REVIEW ARTICLE

Biologic agents and small-molecule inhibitors in systemic autoimmune conditions: an update

Diana Prieto-Peña[1], Bhaskar Dasgupta[2]

1 Department of Rheumatology, Marqués de Valdecilla University Hospital, Valdecilla Biomedical Research Institute (IDIVAL), Santander, Spain
2 Department of Rheumatology, Mid & South Essex NHS Foundation Trust, Southend University Hospital, Westcliff-on-Sea, United Kingdom

KEY WORDS

autoimmune diseases, biologics, biosimilars, targeted therapy

ABSTRACT

The progress in the understanding of the pathophysiology of rheumatic diseases provided a rational basis for the development of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), which have completely revolutionized the treatment of inflammatory conditions. These agents differ in terms of their effectiveness for controlling specific rheumatic diseases depending on the pivotal cytokine driving the inflammatory process. Cytokine blockers were the first to be developed and rapidly expanded. They include agents that act against tumor necrosis factor α (TNF-α) (etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol) and interleukin (IL) 6 (tocilizumab and sarilumab), IL-1 (anakinra, canakinumab, and rilonacept), IL-17 (secukinumab and ixekizumab), and IL-12/23 (ustekinumab) receptors. Lymphocyte-targeting agents include rituximab and belimumab, which act against B cells by different mechanisms, and abatacept, which is a T cell costimulation modulator. tsDMARDs, also known as small-molecule inhibitors, are oral drugs based on a novel strategy to treat inflammatory diseases. Janus kinase (JAK) inhibitors (tofacitinib, baricitinib, and upadacitinib) and phosphodiesterase 4 inhibitors (apremilast) form this group. The major concern with the use of bDMARDs and tsDMARDs is a higher risk of infections. Performance of blood tests as well as screening for tuberculosis and hepatitis viral infection are mandatory prior to biologic therapy initiation. Adherence to an immunization program is also recommended. Whenever possible, the choice of bDMARDs and tsDMARDs should be guided by the patient's comorbidities. There have been limited data on the use of these drugs during pregnancy, but anti-TNF-α therapy, rituximab, and anakinra seem to be safe. Biologic agents are expensive, but biosimilars have emerged as a cost-effective option with a potential to treat a greater number of patients.

Correspondence to:
Prof. Bhaskar Dasgupta,
Department of Rheumatology,
Mid & South Essex NHS Foundation Trust, Southend University Hospital,
Prittlewell Chase, Westcliff-on-Sea,
Essex, SS0 0RY, United Kingdom,
phone: +44 01702 435555, email:
bhaskar.dasgupta@southend.nhs.uk
Received: May 21, 2020.
Revision accepted: May 28, 2020.
Published online: June 18, 2020.
Pol Arch Intern Med. 2021;
131 (2): 171-181
doi:10.20452/pamw.15438

Introduction Biologic therapy has been the greatest breakthrough in the management of rheumatic diseases. Advances in the understanding of the pathophysiology of inflammatory conditions led to the development of molecular and cellular targeted therapy, which profoundly changed the management of rheumatic diseases. Currently used biologic agents for rheumatic diseases can be classified as cytokine blockers and lymphocyte-targeting agents.[1]

Furthermore, in recent years, targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) have emerged to stay in the armamentarium of the treatment of inflammatory disorders. tsDMARDs are small molecules targeting intracellular transduction pathways. They differ from biologic agents in terms of structure, synthesis, and route of administration. Compared with biologic agents, tsDMARDs are relatively simple chemical compounds that can be manufactured using less complicated production processes. Because of their structural properties, tsDMARDs can be administered orally and they are not prone to induce immunogenicity.

Throughout this review, we provide an updated overview of the mechanisms of action, therapeutic indications, efficacy, and safety of the currently available biologic disease-modifying antirheumatic drugs (bDMARDs) and tsDMARDs, based on the results of randomized clinical trials and real-world studies.

TABLE 1 Main characteristics of anti–tumor necrosis factor α agents

Agent	Structure	Indications	Dosage	
Etanercept	Humanized dimeric fusion protein of IgG1 Fc and TNF receptor that binds TNF-α and TNF-β	RA, PsA, psoriasis, AS, non-radiographic axial spondyloarthritis, and JIA	25-mg s.c. injections twice weekly or 50-mg s.c. injections once weekly	
Infliximab	Chimeric mouse-human IgG1 monoclonal antibody against TNF	RA, PsA, psoriasis, AS, CD, and UC	3–5-mg/kg i.v. infusion followed by 3–5-mg/kg i.v. infusion at 2 and 6 weeks, then every 8 weeks	
Adalimumab	Fully humanized IgG1 monoclonal antibody	RA, PsA, psoriasis, AS, non-radiographic axial spondyloarthritis, CD, UC, JIA, nonanterior non-infectious uveitis and hidradenitis suppurativa	Standard dose	40-mg s.c. injections every other week
			CD, UC, and hidradenitis suppurativa	160 mg on day 1, 80 mg on day 15, then 40-mg s.c. injections every other week
			Psoriasis and uveitis	80 mg on day 1, 40 mg on day 7, then 40-mg s.c. injections every other week
Golimumab	Fully humanized IgG1 monoclonal antibody	RA, PsA, AS, nonradiographic axial spondyloarthritis, UC, and JIA	RA, PsA, AS, non-radiographic axial sponyloarthritis	Weight <100 kg: 50-mg s.c. injections monthly
				Weight >100 kg: 100-mg s.c. injections monthly
			UC	Weight <80 kg: 200 mg on day 1, then 100 mg on day 15, and then 50 mg monthly
				Weight >80 kg: 200 mg on day 1, then 100 mg on day 15, and then 100 mg monthly
Certolizumab	PEGylated Fc-free antigen binding fragment	RA, PsA, psoriasis, AS, non-radiographic axial spondyloarthritis; CD (only FDA)	400-mg s.c. injections at weeks 0, 2, and 4; then, 200 mg every 2 weeks or 400 mg monthly	

Abbreviations: AS, ankylosing spondylitis; CD, Crohn disease; FDA, Food and Drug Administration; Ig, immunoglobulin; i.v., intravenous; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; s.c., subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis

Cytokine blockers Biologic agents targeting cytokines were developed based on the recognition of the pivotal role of proinflammatory cytokines in the pathogenesis of rheumatic diseases. The currently available cytokine blockers include tumor necrosis factor α (TNF-α) inhibitors, interleukin (IL) 6 receptor blockers, IL-1 inhibitors, anti–IL-17 agents, and IL-12/23 blockers.

Tumor necrosis factor α inhibitors Interestingly, anti–TNF-α agents were first designed for the treatment of severe sepsis in the late 1980s,[2] based on the hypothesis that the excessive production of TNF-α was pathogenic in severe sepsis and septic shock. However, clinical trials showed that, far from being effective, anti–TNF-α blockers were even harmful to patients with sepsis.[3]

Fortunately, this initial failure of the pharmaceutical industry led to the development of the first "rational" treatment for rheumatoid arthritis (RA) based on the observation that TNF-α played the central role in the macrophage-related pathogenesis of RA.[4]

Five TNF-α blockers are currently approved for the treatment of rheumatic inflammatory diseases: a single TNF-α receptor soluble fusion protein (etanercept), 3 immunoglobulin G (IgG) monoclonal antibodies against TNF-α (infliximab, adalimumab, and golimumab), and a single anti-TNF-α PEGylated Fab (certolizumab).[5] Structural variations among them are responsible for the different properties and advantages of each agent. The approved indications for and routes of administration of TNF-α inhibitors are summarized in TABLE 1.

The most important concern regarding the prolonged use of TNF-α therapy is the increased risk of serious infections and reactivation of latent tuberculosis. Moreover, TNF-α inhibitors are not recommended in patients with New York Heart Association class III or IV heart failure. A higher incidence of lupus-like syndrome, demyelinating disease, and cutaneous malignancies has been reported in patients receiving anti–TNF-α agents.[6]

Etanercept Etanercept was the first anti–TNF-α agent approved by the United States Food and Drug Administration (FDA) for the management of RA.[7] It is a humanized recombinant dimeric fusion protein between a human Fc molecule of IgG and 2 copies of the ligand-binding portion of the TNF receptor p75, which acts as a "false soluble receptor" with a much higher affinity than endogenous soluble receptor to circulating TNF-α and TNF-β, blocking them from binding to cell surface TNF receptors.[7] In contrast to the other TNF-α inhibitors, etanercept does not bind transmembrane TNF and, consequently, it does not induce lysis of TNF-producing cells.[7]

Etanercept has demonstrated efficacy in the treatment of RA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), psoriasis, axial spondyloarthritis (AS), and nonradiographic axial spondyloarthritis (SpA).[7,8] However, it seems not to be adequate for the treatment of inflammatory bowel disease (IBD) and, paradoxically, its use has been associated with the development of de novo uveitis and the induction of uveitis flares in patients with inflammatory conditions.[9]

An advantageous property of etanercept is lower immunogenicity in comparison with other anti–TNF-α agents. Etanercept forms smaller immune complexes and it only contains foreign epitopes in the fusion part of its structure, which may prevent the formation of neutralizing antidrug antibodies.[10] This may explain why etanercept monotherapy also shows good prolonged responses.[8]

Regarding safety, a meta-analysis of randomized clinical trials showed that the incidence rate of serious infections among the users of anti–TNF-α agents was lowest for etanercept.[11] A lower risk of latent tuberculosis reactivation has been also reported, which suggests that the lack of binding to transmembrane TNF could explain these insights.[12]

Infliximab Infliximab is a chimeric mouse-human monoclonal antibody that binds both soluble and membrane-bound TNF-α. It is labeled for use in RA, AS, PsA, Ps, Crohn disease (CD), and ulcerative colitis (UC). In long-term safety studies, infliximab showed a favorable safety profile, although a higher risk of serious infections has been observed.[13,14]

Adalimumab Adalimumab differs from infliximab, as it is a fully humanized anti–TNF-α agent resulting in lower immunogenicity. Currently, it is the TNF-α blocker with the widest approved indications including the treatment of RA, PsA, psoriasis, AS, JIA, nonradiographic axial SpA, CD, and UC. Of note, adalimumab is the only biologic agent labeled for use in noninfectious uveitis[15] and hidradenitis suppurativa.

Long-term studies support the safety of adalimumab.[16,17] Rates of lupus-like syndrome and demyelinating disease appear to be lower as compared with infliximab and etanercept therapy.[18-20]

Golimumab Golimumab, like adalimumab, is a fully humanized IgG antibody against TNF-α. It is labeled for the treatment of RA, PsA, AS, nonradiographic axial SpA, UC, and JIA. Its main advantage is that it can be administered as monthly subcutaneous injections. This may be important in selected cases to improve adherence to treatment. The safety profile of golimumab is similar to that of the remaining TNF-α blockers.[21] Noteworthy, no cases of lupus-like syndrome have been reported in patients receiving golimumab.[19]

Certolizumab pegol Certolizumab pegol is an Fc-free, PEGylated anti–TNF-α agent approved for the treatment of RA, PsA, Ps, AS, and nonradiographic axial SpA. It is also licensed for the management of CD by the FDA. Certolizumab pegol differs from other anti–TNF-α agents in the absence of the Fc region that confers advantageous properties,[22] such as a lower antibody-dependent cell-mediated cytotoxicity and lack of transport through the placenta in pregnant women, since certolizumab pegol cannot bind the placental neonatal Fc receptors.[23] Another distinctive feature of certolizumab pegol is that it is PEGylated, which is used to improve drug pharmacokinetics and bioavailability.[22] The safety profile of certolizumab pegol is similar to that of other anti–TNF-α agents.[24]

Interleukin 6 inhibitors Interleukin 6 is known to play an important role in the differentiation of T helper cells. It regulates the balance between IL-17 producing T helper cells (Th17) and regulatory T cells (Tregs).[25] During homeostasis, IL-6 crucially contributes to host defense against stress and infections. However, dysregulated persistent IL-6 synthesis leads to severe inflammatory responses, which can induce chronic inflammatory disorders. In light of these insights, IL-6 blockers can be regarded as promising tools for the treatment of inflammatory diseases.[26,27]

Currently, 2 IL-6 inhibitors against IL-6 receptor are available: tocilizumab and sarilumab. Other IL-6 blocking agents directly targeted at IL-6 that have been investigated or are under investigation include sirukumab, olokizumab, and clazakizumab.

Tocilizumab Tocilizumab is a recombinant humanized IgG1 antibody directed against soluble and membrane-bound IL-6 receptors.[28] Tocilizumab was first approved in 2005 in Japan for the treatment of Castleman disease, but its indications were rapidly extended. Currently, it is labeled for use alone or in combination with DMARDs in the treatment of severe active RA, systemic and polyarthritis JIA, and giant cell arteritis (GCA). Noteworthy, tocilizumab is the only approved biologic agent for the management of GCA based on the results of the GiACTA (GiantCell Arteritis Actemra) trial.[29] The blockade of IL-6 was considered a potential therapeutic option in GCA, considering the original observation that IL-6 levels are elevated in GCA and polymyalgia rheumatica[30] and decreased in response to glucocorticoids in patients with GCA. Tocilizumab has been recently approved in Japan for the treatment of Takayasu arteritis.[31] Real-world studies also support its efficacy for the management of large-vessel vasculitis.[32]

Tocilizumab is administered intravenously at a standard dose (8 mg/kg/4 weeks) or subcutaneously (162 mg/week).[28] Long-term studies have demonstrated its good safety profile.[33] The strongest clinical and economic advantage of

TABLE 2 Main characteristics of interleukin 1 inhibitors

Agent	Structure and mechanism of action	IL-1 inhibition	Indications	Dosage
Anakinra	Recombinant inhibitor of the IL-1 type 1 receptor	IL-1α and IL-1β	RA, CAPS, and Still disease	100-mg s.c. injection daily
Canakinumab	Human monoclonal antibody directed against IL-1β	IL-1β	CAPS, Still disease, periodic fever syndromes, TRAPS, HIDS/MKD, FMF, and gouty arthritis	150-mg s.c. injections every 4–8 weeks
Rilonacept	Soluble IL-1 trap fusion protein	IL-1α, IL-1β, and IL-1 receptor	CAPS (only FDA)	160-mg s.c. weekly injection

Abbreviations: CAPS, cryopyrin-associated periodic syndromes; HIDS, hyperimmunoglobulin D syndrome; IL, interleukin; FMF, familial Mediterranean fever; MKD, mevalonate kinase deficiency; TRAPS, tumor necrosis factor receptor–associated periodic syndrome; others, see TABLE 1

this biologic agent for the treatment of RA lies in its effectiveness as monotherapy. The major considerations associated with the use of tocilizumab include an increased risk of infections (particularly skin infections), gastrointestinal perforation in patients with a history of diverticular disease, liver function abnormalities, and worsening of the lipid profile.[6,28]

Sarilumab Sarilumab is a fully IgG1 monoclonal antibody that also binds to both soluble and membrane-bound IL-6 receptors.[34] The FDA and European Medicines Agency (EMA) approved its use for RA as 150-mg or 200-mg subcutaneous injections administered every 2 weeks. In comparison with tocilizumab, sarilumab has a higher affinity for binding the IL-6 receptor and longer half-life, which allows for a reduction in the frequency of administration. The safety profile is similar to that of tocilizumab.[34,35]

Interleukin 1 inhibitors Interleukin 1 inhibitors have shown considerable efficacy in conditions in which inflammasome activation plays a pivotal role, such as gout, adult-onset Still disease,[36] and autoinflammatory disorders.[37] The inflammatory role of IL-1 was discovered when patients with cancer received IL-1 therapy to increase host immune response and developed fever, myalgias, and arthralgias.[38]

Three IL-1 antagonists are currently available: a recombinant inhibitor of the IL-1 type 1 receptor (anakinra), a human monoclonal antibody directed against IL-1β (canakinumab), a soluble IL-1 TRAP fusion protein that neutralizes both IL-1α and IL-1 β (rilonacept), and a newly developed IL-1 inhibitor (gevokizumab). The characteristics of these agents are presented in TABLE 2.

Anakinra Anakinra neutralizes IL-1α and IL-1β by competitively inhibiting their binding to IL-1 type 1 receptor. This biologic agent has a very short half-life (4–6 hours) and, consequently, daily injections are needed.[39] The recommended dose for most disorders is 100 mg/day by subcutaneous administration. Anakinra has demonstrated remarkable safety since its introduction in 2002 for the treatment of RA.[40] It is generally well tolerated, and self-limited injection site reactions are the most common adverse events observed.

Anakinra can be administered as monotherapy or in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or DMARDs. Anakinra is approved for use in patients with RA, cryopyrin-associated periodic syndromes (CAPSs), and Still disease including systemic juvenile idiopathic arthritis and adult-onset Still disease.

Canakinumab Canakinumab is a fully human monoclonal antibody that selectively binds to soluble IL-1β and blocks its interaction with the IL-1 receptor. Canakinumab has a longer half-life (21–28 days) than anakinra, which enables it to be administered as 150-mg subcutaneous injections every 4 to 8 weeks.[41] For the patient, a low frequency of injections may have an important impact on the quality of life and consequently improve long-term adherence. However, the high cost of this drug is not affordable in numerous healthcare settings.[42]

Canakinumab is labelled for the treatment of CAPS, Still disease, periodic fever syndromes, TNF receptor–associated periodic syndrome, hyperimmunoglobulinemia D syndrome/mevalonate kinase deficiency, familial Mediterranean fever, and refractory gouty arthritis. It is usually well tolerated, and its safety is well established. Respiratory tract infections are the most common adverse events reported.

Rilonacept Rilonacept differs from anakinra and canakinumab by its ability to block not only IL-1β but also IL-1α and IL-1 receptors. Rilonacept also acts longer than anakinra, with a half-life of 6 to 8 days. It is administered as a weekly 160-mg subcutaneous injection. The frequently reported adverse events include injection-site reactions and upper respiratory tract infections. It is currently labelled by the FDA for the treatment of CAPS only, but it has also shown efficacy in active JIA in a double-blind, placebo-controlled trial.[43]

Interleukin 17 inhibitors Therapeutic agents targeting IL-17 have demonstrated efficacy in

psoriasis and PsA. The overexpression of IL-17 by Th17 cells leads to the activation of several signal transduction pathways and release of various proinflammatory cytokines including IL-6, IL-8, TNF-α, and IL-1β. Moreover, IL-17 has been found to act synergistically with TNF.[44]

Secukinumab was the first IL-17 inhibitor approved for the treatment of SpA based on the successful outcomes observed in the treatment of cutaneous psoriasis. It is a human IgG1 monoclonal antibody that selectively binds to and neutralizes IL-17A.[45] It is licensed by the FDA and EMA, alone or in combination with methotrexate, for the management of psoriasis, PsA, and AS. The recommended dose of secukinumab is 150 mg administered subcutaneously at weeks 0, 1, 2 and, 3, followed by monthly maintenance dosing starting at week 4. It has been shown to be effective in patients not responding to anti–TNF-α therapy.[45,46] The Assessment of SpondyloArthritis international Society–EULAR guidelines approved switching to either another TNF-α inhibitor or an IL-17 inhibitor after the failure of the first TNF inhibitor use and suggest that it may be more reasonable to switch to an IL-17 inhibitor.[47]

In a recent meta-analysis comparing abatacept, apremilast, secukinumab, and ustekinumab for the treatment of PsA, secukinumab along with abatacept and ustekinumab showed the safest profiles.[48] Given the role of IL-17 in host defense against fungal infections, the most commonly reported infections associated with the use of secukinumab are related to *Candida albicans*. Secukinumab is not recommended for patients with a history of IBD owing to its failure to treat CD.[49]

Ixekizumab is a novel anti–IL-17 humanized IgG4 antibody that has been licensed by the FDA and EMA for the treatment of psoriasis and PsA. The recommended dosage is 160 mg by subcutaneous injection at week 0 followed by 80 mg every 4 weeks thereafter.[50] It has shown promising results in AS as well,[51] which led to its approval by the FDA for the management of this disease.

Interleukin 12 and interleukin 23 inhibitors Both IL--12 and IL-23 are members of the IL-12 cytokine family that share a common subunit named p40. Interleukin 12 is thought to induce Th1 response, whereas IL-23 drives Th-17 response.

Ustekinumab is a fully monoclonal IgG1 antibody targeted against the p40 subunit, which neutralizes both IL-12 and IL-23.[52] It is labelled for the management of psoriasis, PsA, CD, and UC. The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks for PsA (90 mg in patients weighing over 100 kg). Currently, ustekinumab is used in the treatment of PsA with inadequate response to NSAIDs and conventional DMARDs as an alternative to anti–TNF-α agents or following their failure.[53] What is an advantage of this drug, it only requires the administration of 4 injections a year, which can improve therapeutic adherence. However, it seems not to be effective for AS.[54] In contrast to IL-17 inhibitors, ustekinumab has shown effectiveness in the treatment of IBD.[55]

Lymphocyte-targeting agents T cells and B cells play a pivotal role in the development of autoimmunity,[47] secretion of cytokines, and production of autoantibodies that, subsequently, promote the maintenance of inflammatory response. Agents targeting B and T cells have shown effectiveness in the treatment of several rheumatic diseases.

B-cell–targeting therapy Currently, 2 B-cell–targeting agents are labelled for the treatment of autoimmune conditions: rituximab and belimumab.

Rituximab Rituximab is a chimeric antibody against the cell-surface CD20 antigen, which is expressed by pre–B cells and mature B cells.[56] It was originally developed for the treatment of B-lymphocyte malignancies, but its use was soon extended for the treatment of autoimmune disorders as a targeted biologic therapy. Rituximab depletes the number of B cells by various mechanisms: complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis.[57] Rituximab leads to rapid B-cell depletion, which can be maintained for 6 to 12 months.[58] However, CD20 is not expressed by antibody-secreting plasma cells and, therefore, the serum autoantibody levels gradually decrease. The onset of clinical response to rituximab is not immediate and not completely dependent on the extent of B-cell depletion. Some indirect effects on short-lived autoreactive plasma cells, autoreactive T effector cells, regulatory T cells, and monocyte-derived macrophages may also be implicated.[59]

Rituximab is approved for the treatment of refractory RA, being more effective in patients who are either rheumatoid factor or anti–citrullinated peptide antibodies positive.[60] It is usually considered in patients with RA-related interstitial lung disease (ILD). The standard dosage for RA includes 2 intravenous infusions of 500 or 1000 mg given 2 weeks apart (days 1 and 15).[58]

Rituximab is also licensed in combination with glucocorticoids for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis. The recommended regimen consists of 4 infusions of 375 mg/m^2 at weekly intervals.[61] It has been shown to be noninferior to cyclophosphamide for induction treatment,[62,63] being particularly useful in patients with refractory or relapsing disease, in women of childbearing age, and in patients previously treated with cyclophosphamide.[64] Low-dose rituximab has been demonstrated to be superior to azathioprine for remission maintenance therapy.[65]

Rituximab is being used with good results as an off-label medicine for a variety of autoimmune disorders including systemic lupus erythematosus

(SLE),[66] Sjögren syndrome,[67] systemic sclerosis,[68] systemic vasculitis, and inflammatory myositis.[69]

Rituximab is generally well tolerated, and the incidence of serious adverse events associated with its use is low. Major concerns regarding the use of rituximab include the risk of reactivation of hepatitis B virus infection and a higher risk of infections related to low IgG levels.[58] Extremely rare cases of progressive multifocal leukoencephalopathy have been reported in association with the use of rituximab.[70]

Belimumab Belimumab is a human monoclonal antibody that blocks the binding of the soluble B-lymphocyte stimulator to B cells, also known as the B-cell activating factor. Consequently, this drug has a negative impact on the survival of B cells (including autoreactive B cells) and prevents the differentiation of B cells into immunoglobulins producing plasma cells.[71]

Currently, it is the only biologic agent approved for the treatment of nonrenal SLE, being the first new drug to be approved for the management of SLE in the last 50 years.[72,73] The rationale for the use of belimumab is the overexpression of the B-lymphocyte stimulator observed in patients with SLE.[74] It is available as subcutaneous and intravenous formulations. The recommended dosage for intravenous administration is 10-mg/kg infusion on days 0, 12, and 28, and then every 4 weeks. The dosage for subcutaneous formulation is 200 mg once weekly.

Belimumab is well tolerated and has a safety profile similar to that of rituximab. However, both in the Unites States and Europe, it is not recommended for older patients (aged above 65 years) and patients with psychiatric disorders.[71] Coadministration of belimumab with rituximab or cyclophosphamide is not recommended.[71]

T-cell costimulation modulators Abatacept was the first T cell costimulation modulator developed for the treatment of autoimmune diseases. It differs from the other biologic agents by a unique mechanism of action that inhibits the complete activation of T cells and downregulates the pro-inflammatory cytokine cascade.

Abatacept is a fusion protein of the extracellular domain of cytotoxic T-lymphocyte antigen 4 and a fragment of the Fc region of human IgG1. It acts as a suppressor of the costimulatory signal by blocking the interaction between CD28 and CD80 or CD86.[75]

Abatacept is licensed by the FDA and EMA for the treatment of RA, JIA, and PsA. Abatacept seems to be especially useful to patients with seropositive RA[76] and when associated ILD exists.[77]

Abatacept is available as intravenous infusions and as 125-mg weekly subcutaneous injections. For intravenous route use, it is administered as a 30-min intravenous infusion at the following doses: 500 mg for patients with bodyweight exceeding 60 kg, 750 mg for those weighing 60 to 100 kg, 1000 mg for those weighing above 100 kg. Following the initial treatment, abatacept may be administered at 2 and 4 weeks after the first infusion and 4-weekly intervals thereafter.[75]

Both intravenous and subcutaneous abatacept administration is usually well tolerated and immunogenicity rates are low for both preparations.[75] Low incidence rates for malignancies and infections (particularly tuberculosis) have been reported with abatacept in clinical trials.[78,79]

Small-molecule inhibitors of signal transduction pathways or tsDMARDs Small-molecule inhibitors have emerged as effective agents with potential advantages over other biologic agents, including oral administration and low rates of immunogenicity. The currently available small-molecule agents are phosphodiesterase 4 and Janus kinase (JAK) inhibitors.

Phosphodiesterase 4 inhibitors Apremilast was the first targeted synthetic agent against phosphosphodiesterase 4. The inhibition of phosphosphodiesterase 4 prevents cyclic adenosine monophosphate (AMP) from being hydrolyzed to AMP, resulting in increased cyclic AMP levels. This affects multiple intracellular signaling pathways downstream resulting in the broad regulation of multiple proinflammatory cytokines, such as TNF-α, interferon γ, IL-12/23, and IL-17.[80,81]

It is approved by the EMA and FDA for use, alone or in combination with DMARDs, for the treatment of psoriasis and PsA. It is the first biologic agent labelled for the management of oral ulcers associated with Behçet disease.[82,83]

The recommended initial dose is 10 mg on day 1, which should be uptitrated each day until reaching the recommended dose of 30 mg twice daily on day 6.[84]

Despite multiple therapeutic options being available for PsA, apremilast found its place in selected patients. The EULAR guidelines consider it in patients with peripheral arthritis who prefer oral therapy.[85] However, for severe cases of PsA or when axial involvement is present, other biologic agents seem to be superior and preferred.[48]

Apremilast is well tolerated, and diarrhea, nausea, and weight loss constitute the commonly reported adverse effects.[86] An advantage over other biologic agents is the absence of monitoring requirement for liver or renal function tests or screening for tuberculosis or viral diseases at therapy initiation or maintenance.[6]

Janus kinase inhibitors Janus kinase inhibitors are increasingly used for the management of autoimmune diseases. The JAK–STAT pathway has been recognized as the major target to inhibit the effects of a wide range of cytokines.[87,88] The JAK family comprises 4 members: JAK1, JAK2, JAK3, and tyrosine kinase 2. Autoimmune conditions are characterized by various cytokine profiles, thus the inhibition of different JAK members should be tailored to the treatment of individual autoinflammatory conditions.

TABLE 3 Main characteristics of the currently available JAK inhibitors for the treatment of rheumatic diseases

Agent	JAK inhibition	Indications	Dosage		Specific safety concerns apart from general monitoring
Tofacitinib	JAK1/JAK3	RA, PsA, UC	RA and PsA	5 mg twice daily	Caution in patients >65 years due to increased risk of infection
			UC	10 mg twice daily during 8–16 weeks, then 5 mg twice daily	Caution in patients at risk for VTE,[a] particularly in those receiving 10 mg twice daily
					Dose adjustment in moderate liver impairment (Child–Pugh B)
					Hematologic contraindications (ALC <750 cells/mm^3, ANC <1000 cells/mm^3, Hb <9 g/dl)
Baricitinib	JAK1/JAK2	RA	4 mg once daily or 2 mg once daily (age >75 years, renal impairment, frequent infections, stabilization of the treated disease, and probenecid treatment) Dose adjustment if creatine clearance 30–60 ml/min Close lipid monitoring Hematologic contraindications (ALC <500 cells/mm^3, ANC <1000 cells/mm^3, Hb <8 g/dl)		Caution in patients at risk for VTE[a]
Upadacitinib	JAK1	RA	15 mg once daily Close lipid monitoring Hematologic contraindications (ALC <500 cells/mm^3, ANC <1000 cells/mm^3, Hb <8 g/dl)		Caution in patients at risk for VTE[a]

a Risk factors for VTE include previous VTE, patients undergoing major surgery, immobilization, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited thrombophilia, malignancy. Additional VTE risk factors such as age, obesity (body mass index ≥30 kg/m^2), diabetes, hypertension, and smoking status should also be considered.

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; Hb, hemoglobin; JAK, Janus kinase; VTE, venous thromboembolism; others, see TABLE 1

Three JAK inhibitors have currently been available for the treatment of refractory RA: tofacitinib, which inhibits JAK1 and JAK3[89]; baricitinib, which inhibits JAK1 and JAK2[90]; and upadacitinib, which inhibits JAK1. Upadacitinib was developed as a JAK 1 selective inhibitor in order to improve the safety profile by minimizing the effects on JAK3 and JAK2.[91] The main characteristics of JAK inhibitors are summarized in TABLE 3.

Recently, tofacitinib has also been licensed for the treatment of PsA and UC. Several clinical trials using either pan-JAK inhibitors or more selective JAK inhibitors for the treatment of other inflammatory conditions are currently underway.[87]

The major concern with the use of JAK inhibitors is the potential reactivation of herpes zoster virus[92,93] and a higher risk of venous thromboembolism.[93] Generally, tofacitinib is considered more suitable in renal impairment and baricitinib in liver impairment. The EMA has recently recommended that tofacitinib should be used with caution in patients over 65 years of age due to an increased risk of serious infections.

General considerations before biologic therapy initiation and monitoring Biologic agents and tsDMARDs are effective drugs that are not free from risks. In this regard, the British Society for Rheumatology guidelines published in 2019 to ensure safe use of biologic drugs.[6] A systematic literature review on the safety of synthetic and biologic DMARDs to inform the 2019 update of the EULAR recommendation for the management of RA was also recently published.[93] The relevant recommendations are discussed below.

Consideration of comorbidities as part of the process for bDMARDs and tsDMARDs choice **Infections** In patients with a high risk of infections, etanercept or abatacept are recommended as first-line biologic therapy.[6] If the risk of tuberculosis reactivation exists in patients requiring anti–TNF-α therapy, consider etanercept over the remaining anti-TNF agents.[11] In HIV-positive patients, a reasonable benefit-risk ratio exists with anti–TNF-α therapy if HIV infection is controlled and a highly effective antiretroviral therapy is used.[6] The risk of herpes zoster reactivation should particularly be considered at prescription of JAK inhibitors.[93,94]

Malignancy bDMARDs and tsDMARDs should not be introduced in patients during diagnostic workup for cancer or ongoing investigations for malignancy.[6] There is conflicting evidence regarding the risk of skin cancers associated with anti-TNF therapy.[93] Anti-TNF therapy is relatively contraindicated in patients who have been previously treated with high doses of psoralen and ultraviolet A and/or ultraviolet B phototherapy.

In patients with a history of previous malignancy and/or premalignant conditions, rituximab may be considered as the first-line biologic agent.[6] The safe interval for starting biologic therapy after malignancy is not clear, but it varies between 5 and 10 years and depends on the type of malignancy.

TABLE 4 Specific precautions to be considered in rituximab, tocilizumab, and anti–tumor necrosis factor α therapy

Biologic agent	Specific precautions
Rituximab	Check serum immunoglobulins prior to each cycle of rituximab
	Be aware of the development of symptoms suggestive of progressive multifocal leukoencephalopathy.
Tocilizumab	Laboratory monitoring every 4 weeks for neutrophils and alanine transaminase/aspartate aminotransferase
	Serum lipids every 3 months
	Stop therapy if bowel perforation occurs.
Anti–TNF-α therapy	Stop therapy if patients develop worsening heart failure while on anti-TNF therapy and refer to a cardiologist.
	Stop therapy if demyelinating disease occurs.
	Stop therapy if lupus-like syndrome develops during anti-TNF therapy.

Abbreviations: see TABLE 1

Cardiovascular comorbidities Biologics should be used with caution in patients with New York Heart Association class III or IV heart failure, particularly in those receiving anti-TNF therapy. A history of myocardial infarction or cardiovascular events is not a contraindication.[6]

Other comorbidities Further comorbidites, in which biologics should be administered with caution, include:
– interstitial lung disease: rituximab or abatacept may be considered the first-line biologics in patients with ILD related to connective tissue diseases.[6,77]
– uveitis: adalimumab use is the only biologic therapy approved for the treatment of uveitis, although other biologic agents have also demonstrated effectiveness. As mentioned before, etanercept is not recommended.[6,9,15]
– demyelinating disease: anti-TNF therapy should not be administered in patients with a history of multiple sclerosis or other demyelinating diseases.[6,20]
– diverticular disease: caution should be taken with tocilizumab, particularly when used with NSAIDs and/or glucocorticoids.[6,93]
– venous thromboembolism: JAK inhibitors should be used with caution in patients at risk for venous thromboembolism.[93]

Recommended pretreatment investigations The following investigations should be performed prior to therapy initiation:
– blood tests: complete blood count, creatinine/calculated glomerular filtration rate, alanine aminotransferase and/or aspartate aminotransferase, and albumin levels.
– screening for tuberculosis: tuberculin skin test or interferon γ release assay or both and a chest radiograph. Patients with latent tuberculosis should be treated with prophylactic antituberculosis treatment before biologic therapy administration, which can be initiated after completing at least 1 month of antituberculosis treatment. Patients with active tuberculosis should be treated before initiating biologic therapy, which may be started after completing at least 3 months of antituberculosis treatment.[6]
– screening for hepatitis B and C virus infection: hepatitis B and C positivity is not an absolute contraindication for biologic therapy, but risks and benefits should be weighed with a hepatologist, particularly for hepatitis B virus infection, which may require antiviral therapy.[6]
– HIV screening if risk factors for HIV infections exist.
– special considerations: patients starting rituximab therapy: baseline immunoglobulin levels (IgA, IgG, and IgM); patients starting tocilizumab therapy: baseline lipid profile. If abnormal, lipid-lowering treatment is recommended.

Recommendations for monitoring during treatment
General recommendations regarding all biologic agents:[6]
– blood tests every 3 to 6 months
– monitoring of tuberculosis infection during biologic therapy and for at least 6 months after stopping treatment
– hepatitis B virus DNA and hepatitis C virus RNA in patients with an occult or overt hepatitis viral infection
– close follow-up of CD4 count and viral load in patients with HIV infection

Specific precautions that should be considered with rituximab, tocilizumab, and anti- TNF-α therapy are summarized in TABLE 4.

Pregnancy According to the last EULAR[95] and the British Society for Rheumatology guidelines,[96] anti-TNF agents, rituximab, and anakinra are considered relatively safe if biologic therapy is needed. All of them are classified as pregnancy category B. Among them, certolizumab seems to provide an advantageous profile due to its limited transfer through the placenta.

Vaccinations According to the British Society for Rheumatology guidelines on biologic DMARD safety[6] and the vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies,[97] immunization status should be assessed in every patient before initiating bDMARDs and tsDMARDs (including varicella-zoster virus antibody test) and a tailored vaccination schedule should be offered depending on the age and comorbidities of each patient. In patients over 50 years of age, the varicella-zoster virus vaccine is recommended. In addition, hepatitis B immunization should be considered in patients at risk.

Patients who are currently on bDMARDs and tsDMARDs should receive influenza and pneumococcal vaccines. However, live attenuated vaccines, including herpes zoster, oral polio, or rabies vaccines, should be avoided. The human papillomavirus vaccine for cervical cancer is recommended in young women if they have already received part of the vaccination schedule.

Future directions A better understanding of disease pathophysiology is needed for the potential identification of common pathways in autoimmune diseases, which will lead to the development of novel targeted therapies.

Personalized therapeutic strategies and early onset of treatment are now fundamental in clinical practice. Novel therapies will allow for an improvement in the management of autoimmune diseases, tailored to the comorbidities of each patient.

The high cost of currently available biologic agents has forced the pharmacology industry to look for more cost-effective options. In this regard, biosimilars have emerged to rationalize costs and allow a larger number of patients to be treated.[98,99] The development of biosimilars should undergo a rigorous process to ensure similar efficacy, safety, and immunogenicity to the reference biologic originator. Biosimilars based on adalimumab, etanercept, infliximab, and rituximab are currently available.[99] However, there is still controversy as to how to use biosimilars in clinical practice. Therefore, a compendium of consensus-based recommendations for the use of biosimilars for rheumatic diseases has been recently published.[100] The expert task force was formed by rheumatologists, dermatologists, gastroenterologists, and pharmacologists from 10 different countries. Experts agreed that there is enough evidence to support switching from the originator biologic to the respective biosimilar. However, they stated that no switch to or among biosimilars should be initiated without the prior awareness of the patients and the treating healthcare provider. Experts concluded that, given the complex aspects of biosimilars, the treating clinician must be the only one to decide whether to prescribe a biosimilar in place of a bio-originator based on a shared decision with the patient.[100] Further experience with biosimilars is needed, but, certainly, its market is expanding to stay as a necessary alternative to original biologic agents.

Hopefully, new bDMARDs and tsDMARDs will be soon available for the management of rheumatic diseases. A novel target is Bruton tyrosine kinase, whose inhibition seems to be useful for the management of SLE (ClinicalTrials.gov identifier, NCT03878303) and RA (ClinicalTrials.gov identifier, NCT03233230). Another promising biologic agent is mavrilimumab, which inhibits the human granulocyte-macrophage colony-stimulating factor receptor. It is currently being investigated for the treatment of GCA (ClinicalTrials.gov identifier, NCT03827018). As previously mentioned, new IL-6 blocking agents are under investigation for the treatment of GCA and RA, such as sirukumab (ClinicalTrials.gov identifiers, NCT01856309 and NCT02531633), olokizumab (ClinicalTrials.gov identifiers, NCT02760433, NCT03120949, and NCT02760407), and clazakizumab (ClinicalTrials.gov identifier, NCT02015520). Undoubtedly, numerous new JAK inhibitors will be soon available for the management of a wide spectrum of inflammatory conditions, such as tyrosine kinase 2 inhibitors (ClinicalTrials.gov identifiers, NCT03943147, NCT03252587, and NCT03881059) or filgotinib that is a selective JAK1 inhibitor (ClinicalTrials.gov identifiers, NCT02065700, NCT03117270, NCT02914522, and NCT02914561).

ARTICLE INFORMATION

CONFLICT OF INTEREST DP-P received research support from UCB Pharma, Roche, AbbVie, and Lilly outside the submitted work. BD received grants/research support from Roche, Sanofi, and Abbvie, speakers bureau/honoraria from Roche Chugai, and consulting fees from Roche, Sanofi, BMS, and GSK outside the submitted work.

HOW TO CITE Prieto-Peña D, Dasgupta B. Biologic agents and small-molecule inhibitors in systemic autoimmune conditions: an update. Pol Arch Intern Med. 2021; 131: 171-181. doi:10.20452/pamw.15438

REFERENCES

1 Choy EH, Kavanaugh AF, Jones SA. The problem of choice: current biologic agents and future prospects in RA. Nat Rev Rheumatol. 2013; 9: 154-163.

2 Cohen J, Carlet J. INTERSEPT: an international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. International Sepsis Trial Study Group. Crit Care Med. 1996; 24: 1431-1440.

3 Eichacker PQ, Parent C, Kalil A, et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. Am J Respir Crit Care Med. 2002; 166: 1197-1205.

4 Brennan FM, Chantry D, Jackson A, et al. Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. Lancet Lond Engl. 1989; 2: 244-247.

5 Mpofu S, Fatima F, Moots RJ. Anti-TNF-alpha therapies: they are all the same (aren't they?). Rheumatol Oxf Engl. 2005; 44: 271-273.

6 Holroyd CR, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis – executive summary. Rheumatol Oxf Engl. 2019; 58: 220-226.

7 Zhao S, Mysler E, Moots RJ. Etanercept for the treatment of rheumatoid arthritis. Immunotherapy. 2018; 10: 433-445.

8 Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. Arthritis Rheumatol Hoboken NJ. 2019; 71: 1112-1124.

9 Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum. 2007; 56: 3248-3252.

10 Kim MS, Lee SH, Song MY, et al. Comparative analyses of complex formation and binding sites between human tumor necrosis factor-alpha and its three antagonists elucidate their different neutralizing mechanisms. J Mol Biol. 2007; 374: 1374-1388.

11 Strand V, Ahadieh S, French J, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther. 2015; 17: 362.

12 Plessner HL, Lin PL, Kohno T, et al. Neutralization of tumor necrosis factor (TNF) by antibody but not TNF receptor fusion molecule exacerbates chronic murine tuberculosis. J Infect Dis. 2007; 195: 1643-1650.

13 Lichtenstein GR, Feagan BG, Cohen RD, et al. Infliximab for Crohn's disease: more than 13 years of real-world experience. Inflamm Bowel Dis. 2018; 24: 490-501.

14 O'Donnell S, Murphy S, Anwar MM, et al. Safety of infliximab in 10 years of clinical practice. Eur J Gastroenterol Hepatol. 2011; 23: 603-606.

15 Suhler EB, Adán A, Brézin AP, et al. Safety and efficacy of adalimumab in patients with noninfectious uveitis in an ongoing open-label study: VISUAL III. Ophthalmology. 2018; 125: 1075-1087.

16 Sator P. Safety and tolerability of adalimumab for the treatment of psoriasis: a review summarizing 15 years of real-life experience. Ther Adv Chronic Dis. 2018; 9: 147-158.

17 Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis,

juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013; 72: 517-524.

18 Almoallim H, Al-Ghamdi Y, Almaghrabi H, Alyasi O. Anti-tumor necrosis factor-α induced systemic lupus erythematosus. Open Rheumatol J. 2012; 6: 315-319.

19 Williams VL, Cohen PR. TNF alpha antagonist-induced lupus-like syndrome: report and review of the literature with implications for treatment with alternative TNF alpha antagonists. Int J Dermatol. 2011; 50: 619-625.

20 Kemanetzoglou E, Andreadou E. CNS demyelination with TNF-α blockers. Curr Neurol Neurosci Rep. 2017; 17: 36.

21 Krüger K, Burmester GR, Wassenberg S, et al. Effectiveness and safety of golimumab in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis under real-life clinical conditions: non-interventional GO-NICE study in Germany. BMJ Open. 2018; 8: e021082.

22 Goel N, Stephens S. Certolizumab pegol. MAbs. 2010; 2: 137.

23 Tun GSZ, Lobo AJ. Evaluation of pharmacokinetics and pharmacodynamics and clinical efficacy of certolizumab pegol for Crohn's disease. Expert Opin Drug Metab Toxicol. 2015; 11: 317-327.

24 Curtis JR, Mariette X, Gaujoux-Viala C, et al. Long-term safety of certolizumab pegol in rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis and Crohn's disease: a pooled analysis of 11 317 patients across clinical trials. RMD Open. 2019; 5: e000942.

25 Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. Eur J Immunol. 2010; 40: 1830-1835.

26 Kang S, Tanaka T, Kishimoto T. Therapeutic uses of anti-interleukin-6 receptor antibody. Int Immunol. 2015; 27: 21-29.

27 González-Gay MA, Pina T, Prieto-Peña D, et al. The role of biologics in the treatment of giant cell arteritis. Expert Opin Biol Ther. 2019; 19: 65-72.

28 Sheppard M, Laskou F, Stapleton PP, et al. Tocilizumab (Actemra). Hum Vaccines Immunother. 2017; 13: 1972-1988.

29 Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med. 2017; 377: 317-328.

30 Dasgupta B, Panayi GS. Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. Br J Rheumatol. 1990; 29: 456-458.

31 Nakaoka Y, Isobe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis. 2018; 77: 348-354.

32 Calderón-Goercke M, Loricera J, Aldasoro V, et al. Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice. Semin Arthritis Rheum. 2019; 49: 126-135.

33 Yamamoto K, Goto H, Hirao K, et al. Longterm safety of tocilizumab: results from 3 years of followup postmarketing surveillance of 5573 patients with rheumatoid arthritis in Japan. J Rheumatol. 2015; 42: 1368-1375.

34 Boyce EG, Rogan EL, Vyas D, et al. Sarilumab: review of a second IL-6 receptor antagonist indicated for the treatment of rheumatoid arthritis. Ann Pharmacother. 2018; 52: 780-791.

35 Raimondo MG, Biggioggero M, Crotti C, et al. Profile of sarilumab and its potential in the treatment of rheumatoid arthritis. Drug Des Devel Ther. 2017; 11: 1593-1603.

36 Castañeda S, Atienza-Mateo B, Martín-Varillas JL, et al. Anakinra for the treatment of adult-onset Still's disease. Expert Rev Clin Immunol. 2018; 14: 979-992.

37 Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018; 281: 8-27.

38 Dinarello CA, van der Meer JWM. Treating inflammation by blocking interleukin-1 in humans. Semin Immunol. 2013; 25: 469-484.

39 Cvetkovic RS, Keating G. Anakinra. BioDrugs. 2002; 16: 303-311.

40 Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis. 2006; 65: 1006-1012.

41 Dhimolea E. Canakinumab. MAbs. 2010; 2: 3-13.

42 Sfriso P, Bindoli S, Doria A, et al. Canakinumab for the treatment of adult-onset Still's disease. Expert Rev Clin Immunol. 2020; 16: 129-138.

43 Ilowite NT, Prather K, Lokhnygina Y, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2014; 66: 2570-2579.

44 Ruiz de Morales JMG, Puig L, Daudén E, et al. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: an updated review of the evidence focusing in controversies. Autoimmun Rev. 2020; 19: 102429.

45 Blair HA. Secukinumab: a review in ankylosing spondylitis. Drugs. 2019; 79: 433-443.

46 Braun J, Baraliakos X, Deodhar A, et al. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. Ann Rheum Dis. 2017; 76: 1070-1077.

47 van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017; 76: 978-991.

48 Kawalec P, Holko P, Moćko P, Pilc A. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. Rheumatol Int. 2018; 38: 189-201.

49 Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 2012; 61: 1693-1700.

50 Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet. 2017; 389: 2317-2327.

51 van der Heijde D, Cheng-Chung Wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet. 2018; 392: 2441-2451.

52 Weber J, Keam SJ. Ustekinumab. BioDrugs. 2009; 23: 53-61.

53 Dobbin-Sears I, Roberts J, O'Rielly DD, Rahman P. Ustekinumab in psoriatic arthritis and related phenotypes. Ther Adv Chronic Dis. 2018; 9: 191-198.

54 Deodhar A, Gensler LS, Sieper J, et al. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. Arthritis Rheumatol. 2019; 71: 258-270.

55 Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019; 381: 1201-1214.

56 Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994; 83: 435-445.

57 Johnson PW, Glennie MJ. Rituximab: mechanisms and applications. Br J Cancer. 2001; 85: 1619-1623.

58 Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011; 70: 909-920.

59 Dörner T, Kinnman N, Tak PP. Targeting B cells in immune-mediated inflammatory disease: a comprehensive review of mechanisms of action and identification of biomarkers. Pharmacol Ther. 2010; 125: 464-475.

60 Isaacs JD, Cohen SB, Emery P, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis. 2013; 72: 329-336.

61 Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016; 75: 1583-1594.

62 Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010; 363: 221-232.

63 Jones RB, Furuta S, Tervaert JWC, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis. 2015; 74: 1178-1182.

64 Puéchal X. Targeted immunotherapy strategies in ANCA-associated vasculitis. Joint Bone Spine. 2019; 86: 321-326.

65 Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014; 371: 1771-1780.

66 Ramos-Casals M, Soto MJ, Cuadrado MJ, Khamashta MA. Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases. Lupus. 2009; 18: 767-776.

67 Verstappen GM, van Nimwegen JF, Vissink A, et al. The value of rituximab treatment in primary Sjögren's syndrome. Clin Immunol. 2017; 182: 62-71.

68 Elhai M, Boubaya M, Distler O, et al. Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. Ann Rheum Dis. 2019; 78: 979-987.

69 Schioppo T, Ingegnoli F. Current perspective on rituximab in rheumatic diseases. Drug Des Devel Ther. 2017; 11: 2891-2904.

70 Berger JR, Malik V, Lacey S, et al. Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event. J Neurovirol. 2018; 24: 323-331.

71 Blair HA, Duggan ST. Belimumab: a review in systemic lupus erythematosus. Drugs. 2018; 78: 355-366.

72 Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011; 377: 721-731.

73 Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B

lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011; 63: 3918-3930.

74 Hui-Yuen JS, Li XQ, Askanase AD. Belimumab in systemic lupus erythematosus: a perspective review. Ther Adv Musculoskelet Dis. 2015; 7: 115-121.

75 Hervey PS, Keam SJ. Abatacept. BioDrugs. 2006; 20: 53-61.

76 Alten R, Nüsslein HG, Mariette X, et al. Baseline autoantibodies preferentially impact abatacept efficacy in patients with rheumatoid arthritis who are biologic naïve: 6-month results from a real-world, international, prospective study. RMD Open. 2017; 3: e000345.

77 Fernández-Díaz C, Loricera J, Castañeda S, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: a national multicenter study of 63 patients. Semin Arthritis Rheum. 2018; 48: 22-27.

78 Alten R, Kaine J, Keystone E, et al. Long-term safety of subcutaneous abatacept in rheumatoid arthritis: integrated analysis of clinical trial data representing more than four years of treatment. Arthritis Rheumatol. 2014; 66: 1987-1997.

79 Simon TA, Askling J, Lacaille D, et al. Infections requiring hospitalization in the abatacept clinical development program: an epidemiological assessment. Arthritis Res Ther. 2010; 12: R67.

80 Keating GM. Abatacept: a review of its use in the management of rheumatoid arthritis. Drugs. 2013; 73: 1095-1119.

81 Schafer PH, Parton A, Capone L, et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. Cell Signal. 2014; 26: 2016-2029.

82 Hatemi G, Mahr A, Ishigatsubo Y, et al. Trial of apremilast for oral ulcers in behçet's syndrome. N Engl J Med. 2019; 381: 1918-1928.

83 Deeks ED. Apremilast: a review in oral ulcers of Behçet's disease. Drugs. 2020; 80: 181-188.

84 Keating GM. Apremilast: a review in psoriasis and psoriatic arthritis. Drugs. 2017; 77: 459-472.

85 Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2016; 75: 499-510.

86 Shavit E, Shear NH. An update on the safety of apremilast for the treatment of plaque psoriasis. Expert Opin Drug Saf. 2020; 19: 403-408.

87 Mao X, Ren Z, Parker GN, et al. Structural bases of unphosphorylated STAT1 association and receptor binding. Mol Cell. 2005; 17: 761-771.

88 Jamilloux Y, El Jammal T, Vuitton L, et al. JAK inhibitors for the treatment of autoimmune and inflammatory diseases. Autoimmun Rev. 2019; 18: 102390.

89 Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017; 390: 457-468.

90 Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017; 376: 652-662.

91 Biggioggero M, Becciolini A, Crotti C, et al. Upadacitinib and filgotinib: the role of JAK1 selective inhibition in the treatment of rheumatoid arthritis. Drugs Context. 2019; 8: 212595.

92 Winthrop KL, Yamanaka H, Valdez H, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014; 66: 2675-2684.

93 Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020; 79: 760-770.

94 Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017; 13: 234-243.

95 Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016; 75: 795-810.

96 Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016; 55: 1693-1697.

97 Papp KA, Haraoui B, Kumar D, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies – executive summary. J Can Assoc Gastroenterol. 2019; 2: 149-152.

98 Sarzi-Puttini P, Ceribelli A, Marotto D, et al. Systemic rheumatic diseases: from biological agents to small molecules. Autoimmun Rev. 2019; 18: 583-592.

99 Smolen JS, Goncalves J, Quinn M, et al. Era of biosimilars in rheumatology: reshaping the healthcare environment. RMD Open. 2019; 5: e000900.

100 Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis. 2018; 77: 165-174.