

Role of Biological Agents in Treatment of Rheumatoid Arthritis

Shing T. Law^a, Peter C. Taylor^a

^aNuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK, OX3 7LD

Abstract

Advances in understanding of the pathophysiology of rheumatoid arthritis with concurrent advances in protein engineering led to the development of biological disease-modifying antirheumatic drugs which have dramatically revolutionized the treatment of this condition. This review article focuses on the role of biological agents currently employed in the treatment of rheumatoid arthritis, as well as novel biological agents in development.

Keywords: Biological disease-modifying antirheumatic drugs, Review, Rheumatoid arthritis

Introduction:

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease characterized by persistent synovial inflammation and progressive destruction of joints, leading to disability and loss of quality of life. The prevalence of RA is approximately 1% of the population and women are more likely to be affected than men [1]. The goals of treatment in RA include reducing synovial inflammation, pain relief, preventing joint damage, and preventing deterioration of physical function. A number of pro-inflammatory cytokines including tumor necrosis factor (TNF) and interleukin-6 (IL-6) are involved in the pathophysiology of RA. Biological disease-modifying antirheumatic drugs (bDMARDs) are large proteins and those approved to date for the management of RA do not have the capability of crossing the plasma membrane of a cell. Therefore, bDMARDs target extracellular mediators of inflammation with high specificity. These include pro-inflammatory cytokines and cell membrane-associated immune proteins. The management of RA has been revolutionized over the last two decades by bDMARDs such as TNF inhibitors (TNFi). However, protein-derived bDMARDs have the relative disadvantages of requirement for parenteral administration and high production costs. Here, we review the successes and failures of biological agents in the treatment of RA, as well as potential new therapeutic agents in the pipeline.

Tumor necrosis factor inhibition

TNF inhibitors were the first wave of biologic therapies to revolutionize the treatment of RA. Adalimumab is a human monoclonal antibody that is given subcutaneously every two weeks. Etanercept is a TNF-receptor fusion protein that is given subcutaneously every week. Infliximab is a chimeric monoclonal antibody that is transfused intravenously every eight weeks. Golimumab is a human monoclonal antibody to TNF that can be administered subcutaneously every four weeks or

intravenously every eight weeks. Certolizumab pegol is a pegylated antigen-binding fragment of a humanized monoclonal antibody against TNF that is injected subcutaneously every two to four weeks.

The choice of DMARD therapy depends on patient's comorbidities and the presence of contraindications to treatment. Reports of new onset or deterioration of heart failure for infliximab dosed at 10mg/kg led to concerns about use of TNFi in patients with heart failure [2]. However, subsequent studies showed that the rate of heart failure is not increased in patients receiving TNFi, and the risk of symptomatic congestive heart failure was not increased in the high risk group of patients with established heart failure during therapy with TNFi [3].

Biologic DMARDs are associated with an increase in the number of serious infections of the order of six per 1000 patients treated annually, compared to conventional synthetic DMARDs (csDMARDs) [4, 5]. TNF inhibition is associated with increased risk of tuberculosis and therefore screening for and treatment of latent tuberculosis are necessary prior to initiation of TNFi [6].

IL-6 inhibition

IL-6 is a pivotal cytokine in the pathogenesis of RA by driving both innate and adaptive immune responses, as well as the acute phase response. Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody that is approved for the treatment of RA. In the phase III RADIATE study, tocilizumab plus methotrexate is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNFi [7]. Tocilizumab may be administered subcutaneously or intravenously. Their efficacy and safety profiles are similar except that injection site reactions were more common with the subcutaneous route [8].

Tocilizumab has increased risk of lower intestinal perforation compared to csDMARDs and other bDMARDs [9]. Therefore, the presence of a history of diverticulitis is a contraindication to tocilizumab. Clinical providers should be educated that negative markers of inflammation cannot be interpreted during therapy with tocilizumab.

Tocilizumab has paved the way for other IL-6 inhibitors including biologic agents that target IL-6 cytokine (sirukumab, olokizumab, and clazakizumab) or IL-6 receptor (sarilumab) [10, 11]. Sarilumab is the second IL-6 inhibitor to be licensed for the treatment of RA.

IL-6 inhibitors have shown particular benefits as monotherapy for RA when methotrexate is contraindicated or not tolerated. The AMBITION study showed tocilizumab monotherapy was more effective than methotrexate monotherapy in patients with moderate to severe RA in a 24-week, double-blind, double-dummy parallel-group randomised study [12]. ADACTA was a randomized, double-blind, multi-center phase 4 superiority study of patients with severe RA and who were intolerant to or were inappropriate for continued methotrexate treatment. At week 24, patients who were randomly assigned to tocilizumab monotherapy had significantly greater change from baseline in DAS28 compared to adalimumab monotherapy (-3.3 versus -1.8, 95% CI -1.8 to -1.1; $p < 0.0001$) [13]. 16 of 162 (10%) patients in the adalimumab group versus 19 of 162 (12%) in the tocilizumab group had serious adverse events. In a randomized, double-blind, parallel-group phase III trial, sarilumab as monotherapy also demonstrated clear head-to-head superiority over adalimumab monotherapy in methotrexate intolerant subjects [14]. Sarilumab was superior to adalimumab in the primary end point of change from baseline in DAS28-ESR (-

3.28 vs -2.20; $p < 0.0001$). Sarilumab-treated patients achieved significantly higher American College of Rheumatology 20/50/70 response rates (sarilumab: 7.7%/45.7%/23.4%; adalimumab: 58.4%/29.7%/11.9%; all $p \leq 0.0074$) and had significantly greater improvement in Health Assessment Questionnaire-Disability Index ($p = 0.0037$). This evidence led to the European League Against Rheumatism (EULAR) guideline for RA treatment recommendation that in patients who cannot use csDMARD as comedication, IL-6 pathway inhibitors may offer advantages compared with other bDMARDs [15].

CD80 and CD86 inhibition

Abatacept is a fusion protein composed of the Fc region of the human IgG1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). In patients with RA and inadequate response to TNFi, abatacept produced significant clinical and functional benefits [16]. Abatacept binds to CD80 and CD86 molecules (also known as B7-1 and B7-2) to prevent CD28-mediated T cell activation by blocking costimulatory signaling even when the antigen bound to the major histocompatibility complex (MHC) molecule is presented to the T cell receptor. However, inhibition of T cell co-stimulation may not be the primary mechanism of action by which abatacept works in RA. Other anti-T cell therapies such as anti-CD4 [17] and anti-IL-17 [18] have not been efficacious in treating RA. It has been postulated that abatacept may be efficacious in RA primarily by interfering with macrophage migration [19].

ASP2409 represents a new class of CTLA4-Ig molecules with higher binding avidity and selectivity to CD86. A phase I trial of ASP2409 in RA showed that this agent is tolerable and further clinical trials are pending [20].

CD20 inhibition

Rituximab is a genetically engineered chimeric monoclonal antibody that targets CD20+ B cells [21]. B cell depletion is thought to help in RA by reducing auto-antibody production and inhibiting antigen presentation to T cells [19]. At 24 weeks, a single course of rituximab with concomitant methotrexate therapy provided significant and clinically meaningful improvements in disease activity in patients with active longstanding RA who had an inadequate response to one or more TNFi [22].

In a head-to-head, open label, randomized-controlled trial involving seropositive RA patients with inadequate response to csDMARD, initial treatment with rituximab was non-inferior to initial TNFi treatment with either adalimumab or etanercept [23]. Use of rituximab as initial bDMARD strategy was cost saving over 12 months as compared with the TNFi strategy. In the presence of concomitant comorbidities such as multiple sclerosis or lymphoproliferative disorders, rituximab is preferred as the bDMARD of choice. Rituximab is associated with the greatest risk for hepatitis B virus reactivation among RA patients with positive hepatitis B surface antigen who have received a bDMARD and should therefore be avoided in this at-risk patient group [24]. A rare complication that is specific to rituximab, rather than other bDMARDs, is the risk of progressive multifocal leukoencephalopathy [25].

Ocrelizumab is a humanized anti-CD20 antibody approved by the US Food and Drug Administration (FDA) for treatment of multiple sclerosis. Ocrelizumab induces greater B cell depletion than rituximab. Ocrelizumab has demonstrated efficacy in RA [26].

Ofatumumab specifically targets a membrane-proximal epitope on the CD20 molecule distinct from other anti-CD20 antibodies including rituximab and ocrelizumab, and bind the epitope located on the large loop of CD20 which produces a more durable B-cell depletion [27]. Ofatumumab is associated with increased binding of C1q and more potent complement-dependent cytotoxicity. Randomized clinical trials in RA showed ofatumumab to be effective in methotrexate refractory patients and has clinical efficacy comparable to rituximab at week 24 [28].

Other biological agents

The granulocyte-macrophage colony-stimulating factor (GM-CSF) pathway is emerging as a promising therapeutic target in RA. GM-CSF is a pro-inflammatory cytokine that influences the activation, differentiation, and survival of macrophages, dendritic cells, and neutrophils [29]. GM-CSF cytokine and its receptor are upregulated in synovial tissue and circulating mononuclear cells in patients with RA. GSK3196165 is a human monoclonal antibody to GM-CSF cytokine and has demonstrated significant improvements in DAS-28 scores and higher European League Against Rheumatism response rates than RA patients receiving placebo in a phase Ib/IIa randomised, double-blind, placebo-controlled trial [30]. Mavrilimumab is a monoclonal antibody to GM-CSF receptor- α chain. In a phase IIb, double-blind study, patients with active RA and a history of inadequate response to DMARD were randomized to receive either mavrilimumab 100 mg subcutaneously every other week or golimumab 50 mg subcutaneously every four weeks alternating with placebo every four weeks, administered concomitantly with methotrexate [31]. Both treatment regimen demonstrated clinical efficacy, even though the dosing of mavrilimumab was probably suboptimal in this trial as a regime of 150mg mavrilimumab every other week has been shown to produce higher responses than 100 mg [32].

Despite evidence implicating IL-1 in RA pathogenesis, IL-1 antagonists such as anakinra are relatively less efficacious than other approved bDMARDs in treatment of RA [33]. In the case of anakinra, this may be related in part to the pharmacological properties and short half-life.

In contrast to skin psoriasis, treatment with the anti-IL-12/23 antibody ustekinumab and IL-23 antibody guselkumab did not significantly reduce disease activity in RA patients with an inadequate response to methotrexate [34].

Increased levels of IL-17A are found in joints and blood of patients with RA [35, 36] and correlate with RA disease activity. These observations led to its consideration as a therapeutic target. However, clinical trials of anti-IL-17A agents such as secukinumab and brodalumab in patients with RA have shown disappointingly low efficacy [37, 38]. Ixekizumab, a high affinity anti-IL-17A monoclonal antibody, improved RA signs and symptoms in RA patients who were either biologic-naïve or had an inadequate response to TNFi [39]. Overall, however, targeting the IL17A pathway is not considered to be a mechanism of action with competitive efficacy when compared with blockade of proinflammatory cytokines such as TNF or IL-6.

Guidelines for biologics in treatment of RA

EULAR recommends treatment with csDMARDs including methotrexate upon diagnosis of RA [15]. However, many patients with RA do not achieve remission or low disease activity with methotrexate monotherapy [40]. Biologic DMARDs or targeted synthetic DMARDs (tsDMARDs) should be considered if the primary csDMARD does not achieve treatment target in the presence of negative prognostic factors (such as high disease activity, rheumatoid factor positivity, presence of anti-CCP antibodies, erosive arthritis) or if the response to two csDMARDs is insufficient. Although bDMARDs are usually used in conjunction with methotrexate, more than a third of patients are intolerant of methotrexate so approximately 30% of patients in clinical practice are treated with bDMARD monotherapy [41].

Broadly speaking, approved bDMARDs have similar efficacy when used in combination with methotrexate [42]. All bDMARDs demonstrate better efficacy when combined with methotrexate than as monotherapy, an observation that is reflected in EULAR recommendations for the treatment of RA [15]. When used concomitantly with bDMARD, oral methotrexate at 10 mg weekly may provide similar benefit as 20 mg weekly as evidenced by similar clinical outcomes and adalimumab pharmacokinetic profiles [43]. There is a need for further high quality 'head-to-head' studies that directly compare the efficacy of bDMARDs to provide evidence-based prioritization of currently available drugs. And in the event that such evidence is not forthcoming, this would establish a research agenda for identification of stratifiers that would enrich for the likelihood of best patient outcomes and provide the most cost-effective care [42, 44].

The American College of Rheumatology (ACR) conditionally recommends to use csDMARDs in combination over TNFi in patients with previous serious infections, and to use abatacept preferentially over TNFi in these high risk patients, as supported by low level evidence from the ATTEST trial [6, 45, 46].

A treat-to-target approach prevents progression of joint damage and optimizes quality of life. Remission (or at least low disease activity) is the aim of therapy in conjunction with tight control of clinical symptoms and prompt treatment adaptation in a treat-to-target approach [47]. This treat-to-target approach has been adopted by ACR, EULAR and the Asia Pacific League of Associations for Rheumatology in their guideline recommendations.

First line biologic failure

In patients with RA and inadequate response to a TNFi, there is insufficient data to guide whether the subsequent therapeutic choice should be a different TNFi, a bDMARD with a different mechanism of action, or a tsDMARD. In clinical practice, whether the patient has not had any response to bDMARD from its initiation (primary non-responder) or that an initial response was lost over time (secondary non-responder) may guide choice of second line DMARD but evidence from clinical trials to support this strategy is also lacking [42]. Secondary inefficacy to TNFi may be due to development of antidrug antibodies. The ACR recommends non-TNF bDMARD if the first TNFi fails [6], but European League Against Rheumatism (EULAR) recommendations do not give a preference in this context [15]. Recent evidence from the EXXELERATE study indicates that an immediate switch to a second TNFi can give rise to clinical efficacy following primary non response to an initial TNFi [48]. As a general rule, the level of

efficacy with any bDMARD is less when used after a first TNFi failure than when used as a first line bDMARD. Both ACR and EULAR recommend switching to a non-TNF bDMARD or a tsDMARD if a second TNFi fails [6, 15].

Combination therapy with abatacept plus TNFi [49], or IL-1 receptor antagonist plus TNFi [50], or rituximab plus TNFi [51], have demonstrated lack of added benefit and have increased risks of adverse events including serious infections. However, in future we may be able to design drugs that target multiple cytokine pathways to treat RA without unacceptable risks of infection. For example, in collagen-induced arthritis (CIA) mice, a bispecific antibody targeting IL-1 β and IL-17A (FL-BsAb1/17) improved arthritis scores and histological lesions over and above those achieved either monovalent IL-1 β monoclonal antibody or IL-17A monoclonal antibody alone. FL-BsAb1/17 significantly reduced the production of IL-6 induced by IL-1 β or IL-17A in fibroblast like synoviocytes from patients with RA [52].

Tapering or discontinuation of biologic in low disease activity or remission

In patients with RA that have achieved low disease activity or remission off glucocorticoid, many patients may successfully taper bDMARD, and if a flare occurs most of them will regain disease control upon resuming their prior bDMARD regimen [15, 53]. Tapering involves either reduction of the dose or increasing the interval between drug administrations. The benefits of tapering therapy include lower costs and potentially fewer adverse effects. In patients with sustained low disease activity of RA, reduced doses of etanercept (25 mg) can maintain low disease activity at week 88 [54]. A disease activity guided dose reduction strategy of adalimumab or etanercept to treat RA is non-inferior to usual care with regard to major flaring, while resulting in the successful dose reduction or stopping in two thirds of patients [55]. Abrupt discontinuation of bDMARD therapy led to flares in many patients, some of whom did not return to low disease activity after restart of bDMARD therapy [56-58]. Prognostication may help determine which patient subgroups are able to de-escalate therapy and achieve drug-free remission but we need randomized controlled trials in which patients are stratified according to prognostic factors for tapering [42].

Personalized medicine

RA is a heterogeneous disease with variable clinical phenotypes. A treatment strategy that induces disease remission in one patient with RA may be inefficacious for another. There is great interest in biomarkers as response predictors to help physicians personalize bDMARD treatment to individuals. The goal of personalized medicine is to increase therapeutic effectiveness whilst reducing toxicity and costs. The development of multi-omics technologies, along with reducing prices of these platforms, have stimulated the drive towards biomarker discovery and personalized medicine.

As the synovial tissue is the primary site for inflammation in RA, synovial transcriptomic analysis is emerging as a clinically significant methodology to identify disease biomarkers for personalizing therapeutic approach and prognosis. Ultrasound-guided synovial needle biopsy is increasingly adopted by rheumatologists allowing research of inflammatory arthritis and its response to therapeutics at a tissue and cellular level. Advances in technology including single cell sorting to allow specific synovial single cell transcriptomic profiling will transform our understanding of the pathogenesis underlying the heterogeneous manifestations of RA and how treatment can be tailored to individuals.

Anti-therapeutic antibodies

Patients treated with bDMARDs such as TNFi may develop anti-therapeutic antibodies. In patients treated with adalimumab, antibody assays show that the prevalence of anti-therapeutic antibody to adalimumab was approximately 40% after 24 weeks of treatment [59]. Antibody formation was associated with decreasing levels of circulating adalimumab, but no direct effect on disease activity was evident. Monitoring of both the therapeutic drug level and their respective anti-therapeutic antibody level may allow clinicians to personalize treatments for maximal therapeutic outcomes [59].

Pregnancy

RA affects women of childbearing age so rheumatologists must take the prospect of pregnancy into account when choosing DMARD therapy. The topic of bDMARD in the treatment of RA during pregnancy has been reviewed elsewhere [60]. In brief, it is now recognised that it is important for the health of mother and foetus to optimise control of RA disease activity through pregnancy, which may include the use of TNFi, but without concomitant methotrexate, while remaining mindful of any potential harm to the foetus. EULAR have published points to consider for use of anti-rheumatic drugs in pregnancy and they include the recommendation that among biologics, continuation of TNFi should be considered during the first part of pregnancy [61]. Certolizumab pegol has recently been approved by the European Medicines Agency (EMA) for use throughout pregnancy due to the low rate of transplacental passage [62].

Biosimilars

Biosimilars are approved by the EMA or the FDA as having similar efficacy and safety as their respective biological originator. Infliximab biosimilars (SB2 and CTP13) and the originator (Remicade) have similar achievement of ACR20, reduction of radiographic progression, safety and immunogenicity profiles [63, 64]. Similarly, biosimilar Etanercept SB4 has comparable efficacy and safety profile as the originator Enbrel [65]. A randomized, double-blind clinical trial showed that rituximab biosimilar PF-05280586 has similar efficacy and safety profiles as the originator rituximab [66]. EULAR recommends that biosimilars should be preferred if they are significantly cheaper than the originator [15]. The role of biosimilars in RA has been reviewed elsewhere [67].

Malignancy

Compared to csDMARDs, patients on bDMARDs did not have an increased risk of malignancies in general, but the risk of melanoma may be slightly increased (adjusted Hazard Ratio 1.5) [68, 69].

Nanoparticles and nanocarriers

The future of biological agents in the treatment of RA may be revolutionized by nanoparticles and nanocarriers that allow targeted drug delivery. By exploiting the amphiphilic nature of dextran sulfate, Heo et al. produced spherical nanoparticles loaded with methotrexate. These dextran sulfate nanoparticles were selectively taken up by activated macrophages via scavenger receptor class A-mediated endocytosis. When systemically administered into CIA mice, the dextran sulfate nanoparticles effectively accumulated in inflamed joints implying their high specificity to the primary affected site. Moreover, the methotrexate loaded dextran sulfate nanoparticles significantly improved arthritis in CIA mice compared to free methotrexate alone [70]. It is exciting to imagine how nanotechnology may improve the pharmacokinetics of current bDMARDs to improve their efficacy and safety in the treatment of RA.

Conclusion

The treatment of RA has been transformed by the advent of bDMARDs. However, a number of challenges lie ahead. Despite having different mechanisms of action, broadly speaking bDMARDs seem to have remarkably similar efficacy [42]. This may be related to limitations of the outcome measures and underlying study designs, or because they rely on similar downstream signaling pathways. We need high quality 'head-to-head' studies that directly compare the efficacy of bDMARDs to provide evidence-based prioritization of currently available drugs, to optimize patient outcomes and provide cost-effective care [42, 44]. Identification of biomarkers may allow us to personalize therapeutic regimen, and lead to novel therapeutic targets for new biologic agents especially for patients with RA that is refractory to all current DMARDs. In addition to evaluating efficacy outcomes that meet regulatory approval such as symptoms, signs, structural preservation of joints, we need to take a broader perspective to optimally assess the value of bDMARDs by taking into account patient wellbeing, patient related outcomes, reduced mortality, prevention of comorbidities, and work productivity.

References:

1. Gabriel, S.E., *The epidemiology of rheumatoid arthritis*. Rheumatic Disease Clinics of North America, 2001. **27**(2): p. 269-281.
2. Chung, E.S., et al., *Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure - Results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial*. Circulation, 2003. **107**(25): p. 3133-3140.

3. Solomon, D.H., et al., *Heart failure risk among patients with rheumatoid arthritis starting a TNF antagonist*. Annals of the Rheumatic Diseases, 2013. **72**(11): p. 1813-1818.
4. Singh, J.A., et al., *Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis*. Lancet, 2015. **386**(9990): p. 258-265.
5. Lahiri, M. and W.G. Dixon, *Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis*. Best Practice & Research in Clinical Rheumatology, 2015. **29**(2): p. 290-305.
6. Singh, J.A., et al., *2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis*. Arthritis & rheumatology (Hoboken, N.J.), 2016. **68**(1): p. 1-26.
7. Emery, P., et al., *IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial*. Annals of the Rheumatic Diseases, 2008. **67**(11): p. 1516-1523.
8. Burmester, G.R., et al., *Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMATA)*. Annals of the Rheumatic Diseases, 2016. **75**(1): p. 68-74.
9. Strangfeld, A., et al., *Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs*. Annals of the Rheumatic Diseases, 2017. **76**(3): p. 504-510.
10. Aletaha, D., et al., *Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study*. Lancet, 2017. **389**(10075): p. 1206-1217.
11. Takeuchi, T., et al., *Efficacy and safety of olokizumab in Asian patients with moderate-to-severe rheumatoid arthritis, previously exposed to anti-TNF therapy: Results from a randomized phase II trial*. Modern Rheumatology, 2016. **26**(1): p. 15-23.
12. Jones, G., et al., *Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study*. Annals of the Rheumatic Diseases, 2010. **69**(1): p. 88-96.
13. Gabay, C., et al., *Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial*. Lancet, 2013. **381**(9877): p. 1541-1550.
14. Burmester, G.R., et al., *Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial*. Annals of the Rheumatic Diseases, 2017. **76**(5).
15. Smolen, J.S., et al., *EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update*. Annals of the Rheumatic Diseases, 2017. **76**(6): p. 960-977.
16. Genovese, M.C., et al., *Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition*. New England Journal of Medicine, 2005. **353**(11): p. 1114-1123.
17. Vanderlubbe, P.A., et al., *A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CD4 MONOCLONAL-ANTIBODY THERAPY IN EARLY RHEUMATOID-ARTHRITIS*. Arthritis and Rheumatism, 1995. **38**(8): p. 1097-1106.
18. Blanco, F.J., et al., *Secukinumab in Active Rheumatoid Arthritis: A Phase III Randomized, Double-Blind, Active Comparator- and Placebo-Controlled Study*. Arthritis & Rheumatology, 2017. **69**(6): p. 1144-1153.
19. Bonelli, M., et al., *Abatacept (CTLA-4IG) treatment reduces the migratory capacity of monocytes in patients with rheumatoid arthritis*. Arthritis and Rheumatism, 2013. **65**(3): p. 599-607.

20. Zhang, W.H., et al., *A Phase 1 Dose-Escalation Study of ASP2409, a Selective T-Cell Costimulation Inhibitor, in Stable Rheumatoid Arthritis Patients on Methotrexate Therapy*. Clinical Pharmacology in Drug Development, 2016. **5**(4): p. 259-268.
21. Reff, M.E., et al., *DEPLETION OF B-CELLS IN-VIVO BY A CHIMERIC MOUSE-HUMAN MONOCLONAL-ANTIBODY TO CD20*. Blood, 1994. **83**(2): p. 435-445.
22. Cohen, S.B., et al., *Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy - Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks*. Arthritis and Rheumatism, 2006. **54**(9): p. 2793-2806.
23. Porter, D., et al., *Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial*. Lancet, 2016. **388**(10041): p. 239-247.
24. Chen, M.H., et al., *Hepatitis B Virus Reactivation in Rheumatoid Arthritis Patients Undergoing Biologics Treatment*. Journal of Infectious Diseases, 2017. **215**(4): p. 566-573.
25. Molloy, E.S., C.M. Calabrese, and L.H. Calabrese, *The Risk of Progressive Multifocal Leukoencephalopathy in the Biologic Era Prevention and Management*. Rheumatic Disease Clinics of North America, 2017. **43**(1): p. 95-+.
26. Abushouk, A.I., et al., *Safety and efficacy of ocrelizumab in rheumatoid arthritis patients with an inadequate response to methotrexate or tumor necrosis factor inhibitors: a systematic review and meta-analysis*. Rheumatology International, 2017. **37**(7): p. 1053-1064.
27. Pers, Y.M. and C. Jorgensen, *Perspectives of ofatumumab as CD20 targeted therapy in rheumatoid arthritis and other autoimmune diseases*. Immunotherapy, 2016. **8**(9): p. 1091-1096.
28. Taylor, P.C., et al., *Ofatumumab, a fully human anti-CD20 monoclonal antibody, in biological-naïve, rheumatoid arthritis patients with an inadequate response to methotrexate: a randomised, double-blind, placebo-controlled clinical trial*. Ann Rheum Dis, 2011. **70**(12): p. 2119-25.
29. Hamilton, J.A., *GM-CSF as a target in inflammatory/autoimmune disease: current evidence and future therapeutic potential*. Expert Review of Clinical Immunology, 2015. **11**(4): p. 457-465.
30. Behrens, F., et al., *MOR103, a human monoclonal antibody to granulocyte-macrophage colony-stimulating factor, in the treatment of patients with moderate rheumatoid arthritis: results of a phase Ib/IIa randomised, double-blind, placebo-controlled, dose-escalation trial*. Annals of the Rheumatic Diseases, 2015. **74**(6): p. 1058-1064.
31. Weinblatt, M.E., et al., *A Randomized Phase IIb Study of Mavrilimumab and Golimumab in Rheumatoid Arthritis*. Arthritis & Rheumatology, 2018. **70**(1): p. 49-59.
32. Burmester, G.R., et al., *A randomised phase IIb study of mavrilimumab, a novel GM-CSF receptor alpha monoclonal antibody, in the treatment of rheumatoid arthritis*. Annals of the Rheumatic Diseases, 2017. **76**(6): p. 1020-1030.
33. Scott, I.C., et al., *A randomised trial evaluating anakinra in early active rheumatoid arthritis*. Clinical and Experimental Rheumatology, 2016. **34**(1): p. 88-93.
34. Smolen, J.S., et al., *A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate*. Annals of the Rheumatic Diseases, 2017. **76**(5).
35. Chabaud, M., et al., *Human interleukin-17 - A T cell-derived proinflammatory cytokine produced by the rheumatoid synovium*. Arthritis and Rheumatism, 1999. **42**(5): p. 963-970.
36. Li, N., et al., *Pathologic finding of increased expression of interleukin-17 in the synovial tissue of rheumatoid arthritis patients*. International Journal of Clinical and Experimental Pathology, 2013. **6**(7): p. 1375-1379.

37. Genovese, M.C., et al., *Efficacy and safety of secukinumab in patients with rheumatoid arthritis: a phase II, dose-finding, double-blind, randomised, placebo controlled study*. Annals of the Rheumatic Diseases, 2013. **72**(6): p. 863-869.
38. Martin, D.A., et al., *A phase Ib multiple ascending dose study evaluating safety, pharmacokinetics, and early clinical response of brodalumab, a human anti-IL-17R antibody, in methotrexate-resistant rheumatoid arthritis*. Arthritis Research & Therapy, 2013. **15**(5).
39. Genovese, M.C., et al., *A Phase II Randomized Study of Subcutaneous Ixekizumab, an Anti-Interleukin-17 Monoclonal Antibody, in Rheumatoid Arthritis Patients Who Were Naive to Biologic Agents or Had an Inadequate Response to Tumor Necrosis Factor Inhibitors*. Arthritis & Rheumatology, 2014. **66**(7): p. 1693-1704.
40. Braun, J., et al., *Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis*. Arthritis and Rheumatism, 2008. **58**(1): p. 73-81.
41. Nikiphorou, E., et al., *Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort*. Clinical Rheumatology, 2014. **33**(5): p. 609-614.
42. Nam, J.L., et al., *Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis*. Annals of the Rheumatic Diseases, 2017. **76**(6): p. 1108-1113.
43. Burmester, G.R., et al., *Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial*. Annals of the Rheumatic Diseases, 2015. **74**(6): p. 1037-1044.
44. Soliman, M.M., et al., *Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register*. Annals of the Rheumatic Diseases, 2011. **70**(4): p. 583-589.
45. Schiff, M., et al., *Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate*. Annals of the Rheumatic Diseases, 2008. **67**(8): p. 1096-1103.
46. Yun, H., et al., *Risk of hospitalised infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy*. Annals of the Rheumatic Diseases, 2015. **74**(6): p. 1065-1071.
47. Smolen, J.S., et al., *Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force*. Annals of the Rheumatic Diseases, 2016. **75**(1): p. 3-15.
48. Smolen, J.S., et al., *Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study*. Lancet, 2016. **388**(10061): p. 2763-2774.
49. Weinblatt, M., et al., *Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs - A one-year randomized, placebo-controlled study*. Arthritis and Rheumatism, 2006. **54**(9): p. 2807-2816.
50. Genovese, M.C., et al., *Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate*. Arthritis and Rheumatism, 2004. **50**(5): p. 1412-1419.
51. Greenwald, M.W., et al., *Evaluation of the Safety of Rituximab in Combination With a Tumor Necrosis Factor Inhibitor and Methotrexate in Patients With Active Rheumatoid Arthritis Results From a Randomized Controlled Trial*. Arthritis and Rheumatism, 2011. **63**(3): p. 622-632.

52. Wang, Y.X., et al., *A recombinant IgG-like bispecific antibody acting as interleukin-1 beta and interleukin-17A inhibitor exhibits a promising efficacy for rheumatoid arthritis*. Biomedicine & Pharmacotherapy, 2017. **89**: p. 426-437.
53. Haschka, J., et al., *Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study*. Annals of the Rheumatic Diseases, 2016. **75**(1): p. 45-51.
54. Smolen, J.S., et al., *Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial*. Lancet, 2013. **381**(9870): p. 918-929.
55. van Herwaarden, N., et al., *Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial*. Bmj-British Medical Journal, 2015. **350**.
56. Huizinga, T.W.J., et al., *Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study*. Annals of the Rheumatic Diseases, 2015. **74**(1): p. 35-43.
57. Smolen, J.S., et al., *Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial*. Annals of the Rheumatic Diseases, 2015. **74**(5): p. 843-850.
58. van Vollenhoven, R.F., et al., *Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis*. Annals of the Rheumatic Diseases, 2016. **75**(1): p. 52-58.
59. Cludts, I., et al., *Anti-therapeutic antibodies and their clinical impact in patients treated with the TNF antagonist adalimumab*. Cytokine, 2017. **96**: p. 16-23.
60. Forger, F. and P.M. Villiger, *Treatment of rheumatoid arthritis during pregnancy: present and future*. Expert Review of Clinical Immunology, 2016. **12**(9): p. 937-944.
61. Skorpén, C.G., et al., *The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation*. Annals of the Rheumatic Diseases, 2016. **75**(5): p. 795-810.
62. Mariette, X., et al., *Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study*. Annals of the Rheumatic Diseases, 2018. **77**(2): p. 228-233.
63. Choe, J.Y., et al., *A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy*. Annals of the Rheumatic Diseases, 2017. **76**(1): p. 58-64.
64. Yoo, D.H., et al., *A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study*. Arthritis Research & Therapy, 2016. **18**.
65. Emery, P., et al., *A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy*. Annals of the Rheumatic Diseases, 2017. **76**(1): p. 51-57.
66. Williams, J.H., et al., *Comparative assessment of clinical response in patients with rheumatoid arthritis between PF-05280586, a proposed rituximab biosimilar, and rituximab*. British Journal of Clinical Pharmacology, 2016. **82**(6): p. 1568-1579.
67. Kay, J., et al., *Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases*. Annals of the Rheumatic Diseases, 2018. **77**(2): p. 165-174.
68. Mercer, L.K., et al., *Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers*. Annals of the Rheumatic Diseases, 2017. **76**(2): p. 386-391.

69. Ramiro, S., et al., *Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis*. Annals of the Rheumatic Diseases, 2017. **76**(6): p. 1093-1101.
70. Heo, R., et al., *Dextran sulfate nanoparticles as a theranostic nanomedicine for rheumatoid arthritis*. Biomaterials, 2017. **131**: p. 15-26.