 year and a high proportion of dialysis dependence^[39,40]. The advent of angiotensin converting enzyme (ACE) inhibitors has revolutionized the therapy of SRC, with greater than 80% survival at 3 years. ACE inhibitors should be started immediately when SRC is suspected, and supportive care provided with maintenance of electrolyte balance and renal replacement therapy if needed^[39,40]. An initial rise in serum creatinine may occur on starting ACE inhibitors in such patients; however this should not dissuade further use of these agents and they should rather be continued with caution. Often, patients with SRC appropriately treated with ACE inhibitors regain baseline renal function by 6 to 18 mo^[39,40]. In addition to SRC, patients with SSc who develop renal impairment may do so due to glomerulonephritis resulting from overlap with lupus, or pauci-immune glomerulonephritis resulting from overlap with ANCA vasculitis. The clinician needs to have a high index of suspicion to diagnose appropriately such overlap. Such scenarios should be suspected in the presence of active urinary sediments with serologic evidence of lupus or ANCA-associated vasculitis and require a renal biopsy for diagnosis^[39,40]. They should be treated with immunosuppression as in the context of lupus or vasculitis^[39,40].

Musculoskeletal involvement may be in the form of tendon friction rubs, which are usually felt in the long flexor and extensor tendons around the wrist or anterior compartment tendons of the leg^[12]. They portend a grave prognosis with increased risk of subsequent SRC. Patients can have a symmetric inflammatory polyarthritis of upper and lower limbs affecting small and large joints, treated in the same way as inflammatory arthritis in the context of rheumatic diseases. There can be myositis, either clinically evident as neck, trunk and proximal weakness, or subclinical with only muscle enzyme (creatinine phosphokinase, lactate dehydrogenase, aspartate aminotransferase or alanine aminotransferase) elevation and electromyographic/biopsy evidence of inflammatory myositis^[12]. Such patients with polymyositis-scleroderma overlap usually have antibodies to PM-Scl, and an overall better prognosis. Long standing SSc can result in muscle and joint contractures which are a major cause of morbidity^[12].

A proportion of patients with SSc may not have skin tightening (systemic sclerosis sine scleroderma). Such patients tend to be male and have less severe digital ulcers and telangiectasias^[23]. Almost 80% have oesophageal dysmotility and more than half of these patients have evidence of interstitial lung disease^[23].

OUTCOME MEASURES

Health related quality of life in patients with SSc can

be assessed using the SF-36 questionnaire and Health assessment questionnaire-disability index^[41]. A modified version of the HAQ has been devised for patients with SSc (Scleroderma HAQ - SHAQ) and includes visual analog scales (VAS) for 5 domains - general health, Raynaud's, digital ulcers, dyspnea and gastrointestinal manifestations. These are rated on a scale of 0-15 and normalized to the nearest whole number between 0 and 3 to facilitate inclusion in the HAQ^[41]. Other tools used are the Patient Reported Outcome Measures Information System and United Kingdom functional scale^[41].

Measures of hand involvement include finger-to-distal palmar crease distance, an easily measurable index reflecting severity of impairment of hand function. Quantitative scales like Cochin Hand Mobility Scale and Hand Mobility in Scleroderma Scale are generally used in the setting of clinical trials^[42,43]. Oral involvement in the setting of SSc (limited mouth opening, dryness resulting from sicca syndrome) can be quantified using the Mouth Handicap in SSc scale^[44]. Pulmonary hypertension is quantified by right heart catheterization to measure pulmonary arterial pressures or measuring RVSP on transthoracic Doppler echocardiogram. Functional limitation due to the same can be assessed using the 6-min walk test and Borg dyspnea scale. Interstitial lung disease is measured using extent of involvement on HRCT thorax, VAS for dyspnea (as a component of SHAQ) and Mahler transitional dyspnea index. Severity of gastrointestinal involvement can be measured in day-to-day clinical practice using the VAS for gastrointestinal involvement as a component of the SHAQ, and in a clinical trial setting using the detailed questionnaire devised by the University College of Los Angeles (UCLA SCTC GIT 2.0). RP is measured by documenting frequency and severity of Raynaud's attacks, documenting new-onset digital ulcers, VAS for Raynaud's on the SHAQ and the Raynaud's Condition Score (RCS)^[41].

MANAGEMENT

The management of SSc shall be considered under the various subheadings regarding management of Raynaud's, ILD, PH, skin fibrosis and gastrointestinal involvement.

RP AND DIGITAL ULCERS

RP and digital ulcers are the most dramatic features of SSc, and often the most distressing. They account for significant morbidity in these patients. Hence management of RP in SSc is an area of active research. Dihydropyridine calcium channel blocker nifedipine (10-20 mg three times a day) has been proven efficacious in management of RP in a meta-analysis^[45]. Angiotensin receptor blockade with losartan (50 mg/d) has also been proven in RCTs to be comparable to nifedipine for this indication^[46]. Intravenous iloprost (0.5-3 ng/kg per minute continuous infusion for 3-5 d,

repeated at intervals of 6-8 wk) has shown efficacy in improving RP as well as preventing new digital ulcers in randomized trials^[47], however its use is limited by need for hospitalization, cost and availability. Oral dual endothelin receptor blockade with Bosentan (62.5-125 mg twice daily) has failed to improve RP but has shown efficacy in preventing onset of digital ulcers. However, it delayed the healing of existing digital ulcers^[48].

Our group has done pioneering work in studying the role of phosphodiesterase-5 (PDE-5) inhibition in RP associated with SSc^[49]. PDE-5 is a molecule involved in degradation of cyclic GMP (c-GMP), and its inhibition results in vasodilation due to persistence of action of c-GMP on the smooth muscle of the vasculature^[49]. We studied the role of oral tadalafil at a dose of 20 mg alternate day in refractory RP due to SSc, as add-on to prior therapy with nifedipine or losartan, in a cross-over randomized controlled trial design, and demonstrated efficacy in reduction of frequency and severity of Raynaud's attacks and improvement of RCS^[49]. Surprisingly, pre-existing digital ulcers healed quickly and it prevented development of new digital ulcers^[49]. A meta-analysis of PDE-5 inhibition for secondary Raynaud's (which included data from two trials done at our centre) concluded significant benefit in decreasing frequency and severity of Raynaud's attacks as well as improvement in RCS^[50]. These findings have reflected a change in clinical practice regarding the management of SSc-related RP, with the recent guidelines from the Scleroderma Clinical Trials Consortium (SCTC) and CSRG recommending PDE-5 inhibition as a second line therapy for this indication failing initial therapy with calcium channel blockade^[51]. In our experience, use of PDE-5 inhibitors has significantly reduced morbidity due to RP and digital ulcers in our patients with SSc, especially during the winter months.

INTERSTITIAL LUNG DISEASE

SSc-associated ILD is a major cause of morbidity and mortality. Randomized trial evidence on this field is sparse. Two landmark trials published in 2006 explored the role of cyclophosphamide in SSc-ILD. The Scleroderma Lung Study compared oral cyclophosphamide (at a dose up to 2 mg/kg) for 1 year vs placebo in patients with SSc-ILD with FVC less than 70% and HRCT evidence of fibrosis^[52]. There was a small (2.5%) improvement in FVC on oral cyclophosphamide compared with a worsening on placebo therapy. In the subset with dcSSc, improvement in skin thickening was also demonstrated. Both groups did not differ significantly with respect to adverse events^[52]. This effect was maintained until 18 mo and was lost by 24 mo in the absence of further immunosuppression, suggesting need for maintenance immunosuppression therapy^[53]. Another study compared the role of intravenous cyclophosphamide at monthly doses of 600 mg/m² for 6 mo with oral prednisolone (20 mg alternate day) followed by azathioprine with placebo in SSc-ILD. Although the

findings did not reach statistical significance, there was a definite improvement of FVC by 4% in the group receiving intravenous cyclophosphamide^[54]. A comparison of oral cyclophosphamide vs mycophenolate mofetil in SSc-ILD is currently under study (Scleroderma Lung Study II - clinicaltrials.gov identifier NCT00883129). A recent publication from the EUSTAR group demonstrated potential benefit of rituximab in preventing progression of lung fibrosis in SSc based on retrospective data^[55].

PDE-5 inhibition, in addition to vasodilation, has also shown a role in improving endothelial cell dysfunction and favorably affecting vascular remodeling in animal models of pulmonary hypertension. Also effects in decreasing activation of TGF- β activation and ameliorating fibrosis in bleomycin-induced pulmonary fibrosis have been reported^[56,57]. This led us to hypothesize whether PDE-5 inhibition can be a therapeutic modality in SSc-ILD. A recently-concluded double-blind, randomized placebo controlled trial of tadalafil 20 mg every alternate day vs placebo in SSc-ILD conducted at our centre showed significant improvement in patient-reported breathing scale, and a trend towards improvement in pulmonary function, breathing VAS and physician-assessed breathing scale (Abstract number 1679, ACR Annual Conference 2014)^[58]. These promising results suggest potential use of PDE-5 inhibition in SSc-ILD.

Pulmonary hypertension

Since most patients with SSc-related PH have poor response to calcium channel blockers during right heart catheterization, the same are not recommended for PH in SSc^[59]. Endothelin-1 is a key molecule identified in the pathogenesis of vasculopathy in SSc^[12]. Randomized controlled trials support use of non-selective endothelin receptor antagonist bosentan (at doses varying from 62.5 to 250 mg twice a day)^[60,61] and the selective endothelin receptor A antagonist sitaxentan (at doses from 50 to 300 mg once a day)^[60,62,63] in patients in SSc-associated PH. Newer oral endothelin dual receptor antagonist (macitentan) at doses of 3 or 10 mg od was found effective in connective-tissue disease-related pulmonary hypertension^[64]. PDE-5 inhibitors have been widely used in treatment of PH. Shorter acting PDE-5 inhibitor sildenafil (at doses of 20, 40 or 80 mg thrice daily or 50 mg twice or thrice daily) has been proven efficacious in treatment of PH in the setting of SSc^[65,66]. The disadvantage of short half life and hence frequent administration of sildenafil is overcome by using tadalafil (t_{1/2} 17.5 h) at a dose of 40 mg daily, which has shown efficacy in SSc-related PH^[67]. In patients with NYHA Class *de novo* dyspnea (breathlessness at rest), intravenous epoprostenol therapy has been demonstrated to cause significant symptom relief. However its use is limited by need for continuous intravenous administration and rebound worsening on sudden withdrawal of therapy^[68].

Skin fibrosis

Unfortunately, medical therapy for skin fibrosis has not

been effective. Studies on skin tightening in response to therapy have to be interpreted with caution due to the fact that skin tightening spontaneously resolves in a majority of patients with time. Studies on use of methotrexate have provided conflicting data^[69,70]. However the EULAR recommendations mention methotrexate as a possible option for skin involvement in SSc^[71]. Although cyclophosphamide, azathioprine, mycophenolate mofetil and cyclosporine have been reported to benefit skin tightening in SSc, isolated skin involvement is seldom an indication for their clinical use^[71]. Recent studies have proposed a role for B-cell depletion therapy for reduction of skin involvement in SSc, however results from anecdotal reports and small case series has been conflicting^[72].

Gastrointestinal involvement

Dryness of mouth is managed using sugar-free chewing gums, advise regarding oral hygiene, frequent brushing of teeth (including after meals), taking frequent sips of water and use of parasympathomimetics like pilocarpine and cevimeline. Patients with restricted mouth opening are advised to take small frequent, semisolid, energy-rich meals^[32]. Esophageal dysmotility is managed in addition by use of proton pump inhibitors to reduce acid secretion in the stomach and prokinetic agents like metoclopramide, domperidone and itopride. Intestinal small bowel overgrowth is managed by use of rotational courses of antibiotics like quinolones^[32].

Recent studies have shown a beneficial role of hematopoietic stem cell transplant in early severe SSc compared to placebo. The recent Autologous Stem Cell Transplantation International Scleroderma trial^[73] showed that although autologous hematopoietic stem cell transplant was associated with greater mortality at 1 year, longer term follow up at 5.8 years showed a survival benefit compared to intravenous cyclophosphamide. The trial investigators recommended use of less intense conditioning regimens in future studies to attempt reduction of the early mortality.

Despite advances in understanding of pathogenesis and early diagnosis and interventions, outcomes have not changed overall in SSc in the last 40 years, with a still unacceptably high standardized mortality rate of 3.5^[74]. Cardiac and pulmonary diseases remain major causes of death^[74].

CONCLUSION

With active research ongoing with respect to pathogenesis and newer emerging therapeutic modalities, scleroderma is no more an orphan disease. PDE-5 inhibitors and endothelin receptor antagonists are emerging as drugs with substantial benefit in management of SSc. The day does not seem far when there will be an efficacious disease-modifying agent for SSc.

REFERENCES

1 Katsumoto TR, Whitfield ML, Connolly MK. The pathogenesis

of systemic sclerosis. *Annu Rev Pathol* 2011; **6**: 509-537 [PMID: 21090968 DOI: 10.1146/annurev-pathol-011110-130312]

2 Tanaka S, Suto A, Ikeda K, Sanayama Y, Nakagomi D, Iwamoto T, Suzuki K, Kambe N, Matsue H, Matsumura R, Kashiwakuma D, Iwamoto I, Nakajima H. Alteration of circulating miRNAs in SSc: miR-30b regulates the expression of PDGF receptor β . *Rheumatology* (Oxford) 2013; **52**: 1963-1972 [PMID: 23893664 DOI: 10.1093/rheumatology/ket254]

3 Zhou X, Lee JE, Arnett FC, Xiong M, Park MY, Yoo YK, Shin ES, Reveille JD, Mayes MD, Kim JH, Song R, Choi JY, Park JA, Lee YJ, Lee EY, Song YW, Lee EB. HLA-DPB1 and DPB2 are genetic loci for systemic sclerosis: a genome-wide association study in Koreans with replication in North Americans. *Arthritis Rheum* 2009; **60**: 3807-3814 [PMID: 19950302 DOI: 10.1002/art.24982]

4 Radstake TR, Gorlova O, Rueda B, Martin JE, Alizadeh BZ, Palomino-Morales R, Coenen MJ, Vonk MC, Voskuyl AE, Schuerwegh AJ, Broen JC, van Riel PL, van 't Slot R, Italiaander A, Ophoff RA, Riemekasten G, Hunzelmann N, Simeon CP, Ortego-Centeno N, González-Gay MA, González-Escribano MF, Airo P, van Laar J, Herrick A, Worthington J, Hesselstrand R, Smith V, de Keyser F, Houssiau F, Chee MM, Madhok R, Shiels P, Westhovens R, Kreuter A, Kiener H, de Baere E, Witte T, Padykov L, Klareskog L, Beretta L, Scorza R, Lie BA, Hoffmann-Vold AM, Carreira P, Varga J, Hinchcliff M, Gregersen PK, Lee AT, Ying J, Han Y, Weng SF, Amos CI, Wigley FM, Hummers LK, Nelson JL, Agarwal SK, Assassi S, Gourh P, Tan FK, Koeleman BP, Arnett FC, Martin J, Mayes MD. Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus. *Nat Genet* 2010; **42**: 426-429 [PMID: 20383147 DOI: 10.1038/ng.565]

5 Allanore Y, Saad M, Dieudé P, Avouac J, Distler JH, Amouyel P, Matucci-Cerinic M, Riemekasten G, Airo P, Melchers I, Hachulla E, Cusi D, Wichmann HE, Wipff J, Lambert JC, Hunzelmann N, Tiev K, Caramaschi P, Diot E, Kowal-Bielecka O, Valentini G, Mouthon L, Czirájk L, Damjanov N, Salvi E, Conti C, Müller M, Müller-Ladner U, Riccieri V, Ruiz B, Cracowski JL, Letenneur L, Dupuy AM, Meyer O, Kahan A, Munnich A, Boileau C, Martinez M. Genome-wide scan identifies TNIP1, PSORS1C1, and RHOB as novel risk loci for systemic sclerosis. *PLoS Genet* 2011; **7**: e1002091 [PMID: 21750679 DOI: 10.1371/journal.pgen.1002091]

6 Mayes MD, Bossini-Castillo L, Gorlova O, Martin JE, Zhou X, Chen WV, Assassi S, Ying J, Tan FK, Arnett FC, Reveille JD, Guerra S, Teruel M, Carmona FD, Gregersen PK, Lee AT, López-Isac E, Ochoa E, Carreira P, Simeón CP, Castellví I, González-Gay MÁ, Zhenakova A, Padyukov L, Alarcón-Riquelme M, Wijmenga C, Brown M, Beretta L, Riemekasten G, Witte T, Hunzelmann N, Kreuter A, Distler JH, Voskuyl AE, Schuerwegh AJ, Hesselstrand R, Nordin A, Airó P, Lunardi C, Shiels P, van Laar JM, Herrick A, Worthington J, Denton C, Wigley FM, Hummers LK, Varga J, Hinchcliff ME, Baron M, Hudson M, Pope JE, Furst DE, Khanna D, Phillips K, Schiopu E, Segal BM, Molitor JA, Silver RM, Steen VD, Simms RW, Lafyatis RA, Fessler BJ, Frech TM, Alkassab F, Docherty P, Kaminska E, Khalidi N, Jones HN, Markland J, Robinson D, Broen J, Radstake TR, Fonseca C, Koeleman BP, Martin J. Immunochip analysis identifies multiple susceptibility loci for systemic sclerosis. *Am J Hum Genet* 2014; **94**: 47-61 [PMID: 24387989 DOI: 10.1016/j.ajhg.2013.12.002]

7 Broen JC, Radstake TR, Rossato M. The role of genetics and epigenetics in the pathogenesis of systemic sclerosis. *Nat Rev Rheumatol* 2014; **10**: 671-681 [PMID: 25136786 DOI: 10.1038/nrrheum.2014.128]

8 Zhu H, Luo H, Zuo X. MicroRNAs: their involvement in fibrosis pathogenesis and use as diagnostic biomarkers in scleroderma. *Exp Mol Med* 2013; **45**: e41 [PMID: 24052166 DOI: 10.1038/emmm.2013.71]

9 Steen SO, Iversen LV, Carlsen AL, Burton M, Nielsen CT, Jacobsen S, Heegaard NH. The circulating cell-free microRNA profile in systemic sclerosis is distinct from both healthy controls and systemic lupus erythematosus. *J Rheumatol* 2015; **42**: 214-221 [PMID: 25399392 DOI: 10.3899/jrheum.140502]

10 Gardner H, Shearstone JR, Bandaru R, Crowell T, Lynes M, Trojanowska M, Pannu J, Smith E, Jablonska S, Blaszczak M,

- Tan FK, Mayes MD. Gene profiling of scleroderma skin reveals robust signatures of disease that are imperfectly reflected in the transcript profiles of explanted fibroblasts. *Arthritis Rheum* 2006; **54**: 1961-1973 [PMID: 16736506]
- 11 **Yoshizaki A**, Iwata Y, Komura K, Hara T, Ogawa F, Muroi E, Takenaka M, Shimizu K, Hasegawa M, Fujimoto M, Sato S. Clinical significance of serum hyaluronan levels in systemic sclerosis: association with disease severity. *J Rheumatol* 2008; **35**: 1825-1829 [PMID: 18688912]
 - 12 **Gabrielli A**, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med* 2009; **360**: 1989-2003 [PMID: 19420368 DOI: 10.1056/NEJMra0806188]
 - 13 **Jordan S**, Chung J, Distler O. Preclinical and translational research to discover potentially effective antifibrotic therapies in systemic sclerosis. *Curr Opin Rheumatol* 2013; **25**: 679-685 [PMID: 24047603 DOI: 10.1097/01.bor.0000434598.51526.0e]
 - 14 Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; **23**: 581-590 [PMID: 7378088]
 - 15 **LeRoy EC**, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Rowell N, Wollheim F. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; **15**: 202-205 [PMID: 3361530]
 - 16 **LeRoy EC**, Medsger TA. Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; **28**: 1573-1576 [PMID: 11469464]
 - 17 **Matucci-Cerinic M**, Allanore Y, Czirjak L, Tyndall A, Müller-Ladner U, Denton C, Valentini G, Distler O, Fligelstone K, Tyrrel-Kennedy A, Farge D, Kowal-Bielecka O, van den Hoogen F, Cutolo M, Sampaio-Barros PD, Nash P, Takehara K, Furst DE. The challenge of early systemic sclerosis for the EULAR Scleroderma Trial and Research group (EUSTAR) community. It is time to cut the Gordian knot and develop a prevention or rescue strategy. *Ann Rheum Dis* 2009; **68**: 1377-1380 [PMID: 19674983 DOI: 10.1136/ard.2008.106302]
 - 18 **Lepri G**, Guiducci S, Bellando-Randone S, Giani I, Bruni C, Blagojevic J, Carnesecchi G, Radicati A, Pucciani F, Marco MC. Evidence for oesophageal and anorectal involvement in very early systemic sclerosis (VEDOSS): report from a single VEDOSS/EUSTAR centre. *Ann Rheum Dis* 2015; **74**: 124-128 [PMID: 24130266 DOI: 10.1136/annrheumdis-2013-203889]
 - 19 **Avouac J**, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, Miniati I, Tarner IH, Randone SB, Cutolo M, Allanore Y, Distler O, Valentini G, Czirjak L, Müller-Ladner U, Furst DE, Tyndall A, Matucci-Cerinic M. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. *Ann Rheum Dis* 2011; **70**: 476-481 [PMID: 21081523 DOI: 10.1136/ard.2010.136929]
 - 20 **van den Hoogen F**, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA, Carreira PE, Riemekasten G, Clements PJ, Denton CP, Distler O, Allanore Y, Furst DE, Gabrielli A, Mayes MD, van Laar JM, Seibold JR, Czirjak L, Steen VD, Inanc M, Kowal-Bielecka O, Müller-Ladner U, Valentini G, Veale DJ, Vonk MC, Walker UA, Chung L, Collier DH, Csuka ME, Fessler BJ, Guiducci S, Herrick A, Hsu VM, Jimenez S, Kahaleh B, Merkel PA, Sierakowski S, Silver RM, Simms RW, Varga J, Pope JE. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; **65**: 2737-2747 [PMID: 24122180 DOI: 10.1002/art.38098]
 - 21 **Alhajeri H**, Hudson M, Fritzler M, Pope J, Tatibouet S, Markland J, Robinson D, Jones N, Khalidi N, Docherty P, Kaminska E, Masetto A, Sutton E, Mathieu JP, Ligier S, Grodzicky T, LeClerc S, Thorne C, Gyger G, Smith D, Fortin PR, Larché M, Baron M. 2013 American College of Rheumatology/European League against rheumatism classification criteria for systemic sclerosis outperform the 1980 criteria: data from the Canadian Scleroderma Research Group. *Arthritis Care Res (Hoboken)* 2015; **67**: 582-587 [PMID: 25233870 DOI: 10.1002/acr.22451]
 - 22 **Mehra S**, Walker J, Patterson K, Fritzler MJ. Autoantibodies in systemic sclerosis. *Autoimmun Rev* 2013; **12**: 340-354 [PMID: 22743034 DOI: 10.1016/j.autrev.2012.05.011]
 - 23 **Marangoni RG**, Rocha LF, Del Rio AP, Yoshinari NH, Marques-Neto JF, Sampaio-Barros PD. Systemic sclerosis sine scleroderma: distinct features in a large Brazilian cohort. *Rheumatology (Oxford)* 2013; **52**: 1520-1524 [PMID: 23661427 DOI: 10.1093/rheumatology/ket163]
 - 24 **Furst DE**, Clements PJ, Steen VD, Medsger TA, Masi AT, D'Angelo WA, Lachenbruch PA, Grau RG, Seibold JR. The modified Rodnan skin score is an accurate reflection of skin biopsy thickness in systemic sclerosis. *J Rheumatol* 1998; **25**: 84-88 [PMID: 9458208]
 - 25 **Steen VD**, Medsger TA. Improvement in skin thickening in systemic sclerosis associated with improved survival. *Arthritis Rheum* 2001; **44**: 2828-2835 [PMID: 11762943]
 - 26 **Flavahan NA**. A vascular mechanistic approach to understanding Raynaud phenomenon. *Nat Rev Rheumatol* 2015; **11**: 146-158 [PMID: 25536485 DOI: 10.1038/nrrheum.2014.195]
 - 27 **Khanna D**, Furst DE, Allanore Y, Bae S, Bodukam V, Clements PJ, Cutolo M, Czirjak L, Denton CP, Distler O, Walker UA, Matucci-Cerinic M, Müller-Ladner U, Seibold JR, Singh M, Tyndall A. Twenty-two points to consider for clinical trials in systemic sclerosis, based on EULAR standards. *Rheumatology (Oxford)* 2015; **54**: 144-151 [PMID: 25125594 DOI: 10.1093/rheumatology/keu288]
 - 28 **Wells AU**. Interstitial lung disease in systemic sclerosis. *Presse Med* 2014; **43**: e329-e343 [PMID: 25217474 DOI: 10.1016/j.lpm.2014.08.002]
 - 29 **Nikpour M**, Baron M. Mortality in systemic sclerosis: lessons learned from population-based and observational cohort studies. *Curr Opin Rheumatol* 2014; **26**: 131-137 [PMID: 24441644 DOI: 10.1097/BOR.000000000000027]
 - 30 **Fan MH**, Feghali-Bostwick CA, Silver RM. Update on scleroderma-associated interstitial lung disease. *Curr Opin Rheumatol* 2014; **26**: 630-636 [PMID: 25191993 DOI: 10.1097/BOR.0000000000000111]
 - 31 **Parks JL**, Taylor MH, Parks LP, Silver RM. Systemic sclerosis and the heart. *Rheum Dis Clin North Am* 2014; **40**: 87-102 [PMID: 24268011 DOI: 10.1016/j.rdc.2013.10.007]
 - 32 **Thoua NM**, Bunce C, Brough G, Forbes A, Emmanuel AV, Denton CP. Assessment of gastrointestinal symptoms in patients with systemic sclerosis in a UK tertiary referral centre. *Rheumatology (Oxford)* 2010; **49**: 1770-1775 [PMID: 20530510 DOI: 10.1093/rheumatology/keq147]
 - 33 **Howe S**, Eaker EY, Sallustio JE, Peebles C, Tan EM, Williams RC. Antimicrobial neuronal antibodies in scleroderma. *J Clin Invest* 1994; **94**: 761-770 [PMID: 8040331]
 - 34 **Wehrauch TR**, Korting GW. Manometric assessment of oesophageal involvement in progressive systemic sclerosis, morphea and Raynaud's disease. *Br J Dermatol* 1982; **107**: 325-332 [PMID: 7115611]
 - 35 **Reinhardt JF**, Barry WF. Scleroderma of the small bowel. *Am J Roentgenol Radium Ther Nucl Med* 1962; **88**: 687-692 [PMID: 14491280]
 - 36 **Scudamore HH**, Green PA, Hofman HN, Rosevear JW, Tauxe WN. Scleroderma (progressive systemic sclerosis) of the small intestine with malabsorption. Evaluation of intestinal absorption and pancreatic function. *Am J Gastroenterol* 1968; **49**: 193-208 [PMID: 5647483]
 - 37 **Kaye SA**, Lim SG, Taylor M, Patel S, Gillespie S, Black CM. Small bowel bacterial overgrowth in systemic sclerosis: detection using direct and indirect methods and treatment outcome. *Br J Rheumatol* 1995; **34**: 265-269 [PMID: 7728404]
 - 38 **Rigamonti C**, Shand LM, Feudjo M, Bunn CC, Black CM, Denton CP, Burroughs AK. Clinical features and prognosis of primary biliary cirrhosis associated with systemic sclerosis. *Gut* 2006; **55**: 388-394 [PMID: 16150855]

- 39 **Steen VD.** Scleroderma renal crisis. *Rheum Dis Clin North Am* 2003; **29**: 315-333 [PMID: 12841297]
- 40 **Bose N, Chiesa-Vottero A, Chatterjee S.** Scleroderma renal crisis. *Semin Arthritis Rheum* 2014; Epub ahead of print [PMID: 25613774 DOI: 10.1016/j.semarthrit.2014.12.001]
- 41 **Pope J.** Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). *Arthritis Care Res* (Hoboken) 2011; **63** Suppl 11: S98-111 [PMID: 22588774 DOI: 10.1002/acr.20598]
- 42 **Lefevre-Colau MM, Poiraudau S, Fermanian J, Etchepare F, Alnot JY, Le Viet D, Leclercq C, Oberlin C, Bary F, Revel M.** Responsiveness of the Cochin rheumatoid hand disability scale after surgery. *Rheumatology* (Oxford) 2001; **40**: 843-850 [PMID: 11511751]
- 43 **Del Rosso A, Maddali-Bongi S, Sigismondi F, Miniati I, Bandinelli F, Matucci-Cerinic M.** The Italian version of the Hand Mobility in Scleroderma (HAMIS) test: evidence for its validity and reliability. *ClinExpRheumatol* 2010; **28**: S42-S47 [PMID: 21050544]
- 44 **Mouthon L, Rannou F, Bérezné A, Pagnoux C, Arène JP, Foïs E, Cabane J, Guillevin L, Revel M, Fermanian J, Poiraudau S.** Development and validation of a scale for mouth handicap in systemic sclerosis: the Mouth Handicap in Systemic Sclerosis scale. *Ann Rheum Dis* 2007; **66**: 1651-1655 [PMID: 17502364]
- 45 **Thompson AE, Shea B, Welch V, Fenlon D, Pope JE.** Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum* 2001; **44**: 1841-1847 [PMID: 11508437]
- 46 **Dziadzio M, Denton CP, Smith R, Howell K, Blann A, Bowers E, Black CM.** Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum* 1999; **42**: 2646-2655 [PMID: 10616013]
- 47 **Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells G, Silman A.** Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev* 2000; **(2)**: CD000953 [PMID: 10796395]
- 48 **Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, Wigley FM, Black CM, Fessler BJ, Merkel PA, Pope JE, Swiss NJ, Doyle MK, Hellmich B, Medsger TA, Morganti A, Kramer F, Korn JH, Seibold JR.** Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2011; **70**: 32-38 [PMID: 20805294 DOI: 10.1136/ard.2010.130658]
- 49 **Shenoy PD, Kumar S, Jha LK, Choudhary SK, Singh U, Misra R, Agarwal V.** Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheumatology* (Oxford) 2010; **49**: 2420-2428 [PMID: 20837499 DOI: 10.1093/rheumatology/keq291]
- 50 **Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL.** Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Ann Rheum Dis* 2013; **72**: 1696-1699 [PMID: 23426043 DOI: 10.1136/annrheumdis-2012-202836]
- 51 **Walker KM, Pope J.** Treatment of systemic sclerosis complications: what to use when first-line treatment fails--a consensus of systemic sclerosis experts. *Semin Arthritis Rheum* 2012; **42**: 42-55 [PMID: 22464314 DOI: 10.1016/j.semarthrit.2012.01.003]
- 52 **Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, Arriola E, Silver R, Strange C, Bolster M, Seibold JR, Riley DJ, Hsu VM, Varga J, Schraufnagel DE, Theodore A, Simms R, Wise R, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, Rothfield N, Metersky M.** Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; **354**: 2655-2666 [PMID: 16790698]
- 53 **Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, Goldin J, Arriola E, Strange C, Bolster MB, Seibold JR, Riley DJ, Hsu VM, Varga J, Schraufnagel D, Theodore A, Simms R, Wise R, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, Rothfield N, Metersky M, Khanna D, Li N, Li G.** Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med* 2007; **176**: 1026-1034 [PMID: 17717203]
- 54 **Hoyle RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, Roberts C, Desai S, Herrick AL, McHugh NJ, Foley NM, Pearson SB, Emery P, Veale DJ, Denton CP, Wells AU, Black CM, du Bois RM.** A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006; **54**: 3962-3970 [PMID: 17133610]
- 55 **Jordan S, Distler JH, Maurer B, Huscher D, van Laar JM, Allanore Y, Distler O.** Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Ann Rheum Dis* 2015; **74**: 1188-1194 [PMID: 24442885 DOI: 10.1136/annrheumdis-2013-204522]
- 56 **Yildirim A, Ersoy Y, Ercan F, Atukeren P, Gumustas K, Uslu U, Alican I.** Phosphodiesterase-5 inhibition by sildenafil citrate in a rat model of bleomycin-induced lung fibrosis. *PulmPharmacolTher* 2010; **23**: 215-221 [PMID: 19945540 DOI: 10.1016/j.pupt.2009.11.002]
- 57 **Shenoy P, Agarwal V.** Phosphodiesterase inhibitors in the management of autoimmune disease. *Autoimmun Rev* 2010; **9**: 511-515 [PMID: 20149898 DOI: 10.1016/j.autrev.2010.02.012]
- 58 **2014 ACR/ARHP Annual Meeting Abstract Supplement. *Arthritis Rheumatol* 2014; **66** Suppl 10: S1-S1402 [PMID: 25323628]**
- 59 **Mathai SC, Hassoun PM.** Therapy for pulmonary arterial hypertension associated with systemic sclerosis. *Curr Opin Rheumatol* 2009; **21**: 642-648 [PMID: 19667994 DOI: 10.1097/BOR.0b013e3283307dc8]
- 60 **Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galie N.** Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006; **47**: 2049-2056 [PMID: 16697324]
- 61 **Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G.** Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; **346**: 896-903 [PMID: 11907289]
- 62 **Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, McLaughlin V, Hill N, Tapson VF, Robbins IM, Zwicke D, Duncan B, Dixon RA, Frumkin LR.** Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004; **169**: 441-447 [PMID: 14630619]
- 63 **Langleben D, Brock T, Dixon R, Barst R.** STRIDE 1: effects of the selective ET(A) receptor antagonist, sitaxsentan sodium, in a patient population with pulmonary arterial hypertension that meets traditional inclusion criteria of previous pulmonary arterial hypertension trials. *J Cardiovasc Pharmacol* 2004; **44** Suppl 1: S80-S84 [PMID: 15838366]
- 64 **Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BK, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G.** Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; **369**: 809-818 [PMID: 23984728 DOI: 10.1056/NEJMoa1213917]
- 65 **Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G.** Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; **353**: 2148-2157 [PMID: 16291984]
- 66 **Kumar U, Sankalp G, Sreenivas V, Kaur S, Misra D.** Prospective, open-label, uncontrolled pilot study to study safety and efficacy of sildenafil in systemic sclerosis-related pulmonary artery hypertension and cutaneous vascular complications. *Rheumatol Int*

- 2013; **33**: 1047-1052 [PMID: 22833239 DOI: 10.1007/s00296-012-2466-5]
- 67 **Galiè N**, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L, Barst RJ. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; **119**: 2894-2903 [PMID: 19470885 DOI: 10.1161/CIRCULATIONAHA.108.839274]
- 68 **Badesch DB**, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jöbsis MM, Loyd JE, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin VV, Robbins IM, Groves BM, Shapiro S, Medsger TA. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000; **132**: 425-434 [PMID: 10733441]
- 69 **van den Hoogen FH**, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br J Rheumatol* 1996; **35**: 364-372 [PMID: 8624641]
- 70 **Pope JE**, Bellamy N, Seibold JR, Baron M, Ellman M, Carette S, Smith CD, Chalmers IM, Hong P, O'Hanlon D, Kaminska E, Markland J, Sibley J, Catoggio L, Furst DE. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001; **44**: 1351-1358 [PMID: 11407694]
- 71 **Kowal-Bielecka O**, Landewé R, Avouac J, Chwiesko S, Miniati I, Czirjak L, Clements P, Denton C, Farge D, Fligelstone K, Földvari I, Furst DE, Müller-Ladner U, Seibold J, Silver RM, Takehara K, Toth BG, Tyndall A, Valentini G, van den Hoogen F, Wigley F, Zulian F, Matucci-Cerinic M. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009; **68**: 620-628 [PMID: 19147617 DOI: 10.1136/ard.2008.096677]
- 72 **Lafyatis R**, Kissin E, York M, Farina G, Viger K, Fritzler MJ, Merkel PA, Simms RW. B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. *Arthritis Rheum* 2009; **60**: 578-583 [PMID: 19180481 DOI: 10.1002/art.24249]
- 73 **van Laar JM**, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, Schuerwegh AJ, Marijt EW, Vonk MC, Schattenberg AV, Matucci-Cerinic M, Voskuyl AE, van de Loosdrecht AA, Daikeler T, Kötter I, Schmalzing M, Martin T, Lioure B, Weiner SM, Kreuter A, Deligny C, Durand JM, Emery P, Machold KP, Sarrot-Reynauld F, Warnatz K, Adoue DF, Constans J, Tony HP, Del Papa N, Fassas A, Himsel A, Launay D, Lo Monaco A, Philippe P, Quéré I, Rich É, Westhovens R, Griffiths B, Saccardi R, van den Hoogen FH, Fibbe WE, Socié G, Gratwohl A, Tyndall A. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* 2014; **311**: 2490-2498 [PMID: 25058083 DOI: 10.1001/jama.2014.6368]
- 74 **Elhai M**, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* (Oxford) 2012; **51**: 1017-1026 [PMID: 21900368 DOI: 10.1093/rheumatology/ker269]

P- Reviewer: Ghatak S, Martinez-Lostao L

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Jiao XK



Complementary medicine use in rheumatology: A review

Woan H Wong, Anna E Litwic, Elaine M Dennison

Woan H Wong, Anna E Litwic, Elaine M Dennison, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, United Kingdom

Elaine M Dennison, Victoria University of Wellington, Wellington 6004, New Zealand

Author contributions: Wong WH performed literature search under the supervision of Dennison EM, Litwic AE drafted the manuscript; Dennison EM oversaw the project.

Conflict-of-interest statement: None to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Elaine M Dennison, MB, BChir, MA, MSc, PhD, FRCP, Professor, Honorary Consultant in Rheumatology, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Tremona Rd, Southampton SO16 6YD, United Kingdom. emd@mrcc.soton.ac.uk
Telephone: +44-23-80777624
Fax: +44-23-80704021

Received: November 27, 2014
Peer-review started: November 28, 2014
First decision: December 12, 2014
Revised: June 27, 2015
Accepted: July 29, 2015
Article in press: August 3, 2015
Published online: November 12, 2015

Abstract

Complementary and alternative medicine (CAM) use is increasing worldwide; specifically it appears that these

treatment modalities are popular among rheumatology patients. The most commonly reported CAM therapies are herbal medicines, homeopathy, chiropractic, acupuncture and reflexology. Despite high reported rates of CAM use, the number of patients disclosing use to their rheumatologists remains low. This review highlights rates of current CAM use in rheumatology in studies performed worldwide, and discusses potential reasons for nondisclosure of CAM use to clinicians.

Key words: Complementary medicine; Alternative medicine; Rheumatology; Arthritis; Acupuncture

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Complementary and alternative medicine is widely used among rheumatology patients, who often do not inform their consultants that they are using such therapies. This may reflect a fear that clinicians may not approve, or a lack of awareness that the information may be helpful in their management. Increased awareness of the issue, and better education of clinicians and patients is beneficial.

Wong WH, Litwic AE, Dennison EM. Complementary medicine use in rheumatology: A review. *World J Rheumatol* 2015; 5(3): 142-147 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v5/i3/142.htm> DOI: <http://dx.doi.org/10.5499/wjr.v5.i3.142>

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Complementary and alternative medicine (CAM) was defined by Ernst *et al*^[1] as "diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frame works of medicine" Although the terms "com-

Table 1 Usage of complementary and alternative medicine in European Countries^[17]

Treatment	Prevalence of reported use across Europe (%)
Herbal medicine	5.9-48.3
Homeopathy	2-27
Chiropractic	0.4-28.8
Acupuncture	0.44-23
Reflexology	0.4-21

plementary and alternative" are often used together, their meanings differ; according to the United States National Centre for Complementary and Alternative Medicine (NCCAM), "complementary" refers to using non-mainstream treatment alongside conventional medicine, to better cope with a health condition, whereas "alternative" means using non-mainstream treatment in place of conventional medicine to treat a health condition^[2]. A "complementary therapy" may provide a patient with an experience that is pleasant in itself, and improves the patient's ability to cope with a chronic health condition; as the term implies, these therapies are designed to be used alongside conventional therapy. By contrast, an "alternative" therapy is designed to be used in place of conventional treatment. Few studies have examined the mechanism of action of these treatments, although some researchers have postulated an effect on immune function, and invocation of the placebo effect. Many therapies discussed here can be used in either way; homeopathy, acupuncture, chiropractic and osteopathy have been used within either a "complementary" or "alternative" framework.

CAM is often classified into 3 groups: (1) professionally organised alternative therapies such as acupuncture, chiropractic, herbal medicine, homeopathy and osteopathy; (2) complementary therapies, such as aromatherapy, massage, yoga, meditation, hypnotherapy, Alexander technique, shiatsu, reflexology and counselling stress therapy; and (3) alternative disciplines, for example, traditional Chinese medicine, traditional Indian medicine (Ayurveda), anthroposophical medicine, naturopathy as well as crystal therapy, dowsing, iridology and kinesiology^[3].

Documentation of CAM use in rheumatology is important because of potential adverse consequences in some groups of rheumatology patients. For example, spinal manipulation applied by chiropractor therapists among rheumatoid arthritis (RA) patients with atlanto-axial instability may result in neurological complications^[4]. In addition, herbal medications used in CAM may interact with prescribed rheumatology medications^[5].

ROLE OF CAM IN RHEUMATOLOGY

There is some evidence to suggest efficacy of CAM in rheumatic conditions such as osteoarthritis (OA), RA and other types of arthritis^[6-11]. In a recent systematic review

that assessed the efficacy of CAM in the management of OA, capsaicin gel and S-adenosyl methionine were shown to be effective in improving pain in this group of patients^[7]. Another study suggested that acupuncture and massage therapy were effective in reduction of OA related pain^[6]. Finally, in other work administration of rosehip (herbal medicine) was associated with reductions in OA pain compared to placebo^[8]. Macfarlane *et al*^[9] recently undertook a study aimed to evaluate the evidence supporting or refuting CAM use in the treatment of RA and reported that borage seed oil and thunder god vine reduced symptoms in RA. Practising Iyengar yoga was shown by another group to have a beneficial effect on symptoms of RA^[10]. Acupuncture has been demonstrated to be efficacious in crystal arthritis^[11]. However, other studies have suggested that the evidence supporting the effectiveness of CAM in RA and OA is more doubtful^[12]. Hence the literature around the efficacy of CAM in rheumatology is hotly contested, and studies that consider CAM use are often advertised widely and hence more readily available to patients. The efficacy of CAM in rheumatology is not the focus of this review, which aims rather to highlight the widespread use of these therapies in rheumatology patients.

PREVALENCE AND PATTERNS OF CAM USE IN RHEUMATOLOGY

The prevalence of CAM use in the general population is high according to studies worldwide^[13-15]. The prevalence of CAM use is reported to be the lowest in England when compared to other European countries, United States, Australia and Japan^[16]. The top 5 most commonly reported CAM therapies in the European Union are: herbal medicines, homeopathy, chiropractic, acupuncture and reflexology (Table 1)^[17].

Specifically, CAM usage is popular in rheumatology^[18]. Several studies have suggested a high prevalence of CAM use in North America and Australia in rheumatology patients^[19-22]. The highest prevalence of CAM therapy use in rheumatology patients (94%) was reported in a study by Kronenfeld *et al*^[19]. The 3 most popular modalities reported in this study were topical treatments, dietary modification and supplementary vitamins. In another survey of 232 rheumatology patients in the United States, two thirds had used CAM^[20]. Chiropractic therapy was found to be the most popular and most helpful treatment modality. Patients who had OA were more likely to use CAM regularly. In another OA cohort of patients who were followed for 1 year, 44% of patients remained non-users throughout, whereas 12% started CAM, 22% maintained, and 22% stopped use of CAM^[21]. Equal numbers of patients started and stopped using electric stimulators and visiting chiropractors during the study period. Although patients most frequently started herbal remedies, dietary supplements and special diets, a similar number discontinued these therapies, suggesting that use of

Table 2 Reasons for not disclosing usage of complementary and alternative medicine to rheumatologists

Physician did not ask
Patient thought it unnecessary to talk about it
Patient feared negative response from physician
Patient had used CAM before seeing physician
Patient forgot to discuss

CAM: Complementary and alternative medicine.

CAM is often transitory. Another study of RA patients found that nutritional supplements and touch therapies (massage, acupuncture and acupressure) were the most widely used in this patient disease group, with mind body techniques more prevalent among younger patients^[22]. CAM modalities were found to be used in conjunction with mainstream conventional treatments in early as well as later stages of the disease. CAM usage is also popular among Canadian rheumatology patients; in a study of 235 rheumatology patients, 60% of them had ever used CAM remedies and 79% of these patients had used CAM remedies in the previous 12 mo. The study also found that 47% of these patients had tried at least one CAM before their first rheumatology consultation. Results from a nationwide survey in Canada demonstrated that 22% adults with arthritis over 20 years of age had used CAM^[23]. In this group chiropractic services were used most commonly (59.5%) followed by massage (48.5%), acupuncture (25%) and homeopathy (21%).

CAM is also used widely by rheumatology patients in the Middle East. Patients attending rheumatology clinics in Israel tended to use CAM more often compared to patients seen in primary care, internal medicine and other specialties^[24]; this study indicated that in Israel, CAM was used more frequently by patients with fibromyalgia (58%), in contrast to studies from other countries, where the most common rheumatological diagnoses associated with CAM use were RA and OA^[25-28]. In work from Eastern Europe, a study from Turkey reported that 76% ($n = 250$) patients with any form of arthritis used at least one CAM^[25]. Most of them used thermal therapy, similar to a comparable study from the United States^[29].

Finally, CAM use is also common in Australasia; in one Australian study 82% of RA patients, used more than one CAM after diagnosis and more than half of respondents were current users^[30]. The report suggested the most common CAMs used in Australia were dietary manipulation and use of copper bracelets. In contrast, studies in Asian countries suggest other therapies are commonly used. For example in India, Ayurveda and massage therapy were used most commonly (around 80%) in one survey^[28]. This may be because the Government of India strongly supports alternative therapies such as Ayurveda, Homeopathy, Siddha and Unani medicine and CAM practices and modern (allopathic) medicine in India run in parallel^[31]. Similar

observations have been made in Korea, where traditional oriental medical treatment is performed by certified Korea medical doctors and there is a wide acceptance of acupuncture as a basic treatment^[32]. By contrast, Japan has a lower prevalence of CAM use (approximately 35%). In Japan, dietary supplements, particularly ginger extracts were the most popular type of CAM^[33].

USERS OF CAM, PATIENTS' REASONS AND OBJECTIVES FOR USING CAM

There is a documented variation in the use of CAM among different socio-demographic groups. Women are more likely to use CAM than men^[21,23,24,27,29]. There are also differences according to age: middle aged people are most likely to use complementary therapies, while the youngest and oldest age groups are less likely to have done so^[23,25,27,29,34]. Ethnic background appears relevant in CAM usage among adults with arthritis; Caucasian individuals are more likely to use CAM than Blacks, Asians and Hispanics^[21,34,35]. In recent studies, the use of CAM was explored according to three socio-economic indicators. Researchers reported that the use of CAM increases significantly with income, and higher education in most western countries^[23,24,34]. This may be because medical insurance does not cover CAM, and hence low-income population groups may not be able to afford it^[24].

The aims of trying CAM in rheumatology patients is most commonly reported to be to reduce and control pain and stiffness^[20,27,36]. Similarly a wide range of reasons have been suggested for discontinuation of CAM therapy, with the lack of effectiveness and high cost of therapy being most common^[21]. A common source of information about CAM is by "word of mouth", *e.g.*, previous experiences from families, relatives, neighbours and friends^[24,25,27].

DISCLOSURE OF CAM USE TO RHEUMATOLOGISTS

The reported rate of patients disclosing CAM use to rheumatologists ranges from 28% to over 70%^[20,28,32,36-40]. Women are more likely to talk about CAM therapy than men^[37,38]. In one study, rheumatology patients diagnosed with fibromyalgia were more likely to discuss use of CAM with their physician^[20]. When asked directly, many patients suggest that they would welcome and greater involvement of their clinician in providing details of alternative practitioners when requested^[39].

REASONS FOR NOT DISCLOSING USAGE OF CAM TO RHEUMATOLOGISTS

There are various reasons documented for patients not disclosing their CAM use to clinicians (Table 2). Some patients are concerned about a possible negative

response from rheumatologists. This includes the fear that rheumatologists would not continue to provide health care to them or that the rheumatologist would disapprove of them using CAM. Patients may also want to avoid any conflict or embarrassment during their consultation, and may feel that non-disclosure would ensure this^[39,40]. Most rheumatologists do not ask specifically about CAM usage and this may give an impression that the disclosure of the use of CAM is not important in their health care treatment^[20,40]. Sleath *et al.*^[38] suggested that rheumatology patients were more likely to disclose CAM if the rheumatologists involved them in the decision-making process about their treatment and treatment goals.

ATTITUDES OF RHECUMATOLOGISTS TOWARDS CAM

A recent study suggested that physicians in the United Kingdom have a positive attitude towards some CAM modalities^[41]. Among a background prevalence of use of CAM ranging from 12.1% to 32%, 39% to 46% of physicians recommended using CAM.

Similarly, a national survey of rheumatologist in the United States showed that more than half of the respondents considered some CAM therapies to be beneficial and were at least moderately likely to recommend them to the patients^[42]. Female rheumatologists were significantly more likely than men to perceive common CAM therapies as beneficial. Rheumatologists born outside the United States had more favourable attitudes towards CAM overall. Out of 345 rheumatologists, 65% were "very" or "somewhat likely" to recommend body work, followed closely by meditation (64%). Only 10% of them would consider recommending an energy medicine modality, such as Reiki. This could reflect limited availability and experience of this therapy. Massage had the highest perceived benefits, followed by meditation. Acupuncture and spinal manipulation was thought to be either "very" or "moderately" beneficial, whilst 60% of the rheumatologists had indicated that glucosamine and/or chondroitin was not very or at all beneficial.

Another study looked at the referral patterns for 22 CAM therapies^[43]. It showed that half of physicians had referred patients for 8 of the therapies (*i.e.*, acupuncture, behavioural medicine, biofeedback, counselling/psychotherapy, dietary prescriptions, electromagnetic applications such as transcutaneous and percutaneous electrical nerve stimulation, exercise and massage). Counselling/psychotherapy and exercise headed the list of modalities which had been used by more than half of the rheumatologists. However other modalities including meditation, prayer and spiritual direction non-chiropractic, hypnotherapy, herbal medicine, music therapy, magnets, energetic healing and homeopathy were never used by 75% of physicians.

These findings were subsequently supported by a systematic review, which concluded that rheumatologists

in North America showed moderate acceptance towards some types of CAM, particularly body work and meditation practices^[44]. An overwhelming majority of them had recommended these therapies in the past and were willing to continue this practice. That review also indicated that energy medicine had the lowest perceived benefit and received least recommendations and referrals from rheumatologists. A large proportion of rheumatologists had reported no or minor clinical use of CAM therapies such as prayer, spiritual direction and herbal medicine. They believed that the efficacy of these modalities is poor and potentially even harmful.

CONCLUSION

CAM usage is substantially increasing worldwide. Despite high rates of use of CAM therapies the number of patients disclosing it to their rheumatologists is low. There is a need to promote disclosure, particularly with respect to over the counter preparations that may interact with physician prescribed medication.

REFERENCES

- 1 Ernst E, Resch KL, White AR. Complementary medicine. What physicians think of it: a meta-analysis. *Arch Intern Med* 1995; **155**: 2405-2408 [PMID: 7503598 DOI: 10.1001/archinte.1995.00430220059006]
- 2 Nation Center for Complementary and Integrative Health. Complementary, Alternative, or Integrative Health: What's In a Name? Available from: URL: <http://nccam.nih.gov/health/whatiscam>
- 3 Mills SY. Regulation in complementary and alternative medicine. *BMJ* 2001; **322**: 158-160 [PMID: 11159577 DOI: 10.1136/bmj.322.7279.158]
- 4 Beck RW, Holt KR, Fox MA, Hurtgen-Grace KL. Radiographic anomalies that may alter chiropractic intervention strategies found in a New Zealand population. *J Manipulative Physiol Ther* 2004; **27**: 554-559 [PMID: 15614242 DOI: 10.1016/j.jmpt.2004.10.008]
- 5 Holden W, Joseph J, Williamson L. Use of herbal remedies and potential drug interactions in rheumatology outpatients. *Ann Rheum Dis* 2005; **64**: 790 [PMID: 15834065 DOI: 10.1136/ard.2004.029991]
- 6 De Luigi AJ. Complementary and alternative medicine in osteoarthritis. *PM R* 2012; **4**: S122-S133 [PMID: 22632691 DOI: 10.1016/j.pmrj.2012.01.012]
- 7 De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ. Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. *Rheumatology* (Oxford) 2011; **50**: 911-920 [PMID: 21169345 DOI: 10.1093/rheumatology/keq379]
- 8 Christensen R, Bartels EM, Altman RD, Astrup A, Bliddal H. Does the hip powder of *Rosa canina* (rosehip) reduce pain in osteoarthritis patients?--a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 2008; **16**: 965-972 [PMID: 18407528 DOI: 10.1016/j.joca.2008.03.001]
- 9 Macfarlane GJ, El-Metwally A, De Silva V, Ernst E, Dowds GL, Moots RJ. Evidence for the efficacy of complementary and alternative medicines in the management of rheumatoid arthritis: a systematic review. *Rheumatology* (Oxford) 2011; **50**: 1672-1683 [PMID: 21652584 DOI: 10.1093/rheumatology/ker119]
- 10 Evans S, Moieni M, Taub R, Subramanian SK, Tsao JC, Sternlieb B, Zeltzer LK. Iyengar yoga for young adults with rheumatoid arthritis: results from a mixed-methods pilot study. *J Pain Symptom Manage* 2010; **39**: 904-913 [PMID: 20471550 DOI: 10.1016/j.jpain

- symman.2009.09.018]
- 11 **Lee WB**, Woo SH, Min BI, Cho SH. Acupuncture for gouty arthritis: a concise report of a systematic and meta-analysis approach. *Rheumatology* (Oxford) 2013; **52**: 1225-1232 [PMID: 23424263 DOI: 10.1093/rheumatology/ket013]
 - 12 **Ernst E**, Posadzki P. Complementary and alternative medicine for rheumatoid arthritis and osteoarthritis: an overview of systematic reviews. *Curr Pain Headache Rep* 2011; **15**: 431-437 [PMID: 21979101 DOI: 10.1007/s11916-011-0227-x]
 - 13 **Eisenberg DM**, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998; **280**: 1569-1575 [PMID: 9820257 DOI: 10.1001/jama.280.18.1569]
 - 14 **Featherstone C**, Godden D, Gault C, Emslie M, Took-Zozaya M. Prevalence study of concurrent use of complementary and alternative medicine in patients attending primary care services in Scotland. *Am J Public Health* 2003; **93**: 1080-1082 [PMID: 12835187 DOI: 10.2105/AJPH.93.7.1080]
 - 15 **Thomas KJ**, Coleman P, Nicholl JP. Trends in access to complementary or alternative medicines via primary care in England: 1995-2001 results from a follow-up national survey. *Fam Pract* 2003; **20**: 575-577 [PMID: 14507801 DOI: 10.1093/fampra/cmg514]
 - 16 **Hunt KJ**, Coelho HF, Wider B, Perry R, Hung SK, Terry R, Ernst E. Complementary and alternative medicine use in England: results from a national survey. *Int J Clin Pract* 2010; **64**: 1496-1502 [PMID: 20698902 DOI: 10.1111/j.1742-1241.2010.02484.x]
 - 17 **Eardley S**, Bishop FL, Prescott P, Cardini F, Brinkhaus B, Santos-Rey K, Vas J, von Ammon K, Hegyi G, Dragan S, Uehleke B, Fønnebo V, Lewith G. A systematic literature review of complementary and alternative medicine prevalence in EU. *Forsch Komplementmed* 2012; **19** Suppl 2: 18-28 [PMID: 23883941 DOI: 10.1159/000342708]
 - 18 **Ernst E**. Usage of complementary therapies in rheumatology: a systematic review. *Clin Rheumatol* 1998; **17**: 301-305 [PMID: 9776112 DOI: 10.1007/BF01451009]
 - 19 **Kronenfeld JJ**, Wasner C. The use of unorthodox therapies and marginal practitioners. *Soc Sci Med* 1982; **16**: 1119-1125 [PMID: 7112162 DOI: 10.1016/0277-9536(82)90114-9]
 - 20 **Rao JK**, Mihaliak K, Kroenke K, Bradley J, Tierney WM, Weinberger M. Use of complementary therapies for arthritis among patients of rheumatologists. *Ann Intern Med* 1999; **131**: 409-416 [PMID: 10498556 DOI: 10.7326/0003-4819-131-6-199909210-00003]
 - 21 **Rao JK**, Kroenke K, Mihaliak KA, Grambow SC, Weinberger M. Rheumatology patients' use of complementary therapies: results from a one-year longitudinal study. *Arthritis Rheum* 2003; **49**: 619-625 [PMID: 14558046 DOI: 10.1002/art.11377]
 - 22 **Efthimiou P**, Kukar M, Mackenzie CR. Complementary and alternative medicine in rheumatoid arthritis: no longer the last resort! *HSS J* 2010; **6**: 108-111 [PMID: 19784703 DOI: 10.1007/s11420-009-9133-8]
 - 23 **Fautrel B**, Adam V, St-Pierre Y, Joseph L, Clarke AE, Penrod JR. Use of complementary and alternative therapies by patients self-reporting arthritis or rheumatism: results from a nationwide canadian survey. *J Rheumatol* 2002; **29**: 2435-2441 [PMID: 12415605]
 - 24 **Breuer GS**, Orbach H, Elkayam O, Berkun Y, Paran D, Mates M, Neshet G. Use of complementary and alternative medicine among patients attending rheumatology clinics in Israel. *Isr Med Assoc J* 2006; **8**: 184-187 [PMID: 16599054]
 - 25 **Unsal A**, Gözümlü S. Use of complementary and alternative medicine by patients with arthritis. *J Clin Nurs* 2010; **19**: 1129-1138 [PMID: 20492058 DOI: 10.1111/j.1365-2702.2009.03111.x]
 - 26 **Alvarez-Hernández E**, César Casasola-Vargas J, Lino-Pérez L, Burgos-Vargas R, Vázquez-Mellado J. [Complementary and alternative medicine in patients attending a rheumatology department for the first time. Analysis of 800 patients]. *Reumatol Clin* 2006; **2**: 183-189 [PMID: 21794326 DOI: 10.1016/S1699-258X(06)73044-3]
 - 27 **Kim HA**, Seo YI. Use of complementary and alternative medicine by arthritis patients in a university hospital clinic serving rheumatology patients in Korea. *Rheumatol Int* 2003; **23**: 277-281 [PMID: 14634787 DOI: 10.1007/s00296-003-0311-6]
 - 28 **Jadhav MP**, Jadhav PM, Shelke P, Sharma Y, Nadkar M. Assessment of use of complementary alternative medicine and its impact on quality of life in the patients attending rheumatology clinic, in a tertiary care centre in India. *Indian J Med Sci* 2011; **65**: 50-57 [PMID: 23196313 DOI: 10.4103/0019-5359.103961]
 - 29 **Tamhane A**, McGwin G, Redden DT, Hughes LB, Brown EE, Westfall AO, Conn DL, Jonas BL, Smith EA, Brasington RD, Moreland LW, Bridges SL, Callahan LF. Complementary and alternative medicine use in African Americans with rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2014; **66**: 180-189 [PMID: 23983105 DOI: 10.1002/acr.22148]
 - 30 **Kestin M**, Miller L, Littlejohn G, Wahlqvist M. The use of unproven remedies for rheumatoid arthritis in Australia. *Med J Aust* 1985; **143**: 516-518 [PMID: 4069052]
 - 31 **Subbarayappa BV**. Siddha medicine: an overview. *Lancet* 1997; **350**: 1841-1844 [PMID: 9428267 DOI: 10.1016/S0140-6736(97)04223-2]
 - 32 **Lee MS**, Lee MS, Yang CY, Lee SI, Joo MC, Shin BC, Yoo WH, Shin YI. Use of complementary and alternative medicine by rheumatoid arthritis patients in Korea. *Clin Rheumatol* 2008; **27**: 29-33 [PMID: 17541497 DOI: 10.1007/s10067-007-0646-6]
 - 33 **Kajiyama H**, Akama H, Yamanaka H, Shoji A, Matsuda Y, Tanaka E, Nakajima A, Terai C, Hara M, Tomatsu T, Saitoh T, Kamatani N. One third of Japanese patients with rheumatoid arthritis use complementary and alternative medicine. *Mod Rheumatol* 2006; **16**: 355-359 [PMID: 17164996 DOI: 10.3109/s10165-006-0521-3]
 - 34 **Anderson DL**, Shane-McWhorter L, Crouch BI, Andersen SJ. Prevalence and patterns of alternative medication use in a university hospital outpatient clinic serving rheumatology and geriatric patients. *Pharmacotherapy* 2000; **20**: 958-966 [PMID: 10939557 DOI: 10.1592/phco.20.11.958.35257]
 - 35 **Hoerster KD**, Butler DA, Mayer JA, Finlayson T, Gallo LC. Use of conventional care and complementary/alternative medicine among US adults with arthritis. *Prev Med* 2012; **54**: 13-17 [PMID: 21889528 DOI: 10.1016/j.ypmed.2011.08.023]
 - 36 **Klingberg E**, Wallerstedt SM, Torstenson T, Häwi G, Forsblad-d'Elia H. The use of complementary and alternative medicine in outpatients with inflammatory rheumatic diseases in Sweden. *Scand J Rheumatol* 2009; **38**: 472-480 [PMID: 19922024 DOI: 10.3109/03009740902994280]
 - 37 **Wallen GR**, Brooks AT. To Tell or Not to Tell: Shared Decision Making, CAM Use and Disclosure Among Underserved Patients with Rheumatic Diseases. *Integr Med Insights* 2012; **7**: 15-22 [PMID: 23071389 DOI: 10.4137/IMI.S10333]
 - 38 **Sleath B**, Callahan LF, Devellis RF, Beard A. Arthritis patients' perceptions of rheumatologists' participatory decision-making style and communication about complementary and alternative medicine. *Arthritis Rheum* 2008; **59**: 416-421 [PMID: 18311753 DOI: 10.1002/art.23307]
 - 39 **Visser GJ**, Peters L, Rasker JJ. Rheumatologists and their patients who seek alternative care: an agreement to disagree. *Br J Rheumatol* 1992; **31**: 485-490 [PMID: 1628171 DOI: 10.1093/rheumatology/31.7.485]
 - 40 **Robinson A**, McGrail MR. Disclosure of CAM use to medical practitioners: a review of qualitative and quantitative studies. *Complement Ther Med* 2004; **12**: 90-98 [PMID: 15561518 DOI: 10.1016/j.ctim.2004.09.006]
 - 41 **Posadzki P**, Watson LK, Alotaibi A, Ernst E. Prevalence of use of complementary and alternative medicine (CAM) by patients/consumers in the UK: systematic review of surveys. *Clin Med* 2013; **13**: 126-131 [PMID: 23681857 DOI: 10.7861/clinmedicine.13-2-126.]
 - 42 **Manek NJ**, Crowson CS, Ottenberg AL, Curlin FA, Kaptchuk TJ, Tilburt JC. What rheumatologists in the United States think of complementary and alternative medicine: results of a national survey. *BMC Complement Altern Med* 2010; **10**: 5 [PMID: 20811753 DOI: 10.1186/1475-2875-10-5]

20109215 DOI: 10.1186/1472-6882-10-5]

- 43 **Berman BM**, Bausell RB, Lee WL. Use and referral patterns for 22 complementary and alternative medical therapies by members of the American College of Rheumatology: results of a national survey. *Arch Intern Med* 2002; **162**: 766-770 [PMID: 11926849

DOI: 10.1001/archinte.162.7.766]

- 44 **Grainger R**, Walker J. Rheumatologists' opinions towards complementary and alternative medicine: A systematic review. *Clin Rheumatol* 2014; **33**: 3-9 [PMID: 23990027 DOI: 10.1007/s10067-013-2379-z]

P- Reviewer: Mezalek ZT, Song JX

S- Editor: Tian YL **L- Editor:** A **E- Editor:** Jiao XK





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

