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EDITOR-IN-CHIEF

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

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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>
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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.

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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

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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

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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.

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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. Jakubzick *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

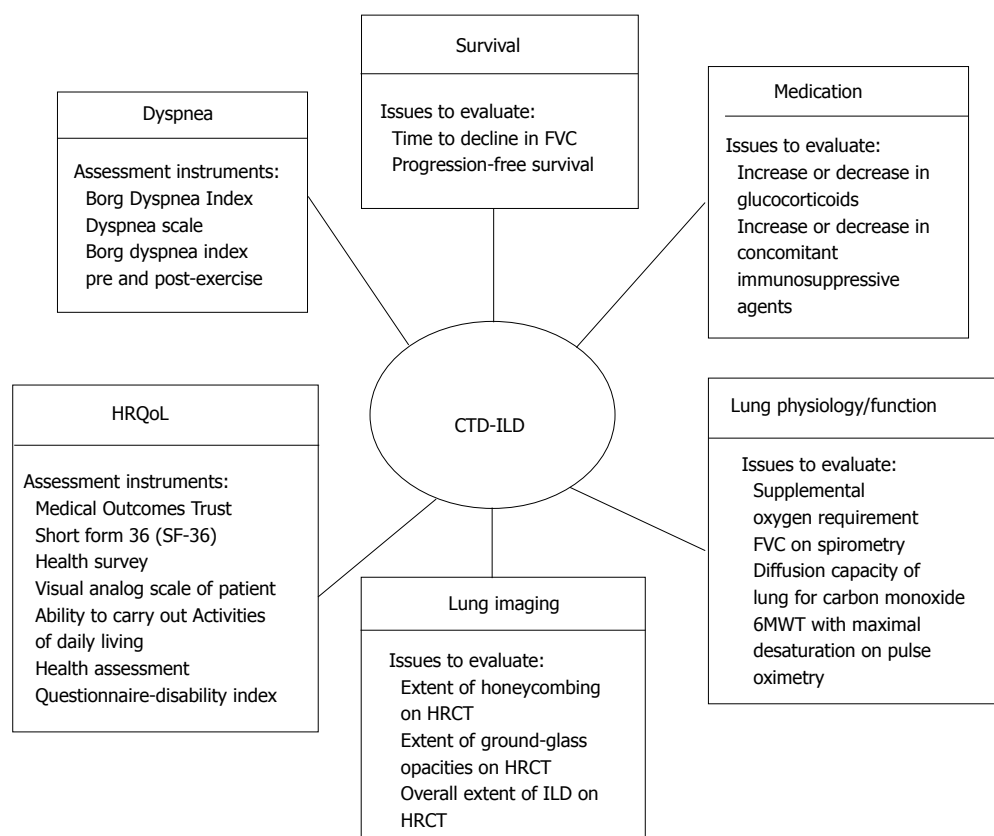


Figure 1 Suggested instruments to assess connective tissue disease associated interstitial lung disease, based on the Delphi Technique^[101]. CTD-ILD: Connective tissue disease associated-interstitial lung disease; FVC: Forced vital capacity; HRQoL: Health-related quality of life; HRCT: High-resolution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

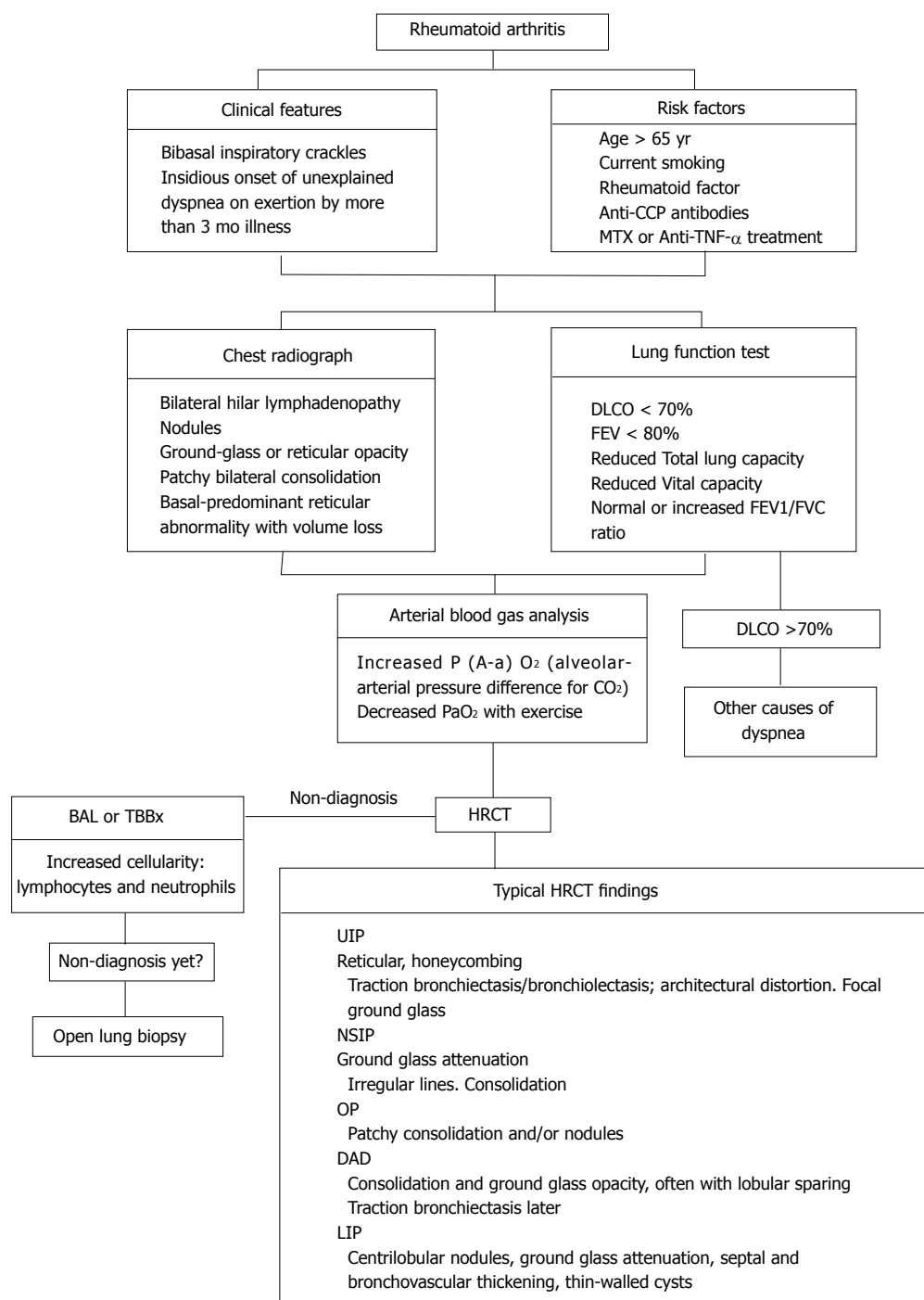


Figure 2 Recommendations for the diagnosis of interstitial lung disease in rheumatoid arthritis patients. Anti-CCP: Anti-cyclic citrullinated peptide; MTX: methotrexate; Anti-TNF- α : Anti-tumor necrosis factor- α ; DLCO: Diffusing capacity of the lung for carbon monoxide; FEV: Forced expiratory volume; 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. Yannopoulos *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.

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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.

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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

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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

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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.

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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

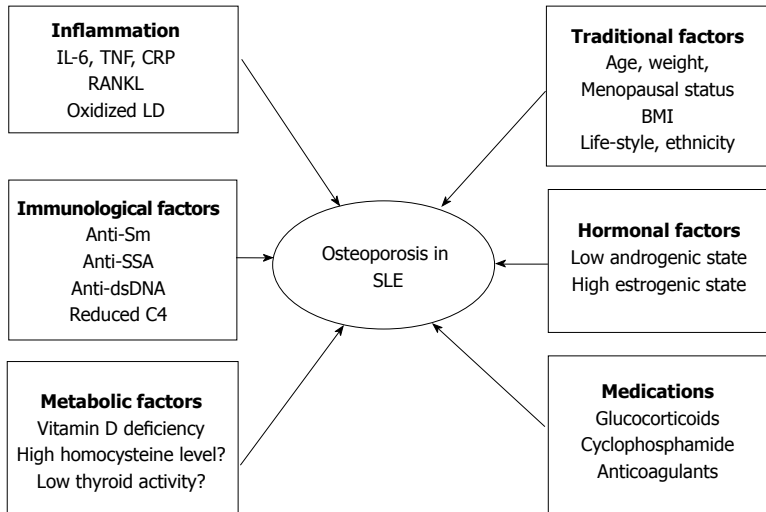


Figure 1 Risk factors of osteoporosis in systemic lupus erythematosus. SLE: Systemic lupus erythematosus; IL-6: Interleukin-6; TNF: Tumor necrosis factor; CRP: C-reactive protein; RANKL: Receptor activator of nuclear factor- κ B ligand; LDL: Low-density lipoprotein; BMI: Body mass index; Anti-Sm: Anti-Smith;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

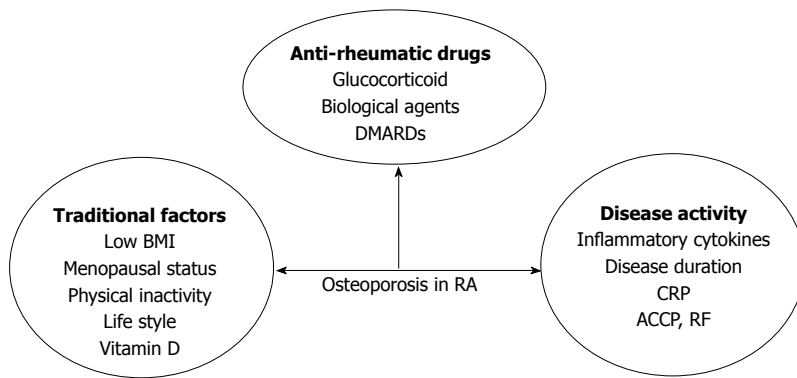


Figure 2 Risk factors for osteoporosis in rheumatoid arthritis. RA: Rheumatoid arthritis; BMI: Body mass index; DMARDs: Disease-modifying antirheumatic drugs; CRP: C-reactive protein; ACCP: Anti-cyclic citrullinated peptide; RF: Rheumatoid factor.

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 up-regulation 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.

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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

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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

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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

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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.

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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

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 latters. 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 $\geq 150 \mu\text{mol/L}$) 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.

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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
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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

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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

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

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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.

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