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## Use of biologic agents for rheumatic diseases in pregnancy

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### Abstract

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

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

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

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

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### INTRODUCTION

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

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

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

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

### Search strategy

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

## USE OF ANTI-CYTOKINES DURING PREGNANCY

### Tumor necrosis factor inhibitors

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

### Anakinra

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

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

### Tocilizumab

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

## ANTI-CELLULAR THERAPY DURING PREGNANCY

### Rituximab

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

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

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

### Abatacept

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

## CONCLUSION

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

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

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

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## Pathogenetic mechanisms of antiphospholipid antibody production in antiphospholipid syndrome

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### Abstract

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

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

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

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

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## INTRODUCTION

Antiphospholipid syndrome (APS) is a multisystemic autoimmune disease, whose pathology is driven by the action of antiphospholipid antibodies (aPL), and is characterized by recurrent thrombosis and pregnancy morbidity<sup>[1]</sup>. These antibodies are heterogenous, have numerous antigenic targets and interact with numerous negatively charged phospholipids (PLs) and protein complexes. However, during the 1990s, several groups showed simultaneously that  $\beta_2$ -glycoprotein I ( $\beta_2$ GP I), and prothrombin, are the major antigenic targets of aPL. More than 90% of binding activity in APS patients target these 2 antigens<sup>[2-4]</sup>.

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

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

## GENETIC STUDIES-DATA FROM APS ANIMAL MODELS

The first evidence of a genetic component to the production of pathogenic aPL in APS was provided by studies in mice. In NZW x BXSB F1 (W/B F1) male mice, the spontaneous production of pathogenic aPL, namely IgG aCL that display  $\beta_2$ GP I -dependent binding to cardiolipin, has been reported<sup>[10]</sup>. Indeed, these W/B F1 male mice are SLE-prone mice that, in addition to aCL, develop autoantibodies to negatively charged PLs such as phosphatidylserine (PS) and phosphatidylinositol, circulating immune complexes, and nephritis. Thrombocytopenia and myocardial infarction on the background of degenerative coronary vascular disease is often found in these mice, which is akin to features of SLE and APS<sup>[10-12]</sup>. The failure of either central or peripheral T-cell tolerance mechanisms is an important aspect of the production of self-reactive autoantibodies in autoimmune diseases. Gene analysis showed that the genes responsible for the development of pathogenic aCL in these mice used certain  $V_H$  and  $V_K$  genes preferentially, while those for non-pathogenic aCL utilized random  $V$  gene combinations. This indicates antigen-driven rather than germ-line encoded antibody production<sup>[13]</sup>. In this study, the pathogenic aCL showed a 91.5% homology to a known germ-line  $V_H$  gene, suggesting that the pathogenic aPL were generated by somatic mutations. Similarly, in MRL-lpr/lpr mice (lupus prone mice), numerous somatic mutations in the  $V_H$  region of a gene encoding a monoclonal aCL compared to the related germ-line  $V_H$  gene were noted, indicating antigen-driven stimulation and a possible failure in peripheral tolerance mechanisms<sup>[14]</sup>. aCL are also produced in normal C57BL/6J mice, with estrogen treatment increasing the incidence and levels of these antibodies, underscoring the role that environmental factors such as hormones may play in modifying genetic susceptibility in APS patients<sup>[15]</sup>. However, the aCL that are produced in these mice are not  $\beta_2$ GP I dependent but instead show diminished binding to cardiolipin in the presence of the  $\beta_2$ GP I cofactor<sup>[16]</sup>. Interestingly, an additional lupus murine model (NZW x NZB F1 mice) failed to produce aCL despite the production of other autoantibodies such as anti-dsDNA<sup>[17]</sup>.

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



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

The first direct evidence of certain MHC II alleles being involved in the induction of pathogenic aPL and development of APS clinical manifestations came from Papalardo *et al.*<sup>[21]</sup> Utilizing a  $\beta_2$ GP I –induced aPL production in mice, this group showed that thrombogenic aPL production and tissue factor upregulation occur in wild type mice after immunization with human  $\beta_2$ GP I but do not occur in MHC- II knockout [MHC(-/-)] mice. Furthermore, the production of pathogenic aPL after inoculation with  $\beta_2$ GP I was restored in MHC(-/-) that were modified to express human DQ6, DR4 or DQ8 genes. Interestingly, the quantity of pathogenic aPL that was produced varied among these 3 transgenic mouse groups. These studies confirm the involvement of certain haplotypes in the induction of aPL as well as their varied importance<sup>[21]</sup>.

## HUMAN GENETIC ASSOCIATIONS IN APS

### *Human leukocyte antigen associations*

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

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

correlated with aPL such as lupus anticoagulant (LA) and aCL, and other autoantibodies in families<sup>[23,24]</sup>. The frequent finding of aCL in first-degree relatives of patients with PAPS or secondary antiphospholipid syndrome (SAPS) has also been demonstrated<sup>[25,26]</sup>. A dominant or co-dominant model for the inheritance of APS was suggested by segregation analysis studies in a group of seven families with a 30% prevalence of primary APS among them<sup>[27]</sup>. However, the study failed to find any HLA associations or correlation with other putative genes including  $\beta_2$ GP I and Fas. In an English-Canadian family, the paternal haplotype A30; Cw3; B60; DR4; DRw53; DQw3 was associated with aCL production in secondary APS patients and individuals without disease<sup>[28]</sup>. DR4 and DR7 have also been reported to be associated with the presence of LA in families<sup>[29,30]</sup>. Another study evaluated family members, all who had SLE and a myriad of APS clinical manifestations, and revealed that DR4, DRw53 and DQw7 composed a haplotype found in twins and their mother<sup>[31]</sup>.

Many HLA associations with APS have also been found in population studies of unrelated individuals. HLA-DQw7 (HLA-DQB1\*0301) linked to HLA-DR4 and/or -DR5 was found to be associated with LA in a group of SLE patients<sup>[32]</sup>. DR4 and DRw53 were found to occur more frequently in primary APS<sup>[33]</sup>. Other primary APS associated HLA include DQB1\*0301/4, DQB1\*0604/5/6/7/9, DQA1\*0102, DQA1\*0301/2, DRB1\*04 and DR7<sup>[34-36]</sup>. Similar results were found in a large study of Italian SLE patients, in which HLA-DRB1\*04, -DRB1\*07, -DQA1\*0201, -DQA1\*0301, -DQB1\*0302, -DRB3\*0301 were associated with aCL and DQB1\*0302 with anti- $\beta_2$ GP I<sup>[37]</sup>. In Japanese patients, DRB1\*09 has been reported to be associated with aCL production in patients with lupus-associated APS<sup>[38]</sup>. A strong association exists between anti- $\beta_2$ GP I and HLA-DR4 haplotypes, particularly when linked to HLA-DQ8 (DQB1\*0302) in Caucasian and Mexican Americans, while the association with anti- $\beta_2$ GP I was attributed to the HLA-DRB1\*1302;DQB1\*0604/0605 haplotype in African American and Caucasian British patients with primary APS<sup>[34,39]</sup>. In black American populations, there is evidence that C4A or C4B null alleles are associated with the presence of aCL. It is interesting to note however, that in the Hopkins Lupus Cohort, composed of a significant number of African Americans, patients who were homozygous for C4A deficiency had a lower frequency of aCL and LA than patients without this deficiency<sup>[40-42]</sup>.

### *Non-HLA associations*

Mutations in genes not associated with the MHC region, such as a substitution of valine for leucine at amino acid residue 247 in domain V of  $\beta_2$ GP I, can contribute to APS development. This polymorphism is more prevalent in APS patients, especially those with arterial thrombosis, compared to matched controls and is linked to anti- $\beta_2$ GP I production in these patients<sup>[43-45]</sup>. Other thrombophilia-related genetic factors like factor V Leiden (FVL), prothrombin mutations and deficiencies of antithrombin



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

Peptide	Source	Amino acid sequence	Inhibition of $\beta_2$ GP I binding to CL (%) <sup>1</sup>
GDKV	Gly <sup>274</sup> -Cys <sup>288</sup> in domain V of human B2GPI	GDKVSFFCKNKKC	43
GDKV <sub>2</sub>	Modified GDKV with all six residues between Lys <sup>282</sup> -Lys <sup>287</sup> replaced with Lys	GDKVSFFCKKKKKKC	56
TADL	Thr <sup>77</sup> -Glu <sup>96</sup> of Adv type2 DNA binding protein	TADLAIAKKKKKKRPSKPKE	68
TIFI	Thr <sup>101</sup> -Thr <sup>120</sup> of ULB0-HCMVA from human CMV	TIFILFCCSKEKRKKKQAAT	75
VITT	Val <sup>51</sup> -Ile <sup>70</sup> of US27-HCMVA from human CMV	VITTILYYRRKKKSPSDT	83
SGDF	Ser <sup>237</sup> -Ser <sup>256</sup> of TLP-BACSU from <i>Bacillus subtilis</i>	SGDFEYTYKGKKKKMAFATS	NA

<sup>1</sup>Refers to the percentage of inhibition of 100 nmol/L of beta-2 glycoprotein I binding to cardiolipin produced by 6uM of each peptide. CMV: Cytomegalovirus; NA: Not available;  $\beta_2$ GP I : Beta-2 glycoprotein I ; CL: Cardiolipin.

III, protein C and protein S have also been linked to APS disease manifestations<sup>[46]</sup>.

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

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

## ENVIRONMENTAL FACTORS IN APS

### Infectious agents

Early efforts to induce aPL production in animal models

focused on immunization of animals with theorized antigenic targets. Initial experiments utilized cardiolipin antigens but these failed to allow for production of aPL in animal models<sup>[62]</sup>. After the discovery that the main antigenic target of pathogenic aPL was in fact  $\beta_2$ GP I, subsequent experiments utilized immunization with heterologous  $\beta_2$ GP I rather than pure PLs. This led to the successful induction of aPL production in mice and these antibodies were able to induce pathogenic effects<sup>[2,62]</sup>. Researchers then hypothesized that perhaps molecular mimicry played a key role in pathogenic aPL production. In essence, foreign PL-binding proteins that shared structural similarities to  $\beta_2$ GP I could bind to self PLs in APS patients, and in so doing allow for the assembly of immunogenic complexes that stimulate aPL production.

Subsequent studies made use of a synthesized 15 amino acid peptide, GDKV, which spanned an area of the fifth domain of  $\beta_2$ GP I known to be a major PL-binding site of the molecule. This peptide was able to induce pathogenic aPL and anti- $\beta_2$ GP I production in immunized mice<sup>[63]</sup>. A monoclonal antibody with aPL and anti- $\beta_2$ GP I activity generated from these GDKV-immunized mice was shown to be pathogenic using *in vivo* models for thrombus enhancement and microcirculation<sup>[64]</sup>. A search for candidate peptides with structural similarities to GDKV among libraries of peptides from viral and bacterial agents produced several candidates (Table 1). Similar results in experimental animal models were then reported using these candidate peptides<sup>[65]</sup>. When compared to GDKV, peptides from cytomegalovirus (TIFI and VITT), from adenovirus (TADL) and from *Bacillus subtilis* (SGDF) all bound to PLs with greater affinity and induced higher anti- $\beta_2$ GP I levels in experimental animals. The thrombogenic and proinflammatory capacity of induced antibodies in mice immunized with TIFI was subsequently confirmed<sup>[65,66]</sup>.

An interesting set of experiments that focused on a hexapeptide, TLRVYK, which is a known antigen of pathogenic monoclonal anti- $\beta_2$ GP I, found in micro-organisms provided further evidence of molecular mimicry being involved in aPL production<sup>[67]</sup>. BALB/c mice immunized with *Haemophilus influenzae*, *Neisseria gonorrhoeae* or tetanus toxoid produced high anti-TLRVYK and anti- $\beta_2$ GP I antibodies which were then isolated and passively transferred to naive mice at day 0 of pregnancy. These

antibodies induced a higher frequency of fetal loss, thrombocytopenia and prolonged activated partial thromboplastin times at day 15 after inoculation. Even further evidence comes from a study utilizing protein H found in *Streptococcus pyogenes* isolates. Protein H was able to bind to  $\beta_2$ GP I, induce changes in the conformation of the protein, expose cryptic epitopes and consequently allow for the development of anti- $\beta_2$ GP I antibodies<sup>[68]</sup>.

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

The majority of circulating  $\beta_2$ GP I exists in a reduced form containing unpaired cysteines (free thiols), which are involved in the interaction with platelets and endothelial cells. This abundant pool of free thiols may serve as an antioxidant reservoir protecting cells or critical molecules from oxidative stress and oxidation of  $\beta_2$ GP I has been shown to confer an increase in its immunogenicity through a Th1 immunological mechanism. It is therefore possible that the generation of reactive oxidative and nitrosative species by certain infectious agents could allow for generation of an abundance of oxidized  $\beta_2$ GP I and foster autoantibody production. Indeed, serum from patients with APS assessed by a novel enzyme linked immunoassay (ELISA) assay, have a significant increase in oxidized  $\beta_2$ GP I<sup>[73]</sup> (Figure 1).

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

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

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

### Other environmental agents

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

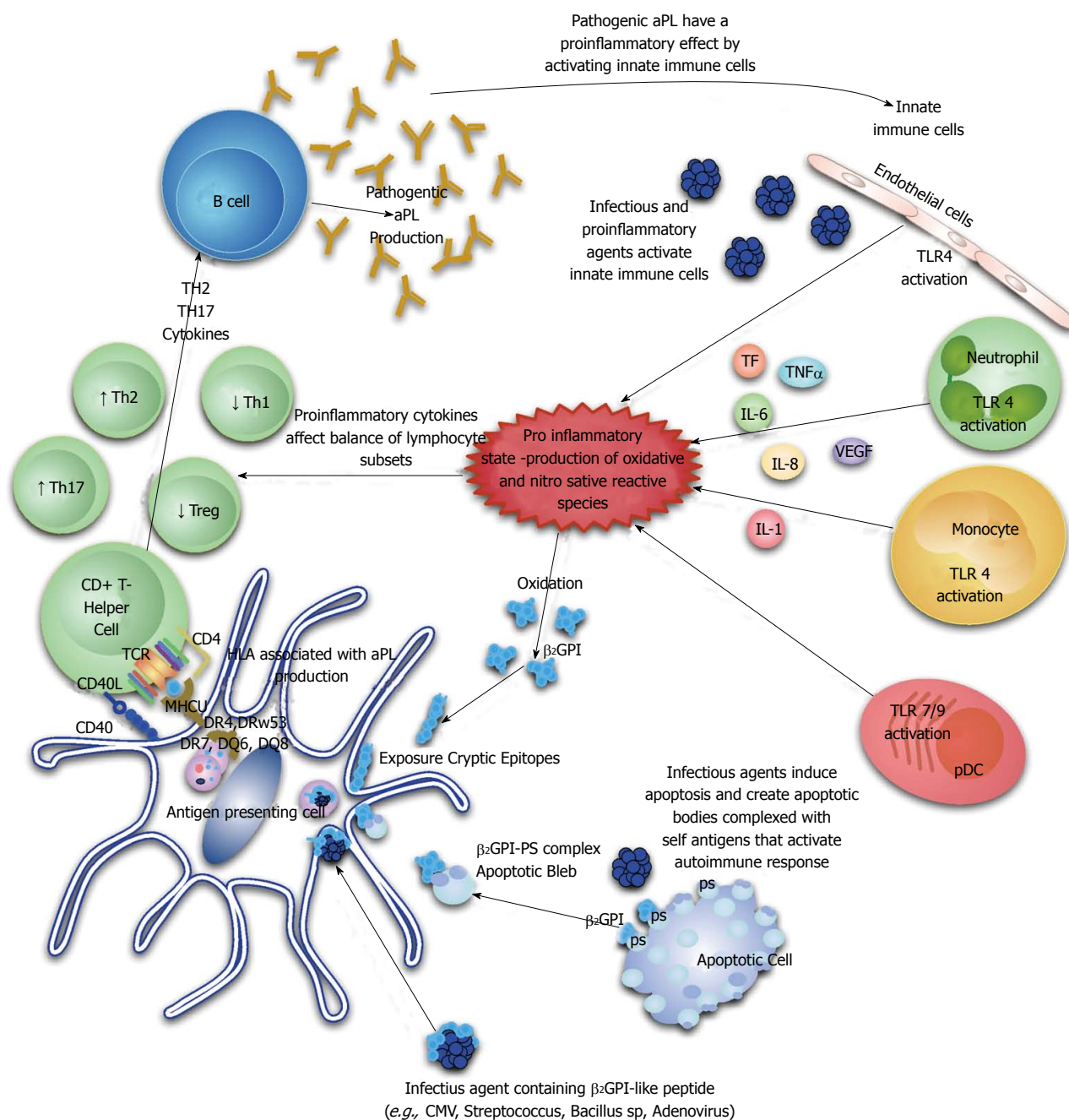
Drugs are able to bind self-antigens, alter their processing and presentation to immune cells and in essence creating neopeptides or expose cryptic epitopes, facilitating autoimmune induction<sup>[82]</sup>. Similar to other non-infectious environmental agents, several drugs have been reported to be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

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

## APOPTOSIS IN APS DEVELOPMENT

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

During apoptosis, a negatively charged PL, PS, which is normally found almost entirely on the inner cytoplasmic leaflet, is transferred to the outer leaflet<sup>[88,89]</sup>. This is important in APS as it provides an antigen for aPL binding and such autoantibodies that bind apoptotic cells *via* interaction with PL- $\beta_2$ GP I complexes have been



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

identified<sup>[90-92]</sup>. Indeed, the antigenic reactivity of several aPL with a complex formed between anionic phospholipid (e.g., PS) and  $\beta_2$ GP I or  $\beta_2$ GP I in isolation<sup>[93]</sup>. During the apoptotic process in autoimmune patients, the sequestration of PS induces specific recognition by macrophages and subsequent removal<sup>[94]</sup>, and the PS/ $\beta_2$ GP I complex recruits anti- $\beta_2$ GP I, which then facilitates apoptotic cell clearance and preserves tissue homeostasis<sup>[95]</sup>.

The concept that apoptosis plays a role in the production of aPL was first proposed by Piroux *et al.*<sup>[92]</sup>. Subsequent studies have provided evidence that apoptotic cells/ $\beta_2$ GP I complexes can act as a source of anti- $\beta_2$ GP I antibodies. Levine *et al.*<sup>[96]</sup> reported that  $\beta_2$ GP

I do not readily bind to the surface of viable cells but rather to the surface of apoptotic cells. Once bound, the exposure of an essential epitope facilitates recognition by aPL from patients with primary APS and SLE. Interestingly, increased aPL production can be induced in mice immunized with apoptotic cells alone or complexed to  $\beta_2$ GP I. A recent study highlighted the importance of the Ro60 receptor in  $\beta_2$ GP I precipitation in apoptotic bodies<sup>[95-99]</sup>.

## CONCLUSION

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



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

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

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### Abstract

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

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

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

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

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## INTRODUCTION

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

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

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

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

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

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

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

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

**Table 1** Summary of knee osteoarthritis grading scales

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

OA: Osteoarthritis.

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

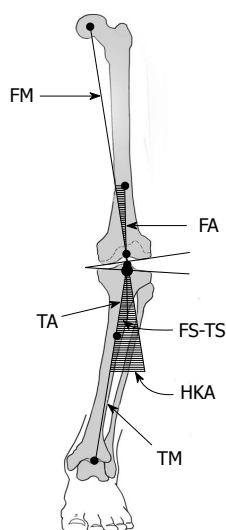
## FRONTAL-PLANE LE ALIGNMENT

### Determination of LE alignment using full-length radiographs

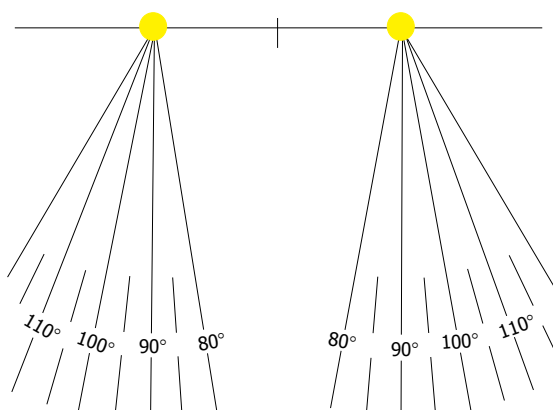
The criterion standard measure of frontal-plane LE alignment is the hip-knee-ankle (HKA) angle, also known

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





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



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

or  $-1^{\circ}$  to  $-1.5^{\circ}$ <sup>[49-51]</sup>.

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

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

### LE positioning

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

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

### Determination of LE alignment using knee radiographs

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

There are concerns that the FS-TS angle does not



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

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

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

### Summary and recommendations

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

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

## GRADING THE SEVERITY OF TF OA

### Global scales

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

### KL Grading scale

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

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

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

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

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

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

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

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

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

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

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

### Other Global scales

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

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

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

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

### Composite scales

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

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

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

### Compartmental Grading scale for knee OA

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

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

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

### Individual OA Feature Grading scales

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

### OA Research Society International Atlas

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



most sensitive to change over time.

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

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

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

### Other Individual OA Feature Scales

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

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

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

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

### Digital evaluations

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

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

### Summary and recommendations

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

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

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

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

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

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## Safety of biologic therapies during pregnancy in women with rheumatic disease

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### Abstract

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

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

**Key words:** Pregnancy; Biologic therapy; Monoclonal

antibodies; Rheumatic diseases; Safety

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

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## INTRODUCTION

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

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

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

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

## BIOLOGICAL AGENTS TARGETING CYTOKINES

### *Tumor necrosis factor inhibitors*

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

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

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

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

Nevertheless, because these results are very limited,



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

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

<sup>1</sup>Remicade®, Inflectra® and Remsima®; <sup>2</sup>Humira® and Trudexa®.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Because the immune system is not yet completely

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

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

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

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

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

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

Although only limited short-term experiences are

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

### Others biological agents targeting cytokines

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

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

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

## BIOLOGICAL AGENTS TARGETING CELLS

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

### RTX

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

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

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

### Belimumab

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

### Abatacept

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

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

## CONCLUSION

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

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

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## Current review of trapeziometacarpal osteoarthritis (rhizarthrosis)

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### Abstract

Trapeziometacarpal (TMC) joint is the secondly affected

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

**Key words:** Osteoarthritis; Thumb; Trapeziometacarpal joint; Rhizarthrosis

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

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## INTRODUCTION

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

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

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

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

## LIGAMENTOUS ANATOMY OF THE TMC JOINT

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

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

summarized in Table 1<sup>[19]</sup>.

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

## DIAGNOSIS

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

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

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

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

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



**Table 1** Main ligaments of the trapeziometacarpal joint

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

arthritis<sup>[19]</sup>. But careful and proper clinical and radiological evaluations will differentiate rhizarthrosis from the aforementioned clinical entities.

## TREATMENT

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

### Non-surgical treatment

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

### Surgical treatment

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

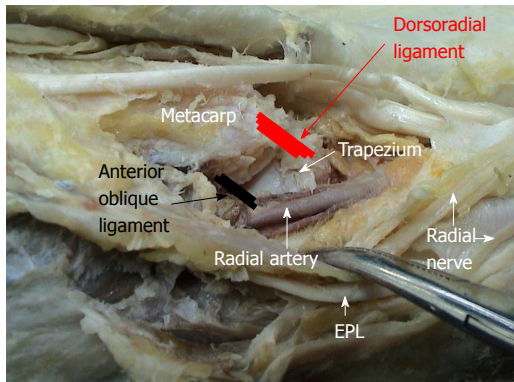
### Trapeziectomy with or without tendon interposition or ligament reconstruction

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

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

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

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



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

**Table 2** Eaton-Littler classification of rhizarthrosis

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

TMC: Trapeziometacarpal; ST: Scaphotrapezial.

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

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

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

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

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

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

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

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

## CONCLUSION

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

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

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### Abstract

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

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

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

pathogenesis of rheumatic diseases.

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## INTRODUCTION

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

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

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

## H. PYLORI -INDUCED IMMUNOLOGIC RESPONSE

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

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

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

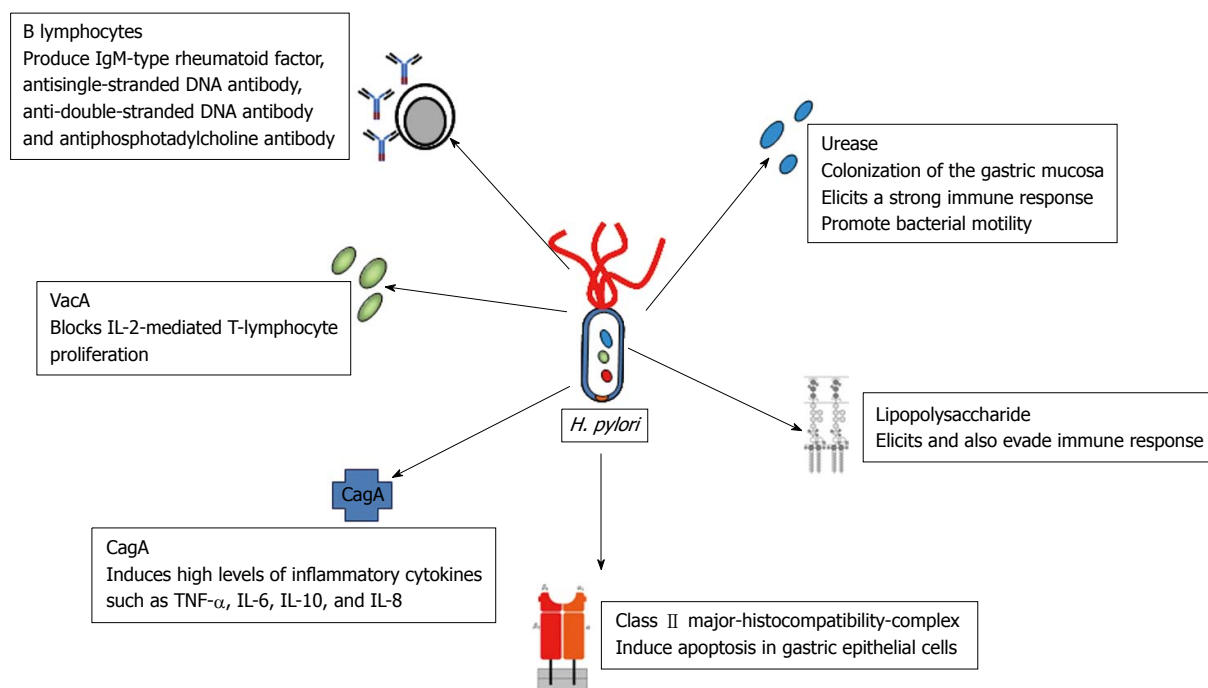
A study by Jackson *et al*<sup>[17]</sup> shows elevated C-reactive protein in chronic *H. pylori* infected patients. Few other reports have demonstrated that chronic *H. pylori* infection leads to activation and survival of B lymphocytes to produce rheumatoid factor (IgM), antisingle-stranded DNA (anti-ssDNA)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

## H. PYLORI-ASSOCIATED RHEUMATOID ARTHRITIS

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

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

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



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

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

## H. PYLORI-ASSOCIATED SYSTEMIC LUPUS ERYTHEMATOSUS

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

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

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

## H. PYLORI-ASSOCIATED FIBROMYALGIA

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

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

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

## CONCLUSION

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

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

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### Abstract

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

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

**Key words:** Neutrophilic dermatosis; Pathergy; Koebner phenomenon; Autoinflammatory disorder

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

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## INTRODUCTION

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

## CLINICAL FEATURES

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

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

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

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

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

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

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

## ATYPICAL SUBSETS

### Peristomal PG

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

### Superficial granulomatous PG

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

### Drug-induced PG

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

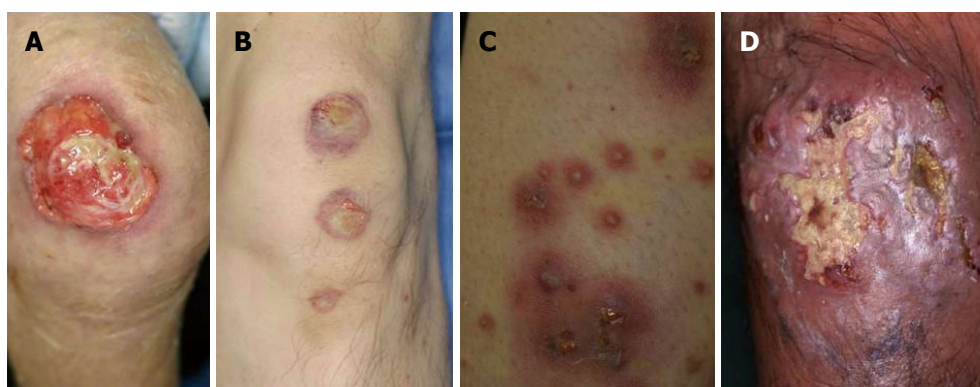


Figure 1 Clinical features of pyoderma gangrenosum involving lower legs. Ulcerative type (A), bullous type (B), pustular type (C), and vegetative type (D).



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

### ***Pyodermatitis-pyostomatitis vegetans***

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

## **ASSOCIATED DISEASES**

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

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

## **AUTOINFLAMMATORY DISEASES**

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



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

## ASSOCIATION WITH OTHER NEUTROPHILIC DISORDERS

### *Hidradenitis suppurativa*

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

### *Psoriasis*

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

### *Palmoplantar pustulosis*

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

## HISTOPATHOLOGY

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

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

## PATHOGENESIS

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

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

## PATHERGY

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

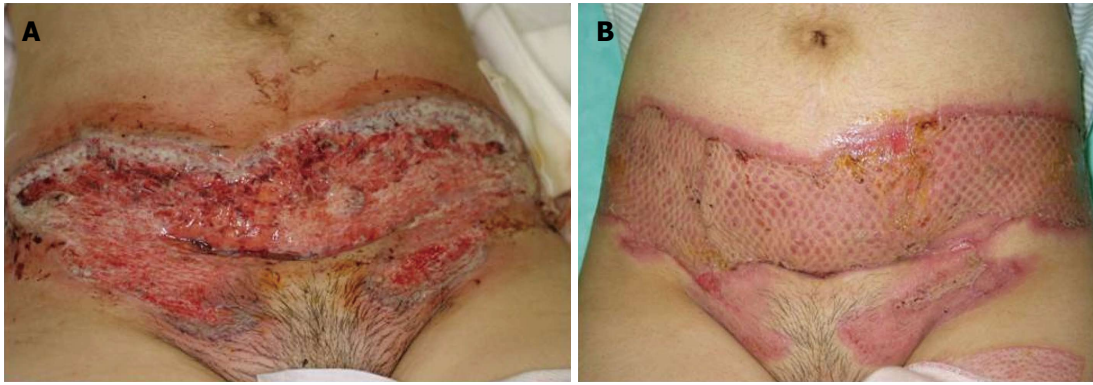


Figure 3 Pyoderma gangrenosum triggered by caesarean operation (A), which was surgically treated by mesh grafting with oral prednisolone (B).

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

## DIFFERENTIAL DIAGNOSIS

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

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

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

## THERAPY

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

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

## CONCLUSION

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

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

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### Abstract

**AIM:** To evaluate the effectiveness of the biological disease-modifying antirheumatic drugs (bDMARD) in the treatment of rheumatoid arthritis through a systematic review of observational studies.

**METHODS:** The studies were searched in the PubMed, EMBASE, Cochrane Controlled Trials Register and LILACS databases (until August 2014), in the grey literature and conducted a manual search. The assessed criteria of effectiveness included the EULAR, the disease activity score (DAS), the Clinical Disease Activity Index, the Simplified Disease Activity Index, the American College of Rheumatology and the Health Assessment Questionnaire. The meta-analysis was performed with Review Manager® 5.2 software using a random effects model. A total of 35 studies were included in this review.

**RESULTS:** The participants anti-tumor necrosis factor inhibitors (TNF) naïve, who used adalimumab ( $P = 0.0002$ ) and etanercept ( $P = 0.0006$ ) exhibited greater good EULAR response compared to the participants who used infliximab. No difference was detected between adalimumab and etanercept ( $P = 0.05$ ). The participants who used etanercept exhibited greater remission according to DAS28 compared to the participants who used infliximab ( $P = 0.01$ ). No differences were detected between adalimumab and infliximab ( $P = 0.12$ ) or etanercept ( $P = 0.79$ ). Better results were obtained with bDMARD associated with methotrexate than with bDMARD alone. The good EULAR response and DAS 28 was better for combination with methotrexate than bDMARD monotherapy ( $P = 0.03$  e  $P < 0.00001$ ). In cases of therapeutic failure, the participants who used rituximab exhibited greater DAS28 reduction compared to those who used anti-TNF agents ( $P = 0.0002$ ). The participants who used etanercept achieved greater good EULAR response compared to those who did not use that drug ( $P = 0.007$ ). Studies that assessed reduction of the CDAI score indicated the superiority of abatacept over rituximab (12.4 *vs* +1.7) and anti-TNF agents (7.6 *vs* 8.3). The present systematic review with meta-analysis found that relative to anti-TNF treatment-naïve patients, adalimumab and etanercept were more effective when combined with methotrexate than when used alone. Furthermore, in case of therapeutic failure with anti-TNF agents; rituximab and abatacept (non anti-TNF) and etanercept (as second anti-TNF) were more effective. However, more studies of effectiveness were found for the rituximab.

**CONCLUSION:** The best treatment for treatment-naïve patients is adalimumab or etanercept combined with methotrexate. For anti-TNF therapeutic failure, the best choice is rituximab, abatacept or etanercept.

**Key words:** Systematic review; Meta-analysis; Effectiveness; Biological disease-modifying antirheumatic drugs; Rheumatoid arthritis

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**Core tip:** Rheumatoid arthritis is a chronic, progressive, systemic inflammatory disease that preferentially affects the synovial membranes of joints, eventually leading to bone and cartilage destruction. Its worldwide prevalence is estimated to be 0.3% to 1%. Observational studies could provide relevant information for deciding the choice of treatments, the elaboration of clinical protocols, and the formulation of health policies. The present systematic review of biological disease-modifying antirheumatic drugs included cohort observational studies that reported treatment results applied in real-life conditions; thus, these studies are able to fill in gaps in knowledge left by clinical trials.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory disease that preferentially affects the synovial membranes of joints, eventually resulting in destruction of bone and cartilage<sup>[1]</sup>. Its worldwide prevalence is estimated to be 0.3% to 1%<sup>[2]</sup>.

Treatment of RA includes non-steroidal anti-inflammatory drugs, corticoids and synthetic (sDMARD) and biological [biological disease-modifying antirheumatic drugs (bDMARD)] disease-modifying antirheumatic drugs. bDMARD are indicated for individuals with persistent disease activity despite the use of sDMARD<sup>[3-5]</sup>. Tumor necrosis factor inhibitors (anti-TNF) are inhibitors of tumor necrosis factor alpha, rituximab is depleting B lymphocyte, abatacept is blocking of costimulation of T lymphocyte and tocilizumab is a blocking interleukin-6 receptor. Among the bDMARD, anti-TNF represent the first choice after failure of regimens that included sDMARD, and there is more evidence of the post-marketing efficacy and safety for anti-TNF agents<sup>[4,5]</sup>. Nevertheless, anti-TNF could eventually exhibit therapeutic failure, in which case another anti-TNF drug or another class of bDMARD might be used<sup>[6,7]</sup>.

Appropriate knowledge of the effectiveness profiles of all of these strategies is relevant for choosing the best option for each patient. In this regard, observational studies are particularly interesting, as they seek to understand treatments in the actual practice setting. Thus, this type of study could contribute to decide the choice of treatments, the elaboration of clinical protocols, and the formulation of health policies. The present systematic review selected cohort observational studies. These types of studies more accurately represent real-life conditions (actual practice setting) and are able to provide complementary data to the results of randomized clinical studies conducted in controlled conditions<sup>[8]</sup>.

The aim of the present study was to assess the effectiveness of the anti-TNFs adalimumab, etanercept, infliximab, golimumab and certolizumab pegol and of the non anti-TNF rituximab, tocilizumab and abatacept, in the treatment of active RA by means of a systematic review with meta-analysis.

## MATERIALS AND METHODS

This systematic review followed the recommendations in the Cochrane Collaboration Handbook and was elaborated using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)<sup>[9,10]</sup>.

**Table 1** Search strategies

<p>PubMed</p> <p>((Arthritis, Rheumatoid[Text Word] or "Arthritis, Rheumatoid"[Mesh]) and (((((((((((rituximab[Text Word] or Mabthera[Text Word]) or Rituxan[Text Word]) or IDEC-C2B8 antibody[Text Word]) or "rituximab"[Supplementary Concept]) or ((((((TNFR-Fc fusion protein[Text Word] or TNR 001[Text Word]) or TNR-001[Text Word]) or TNF receptor type II-IgG fusion protein[Text Word]) or recombinant human dimeric TNF receptor type II-IgG fusion protein[Text Word]) or Enbrel[Text Word]) or etanercept[Text Word]) or "TNFR-Fc fusion protein"[Supplementary Concept])) or (((infiximab[Text Word] or monoclonal antibody cA2[Text Word]) or MAb cA2[Text Word]) or Remicade[Text Word]) or "infiximab"[Supplementary Concept])) or ((adalimumab[Text Word] or Humira[Text Word]) or "adalimumab"[Supplementary Concept])) or (((certolizumab[Text Word] or CDP870[Text Word]) or CDP 870[Text Word]) or Cimzia[Text Word]) or certolizumab pegol[Text Word]) or "certolizumab pegol"[Supplementary Concept])) or (((((((((((abatacept[Text Word] or BMS 188667[Text Word]) or BMS-188667[Text Word]) or nulojix[Text Word]) or CTLA-4-Ig[Text Word]) or cytotoxic T lymphocyte-associated antigen 4-immunoglobulin[Text Word]) or CTLA4-Fc[Text Word]) or CTLA4-Ig[Text Word]) or LEA29Y[Text Word]) or Orenia[Text Word]) or BELATACEPT[Text Word]) or BMS-224818[Text Word]) or "abatacept"[Supplementary Concept])) or ((tocilizumab[Text Word] or atlizumab[Text Word]) or Actemra[Text Word]) or "tocilizumab"[Supplementary Concept])) or ("golimumab"[Supplementary Concept] or Simponi[Text Word] or golimumab[Text Word])))) and ("Cohort Studies"[Mesh]) or (((cohort*[Text Word] or controlled clinical trial[Publication Type]) or epidemiologic methods))</p> <p>EMBASE</p> <p>"golimumab"/exp and [embase]/lim or ("cnto\$148" and [embase]/lim) or ("simponi" and [embase]/lim) or ("tocilizumab"/exp and [embase]/lim) or ("actemra" and [embase]/lim) or ("actemra 200" and [embase]/lim) or ("atlizumab" and [embase]/lim) or ("r\$1569" and [embase]/lim) or ("roactemra" and [embase]/lim) or ("abatacept"/exp and [embase]/lim) or ("bms\$188667" and [embase]/lim) or ("ctla4\$ig" and [embase]/lim) or ("ctla4 immunoglobulin" and [embase]/lim) or ("ctla4 immunoglobulin g" and [embase]/lim) or ("orencia" and [embase]/lim) or ("certolizumab pegol"/exp and [embase]/lim) or ("cdp\$870" and [embase]/lim) or ("cimzia" and [embase]/lim) or ("pha\$738144" and [embase]/lim) or ("adalimumab"/exp and [embase]/lim) or ("humira"/exp and [embase]/lim) or ("monoclonal antibody d2e7" and [embase]/lim) or ("trudexa" and [embase]/lim) or ("infiximab"/exp and [embase]/lim) or ("avakine" and [embase]/lim) or ("inflectra" and [embase]/lim) or ("remicade" and [embase]/lim) or ("remsima" and [embase]/lim) or ("revellex" and [embase]/lim) or ("etanercept"/exp and [embase]/lim) or ("embrel" and [embase]/lim) or ("enbrel" and [embase]/lim) or ("recombinant tumor necrosis factor receptor fc fusion protein" and [embase]/lim) or ("tnr\$001" and [embase]/lim) or ("tumor necrosis factor receptor fc fusion protein" and [embase]/lim) or ("rituximab"/exp and [embase]/lim) or ("idec c2b8" and [embase]/lim) or ("mabthera" and [embase]/lim) or ("monoclonal antibody idec c2b8" and [embase]/lim) or ("reditux" and [embase]/lim) or ("rituxan" and [embase]/lim) or ("rituxin" and [embase]/lim) or ("rheumatoid arthritis"/exp and [embase]/lim) or ("arthritis, rheumatoid" and [embase]/lim) and ("cohort analysis"/exp and [embase]/lim or ("longitudinal study"/exp and [embase]/lim) or ("prospective study"/exp and [embase]/lim) or ("follow up"/exp and [embase]/lim) or ("cohort\$" and [embase]/lim))</p> <p>Cochrane Controlled Trials Register</p> <p>#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees</p> <p>#2 Rheumatoid Arthritis in Trials</p> <p>#3 golimumab in Trials</p> <p>#4 tocilizumab in Trials</p> <p>#5 abatacept in Trials</p> <p>#6 certolizumab pegol in Trials</p> <p>#7 adalimumab in Trials</p> <p>#8 infiximab in Trials</p> <p>#9 etanercept in Trials</p> <p>#10 rituximab in Trials</p> <p>#11 #1 or #2 in Trials</p> <p>#12 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 in Trials</p> <p>#13 #11 and #12</p> <p>LILACS</p> <p>(tw:((mh:(arthritis, rheumatoid)) or (tw:(artrite reumatoide)) or (tw:(arthritis reumatoide)) )) and (tw:((tw:(adalimumab)) or (tw:(etanercept)) or (tw:(infiximab)) or (tw:(rituximab)) or (tw:(golimumab)) or (tw:(tocilizumab)) or (tw:(abatacept)) or (tw:(certolizumab pegol))))</p>
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**Eligibility criteria**

We included prospective and retrospective cohort studies and database records of patients with RA whose diagnoses were confirmed based on the ACR 1987 and the more recent ACR/EULAR 2010 criteria. Studies that accessed the effectiveness of adalimumab, etanercept, infiximab, golimumab, certolizumab pegol, rituximab, tocilizumab and abatacept between themselves, in monotherapy or combined with sDMARD were evaluated for inclusion.

**Study search**

We performed an electronic search of relevant articles published before August 2014 in the PubMed, EMBASE, Cochrane Controlled Trials Register and LILACS databases. Several combinations of terms corresponding

to the disease, interventions and type of study were used in the search strategy (Table 1).

In addition, we conducted a manual search in the 2012 and 2013 editions of four rheumatology journals (Journal Rheumatology, Rheumatology, Rheumatology International and the Brazilian Journal of Rheumatology) and in the abstracts of the ACR and the EULAR meetings. Also, we searched for grey literature in the Digital Library of Theses and Dissertations of University of São Paulo, and ProQuest Dissertation and Theses Database.

**Study selection and data collection processes**

We performed the study selection in duplicate by four independent examiners (JBS, JOC, HAOJ, LLPL). The steps included analysis of titles, abstracts, and analysis of the full-texts of articles. Divergences were analyzed by

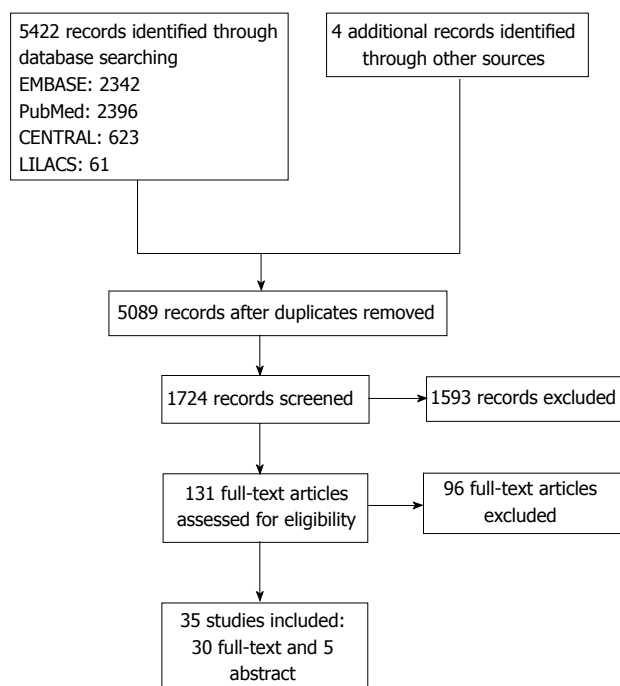


Figure 1 Study flow diagram.

another reviewer (VEA). Data collection was performed by four investigators (JBS, JOC, HAOJ, LLPL). The authors were contacted for additional information whenever needed. We assessed effectiveness as indicated by the rate of response to bDMARD according to the criteria of ACR and EULAR. We also analysed the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS28) and the Health Assessment Questionnaire (HAQ).

### Assessment of methodological quality

The methodological quality of each study was assessed by four examiners (JBS, JOC, HAOJ, LLPL); divergences were solved by consensus. For that purpose, we used the Newcastle-Ottawa scale, as recommended by the Cochrane Collaboration in the case of observational studies<sup>[11]</sup>. This scale assesses studies in three major domains: selection of the study groups, comparability of groups, and ascertainment of exposure and of results of interest. The maximum total score is nine stars, and scores above six stars are indicative of high methodological quality.

Funding sources were identified to establish potential sources of bias. Publication bias was assessed by funnel plot analysis of the results of EULAR responses and DAS28.

### Statistical analysis

We used the Software Review Manager<sup>®</sup> 5.2 to perform the meta-analyses. The results are expressed as relative risks (dichotomous variables) or means differences (continuous variables) with the corresponding 95% CIs. Values of  $I^2 > 40\%$  and  $P < 0.10$  on the  $\chi^2$  test were considered as indicative of significant heterogeneity. The

causes of heterogeneity were investigated by excluding one study at a time and checking the changes in  $I^2$  and  $P$  values.

## RESULTS

### Study inclusion

A total of 5422 articles were found in the investigated electronic databases, and a further four after manual search. Following the exclusion of duplicates, 5089 articles were selected for title analysis, from which 1724 were selected for abstract analysis, and finally 131 for full-text reading. Following full-text reading, 35 studies were included in the review, corresponding to 30 full-text articles<sup>[12-42]</sup> and five abstracts<sup>[43-47]</sup> (Figure 1). No observational study assessed the medicines golimumab or certolizumab pegol.

### Characteristics of the studies

Among the 35 observational studies included, 16 were registry studies and 19 were cohort studies; eight were retrospective, and 27 were prospective. The study duration varied from 15 to 80 mo, though this information was not provided by some authors. The participants were followed from three to 48 mo. Five studies were funded by pharmaceutical companies, two studies were not funded by the pharmaceutical industry, and 16 had mixed funding; in the remainder articles the authors did not disclose the funding source. Nine studies assessed anti-TNF naïve participants, and 11 studies assessed cases of therapeutic failure with at least one anti-TNF agent; the remainder of the studies did not inform whether therapeutic failure had occurred or did not separate patients into subgroups (Table 2). Disease duration varied from 6 to 20 years. Approximately 50% of the participants used glucocorticoids and the use of sDMARD varied from 31% to 100%. In most of the studies, the DAS28 score was  $> 5.1$ , which indicates high disease activity. The HAQ score varied from 0.4 to 2.2 (Figure 2).

### Methodological quality

From the 35 analyzed studies, two achieved the highest score on the Newcastle-Ottawa scale, nine stars; 14, eight stars; seven, seven stars; 10, six stars; and two, five stars (Table 3). The funnel plot did not exhibit asymmetry relative to outcomes in the DAS 28 and EULAR response, which indicated the absence of publication bias, and thus of overestimation of the intervention effects calculated in the meta-analysis (data not shown).

### Data synthesis

A total of 22 studies assessed the drugs adalimumab, etanercept and infliximab; nine studies assessed anti-TNF naïve patients only and seven anti-TNF naïve participants and cases of therapeutic failure; six studies did not inform whether therapeutic failure had occurred. Nineteen of those studies were included in the meta-analyses of EULAR responses, DAS28, remission



Table 2 Characteristics of included studies

N study	Ref.	Type of study	Time horizon	Patient	Intervention	Country conducting the study	Funding Sources	Duration of the study (mo)	Follow-up (mo)
1	Geborek <i>et al</i> <sup>[12]</sup>	Cohort	Prospective	Naive	ETA <i>vs</i> IFX <i>vs</i> LEF	Sweden	NR	24	12
2	Van Vollenhoven <i>et al</i> <sup>[13]</sup>	Registry	Prospective	NR	ETA <i>vs</i> ETA + MTX	Sweden	Mixed	NR	12
3	Cohen <i>et al</i> <sup>[14]</sup>	Cohort	Retrospective	Therapeutic failure	IFX <i>vs</i> ETA	France	NR	48	3
4	Finckh <i>et al</i> <sup>[15]</sup>	Registry	Prospective	Mixed	ADA <i>vs</i> ETA <i>vs</i> IFX	Switzerland	Mixed	80	12
5	Heiberg <i>et al</i> <sup>[16]</sup>	Cohort	Prospective	Mixed	ADA	Norway	Mixed	NR	12
6	Hyrich <i>et al</i> <sup>[17,18]</sup>	Registry	Prospective	NR	monotherapy <i>vs</i> ADA + MTX ETA monotherapy <i>vs</i> ETA + MTX <i>vs</i> ETA + DMARD and ADA monotherapy <i>vs</i> ADA + MTX <i>vs</i> ADA + DMARD	England	Pharmaceutical industry	NR	6
7	Kristensen <i>et al</i> <sup>[19]</sup>	Cohort	Prospective	Naive	ETA <i>vs</i> IFX	Sweden	Mixed	55	36
8	Bernal Rivera <i>et al</i> <sup>[20]</sup>	Cohort	Prospective	Naive	ADA <i>vs</i> ETA <i>vs</i> IFX	Spain	NR	24	12
9	Kristensen <i>et al</i> <sup>[19]</sup>	Cohort	Prospective	Naive	ETA <i>vs</i> IFX	Spain	NR	72	6
10	Radstake <i>et al</i> <sup>[23]</sup>	Cohort	Prospective	NR	IFX <i>vs</i> ADA	The Netherlands	Mixed	NR	6
12	Bazzani <i>et al</i> <sup>[24]</sup>	Registry	Prospective	Mixed	ADA <i>vs</i> ETA <i>vs</i> IFX	Italy	Pharmaceutical industry	25.29	36
13	Greenwood <i>et al</i> <sup>[47]</sup>	Cohort	Retrospective	NR	ADA <i>vs</i> ETA <i>vs</i> IFX	England	NR	NR	12
14	Laas <i>et al</i> <sup>[25]</sup>	Cohort	Prospective	Naive	ETA <i>vs</i> ADA	Finland	No pharmaceutical industry	36	3
15	Arenere Mendoza <i>et al</i> <sup>[26]</sup>	Cohort	Retrospective	Mixed	ADA <i>vs</i> ETA <i>vs</i> IFX	Spain	NR	80	12
16	Buch <i>et al</i> <sup>[46]</sup>	Cohort	Prospective	Therapeutic failure	RTX <i>vs</i> anti-TNF	England	NR	NR	6
17	Canh�o <i>et al</i> <sup>[27]</sup>	Registry	Prospective	Naive	ADA <i>vs</i> ETA <i>vs</i> IFX	Portugal	Mixed	NR	12
18	Hetland <i>et al</i> <sup>[28]</sup>	Registry	Prospective	Naive	ADA <i>vs</i> ETA <i>vs</i> IFX	Denmark	Mixed	86	12
19	Blom <i>et al</i> <sup>[29]</sup>	Registry	Prospective	Therapeutic failure	RTX <i>vs</i> anti-TNF	The Netherlands	Mixed	NR	12
20	Chatzidionysiou <i>et al</i> <sup>[30]</sup>	Registry	Prospective	Mixed	RTX monotherapy <i>vs</i> RTX + MTX <i>vs</i> RTX + LEF	Europe	Pharmaceutical industry	NR	12
21	Gotenberg <i>et al</i> <sup>[45]</sup>	Registry	Prospective	Mixed	RTX <i>vs</i> ABAT	France	NR	NR	6
22	Iannone <i>et al</i> <sup>[32]</sup>	Registry	Prospective	NR	ADA <i>vs</i> ETA <i>vs</i> IFX	Italy	NR	NR	48
23	Leffers <i>et al</i> <sup>[33]</sup>	Registry	Prospective	Mixed	ABAT <i>vs</i> TOCI	Denmark	Mixed	NR	48
24	Martinez-P�rez <i>et al</i> <sup>[44]</sup>	Cohort	Retrospective	Mixed	RTX <i>vs</i> IFX	Spain	NR	NR	12
25	Wakabayashi <i>et al</i> <sup>[34]</sup>	Cohort	Retrospective	Therapeutic failure	TOCI <i>vs</i> ETA	Japan	No pharmaceutical industry	60	12
26	Finckh <i>et al</i> <sup>[36]</sup>	Cohort	Prospective	Therapeutic failure	RTX <i>vs</i> anti-TNF	Switzerland	Mixed	NR	24
27	Gomez-Reino <i>et al</i> <sup>[35]</sup>	Cohort	Prospective	Therapeutic failure	RTX <i>vs</i> anti-TNF	Spain	Pharmaceutical industry	36	12
28	Greenberg <i>et al</i> <sup>[37]</sup>	Registry	Prospective	Naive	ADA <i>vs</i> ETA <i>vs</i> IFX	United States	Mixed	74	24
29	Kekow <i>et al</i> <sup>[38]</sup>	Cohort	Retrospective	Therapeutic failure	RTX <i>vs</i> anti-TNF	Germany	Pharmaceutical industry	NR	6
30	Schabert <i>et al</i> <sup>[39]</sup>	Cohort	Retrospective	NR	ADA <i>vs</i> ETA <i>vs</i> IFX	United States	Mixed	15	12

31	Chatzidionysiou <i>et al</i> <sup>[40]</sup>	Registry	Prospective	Therapeutic failure	Anti-TNF <i>vs</i> ETA <i>vs</i> ADA	Stockholm	NR	NR	6
32	Keystone <i>et al</i> <sup>[43]</sup>	Cohort	Retrospective	Therapeutic failure	ABAT <i>vs</i> TOCI	Canada	NR	NR	12
33	Emery <i>et al</i> <sup>[41]</sup>	Cohort	Prospective	Therapeutic failure	RTX <i>vs</i> anti-TNF	Multicentre	Mixed	NR	12
34	Flouri <i>et al</i> <sup>[42]</sup>	Registry	Prospective	Mixed	ADA <i>vs</i> ETA <i>vs</i> IFX	Greece	Mixed	60	12
35	Harrold <i>et al</i> <sup>[31]</sup>	Registry	Prospective	Therapeutic failure	ABAT <i>vs</i> TOCI	United States	Mixed	NR	12

ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; RTX: Rituximab; ABAT: Abatacept; TOCI: Tocilizumab; LEF: Leflunomid; MTX: Methotrexate; sDMARD: Synthetic disease-modifying antirheumatic drugs; NR: Not reported.

according to DAS28, CDAI, SDAI, ACR20, 50 and 70, and HAQ (Table 4).

The good EULAR response for the participants who used etanercept was no different as that for the participants who used infliximab ( $P = 0.08$ ) (Figure 3). However, the meta-analysis exhibited high heterogeneity. Following exclusion of the studies by Kristensen *et al*<sup>[19]</sup> (2006) and Hyrich *et al*<sup>[17]</sup> (2006), the heterogeneity was lowered, and the results became favorable to etanercept ( $P < 0.0001$ ). No difference was found between adalimumab and etanercept ( $P = 0.80$ ) (Figure 4). That meta-analysis also exhibited high heterogeneity; and after the exclusion of the study by Iannone *et al*<sup>[32]</sup> (2011), no heterogeneity was detected ( $P = 0.05$ ). The participants who used adalimumab presented higher good EULAR response compared to those who used infliximab ( $P = 0.009$ ) (Figure 5). However, that meta-analysis exhibited high heterogeneity. Following exclusion of the study by Iannone *et al*<sup>[32]</sup> (2011), the heterogeneity was lowered ( $P < 0.00001$ ). Comparison of etanercept *vs* infliximab, adalimumab *vs* etanercept, and adalimumab *vs* infliximab found similar results relative to moderate EULAR response ( $P > 0.05$ ). Regarding the EULAR no response, the results were favorable to infliximab compared to etanercept ( $P = 0.01$ ), while no difference was detected between adalimumab and infliximab ( $P = 0.09$ ) or etanercept ( $P = 0.60$ ). The study by Gotteberg *et al*<sup>[45]</sup> (2011), which was not included in the meta-analysis due to the lack of studies comparing abatacept and rituximab, did not detect a difference in the EULAR responses between the two drugs ( $P > 0.05$ ). Additionally, the study by Leffers *et al*<sup>[33]</sup> could not be included in the meta-analysis for the same reason and did not detect a difference in the EULAR responses between abatacept and tocilizumab ( $P > 0.05$ ).

The participants who used etanercept exhibited greater remission according to DAS28 compared to the participants who used infliximab ( $P < 0.0001$ ). Comparison of adalimumab and infliximab did not reveal a significant difference ( $P = 0.23$ ). However, that meta-analysis exhibited moderate heterogeneity. Following exclusion of the study by Iannone *et al*<sup>[32]</sup>, the heterogeneity was lowered, and the result became favorable to adalimumab ( $P = 0.001$ ). No significant difference was detected between adalimumab and etanercept ( $P = 0.63$ ). However, the meta-analysis

exhibited high heterogeneity. Following exclusion of the study by Iannone *et al*<sup>[32]</sup>, heterogeneity was lowered ( $P = 0.21$ ). The participants who used etanercept exhibited greater reduction in the DAS28 score compared to the participants who used infliximab ( $P = 0.03$ ). Significant differences were not detected between adalimumab and etanercept ( $P = 0.36$ ) or infliximab ( $P = 0.52$ ). Comparison of etanercept *vs* infliximab or adalimumab did not reveal any statistically significant differences relative to DAS28 ( $P > 0.05$ ). The study by Arenere Mendoza *et al*<sup>[26]</sup> (2010), which was not included in the meta-analysis due to the lack of studies that analyzed the DAS28 outcome, did not report differences between adalimumab and infliximab ( $P > 0.05$ ). The study by Greenwood *et al*<sup>[47]</sup> (2009), which was not included in the meta-analysis due to lack of data, did not report significant differences in the DAS28 response when comparing adalimumab *vs* etanercept, infliximab *vs* adalimumab, and infliximab *vs* etanercept ( $P > 0.05$ ). The study by Gotteberg *et al*<sup>[45]</sup> (2011), which was also not included in meta-analysis, did not report a difference relative to DAS28 outcome between abatacept and rituximab ( $P > 0.05$ ). The study by Leffers *et al*<sup>[33]</sup> (2011) also did not report a difference between abatacept and tocilizumab relative to DAS28 remission ( $P > 0.05$ ).

In regard to the ACR20 outcome, the comparison of etanercept *vs* adalimumab or infliximab presented similar results ( $P > 0.05$ ). Comparisons of etanercept *vs* infliximab, etanercept *vs* adalimumab, and infliximab *vs* adalimumab did not reveal differences relative to the outcomes of CDAI and SDAI remission, ACR50 and ACR70 ( $P > 0.05$ ).

The HAQ scores of the participants who used adalimumab ( $P = 0.0009$ ) and etanercept ( $P = 0.04$ ) were better compared to the participants who used infliximab. Adalimumab and etanercept were not different in regard to that outcome ( $P = 0.23$ ). Adalimumab and etanercept were also not different in terms of the HAQ reduction outcome ( $P = 0.16$ ). The study by Martinez-Pérez *et al*<sup>[44]</sup> (2011), which was not included in the meta-analysis due to the lack of studies comparing infliximab and rituximab, did not report a difference with respect to HAQ ( $P > 0.05$ ). The study by Leffers *et al*<sup>[33]</sup> (2011), which was also not included in the meta-analysis, did not report a significant difference in HAQ between abatacept and tocilizumab ( $P > 0.05$ ).

N study	Author, Year, Study, Intervention	n	Age (yr)	Male sex (%)	Disease duration, years	Previous anti-TNF (% ou DP)	Previous sDMARD (% ou DP)	Concomitant sDMARD (% ou DP)	Concomitant MTX (% ou DP)	Concomitant steroids (% ou DP)	DAS 28 (DP)	HAQ (DP)
1	Geborek <i>et al</i> <sup>[12]</sup>											
	ETA	166	54.0	22	14.9	NR	4.5	0.7	NR	NR	5.8	1.55
	IFX	135	55.4	21	14.1	NR	4.0	1.0	NR	NR	5.6	1.47
	Value p ETA vs IFX	NA	NS	NS	NS	NR	NS	< 0.001	NR	NR	NS	NS
2	Van Vollenhoven <i>et al</i> <sup>[13]</sup>											
	ETA monotherapy	40	53.3 (2.0)	30	12.7 (1.5)	NR	NR	NR	NR	NR	NR	1.62 (0.08)
	ETA + MTX	57	51.1 (1.7)	9	14.5 (1.3)	NR	NR	NR	NR	NR	NR	1.86 (0.09)
	Value P	NA	NS	< 0.02	NS	NR	NR	NR	NR	NR	NR	NS
3	Cohen <i>et al</i> <sup>[14]</sup>											
	IFX to ETA	24	53.6 (11.3)	12.5	12.2 (9.6)	NR	4.1 (1.8)	NR	NR	NR	5.6 (1.1)	NR
	ETA to IFX	14	55.8 (12.8)	28.6	15.7 (8.9)	NR	4.6 (1.8)	NR	NR	NR	5.9 (1.2)	NR
	Value P	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
4	Finckh <i>et al</i> <sup>[15]</sup>											
	ADA	317	53.0 (51.4-54.7)	26	10.1 (5.6-17.5)	39	NR	53	NR	41	4.19 (4.02-4.36)	1.25 (1.18-1.33)
	IFX	362	53.1 (51.7-54.5)	25	10.2 (5.0-16.5)	12	NR	93	NR	56	4.54 (4.38-4.7)	1.37 (1.29-1.44)
	ETA	519	54.4 (53.2-55.6)	26	10.3 (5.7-15.9)	7	NR	64	NR	60	4.72 (4.59-4.85)	1.37 (1.31-1.43)
	Value P		0.24	0.89	0.97	< 0.001	NR	NR	NR	< 0.001	< 0.001	0.04
5	Heiberg <i>et al</i> <sup>[16]</sup>											
	ADA	84	56.1 (12.9)	21.4	13.5 (9.7)	46	4.9 (2.5)	NR	NR	5.4 (4.7)	5.5 (1.2)	1.89 (0.57)
	ADA+MTX	99	52.4 (14.4)	21.2	11.8 (9.7)	42	3.8 (3.2)	NR	NR	3.4 (4.1)	5.4 (1.2)	1.84 (0.45)
	Value P	NA	0.07	0.97	0.26	0.29	0.01	NR	NR	< 0.01	0.60	0.52
6	Hyrich <i>et al</i> <sup>[17]</sup>											
	ETA monotherapy	763	58 (12)	20	16 (10)	NR	5.0 (2)	NR	NR	54	6.8 (1.0)	2.2 (0.5)
	ETA + MTX	250	54 (12)	24	13 (8)	NR	4.0 (2)	NR	NR	44	6.6 (0.9)	2.1 (0.5)
	ETA + sDMARD	245	55 (12)	21	15 (9)	NR	5.0 (2)	NR	NR	51	6.6 (0.9)	2.1 (0.5)
	IFX monotherapy	128	59 (12)	21	16 (11)	NR	5.0 (2)	NR	NR	69	6.8 (1.1)	2.2 (0.5)
	IFX + MTX	1204	55 (12)	23	14 (9)	NR	4.0 (2)	NR	NR	48	6.7 (0.9)	2.1 (0.5)
	IFX + sDMARD	121	58 (12)	26	14 (9)	NR	5.0 (2)	NR	NR	59	6.8 (1.1)	2.2 (0.6)
	Value P ETA	NA	< 0.001	0.27	0.005	NR	< 0.001	NR	NR	0.01	< 0.001	< 0.001
	Value P IFX	NA	< 0.001	0.65	0.11	NR	< 0.001	NR	NR	< 0.001	0.50	0.03
	Hyrich <i>et al</i> <sup>[18]</sup>											
	ETA	1413	56 (12)	22	15 (9)	NR	4.5 (1.7)	46	27	50	6.7 (1.0)	2.1 (0.5)
	IFX	1810	55 (12)	23	14 (9)	NR	4.2 (1.7)	93	85	50	6.7 (1.0)	2.1 (0.5)
	Value P	NA	NS	NS	NS	NR	NS	< 0.05	< 0.05	NS	NS	NS
7	Kristensen <i>et al</i> <sup>[19]</sup>											
	ETA	309	55.1 (13.0)	18	14.7 (10.1)	NR	4.2 (2.05)	NR	31	NR	5.9 (1.06)	1.6 (0.64)
	IFX	640	56.2 (14.0)	25	12.7 (10.0)	NR	3.6 (1.98)	NR	73	NR	5.6 (1.20)	1.4 (0.62)
	Value P	NA	NR	0.021	< 0.001	NR	< 0.001	NR	< 0.001	NR	< 0.001	0.002
8	Bernal Rivera <i>et al</i> <sup>[20]</sup>											
	ETA total	49	45.3 (5.3)	37	9.9 (2.0)	NR	3.2 (0.26)	NR	65	43	6.3 (0.4)	NR
	ETA + MTX	32	NR	NR	NR	NR	NR	NR	NR	NR	6.2 (0.4)	NR
	ETA monotherapy	10	NR	NR	NR	NR	NR	NR	NR	NR	5.7 (0.9)	NR
	ADA total	50	51.5 (3.7)	42	12.4 (1.9)	NR	3.1 (0.4)	NR	42	52	6.7 (0.3)	NR
	ADA + MTX	21	NR	NR	NR	NR	NR	NR	NR	NR	6.7 (0.5)	NR
	ADA monotherapy	15	NR	NR	NR	NR	NR	NR	NR	NR	6.5 (0.7)	NR
	Value P	NA	NS	NS	NS	NR	NS	NS	NS	NS	NS	NR
9	Fernández-Nebro <i>et al</i> <sup>[21]</sup>											
	IFX	60	54 (11.6)	12	9.6 (7.9)	NR	3.8 (1.5)	NR	83	65	6.2 (1.3)	1.78 (0.56)
	ETA	79	54 (12.4)	24	9.9 (7.9)	NR	3.6 ± 1.3	NR	52	67	5.9 (1.4)	1.71 (0.65)
	ADA	22	54 (10.4)	18	9.5 (8.3)	NR	3.8 ± 1.5	NR	50	48	6.2 (0.9)	1.74 (0.71)
	Value P	NA	NS	NS	NS	NR	NS	NR	< 0.05	NS	NS	NS
10	Radstake <i>et al</i> <sup>[23]</sup>											
	IFX	35	57 (10)	14	NR	NR	NR	NR	100	NR	5.6 (1.2)	NR
	ADA	34	56 (10)	21	NR	NR	NR	NR	41	NR	5.7 (1.0)	NR
	Value P	NA	NS	NS	NR	NR	NR	NR	NS	NR	NS	NR
11	Kievit <i>et al</i> <sup>[22]</sup>											
	ADA	267	55.1 (12.6)	30	7.7 (2.7-13.6)	NR	3.0 (2-4)	NR	NR	NR	5.3 (1.3)	1.3 (0.7)
	ETA	289	54.6 (14.2)	31.1	6 (2.1-13.4)	NR	3.0 (2-4.75)	NR	NR	NR	5.5 (1.2)	1.4 (0.7)
	IFX	151	57.8 (13.4)	29.8	7.7 (2.7-14.1)	NR	3.0 (2-5)	NR	NR	NR	5.2 (1.3)	1.4 (0.7)
	Value P	NA	0.05	0.939	0.356	NR	0.385	NR	NR	NR	0.059	0.176

12	Bazzani <i>et al</i> <sup>[24]</sup>											
	IFX	498	NR	NR	NR	NR	NR	NR	NR	NR	6.01	1.5
	ETA	229	NR	NR	NR	NR	NR	NR	NR	NR	6.05	1.23
	ADA	283	NR	NR	NR	NR	NR	NR	NR	NR	5.76	1.2
13	Value P	NA	NS	NR	NS	NR	NS	NR	NR	NR	< 0.05	< 0.05
	Greenwood <i>et al</i> <sup>[47]</sup>											
	IFX	74	55	28	14	NR	NR	NR	NR	NR	6.86	NR
	ETA	108	57	28	14	NR	NR	NR	NR	NR	6.59	NR
14	ADA	27	55	30	12	NR	NR	NR	NR	NR	6.44	NR
	Value P	NA	NS	NS	NS	NR	NR	NR	NR	NR	NS	NR
	Laas <i>et al</i> <sup>[25]</sup>											
	ETA	58	50 (14)	26	16 (1-47)	NR	NR	NR	53	NR	NR	1.22 (0.68)
15	ADA	39	55 (11)	24	17 (1-37)	NR	NR	NR	54	NR	NR	1.14 (0.72)
	Value P	NA	NS	NS	NS	NR	NR	NR	NS	NR	NR	NR
	Arenere Mendoza <i>et al</i> <sup>[26]</sup>											
	IFX	38	53.4 (14.0)	23.7	9.3 (8.0)	NR	NR	NR	NR	NR	5.60 (1.10)	1.6 (0.7)
16	ETA	44	50.5 (15.0)	15.9	11.9 (9.5)	NR	NR	NR	NR	NR	5.54 (1.27)	1.2 (0.7)
	ADA	37	52.3 (12.8)	16.2	8.1 (6.2)	NR	NR	NR	NR	NR	5.60 (0.88)	1.1 (0.5)
	Value P	NA	0.695	0.606	0.121	NR	NR	NR	NR	NR	0.836	0.051
	Buch <i>et al</i> <sup>[46]</sup>											
17	RTX	101	NR	NR	NR	1.93 (0.77)	NR	NR	NR	NR	6.30 (1.84)	NR
	Anti-TNF	101	NR	NR	NR	1.17 (0.38)	NR	NR	NR	NR	6.29 (1.07)	NR
	Value P	NA	NR	NR	NR	NS	NR	NR	NR	NR	NS	NR
	Canhão <i>et al</i> <sup>[27]</sup>											
18	IFX	206	54.1 (11.9)	15.1	11.2 (9.4)	NR	NR	95.1	NR	73.8	5.9 (1.1)	1.53 (0.62)
	ETA	250	52.4 (12.1)	9.2	10.4 (8.6)	NR	NR	82.4	NR	74.4	5.8 (1.2)	1.55 (0.57)
	ADA	161	50.9 (12.0)	11.8	9.5 (7.6)	NR	NR	86.3	NR	62.1	5.5 (1.1)	1.3 (0.6)
	Value P	NA	0.04	0.16	0.21	NR	NR	0.0001	NR	0.02	0.02	0.008
	Value p IFX vs ETA	NA	NS	NS	NS	NR	NR	NS	NR	NS	NS	NS
	Value p IFX vs ADA	NA	0.01	NS	NS	NR	NR	NS	NR	NS	0.007	0.01
	Value p ETA vs ADA	NA	NS	NS	NS	NR	NR	NS	NR	NS	NS	0.003
	Hetland <i>et al</i> <sup>[28]</sup>											
19	ADA	544	56 (15-85)	25	9 (0-51)	NR	3.0 (0-8)	NR	70	40	5.3 (3.3-8.3)	NR
	ETA	425	58 (19-89)	28	8 (0-47)	NR	3.0 (0-8)	NR	61	43	5.4 (3.3-8.4)	NR
	IFX	908	57 (17-85)	27	9 (0-68)	NR	3.0 (0-9)	NR	87	50	5.4 (3.3-8.3)	NR
	Value p	NA	0.30	0.58	0.24	NR	0.0044	NR	< 0.0001	< 0.0001	0.035	NR
20	Blom <i>et al</i> <sup>[29]</sup>											
	Terceiro anti-TNF	64	53.3 (12.9)	28	8.9 (9.2)	100	4.0 (2.0)	NR	53	38	5.1 (1.30)	1.51 (0.64)
	RTX	90	56.6 (12.2)	27	10.9 (13.7)	100	4.0 (2.3)	NR	49	44	5.32 (1.25)	1.52 (0.78)
	Value P	NA	NS	NS	NS	NS	NS	NR	NS	NS	NS	NS
21	Chatzidionysiou <i>et al</i> <sup>[30]</sup>											
	RTX	505	55.2 (12.9)	18.9	13.2 (10.1)	1.0 (0.8)	2.8 (1.8)	NR	NR	56.6	5.7 (1.3)	1.7 (0.7)
	RTX + MTX	1195	51.9 (13.1)	18.7	11.7 (8.8)	0.9 (0.8)	2.6 (1.5)	NR	NR	59.9	5.9 (1.3)	1.6 (0.7)
	RTX + LEF	177	52.3 (12.1)	16.9	11.4 (7.9)	0.6 (0.8)	2.5 (1.4)	NR	NR	53.2	5.9 (1.2)	1.6 (0.7)
	Value p RTX vs RTX + MTX	NA	< 0.0001	NS	0.003	0.01	0.003	NR	NR	NS	0.02	NS
	Value p RTX vs RTX + LEF	NA	0.001	NS	0.04	< 0.0001	0.05	NR	NR	NS	NS	NS
22	Value p RTX + MTX vs RTX + LEF	NA	NS	NS	NS	0.001	NS	NR	NR	NS	NS	NS
	Gotenberg <i>et al</i> <sup>[45]</sup>											
	RTX	1732	NR	NR	NR	78.8	3.1 (1.4)	NR	NR	NR	5.6 (1.2)	NR
	ABAT	508	NR	NR	NR	89.3	2.8 (1.4)	NR	NR	NR	5.3 (1.3)	NR
23	Value P	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Iannone <i>et al</i> <sup>[32]</sup>											
	ADA	324	54.5 (12)	17.7	11.5 (8.8)	NR	97	25	NR	29	5.37 (1.5)	1.28 (0.5)
	ETA	311	53.5 (14)	13.8	10.7 (8.6)	NR	99	31	NR	44	5.71 (1.5)	1.6 (0.7)
24	IFX	218	51.9 (13)	21.1	9.9 (7.7)	NR	96	44	NR	30	5.6 (1.4)	1.5 (0.6)
	Value p	NA	0.06	NR	0.17	NR	0.19	0.01	NR	0.06	0.04	0.03
	Leffers <i>et al</i> <sup>[33]</sup>											
	ABAT	104	54 (23-82)	22	8 (1-38)	97	3.0 (0-8)	NR	NR	45	5.3 (2.6-7.5)	NR
25	TOCI	97	56 (20-81)	26	7 (1-45)	98	3.0 (1-8)	NR	NR	38	5.4 (1.6-7.8)	NR
	Value p	NA	NS	NS	NS	NS	NS	NR	NR	NS	NS	NR
	Martínez-Pérez <i>et al</i> <sup>[44]</sup>											
	IFX	23	NR	28.6	NR	4.8	NR	NR	NR	NR	NR	1.996 (0.764)
26	RTX	19	NR		NR	100	NR	NR	NR	NR	NR	1.680 (0.763)
	Value P	NA	NR	NA	NR	NR	NR	NR	NR	NR	NR	NR



25	Wakabayashi <i>et al</i> <sup>[34]</sup>											
	ETA	16	57.0 (14.1)	25	10.8 (9.5)	100	NR	NR	NR	100	5.4 (1.3)	NR
	TOCI	23	54.6 (14.6)	13	6.8 (6.4)	100	NR	NR	NR	95.6	4.9 (1.7)	NR
	Value P	NA	0.5389	0.4151	0.2377	NS	NR	NR	NR	1,000	0.3246	NR
26	Finckh <i>et al</i> <sup>[36]</sup>											
	Anti-TNF	163	56 (44-64)	19	11 (0.5)	100	NR	74	NR	48	4.2 (0.08)	1.13 (0.04)
	RTX	155	58 (47-66)	25	12 (0.8)	100	NR	79	NR	56	4.7 (0.14)	1.27 (0.07)
	Value P		0.15	0.18	0.13	NS	NR	0.30	NR	0.16	0.003	0.07
27	Gomez-Reino <i>et al</i> <sup>[35]</sup>						> 2 DMARD					
	RTX	575	55.3 (12.8)	18	NR	100	92.7	NR	NR	NR	5.5 (1.20)	NR
	anti-TNF	513	54.5 (13.5)	19.5	NR	100	86.6	NR	NR	NR	5.0 (1.30)	NR
	Value P	NA	0.364	0.400	NR	NS	0.0028	NR	NR	NR	< 0.0001	NR
28	Greenberg <i>et al</i> <sup>[37]</sup>											
	ADA	460	55 (12)	22	8.9 (9.5)	NR	0.7 (1.0)	NR	NR	35	4.49 (1.6)	0.5 (0.5)
	ETA	480	54 (13)	24	8.8 (9.2)	NR	0.7 (1.0)	NR	NR	33	4.48 (1.4)	0.5 (0.5)
	IFX	535	61 (13)	28	9.6 (9.9)	NR	0.7 (1.0)	NR	NR	33	4.53 (1.4)	0.4 (0.5)
	Value P	NA	< 0.001	0.06	< 0.001	NR	0.73	NR	NR	0.80	0.91	0.11
29	Kekow <i>et al</i> <sup>[38]</sup>											
	RTX	90	57 (27-79)	26.7	7.3 (0.9-30.6)	100	80	83.3	NR	NR	5.6 (0.1)	1.8 (0.1)
	anti-TNF	106	58 (21-83)	18.9	8.4 (0.2-38.3)	100	86.7	82.1	NR	NR	5.4 (0.1)	1.6 (0.2)
	Value P	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
30	Schabert <i>et al</i> <sup>[39]</sup>											
	ETA	218	55.1 (11.6)	15.6	18.52 (10.88)	NR	NR	NR	62.8	61	NR	1.20 (0.73)
	IFX	93	60.2 (12.8)	16.1	19.66 (11.36)	NR	NR	NR	66.7	50.5	NR	1.24 (0.72)
	ADA	40	56.6 (13.0)	30	19.16 (10.9)	NR	NR	NR	62.5	52.5	NR	0.92 (0.76)
	Value p IFX vs ETA	NA	< 0.001	NS	NS	NR	NR	NR	NS	NS	NR	NS
	Value p IFX vs ADA	NA	NS	< 0.05	NS	NR	NR	NR	NS	NS	NR	< 0.05
	Value p ETA vs ADA	NA	NS	< 0.05	NS	NR	NR	NR	NS	NS	NR	< 0.05
31	Chatzidionysiou <i>et al</i> <sup>[40]</sup>											
	Anti-TNF (ADA ou IFX)	161	55.8 (13.8)	21.1	6 (3-15)	100	NR	68.9	NR	45.3	4.87 (1.27)	1.14 (0.65)
	ETA	98	52.7 (14.4)	12.2	7 (2-15)	100	NR	71.4	NR	54.1	4.86 (1.21)	1.14 (0.62)
	RTX	69	60.3 (14.0)	15.9	9 (3-16)	100	NR	59.4	NR	58.0	5.30 (1.29)	1.43 (0.57)
	Value P	NA	< 0.05	NS	NS	NS	NR	NS	NR	NS	NS	< 0.05
32	Keystone <i>et al</i> <sup>[43]</sup>											
	ABAT	24	NR	NR	NR	11 (45.8)	NR	NR	NR	NR	NR	NR
	RTX	37	NR	NR	NR	9 (33.3)	NR	NR	NR	NR	NR	NR
	Value P	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
33	Emery <i>et al</i> <sup>[41]</sup>											
	RTX	405	56.5 (12.6)	23	9.1 (7.7)	NR	2.2 (1.1)	NR	NR	293 (72.3)	5.2 (1.2)	1.5 (0.8)
	Anti-TNF	323	54.7 (13.3)	20	7.8 (6.8)	NR	2.3 (1.3)	NR	NR	229 (70.9)	4.8 (1.3)	1.3 (0.8)
	Value p	NA	0.0611	0.2376	0.1044	NR	0.3853	NR	NR	0.6666	<0.0001	0.0945
34	Flouri <i>et al</i> <sup>[42]</sup>											
	IFX	560	58 (17)	26	8.5 (12.7)	7.0	2.0 (1)	93	NR	59	5.4 (1.5)	1.0 (0.9)
	ADA	435	59 (18)	19	7.8 (12.8)	29.7	2.0 (1)	88	NR	55	5.6 (1.6)	1.0 (0.9)
	ETA	302	57 (19)	20	7.4 (10.6)	33.4	2.0 (1)	87	NR	53	5.7 (1.6)	1.0 (0.9)
	Value P	NA	0.995	0.995	0.354	< 0.001	0.229	0.017	NR	0.259	0.331	0.634
	Value p IFX vs ETA	NA	NS	NS	NS	< 0.05	NS	< 0.05	NR	NS	NS	NS
	Value p IFX vs ADA	NA	NS	< 0.05	NS	< 0.05	NS	< 0.05	NR	NS	NS	NS
	Value p ETA vs ADA	NA	NS	NS	NS	NS	NS	NS	NR	NS	NS	NS
35	Harrold <i>et al</i> <sup>[31]</sup>											
	ABAT	431	57.6 (12.4)	17.6	13.3 (10.0)	NR	NR	NR	55.2	39.4	NR	0.7 (0.5)
	Anti-TNF	746	57.2 (11.7)	20.9	12.1 (9.8)	NR	NR	NR	55.5	33.0	NR	0.6 (0.5)
	Value P	NA	0.578	0.196	0.045	NR	NR	NR	0.951	0.027	NR	0.047

**Figure 2 Patient characteristics of included articles.** ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; RTX: Rituximab; ABAT: Abatacept; TOCI: Tocilizumab; MTX: Methotrexate; sDMARD: Synthetic disease-modifying antirheumatic drugs; NR: Not reported; NS: Not significant; NA: Not applicable.

Table 3 Quality assessment of articles for Newcastle Ottawa scale

N study	Ref.	Selection				Comparability	Results			Total
		Representativeness of the cases	Selection of controls	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	
1	Geborek <i>et al</i> <sup>[12]</sup>	1	1	1	1	2	0	1 (12 mo)	1	8
2	Van Vollenhoven <i>et al</i> <sup>[13]</sup>	0	1	1	1	2	0	1 (24 mo)	0	6
3	Cohen <i>et al</i> <sup>[14]</sup>	1	1	1	1	1	0	1 (3 mo)	0	6
4	Finckh <i>et al</i> <sup>[15]</sup>	1	1	1	0	1	1	1 (12 mo)	1	7
5	Heiberg <i>et al</i> <sup>[16]</sup>	1	1	1	1	2	0	1 (6 mo)	1	8
6	Hyrich <i>et al</i> <sup>[17,18]</sup>	1	1	1	1	2	0	1 (6 mo)	1	8
7	Kristensen <i>et al</i> <sup>[19]</sup>	1	1	1	0	2	0	1 (36 mo)	0	6
8	Bernal Rivera <i>et al</i> <sup>[20]</sup>	1	1	1	0	2	0	1 (12 mo )	1	7
9	Fernández-Nebro <i>et al</i> <sup>[21]</sup>	1	1	1	1	2	0	1 (6 mo)	1	8
10	Radstake <i>et al</i> <sup>[23]</sup>	0	1	1	1	2	0	1 (6 mo)	0	6
11	Kievit <i>et al</i> <sup>[22]</sup>	1	1	1	1	2	0	1 (6 mo)	0	7
12	Bazzani <i>et al</i> <sup>[24]</sup>	1	1	1	0	2	1	1 (6 mo)	1	8
13	Greenwood <i>et al</i> <sup>[47]</sup>	0	1	1	1	2	0	1 (12 mo)	0	6
14	Laas <i>et al</i> <sup>[25]</sup>	1	1	1	1	2	1	1 (3 mo)	1	9
15	Arenere Mendoza <i>et al</i> <sup>[26]</sup>	1	1	1	1	2	0	1 (12 mo)	0	7
16	Buch <i>et al</i> <sup>[46]</sup>	1	1	1	0	2	0	1 (6 mo)	0	6
17	Canhão <i>et al</i> <sup>[27]</sup>	1	1	1	0	2	0	1 (12 mo)	1	7
18	Hetland <i>et al</i> <sup>[28]</sup>	1	1	1	1	2	0	1 (12 mo)	1	8
19	Blom <i>et al</i> <sup>[29]</sup>	1	1	1	1	2	1	1 (12 mo)	1	9
20	Chatzidionysiou <i>et al</i> <sup>[30]</sup>	1	1	1	1	2	0	1 (12 mo)	0	7
21	Gotenberg <i>et al</i> <sup>[45]</sup>	1	1	1	1	2	0	1 (6 mo)	1	8
22	Iannone <i>et al</i> <sup>[32]</sup>	1	1	1	0	2	0	1 (48 mo)	0	6
23	Leffers <i>et al</i> <sup>[33]</sup>	1	1	1	1	2	0	1 (12 mo)	0	7
24	Martínez-Pérez <i>et al</i> <sup>[44]</sup>	0	1	0	1	2	0	1 (12 mo)	0	5
25	Wakabayashi <i>et al</i> <sup>[34]</sup>	0	1	1	1	2	1	1 (12 mo)	1	8
26	Finckh <i>et al</i> <sup>[36]</sup>	1	1	1	1	1	1	1 (24 mo)	1	8
27	Gomez-Reino <i>et al</i> <sup>[35]</sup>	1	1	1	0	2	1	1 (12 mo)	1	8
28	Greenberg <i>et al</i> <sup>[37]</sup>	1	1	1	1	2	0	1 (24 mo)	1	8
29	Kekow <i>et al</i> <sup>[38]</sup>	1	1	1	1	2	0	1 (6 mo)	1	8
30	Schabert <i>et al</i> <sup>[39]</sup>	1	1	1	1	1	1	1 (12 mo)	1	8
31	Chatzidionysiou <i>et al</i> <sup>[40]</sup>	1	1	1	0	2	0	1 (6 mo)	0	6
32	Keystone <i>et al</i> <sup>[43]</sup>	0	1	1	0	2	0	1 (12 mo)	0	5
33	Emery <i>et al</i> <sup>[41]</sup>	1	1	1	0	2	0	1 (12 mo)	0	6
34	Flouri <i>et al</i> <sup>[42]</sup>	1	1	1	1	2	0	1 (12 mo)	1	8
35	Harrold <i>et al</i> <sup>[31]</sup>	1	1	1	0	2	0	1 (12 mo)	0	6

**Anti-TNF naïve patients:** Nine studies assessed anti-TNF-naïve individuals only, from which seven were included in the meta-analysis that assessed the outcomes of EULAR, remission according to DAS28 and CDAI, and ACR20, 50, 70 (Table 5).

The good EULAR response for the participants who used etanercept were the same as those of the participants who used infliximab ( $P = 0.17$ ). However, that meta-analysis exhibited high heterogeneity. Following exclusion of the study by Kristensen *et al*<sup>[19]</sup> (2006), the heterogeneity was low, and the results became favorable to etanercept ( $P = 0.0006$ ). No difference was detected between adalimumab and etanercept ( $P = 0.05$ ). The participants who used adalimumab exhibited greater good EULAR response compared to the participants who used infliximab ( $P = 0.0002$ ). The results relative to the moderate EULAR response outcome were similar in the comparisons of etanercept vs infliximab, adalimumab vs etanercept, and adalimumab vs infliximab ( $P > 0.05$ ). With regard to the EULAR no response, the results were favorable to infliximab compared to etanercept ( $P =$

0.004) or adalimumab ( $P < 0.00001$ ) and to etanercept compared to adalimumab ( $P = 0.004$ ).

The participants who used etanercept exhibited greater remission according to DAS28 compared to the participants who used infliximab ( $P = 0.01$ ). No differences were detected between adalimumab and infliximab ( $P = 0.12$ ) or etanercept ( $P = 0.79$ ).

With regard to the ACR20 outcome, the results of etanercept vs adalimumab or infliximab were not different ( $P > 0.05$ ). No differences were detected for the outcomes of ACR50 and 70 and the remission according to CDAI between etanercept and infliximab, etanercept and adalimumab, and infliximab and adalimumab ( $P > 0.05$ ). Only the study by Greenberg *et al*<sup>[37]</sup> (2012) compared the ACR20 outcome between adalimumab and infliximab ( $P > 0.05$ ). The study by Geborek *et al*<sup>[12]</sup> (2002), which was not included in the meta-analysis because it reported graphical data without numerical values; showed that the ACR 20 response was better with etanercept compared to infliximab ( $P < 0.05$ ), while no differences were detected relative to ACR50 and 70.

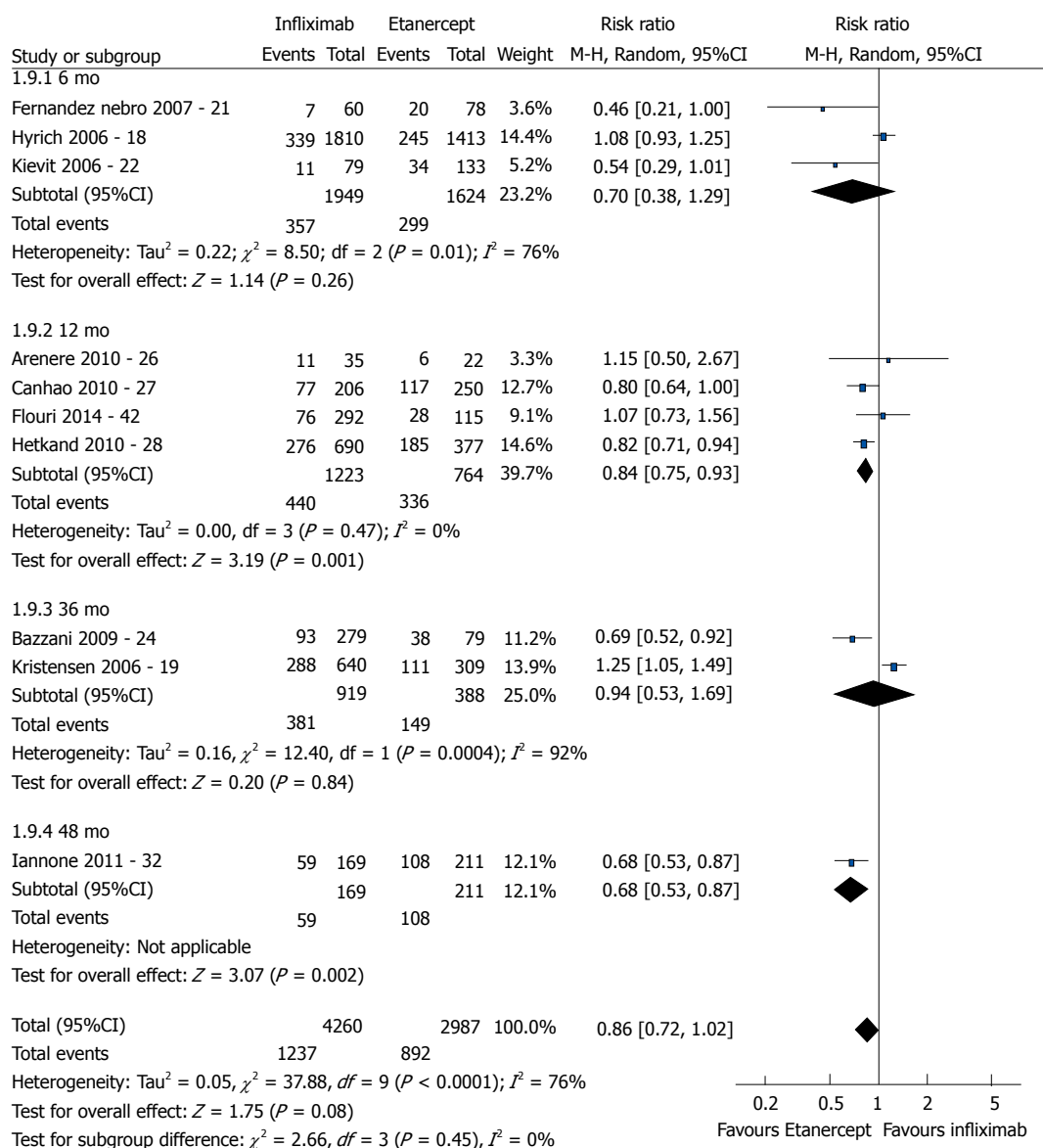


Figure 3 EULAR good response - Etanercept vs Infliximab.

The study by Kievit *et al.*<sup>[22]</sup> (2008) assessed the HAQ reduction outcome and found that the results were better with adalimumab compared to infliximab ( $P < 0.05$ ). Kievit *et al.*<sup>[22]</sup> (2008) and Laas *et al.*<sup>[25]</sup> (2009) did not detect a difference between adalimumab and etanercept ( $P = 0.16$ ).

**Patients with anti-TNF therapeutic failure:** Eleven studies assessed anti-TNF therapeutic failure only, from which nine were included in the meta-analyses that assessed the outcomes of EULAR response and DAS28 reduction (Table 6).

The participants who used rituximab exhibited greater DAS28 reduction compared to those who used anti-TNF agents ( $P = 0.0002$ ); however, the EULAR responses did not differ between these groups ( $P > 0.05$ ). In addition, all of the corresponding meta-analyses exhibited high statistical heterogeneity. The study by Blom *et al.*<sup>[29]</sup> (2011), which was not included in the meta-analysis

because it did not report the DAS28 absolute scores, also detected lower scores for the participants who used rituximab compared to those who used anti-TNF ( $P = 0.004$ ). Among four studies that assessed HAQ, only the Finckh *et al.*<sup>[36]</sup> study (2012) found that the participants who used rituximab exhibited greater score reductions compared to those who used anti-TNF, which did not represent a clinically significant improvement (e.g., a reduction of 0.22 points in the HAQ score).

The participants who used etanercept achieved greater good EULAR response compared to those who did not use that drug ( $P = 0.007$ ); that difference resulted from one study that compared etanercept vs rituximab<sup>[37]</sup>. With regard to the DAS28 score reduction, no differences were reported between the groups ( $P = 0.71$ ).

The abstracts of studies that assessed reduction of the CDAI score indicated the superiority of abatacept over rituximab (12.4 vs +1.7) and anti-TNF agents (7.6

**Table 4** Meta-analysis of the outcomes for patients with treatment-naïve and therapeutic failure

Intervention	Outcomes	Studies (references)	Partici-pants	Relative risk (95%CI) or other mesure	I <sup>2</sup> (%)	P value
IFX <i>vs</i> ETA	EULAR good response	10 (18,19,21,22,24, 26,27, 28, 32,42)	7247	0.86 [0.72-1.02]	76	< 0.0001
	EULAR moderate response	9 (18,19,21,22,24, 26, 28, 32,42)	6791	0.98 [0.84-1.15]	78	< 0.0001
	EULAR no response	9 (18,19,21,22,24, 26, 28, 32,42)	6791	1.20 [1.05-1.38]	46	0.06
	DAS 28 remission	7 (21,26,27,28,32,37,42)	2868	0.70 [0.59-0.84]	0	0.51
	DAS 28	2 (21,26)	196	0.40 [-0.27- 1.07]	59	0.12
	DAS 28 reduction	2 (15,22)	1321	0.40 [0.04-0.77]	77	0.04
	CDAI remission	4 (27,28,37,42)	2293	0.90 [0.74-1.09]	0	0.89
	SDAI remission	2 (27,42)	840	0.87 [0.61-1.26]	0	0.9
	HAQ	3 (21,26,39)	495	0.14 [0.00-0.27]	0	0.51
	ACR 20	2 (19,37)	1309	0.95 [0.86-1.06]	0	0.47
	ACR50	3 (19,28,37)	2315	0.92 [0.81-1.03]	10	0.33
	ACR70	3 (19,28,37)	2315	0.88 [0.57-1.36]	79	0.009
ADA <i>vs</i> ETA	EULAR good response	8 (20,22,24,26,27,28,32,42)	2492	0.97 [0.79-1.20]	73	0.0005
	EULAR moderate response	7 (20,22,24,26,28,32,42)	2080	1.00 [0.89-1.12]	0	0.48
	EULAR no response	7 (20,22,24,26,28,32,42)	2080	0.90 [0.62-1.32]	76	0.0003
	DAS 28 remission	6 (26,27,28,32,37,42)	2412	0.93 [0.68-1.26]	80	0.0001
	DAS 28	2 (20,26)	180	-0.09 [-0.25-0.06]	0	0.73
	DAS 28 reduction	2 (15,22)	1392	0.17 [-0.19-0.52]	68	0.08
	CDAI remission	4 (27,28,37,42)	1883	1.16 [0.77-1.74]	70	0.02
	SDAI remission	2 (27,42)	641	1.40 [0.76-2.59]	55	0.13
	HAQ	2 (26,39)	339	-0.15 [-0.39-0.10]	49	0.16
	HAQ reduction	2 (22,25)	653	-0.07 [-0.16-0.03]	0	0.92
	ACR 20	2 (20,37)	445	0.89 [0.71-1.12]	0	0.68
	ACR 50	3 (20,28,37)	1217	1.09 [0.91-1.31]	18	0.3
	ACR 70	3 (20,28,37)	1436	1.15 [0.92-1.43]	0	0.82
IFX <i>vs</i> ADA	EULAR good response	8 (22,23,24,26,27,28,32,42)	3025	1.25 [1.06-1.47]	57	0.02
	EULAR moderate response	7 (22,23,24,26,28,32,42)	2657	0.91 [0.79-1.04]	31	0.19
	EULAR no response	7 (22,23,24,26,28,32,42)	2657	0.77 [0.56-1.05]	75	0.0006
	DAS 28 remission	6 (26,27,28,32,37,42)	2760	1.15 [0.91-1.46]	63	0.02
	DAS 28 reduction	2 (15,22)	1097	-0.24 [-0.96-0.48]	91	0.001
	CDAI remission	4 (27,28,37,42)	2332	1.30 [0.90-1.88]	68	0.02
	SDAI remission	2 (27,42)	765	1.66 [0.94-2.93]	61	0.11
	HAQ	2 (26,39)	182	-0.33 [-0.53-0.13]	0	0.92
	ACR 50	2 (28,37)	1458	1.14 [0.71-1.84]	79	0.03
	ACR 70	2 (28,37)	1458	1.41 [0.81-2.44]	72	0.06

A value of  $I^2 > 40\%$  indicates statistical heterogeneity between the studies. A value of  $P < 0.10$  from the chi-square test indicates statistical heterogeneity between the studies. CI: Confidence interval; ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; EULAR: European League Against Rheumatism; DAS 28: Disease activity score; SDAI: Simplified disease activity index; CDAI: Clinical disease activity; HAQ: Health Assessment Questionnaire; ACR: American College Rheumatology.

*vs* 8.3); those results could not be assessed in the meta-analysis due to the lack of data<sup>[28,41]</sup>. Harrold *et al.*<sup>[31]</sup> (2014) also assessed ACR20 and 50 outcomes and did not detect any differences between the groups treated with abatacept or anti-TNF agents [0.87 (0.59; 1.29) and 0.86 (0.58; 1.27), respectively].

**Patients who used bDMARD in monotherapy or in combination with methotrexate:** Four studies assessed individuals treated with bDMARD monotherapy or in combination with methotrexate, and three were included in the meta-analysis that assessed EULAR response, DAS28 and HAQ outcomes (Table 7).

Regarding the good EULAR response, combination with methotrexate was better than bDMARD monotherapy ( $P = 0.03$ ) (Figure 6). No difference was found relative to DAS28 between bDMARD monotherapy and combination with methotrexate ( $P = 0.07$ ). However, this meta-analysis exhibited high heterogeneity. Following exclusion of the study by Chatzidionysiou *et al.*<sup>[30]</sup> (2012)<sup>[30]</sup>, no heterogeneity was detected, and the results

became favorable to the combination with methotrexate ( $P < 0.00001$ ). The study by van Vollenhoven *et al.*<sup>[13]</sup> (2003), which was not included in the meta-analysis because it reported graphical data without numerical values, reported a difference in DAS28 favorable to combination with methotrexate compared to bDMARD monotherapy ( $P < 0.05$ ). The study by Heiberg *et al.*<sup>[16]</sup> (2006), which was not included in the meta-analysis due to the lack of studies that assessed the DAS28 reduction outcome, reported a difference favorable to bDMARD in combination with methotrexate ( $P < 0.05$ ). With regard to the HAQ score outcome, the best results were exhibited by bDMARD in combination with methotrexate ( $P = 0.009$ ).

## DISCUSSION

Patients who used adalimumab and etanercept presented similar results among them and better outcomes compared to patients under infliximab therapy. The analysis of subgroup of anti-TNF naïve participants



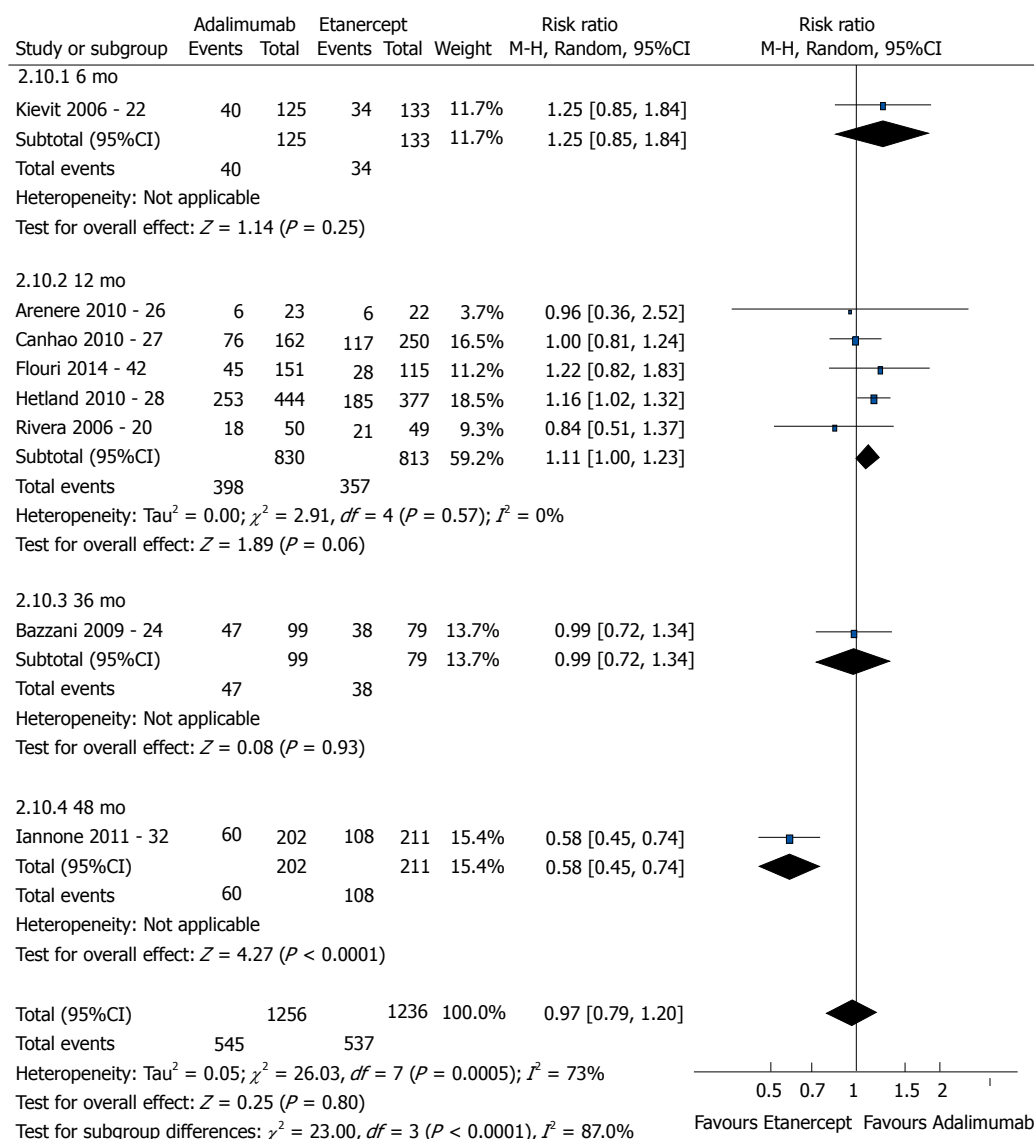


Figure 4 EULAR good response - Etanercept vs Adalimumab.

showed better results for adalimumab and etanercept compared to infliximab. The results were similar to the group with all patients (anti-TNF naïve and/or therapeutic failure), probably because most of the participants under treatment were anti-TNF naïve. The use of bDMARD in combination with methotrexate exhibited greater results than bDMARD monotherapy. Rituximab, etanercept and abatacept proved to be effective therapeutic options following therapeutic failure with anti-TNF agents. However, most of the studies on therapeutic failure assessed rituximab; thus, more studies comparing other drugs are needed to contribute to the choice of third-line agents in actual clinical practice.

Systematic reviews that performed indirect comparison meta-analyses of randomized clinical trials that assessed the efficacy of the anti-TNFs adalimumab, etanercept and infliximab reported similar results<sup>[48-50]</sup>. One meta-analysis found that the efficacy of etanercept was lower compared to that of infliximab and adalimumab; however, the patients selection for the

study was different: the study divided patients by those on etanercept (methotrexate-naïve individuals) and other drugs (patients resistant to methotrexate), which makes the comparison of the results between the medicines difficult<sup>[51]</sup>. The difference of these studies relative to ours might be most likely due to the characteristics of the participants and the low dose of infliximab (3 mg/kg). Some studies reported that patients using infliximab required dose escalation more often compared to those who used etanercept and adalimumab<sup>[52,53]</sup>. Dose escalation might increase the cost of treatment with infliximab<sup>[52]</sup> and might thus result in moderate effectiveness<sup>[54]</sup>. In addition, Pascual-Salcedo *et al.*<sup>[55]</sup> observed that the production of anti-infliximab antibodies is associated with loss of clinical response<sup>[55]</sup>.

The superiority of the combination of bDMARD and sDMARD compared to bDMARD monotherapy was also reported in other recent meta-analyses<sup>[51,56]</sup>. In particular, the same pattern was reported for etanercept in combination with methotrexate in a randomized clinical

**Table 5** Meta-analysis of the outcomes for anti-tumor necrosis factor naïve patients

Intervention	Outcomes	Studies (references)	<i>n</i>	RR (95%CI) or other mesure	<i>I</i> <sup>2</sup> (%)	<i>P</i> value
IFX <i>vs</i> ETA	EULAR good response	5 (19, 21, 22, 27, 28)	2822	0.82 [0.62-1.09]	82	0.0001
	EULAR moderate response	4 (19, 21, 22, 28)	2366	0.90 [0.61-1.33]	90	< 0.00001
	EULAR no response	4 (19, 21, 22, 28)	2366	1.29 [1.09-1.53]	27	0.25
	DAS 28 remission	4 (21, 27, 28, 37)	1804	0.82 [0.70-0.95]	0	0.4
	ACR 20	2 (19, 37)	1309	0.95 [0.86-1.06]	0	0.47
	ACR50	3 (19, 28, 37)	2315	0.92 [0.81-1.03]	10	0.33
	ACR70	3 (19, 28, 37)	2315	0.88 [0.57-1.36]	79	0.009
	CDAI remission	3 (27, 28, 37)	1876	0.88 [0.72-1.08]	0	0.93
ADA <i>vs</i> ETA	EULAR good response	4 (20, 22, 27, 28)	1590	1.11 [1.00-1.23]	0	0.4
	EULAR moderate response	3 (20, 22, 28)	1178	1.01 [0.83-1.24]	19	0.29
	EULAR no response	3 (20, 22, 28)	1178	0.69 [0.53-0.89]	11	0.32
	DAS 28 remission	3 (27, 28, 37)	1380	1.03 [0.82-1.29]	37	0.21
	ACR 20	2 (20, 37)	445	0.89 [0.71-1.12]	0	0.68
	ACR 50	3 (20, 28, 37)	1217	1.09 [0.91-1.31]	18	0.3
	ACR 70	3 (20, 28, 37)	1436	1.15 [0.92-1.43]	0	0.82
	HAQ reduction	2 (22, 25)	653	-0.07 [-0.16-0.03]	0	0.92
IFX <i>vs</i> ADA	CDAI remission	3 (27, 28, 37)	1601	1.02 [0.67-1.56]	72	0.03
	EULAR good response	3 (22, 27, 28)	1706	1.42 [1.18-1.72]	42	0.18
	EULAR moderate response	2 (22, 28)	1338	0.96 [0.58-1.59]	80	0.03
	EULAR no response	2 (22, 28)	1338	0.56 [0.45-0.69]	0	0.88
	DAS 28 remission	3 (27, 28)	1648	1.23 [0.95-1.59]	48	0.15
	ACR 50	2 (28, 37)	1458	1.14 [0.71-1.84]	79	0.03
	ACR 70	2 (28, 37)	1458	1.41 [0.81-2.44]	72	0.06
	CDAI remission	3 (27, 28, 37)	1875	1.17 [0.75-1.82]	75	0.02

A value of  $I^2 > 40\%$  indicates statistical heterogeneity between the studies. A value of  $P < 0.10$  from the chi-square test indicates statistical heterogeneity between the studies. CI: Confidence interval; ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; EULAR: European League Against Rheumatism; DAS 28: Disease activity score; CDAI: Clinical disease activity; HAQ: Health assessment questionnaire; ACR: American College Rheumatology.

**Table 6** Meta-analysis of the outcomes for patients with anti-tumor necrosis factor therapeutic failure

Intervention	Outcomes	Studies (references)	<i>n</i>	Relative risk (95%CI) or other mesure	<i>I</i> <sup>2</sup> (%)	<i>P</i> value
RTX <i>vs</i> anti-TNF	EULAR good response	4 (35, 38, 40, 46)	1608	0.96 [0.60-1.54]	74	0.009
	EULAR moderate response	5 (29, 35, 38, 40, 46)	1706	1.02 [0.79-1.32]	66	0.02
	EULAR no response	3 (35, 38, 40)	1406	1.00 [0.53-1.89]	85	0.001
	DAS 28 reduction	6 (35, 36, 38, 40, 41, 46)	1584	0.42 [-0.65--0.20]	62	0.02
ETA <i>vs</i> control	EULAR good response	2 (14, 40)	173	2.11 [1.23-3.62]	0	0.48
	IFX		38	1.60 [0.63-4.09]		
	RTX		135	2.42 [1.25-4.68]		
	DAS 28 reduction	2 (34, 40)	152	0.15 [-0.65-0.95]	77	0.04
	RTX		113	-0.22 [-0.64-0.20]		
	TOCI		39	0.60 [-0.05-1.25]		

A value of  $I^2 > 40\%$  indicates statistical heterogeneity between the studies. A value of  $P < 0.10$  from the chi-square test indicates statistical heterogeneity between the studies. CI: Confidence interval; RTX: Rituximab; ETA: Etanercept; IFX: Infliximab; TOCI: Tocilizumab; EULAR: European League Against Rheumatism; DAS 28: Disease activity score.

trial<sup>[57,58]</sup>. The fact that infliximab should be administered in combination with methotrexate is well established<sup>[59]</sup>.

Despite the publication of recent studies on the subject, the definition of the best strategy for patients who exhibit therapeutic failure to at least one anti-TNF agent still poses a challenge<sup>[60]</sup>. Some studies assessed subgroups in an attempt to identify profiles of patients who will benefit from treatment with rituximab. Thus, whereas testing positive for rheumatoid factor did not induce significant changes in the results<sup>[61]</sup>, rituximab proved to be more effective in individuals who tested positive for rheumatoid factor and for anti-cyclic citrullinated peptide antibody<sup>[39]</sup>.

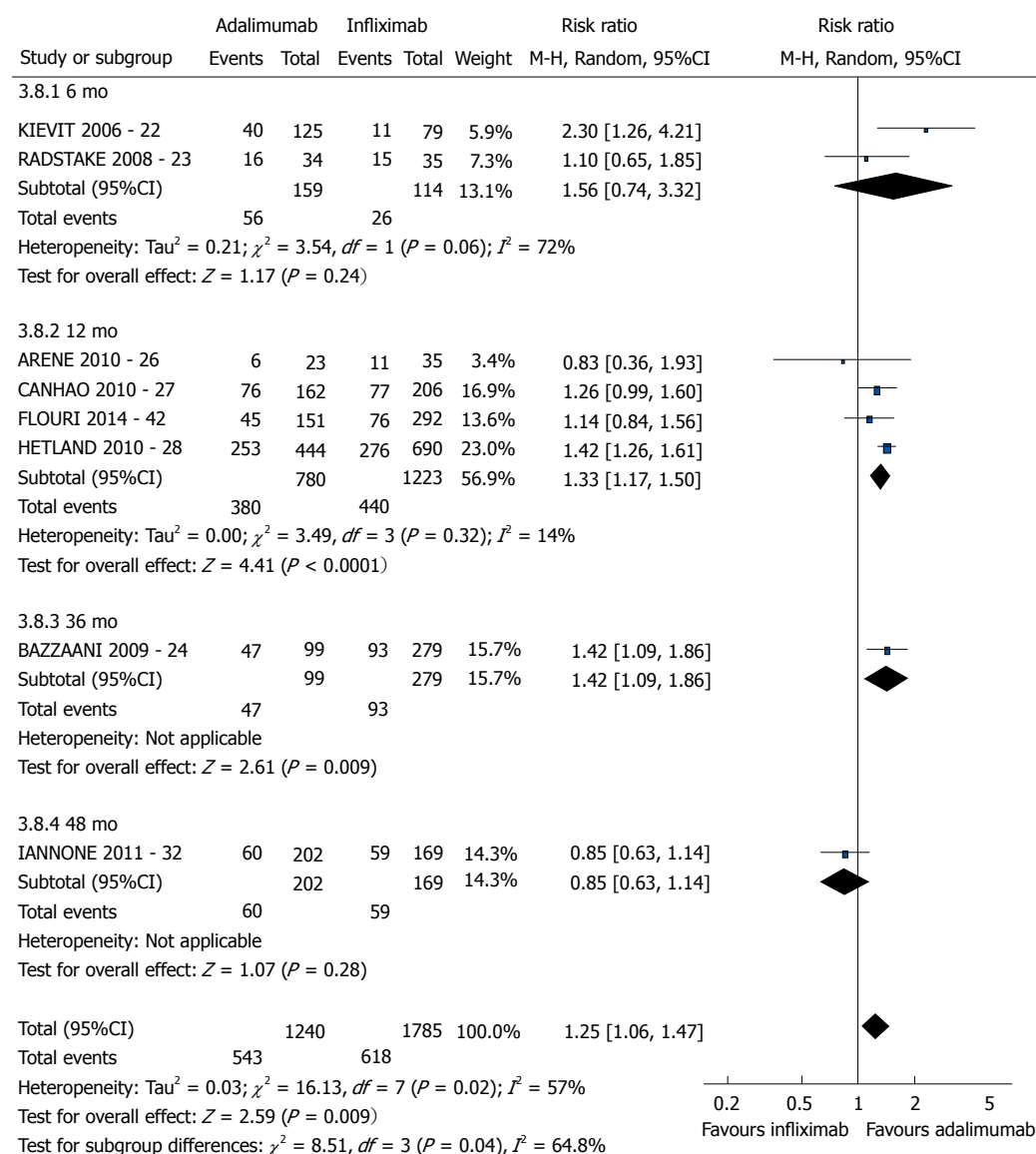
One of the limitations of systematic reviews with meta-analysis of cohort studies concerns selection bias, which is intrinsic to the design of such studies, as the participants are not randomized but might be allocated to a given treatment based on their patient and physician preferences. A consequence of that limitation was the difference noted among the groups at the onset of treatment that, as a whole, manifested as poorer prognosis in the participants from the rituximab group relative to the numbers of anti-TNF and sDMARD previously used, older age, and greater DAS28 and HAQ scores at baseline<sup>[22,36,41]</sup>.

One further limitation is related to the fact that

**Table 7** Meta-analysis of the outcomes for patients in treatment with biological monotherapy *vs* biological in combination with methotrexate

Intervention	Outcomes	Studies (references)	Participants	Relative risk (95%CI) or other measure	$I^2$ (%)	$P$ value
bDMARD	EULAR good response	3 (16,17, 30)	3000	0.57 [0.34-0.95]	82	0.0008
monotherapy <i>vs</i>	DAS 28	3 (17, 20, 30)	2913	0.25 [-0.02-0.52]	69	0.01
bDMARD + MTX	HAQ	2 (165, 30)	655	0.13 [0.03-0.22]	0	0.43

A value of  $I^2 > 40\%$  indicates statistical heterogeneity between the studies. A value of  $P < 0.10$  from the  $\chi^2$  test indicates statistical heterogeneity between the studies. CI: Confidence interval; bDMARD: Biological disease-modifying antirheumatic drugs; MTX: Methotrexate; EULAR: European League Against Rheumatism; DAS 28: Disease activity score; HAQ: Health Assessment Questionnaire.

**Figure 5** EULAR good response - Infliximab vs Adalimumab.

observational studies are conducted under real-life non-controlled conditions. For that reason, differences were detected in the number of participants among the groups, in the disease activity, and in the lack of dose standardization, especially in the case of infliximab. Moreover, observational studies have the advantage of recruiting large numbers of participants. These types of

studies more accurately represent real-life conditions and are able to provide complementary data to the results of randomized clinical studies. Some studies reported that the participants in randomized controlled clinical trials exhibited greater disease activity and fewer associated comorbidities compared to those patients treated in the actual practice setting. The practice of prescribing

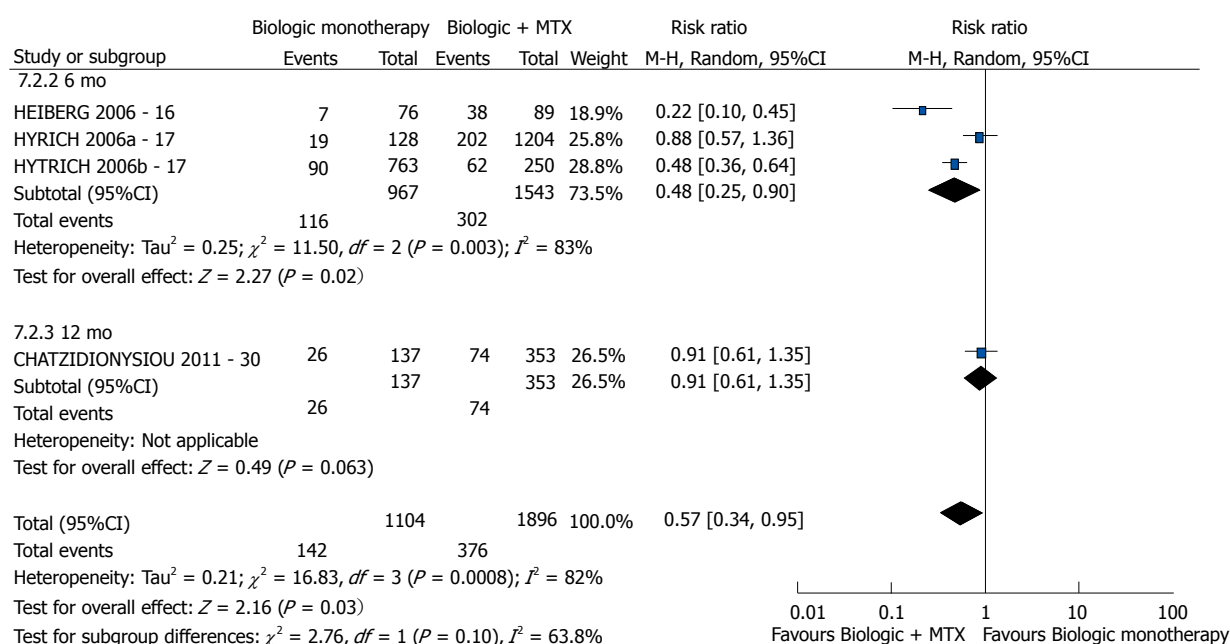


Figure 6 EULAR good response - Biologic monotherapy vs Biologic + MTX.

has been modified over time in real-life. bDMARDs (specially in clinical trials) were prescribed only when patients presented high activity of disease and, now, the medicines are prescribed when the activity is moderate or high<sup>[62-64]</sup>. Kievit *et al.*<sup>[65]</sup> (2007) called attention to the reduction of the external validity of randomized clinical trials<sup>[65]</sup>, while another study found similar rates of response in both randomized clinical trials and clinical practice<sup>[62]</sup>.

Nevertheless, all of the assessed therapies were effective to reduce the disease activity and might be considered as therapeutic alternatives as they are proven to exhibit benefits such as greater comfort, less adverse effects and lower cost.

The results of the observational studies included in this review, which reflect the "real-life" use of bDMARD. The best choice for bDMARD treatment-naïve individuals are adalimumab or etanercept in combination with methotrexate. In cases of therapeutic failure with anti-TNF agents rituximab or abatacept (non anti-TNF) or etanercept (as second anti-TNF) might be used; however, more studies of effectiveness were found for rituximab.

## COMMENTS

### Background

Observational studies could provide relevant information for deciding the choice of treatments, the elaboration of clinical protocols, and the formulation of health policies. The present systematic review of biological disease-modifying antirheumatic drugs included cohort observational studies that reported treatment results applied in real-life conditions; thus, these studies are able to fill in gaps in knowledge left by clinical trials.

### Research frontiers

This study evaluate, by systematic review and metanalysis, the effectiveness of biological disease-modifying antirheumatic drugs (bDMARD) for treatment of rheumatoid arthritis for naïve and therapeutic failure patients.

### Innovations and breakthroughs

The innovations of this study is that do not exist others studies evaluating the direct comparison between bDMARD adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, rituximab, tocilizumab and abatacept in the real-world. Furthermore, the study assess naïve and therapeutic failure patients groups.

### Applications

That study is able to fill in gaps in knowledge left by clinical trials with bDMARD adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, rituximab, tocilizumab and abatacept. Furthermore, do not exist others studies evaluating the direct comparison. Then provide relevant information for deciding the choice of treatments.

### Terminology

The Disease Activity Score (DAS) is a clinical index of rheumatoid arthritis (RA) disease activity that combines information from swollen joints, tender joints, the acute phase response and general health. The EULAR response criteria is a classified response criteria which classifies the patients individual as non, moderate or good responders dependent on the change and the level of the DAS and DAS28. The ACR score represents a percentage. An ACR20 score means that a person's RA has improved by 20%, an ACR50 score means it has improved by 50%, and an ACR70 score means it has improved by 70%. The CDAl is a clinical index of RA disease activity that combines information from swollen joints, tender joints and general health. The HAQ is one of the first self-report functional status (disability) measures.

### Peer-review

The authors present an extensive revision about the effectiveness of the biological treatment for rheumatoid arthritis. The paper is well written. It explores the best treatment options for patients with DMARDs failure and provides useful and practical information for clinicians involved in the care of patients with this disease.

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