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

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Article type: Review article

Received: May 21, 2020.

Accepted: May 28, 2020.

Published online: June 18, 2020.

ISSN: 1897-9483
Biologic agents and small-molecule inhibitors in systemic autoimmune conditions: an update

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Short title: Biological therapy and small-molecule inhibitors in autoimmune conditions.

Key words: autoimmune diseases, biologics, biosimilars, targeted, therapy

Conflict of interests statement

DP-P reports research support from UCB Pharma, Roche, AbbVie, and Lilly outside the submitted work. BD reports grants/research support from Roche, Sanofi, Abbvie; speakers bureau/honoraria from Roche Chugai and consulting fees from Roche, Sanofi, BMS and GSK outside the submitted work.
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 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 TNFα (etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol), IL-6 receptor (tocilizumab and sarilumab), IL-1 (anakinra, canakinumab, and rilonacept), IL-17 (secukinumab and ixekizumab) and IL12/23 (ustekinumab). Lymphocyte-targeting agents include rituximab and belimumab which act against B cells by different mechanisms and, abatacept which is a T cell co-stimulation modulator. tsDMARDs, also known as small-molecule inhibitors, are oral drugs with a novel strategy to treat inflammatory diseases. JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) and phosphodiesterase 4 inhibitor (apremilast) form this group.

The major concern with the use of bDMARDs and tsDMARDs is a higher risk for infections. Performance of blood tests, tuberculosis, and hepatitis viral infection screening is mandatory before the onset of biologic therapy. Adherence to an immunization program is also recommended. Whenever possible, the choice of bDMARDs and tsDMARDs should be influenced by the co-morbidities of each patient. During pregnancy limited data exits, but anti-TNFα, rituximab, and anakinra seem to be safe. Biologic agents are expensive, but biosimilar have raised as a more cost-effective option and an opportunity to treat a greater number of patients.
Introduction

Biologic therapy has been the greatest breakthrough in the management of rheumatic diseases. The advance in the acknowledgment of the pathophysiology of inflammatory conditions led to the development of molecular and cellular targeted therapy which profoundly changed the management of rheumatic diseases. Current biologic interventions in rheumatic diseases can be classified as cytokine blockers and lymphocyte-targeting agents [1].

Furthermore, in recent years, 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 to biologic agents, tsDMARDs are relatively simple chemical compounds that can be manufactured by less complicated production processes. Because of its structural properties tsDMARDs, can be orally administered 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 bDMARDs and tsDMARDs, based on the results of randomized clinical trials and real-life studies.

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 are tumor necrosis factor (TNF)-α inhibitors, interleukin (IL)-6 receptor blockers, IL-1 inhibitors, anti-IL17 agents, and IL12/23 blockers.
**TNF-α inhibitors**

Interestingly, anti-TNF-α agents were firstly 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 for being effective, anti-TNF-α blockers were even harmful to the treatment of sepsis[3].

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

Five TNF-α blockers are currently approved for the treatment of rheumatic inflammatory diseases: one TNF-α receptor soluble fusion protein (etanercept (ETN)), three IgG monoclonal antibodies against TNF-α (infliximab (IFX), adalimumab (ADA) and golimumab (GLM)) and one anti-TNF-α PEGylated Fab (certolizumab (CZP))[5]. The structural variations between them are responsible for the different properties and advantages of each agent. Table 1 summarizes the approved indications and route of administration of TNF-α inhibitors.

The most important concerns with prolonged use of TNF-α therapy are increased risk for serious infections and reactivation of latent tuberculosis. TNF-α inhibitors are not recommended in patients with class III or IV cardiac failure. A higher incidence of lupus-like syndrome, demyelinating disease, and cutaneous malignancies have been reported in patients receiving anti-TNFα agents[6].

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

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

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

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

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

**Adalimumab**

ADA differs from IFX in that it is a fully- humanized anti-TNF α agent resulting in less immunogenicity. Currently, it is the TNF α blocker with the widest approved indications, including RA, PsA, psoriasis, AS, JIA, non-radiographic axial SpA, CD, and UC. Of note, ADA is the only biological therapy labeled for non-infectious uveitis [15] and hidradenitis suppurativa.

Long-term studies support the safety of ADA[16,17]. Rates of the lupus-like syndrome and demyelinating disease appear to be lower as compared to IFX and ETN[18–20].

**Golimumab**

GLM, like ADA, is a fully- humanized IgG antibody against TNF α. It is labeled for the treatment of RA, PsA, AS, non-radiographic axial spondyloarthritis, UC, and JIA. The main advantage is that it can be administered as monthly subcutaneous (SC) injections. This can be important in selected cases to improve adherence to treatment. The safety profile of GLM is comparable to the remaining TNF α blockers[21]. Noteworthy, no cases of lupus-like syndrome have been reported in patients under GLM[19].

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

**IL-6 inhibitors**

IL-6 is known to play an important role in the differentiation of T helper cells. IL-6 regulates the balance between IL-17 producing Th helper cells (Th17) and regulatory T-cells (Treg)[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 the development of 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, two IL-6 inhibitors against IL-6 receptor are available: Tocilizumab (TCZ) and Sarilumab. Other IL-6 blocking agents directly targeted on IL-6 that have been investigated or under investigation are sirukumab, olokizumab, and clazakizumab.

**Tocilizumab**

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

TCZ is administered IV at a standard dose (8 mg/kg/4 weeks) or SC (162 mg/week)[28]. The safety profile of TCZ has shown to be good in long-term studies [33]. The strongest clinical and economic advantage of this biological agent for the treatment of RA is its effectiveness as monotherapy. The major considerations when using TCZ are increased risk of infections (particularly, skin infections), gastrointestinal perforation in patients who have history of diverticular disease, liver function abnormalities, and worsening of lipid profile [6,28].

**Sarilumab**

Sarilumab is a fully IgG1 monoclonal antibody that also binds to both soluble and membrane bound IL6 receptor[34]. It is approved as 150 mg or 200 mg sc injections administered every 2 weeks for RA by the United States (US) food and drug administration (FDA) and European medicine agency (EMA). In comparison with TCZ, Sarilumab has a higher affinity for binding the IL6 receptor and longer half-life which allows for a reduction of the frequency of administration. The safety profile is similar to TCZ [34,35].

**IL-1 blockers**
IL-1 inhibitors have shown considerable efficacy in conditions where activation of inflammasome plays a pivotal role, such as gout, adult onset still disease (AOSD) [36], and autoinflammatory disorders[37]. The inflammatory role of IL-1 was discovered when patients with cancer administered IL-1 therapy to increase host immune response, 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) and a soluble IL-1 trap fusion protein that neutralizes both IL-1α and IL-1β (rilonacept) and a novel IL-1 inhibitor has been developed (gevokizumab). Table 2 summarizes the characteristics of these agents.

**Anakinra**

Anakinra (ANK) neutralizes IL-1α and IL-1 β by competitively inhibiting their binding to IL-1 type 1 receptor. This biological 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. ANK has shown remarkable safety since its introduction in 2002 for the treatment of RA[40]. It is generally well-tolerated, self-limited injection site reactions being the most common adverse event.

ANK can be administered as monotherapy or in combination with NSAIDs and/or DMARDs. ANK is approved for patients with RA, cryopyrin-associated periodic syndromes (CAPS), and Still’s disease including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still’s Disease (AOSD).

**Canakinumab**

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

CANA is labelled for treatment of CAPS, Still’s disease, periodic fever syndromes, tumor necrosis factor receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/ mevalonate kinase deficiency (MKD), familial Mediterranean fever (FMF) and refractory gouty arthritis. It is usually well-tolerated, and its safety is well established. Respiratory tract infections are the most common adverse event observed.

**Rilonacept**

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

**IL-17 inhibitors**

Therapeutic agents targeting IL-17 have shown efficacy in Ps and PsA. The overexpression of IL-17 by Th17 cells leads to activation of several signal transduction pathways and the release of various proinflammatory cytokines including IL-6, IL-8, TNF α and IL-1B. Moreover, IL-17 has been found to act synergistically with TNF [44].
Secukinumab was the first IL-17 inhibitor to be approved for the treatment of SpA considering the successful results obtained in the treatment of cutaneous Ps. It is a human IgG1 monoclonal antibody that selectively binds to and neutralized IL-17A[45]. It is licensed by the FDA and EMA, alone or in combination with MTX, for the management of Ps, PsA, and AS. The recommended dosage of secukinumab is 150 mg SC administered at weeks 0, 1, 2, 3, and 4 followed by 4-weekly administration. It has been shown to be effective in patients who have failed anti-TNF α therapy[45,46]. The ASAS-EULAR guidelines allow switching to either another TNFα inhibitor or an IL-17 inhibitor after the failure of the first TNF inhibitor, while stating that it may be more rational 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 profile[48]. Given the role of IL-17 in host defence against fungal infections, the most commonly reported infections with Secukinumab are related to Candida albicans. Secukinumab is not recommended for patients with inflammatory bowel disease history based on its failure to treat Crohn’s disease[49].

Ixekizumab is a novel anti-IL-17 humanized IgG4 antibody which has been licensed by FDA and EMA for the treatment of Ps and PsA. The recommended dose is 160mg by SC 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 AS.

**IL-12/IL-23 inhibitors**
IL-12 and IL-23 are members of the IL-12 cytokine family which share a common subunit named p40. IL-12 is thought to induce Th1 response whereas IL-23 drives the expression of Th-17 response.

**Ustekinumab** is a fully monoclonal IgG1 antibody targeted against the p40 subunit, that neutralizes both IL-12 and IL-23[52]. It is labelled for the management of Ps, 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 if 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, or after the failure of anti-TNF-α agents [53]. An advantage of this drug is that it only requires the administration of 4 injections a year, which can improve the therapeutic adherence. However, it seems to be not useful for axial spondylarthritis[54].

In contrast to IL-17 inhibitors, Ustekinumab has shown effectiveness in the treatment of inflammatory bowel disease[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 perpetuation of the inflammatory response. Agents targeting B-cells and T-cells have shown effectiveness in the treatment of several rheumatic diseases.

**B-cell targeting therapy**

Currently two B-cell targeting agents are labelled for the treatment of autoimmune conditions: Rituximab (RTX) and Belimumab.

**Rituximab**
RTX 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 expanded for the treatment of autoimmune disorders as a targeted biologic treatment. RTX depletes the number of B cells by different mechanisms: complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis[57]. RTX leads to a rapid B-cell depletion that 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 reduce gradually. The onset of clinical response to RTX is not immediate and is not completely dependent on the extent of B-cell depletion. Some indirect mechanisms on short-lived autoreactive plasma cells, autoreactive T-effector cells, regulatory T cells, and monocyte-derived macrophages may also be implicated[59].

RTX is approved for the treatment of refractory RA, being more effective in patients who are either rheumatoid factor (RF) or anticitrullinated-peptide antibodies (ACPA) positive[60]. It is usually considered in patients with RA-related interstitial lung disease (ILD). The standard dosage regimen for RA is two IV infusions of 500 or 1,000 mg given two weeks apart (days 1 and 15)[58].

RTX is also license in combination with glucocorticoids for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The recommended regimen consists of 4 infusions of 375 mg/m2 at weekly intervals[61]. It has shown to be non-inferior than 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]. Lower dose RTX has been shown to be superior to AZA for remission maintenance therapy [65].
RTX is being used with good results as an off-label treatment for a variety of autoimmune disorders including SLE [66], Sjögren’s syndrome[67], systemic sclerosis[68], systemic vasculitis and inflammatory myositis[69].

RTX is generally well tolerated and the incidence of serious adverse events is low. Major concerns with the use of RTX are the risk of hepatitis B reactivation and a higher risk of infections related to low IgG levels[58]. Extremely rare cases of progressive multifocal leukoencephalopathy have been reported with the use of RTX[70].

**Belimumab**

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

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

Belimumab is well-tolerated with a safety profile similar to RTX. However, both in the USA and Europe, it is not recommended for older patients (aged > 65 years) and patients with psychiatric disorders [71]. Coadministration of Belimumab with RTX or cyclophosphamide is not recommended[71].

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

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

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

Abatacept is available as IV infusions and as 125mg weekly SC injections. For IV presentation it is administered as a 30-min intravenous infusion at the following doses: 500mg for patients with a bodyweight < 60 kg; 750mg for those weighing 60-100 kg; 1000 mg for those weighing > 100kg. After the initial treatment, Abatacept may be administered at 2 and 4 weeks after the first infusion and 4-weekly intervals thereafter[75].

Both IV and SC Abatacept are 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 (PD) 4 and Janus kinase (JAK) inhibitors.
Phosphodiesterase 4 inhibitor

Apremilast was the first targeted synthetic agent against phosphodiesterase (PD) 4. The inhibition of PDE4 prevents cAMP from being hydrolysed to AMP, resulting in increased cAMP levels. This affects multiple intracellular signaling pathways downstream resulting in broad regulation of multiple pro-inflammatory cytokines, such as TNF-α, INF-γ, IL-12/23, and IL-17[80,81].

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

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

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

Apremilast is well-tolerated, with diarrhea, nausea, and weight loss the commonly reported side effects[86]. An advantage over other biologic agents is absence of monitoring requirement for liver or renal function tests nor the screening for tuberculosis or viral diseases at initiation or maintenance[6].

JAK inhibitors

Janus kinase (JAK) inhibitors are increasingly used for the management of autoimmune diseases. The JAK-STAT pathway has been recognized as a major target to inhibit the
effects of a wide range of cytokines[87,88]. JAK family comprises four members: JAK1, JAK2, JAK3, and TYK2. Autoimmune conditions are characterized by different cytokines profiles, thus the inhibition of different JAK members should be tailored to the treatment of individual autoinflammatory conditions.

Three JAK inhibitors have currently available for the treatment of refractory RA: Tofacitinib, which inhibits JAK1 and 3 [89]; Baricitinib which inhibits JAK 1 and 2 [90] and; Upadacitinib which inhibits JAK 1. Upadacitinib was developed as a JAK 1 selective inhibitor in order to improve the safety profile by minimizing the effects on JAK 3 and JAK2[91]. Table 3 summarizes the main characteristics of JAK inhibitors.

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

The major concern with the use of JAK inhibitors is the potential reactivation of Herpes Zoster virus [92,93] and a higher risk for venous thromboembolism [93]. In general terms, tofacitinib is considered more suitable in renal impairment and baricitinib for those with 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 onset and monitoring**

Biologic agents and tsDMARDs are effective drugs that are not exempt from risks. In this regard, the British Society for Rheumatology published guidelines in 2019 to ensure safe use of biologic drugs[6]. A systematic literature review about the safety of synthetic and biological DMARDs to inform the 2019 update of the EULAR
recommendation for the management of RA was also recently published[93]. A summary of the important recommendations is discussed below.

Consideration of comorbidities as part of the process for bDMARDs and tsDMARDs choice

Infections

In patients with a high risk of infections, ETN, or ABA are recommended as first-line biologic therapy[6]. If the risk of TB reactivation exists in patients requiring anti-TNF-α therapy, consider ETN over the remaining anti-TNF agents[11]. In human immunodeficiency virus (HIV) positive patients, a reasonable benefit-risk ratio exists with anti-TNFα therapy if HIV infection is controlled and a highly active antiretroviral therapy is given[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 commenced in patients at cancer diagnosis or during ongoing investigations for malignancy[6]. There is conflicting evidence regarding the risk of skin cancers with anti-TNF therapy[93]. Anti-TNF therapy is relatively contraindicated in patients who have had prior treatment with high doses of psoralen and ultraviolet A (PUVA) and/or ultraviolet B (UVB) phototherapy.

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

Cardiovascular comorbidities
Biologics should be used with caution in patients with class III or IV cardiac failure, particularly with anti-TNF therapy. History of previous myocardial infarction or cardiovascular events is not a contraindication[6].

Other comorbidities

- *Interstitial lung disease*: RTX or ABA may be considered a first-line biologics in patients with ILD related to connective tissue diseases (CTD)[6,77].

- *Uveitis*: ADA is the only biologic therapy approved for the treatment of uveitis, although other biologic agents have also demonstrated effectiveness. As mentioned before, ETN is not recommended[6,9,15].

- *Demyelinating disease*: anti-TNF therapy should not be given when there is a previous history of multiple sclerosis or other demyelinating diseases[6,20].

- *Diverticular disease*: caution should be taken with TCZ, particularly when used with NSAIDs and/or glucocorticoids[6,93].

- *Venous thromboembolism*: JAK inhibitors should be used with caution in patients with risk for venous thromboembolism[93].

Recommended pre-treatment investigations

- **Blood tests**: Full blood count, creatinine/calculated glomerular filtration rate (GFR), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and albumin.

- **TB screening**: tuberculin skin test (TST) or IFN-y release assay (IGRA) or both and a chest radiograph. Patients with latent TB should be treated with prophylactic anti-TB treatment before biologic therapy which can be initiated after completing at least 1 month of anti-TB treatment. Patients with active TB
should be treated before starting biologic therapy which may be started after completing at least 3 months of anti-TB treatment[6].

- **Hepatitis B and C screening:** Hepatitis B and C positivity is not an absolute contraindication for biologic therapy, but a risk-benefit decision has to be taken with a hepatologist, particularly for hepatitis B infection which may require antiviral therapy[6].

- **HIV screening** if risk factors for HIV infections exist.

- **Special considerations:**
  - Patients starting RTX: baseline immunoglobulins (IgA, IgG, and IgM)
  - Patients starting TCZ: baseline lipid profile. If abnormal, lipid-lowering treatment is recommended.

*Recommendations for monitoring during treatment*

General recommendations with all biologic agents[6]:

- Blood tests every 3-6 months.
- Monitoring of TB 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 viral hepatitis infection.
- Close follow-up of CD4 count and viral load in patients with HIV infection.

Table 4 summarizes specific precautions that should be taken with RTX, TCZ, and anti-TNF alpha therapy.

**Pregnancy**

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

**Vaccinations**

According to the British Society for Rheumatology biologic DMARD safety guidelines[6] and the Vaccination Guidelines for Patients with immune-mediated disorders on immunosuppressive therapies [97], immunization status should be assessed in every patient before the onset of bDMARDs and tsDMARDs (including varicella-zoster virus antibody test) and, a tailored vaccine 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 for at risk patients.

Patients who are currently under 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**

Improved 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 of the management of autoimmune diseases tailored in accordance with the co-morbidities of each patient.
The high cost of current available biologic agents has forced the pharmacology industry to look for more cost-effective options. In this regard, biosimilars have emerged intending to rationalize costs and allow a larger number of patients to be treated [98,99]. The development of biosimilars must undergo a rigorous process to ensure similar efficacy, safety, and immunogenicity to the reference biologic originator. Biosimilars based on ADA, ETN, IFX, and RTX are currently available [99]. However, there is still controversy on how to use biosimilars in clinical practice. In this regard, 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 ten 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 biological agents.

Hopefully, new bDMARDs and tsDMARDs will be soon available for the management of rheumatic diseases. A novel target is Bruton’s tyrosine kinase (BTK) which inhibition seems to be useful for the management of SLE (NCT03878303) and RA (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 (NCT03827018). As previously mentioned, new IL-6 blocking agents are under investigation for the treatment of GCA and RA such as
sirukumab (NCT01856309, NCT02531633), olokizumab (NCT02760433, NCT03120949, NCT02760407), and clazakizumab (NCT02015520). Undoubtedly, numerous new JAK inhibitors will be soon available for the management of a wide spectrum of inflammatory conditions, such as TYK2 inhibitors (NCT03943147, NCT03252587, NCT03881059) or filgotinib which is a selective JAK1 inhibitor (NCT02065700, NCT03117270, NCT02914522, NCT02914561).

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### TABLE 1. Main characteristics of anti-TNF α agents.

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

AS: ankylosing spondylitis, CD: Crohn’s disease; JIA: juvenile idiopathic arthritis, Ps: psoriasis, PsA: psoriatic arthritis, RA: rheumatoid arthritis; UC: ulcerative colitis
**TABLE 2.** Main characteristics of IL-1 inhibitors.

| Structure and mechanism of action | IL-1 inhibition | Indications | Dosage |
|-----------------------------------|-----------------|-------------|--------|
| **Anakinra**                      | IL-1α and IL-1β | RA, CAPS and Still’s disease | 100 mg SC injection daily |
| **Canakinumab**                   | IL-1β           | CAPS, Still’s disease, periodic fever syndromes, TRAPS, HIDS/MKD, FMF and gouty arthritis | 150 mg SC injections every 4-8 weeks. |
| **Rilonacept**                    | IL-1α, IL-1β and IL-1 receptor | CAPS (only FDA) | 160 mg SC weekly injection |

CAPS: cryopyrin-associated periodic syndromes; HIDS: hyperimmunoglobulin D syndrome, FMF: familial mediterranean fever, RA: rheumatoid arthritis; MKD: mevelonate kinase deficiency; TRAPS: tumor necrosis factor receptor associated periodic syndrome.
### TABLE 3. Main characteristics of the currently available JAK inhibitors for the treatment of rheumatic diseases.

| JAK inhibition | Indications | Dosage | Specific safety concerns apart from general monitoring |
|----------------|-------------|--------|------------------------------------------------------|
| **Tofacitinib** | JAK1/JA K3 | RA, PsA, UC | RA and PsA: 5mg twice daily<br>UC: 10 mg twice daily x 8-16 weeks, then 5mg twice daily | - Caution in patients > 65 years due to increased risk of infection.<br>- Caution in patients with risk for VTE*. Particularly, in patients receiving 10mg twice daily.<br>- Dose adjustment in moderate liver impairment (Child Pugh B)<br>- Hematologic contraindications (ALC < 750 cells/mm3, ANC < 1000 cells/mm3, Hb < 9 mg/dL) |
| **Baricitinib** | JAK1/JA K2 | RA | 4mg once daily<br>2mg once daily (patients > 75 years, renal impairment, frequent infections, stabilisation of treated disease and, probenecid treatment) | - Caution in patients with risk for VTE*.<br>- Dose adjustment if creatine clearance 30-60mL/min.<br>- Close lipid monitoring.<br>- Hematologic contraindications (ALC < 500 cells/mm3, ANC < 1000 cells/mm3, Hb < 8 mg/dL) |
| **Upadacitinib** | JAK 1 | RA | 15mg once daily | - Caution in patients with risk for VTE*.<br>- Close lipid monitoring.<br>- Hematologic contraindications (ALC < 500 cells/mm3, ANC < 1000 cells/mm3, Hb < 8 mg/dL) |

ALC: absolute lymphocyte count, ANC: absolute neutrophil count, Hb: haemoglobin, PsA: psoriatic arthritis, RA: rheumatoid arthritis, UC: ulcerative colitis, VTE: venous thromboembolism.

* VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy.

Additional VTE risk factors such as age, obesity (BMI ≥30), diabetes, hypertension, smoking status should also be considered.
**TABLE 4.** Specific precautions to be taken with Rituximab, Tocilizumab and anti-TNF alpha therapy.

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