

Monoclonal antibodies in rheumatoid arthritis

Monoclonal antibodies are a group of complex and effective biologic agents used in the treatment of rheumatoid arthritis and other immune-mediated inflammatory diseases. They now represent an important series of options in the treatment of rheumatoid arthritis. In this review, we discuss the efficacy and safety of these agents. In addition, information regarding upcoming monoclonal agents and biosimilars is presented.

KEYWORDS: adalimumab • anakinra • anakinra safety • B-cell depletion therapy • certolizumab • golimumab • IL-1 inhibition • IL-6 inhibition • infliximab • monoclonal antibody • rheumatoid arthritis treatment • rituximab • TNF inhibition safety • TNF inhibitors • tocilizumab • tocilizumab safety

Marc Cohen^{*1},
Mohammed A Omair²
& Edward C Keystone³

¹Division of Rheumatology, University of Colorado Medical Center, Denver, CO, USA

²Division of Rheumatology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

³The Rebecca MacDonald Centre for Arthritis & Autoimmune Diseases, Mount Sinai Hospital, University of Toronto, Toronto, Canada

*Author for correspondence:
Tel.: +1 720 345 8964
mcohen@rheumdoc.net

The treatment of rheumatoid arthritis (RA) has dramatically changed in the last decade since the introduction of the biological agents. Achieving remission in the clinical, functional and radiographic domains has become an achievable target [1]. Clinical studies involving biologic agents in RA have been essential to the recent progress in RA treatment. Monoclonal antibodies directed against the pathogenic cytokine and cellular elements within the RA synovium have been the most common form of biologic developed. Monoclonal antibodies (mAbs) are monospecific antibodies that are produced by immune cells that are all clones of a unique parent cell. Initial studies using mAbs in RA utilized anti-CD4, anti-CD7 and CAMPATH-1H as targets, with varying degrees of efficacy and with significant safety concerns [2–10]. Over the last decade, however, directed against a number of different target molecules mAbs have received US FDA approval for the treatment of RA. These are directed against TNF- α , CD20-positive B cells, IL-1 and IL-6. Other biological agents approved for the treatment of RA are not monoclonal antibodies but fusion proteins and include etanercept and abatacept.

Monoclonal antibodies directed against TNF- α

The central role of TNF- α in the pathogenesis of RA was initially described in the mid-1980s [11–13]. TNF- α is a key mediator of the inflammation-induced joint damage that is a hallmark of this disease. Monoclonal antibodies to TNF bind soluble and transmembrane TNF, thereby downregulating TNF-induced

immune responses including adhesion molecule expression, cytokine production, matrix metalloproteinase production, neutrophil activities, dendritic cell function and osteoclast differentiation [14]. Monoclonal antibodies to TNF, except for certolizumab, have the ability to lyse TNF-expressing cells in the presence of complement [15]. It has been widely and repeatedly demonstrated that reduction in TNF- α levels improves the signs and symptoms of RA and reduces radiographic progression. Currently there are four mAbs approved for the treatment of RA.

■ Infliximab

Infliximab is a chimeric IgG1 mAb that consists of human constant regions and murine variable regions [16]. It is only available in the intravenous form, and should be used in combination with methotrexate (MTX) if possible. The starting dose is 3 mg/kg and can increase up to 10 mg/kg with an interval between doses ranging from 4 to 8 weeks. It was approved by the FDA/EMA in combination with MTX for the treatment of moderate-to-severe RA in, or soon after, 2001. Initially called cA2, it was first evaluated in 1993 by Elliott *et al.* in 20 refractory RA patients with an excellent response in all outcome measures and reasonably good tolerance with acceptable adverse events (AEs) [17]. These promising results were confirmed by the first multicenter trial in 1994 [18]. Multiple, randomized controlled trials comparing its effectiveness to placebo showed greater improvement in disease activity, functional outcomes and radiographic inhibition [16–22]. In the pivotal ATTRACT trial, Lipsky *et al.* reported on 428 patients with

severe, longstanding erosive disease randomized to receive infliximab 3 or 10 mg/kg every 4 or 8 weeks plus MTX or MTX with placebo infusion every 4 weeks [19]. At week 30, ACR20 response criteria were achieved in more than 50% of patients receiving infliximab compared with 20% of patients receiving placebo. At week 54, radiographic data demonstrated a significantly higher rate of bone erosion and joint space narrowing in patients treated with placebo compared with those treated with infliximab. The observed clinical response rates were maintained over 102 weeks, and infliximab-treated patients maintained less radiographic progression, greater improvements in Health Assessment Questionnaire and improved Short Form-36 physical component summary scores. In a later subanalysis of the same study, Smolen *et al.* demonstrated radiographic benefit in patients who had no clinical improvement (defined as ACR20 nonresponders), suggesting a dissociation between the clinical and radiographic responses [21].

The efficacy of infliximab was also demonstrated in RA patients with early (less than 3 years) disease and no prior treatment with MTX [22]. In the ASPIRE trial, 1049 patients were randomized to receive MTX with placebo, or MTX with infliximab 3 or 6 mg/kg. At week 54, the median improvements in ACR-N were significantly higher in those patients receiving infliximab compared with placebo, as were ACR20/50/70 response rates and Health Assessment Questionnaire improvements; the infliximab groups also demonstrated less radiographic progression.

In ATTRACT and ASPIRE trials, the different infliximab dose regimens were statistically powered to differentiate between them. The possibility that more drugs might be more efficacious has been evaluated, and in fact most RA patients receive some form of infliximab dose escalation. Some patients who flare during the 8-week dose interval may no longer have sufficient active drug, probably due to early elimination, suggesting that interval shortening should be done to improve outcomes first, but dosing increases are also seen [16,23,24]. Given that infliximab is comprised of a significant proportion of murine protein it was anticipated that patients would develop antichimeric antibodies that could impair the efficacy and increase the risk of infusion reactions. The combination of infliximab and MTX results in a substantial reduction in antichimeric antibody and increased serum infliximab levels. Immunogenicity of infliximab

has been shown to have an effect on long-term sustainability and increase infusion reactions in some patients.

■ Adalimumab

Adalimumab is a human recombinant IgG1 mAb that has no murine component and is produced by phage display technology. It was FDA/EMA approved in, or soon after, 2002 for the treatment of moderate-to-severe RA as monotherapy or in combination with disease-modifying antirheumatic drugs (DMARDs). It is available in the subcutaneous form at a dose of 40 mg every 2 weeks. Adalimumab was evaluated in many randomized controlled trials assessing its response in both early and late disease in combination with MTX or as monotherapy [25–35]. In the PREMIER study, which evaluated 799 patients with less than 3 years of disease who were MTX naive, the combination of MTX and adalimumab was superior to adalimumab or MTX monotherapy [25]. At 1 year, 62% of the patients treated with combination therapy achieved an ACR50 response rate compared with 46 and 41% of patients receiving MTX or adalimumab monotherapy, respectively. The change in the Sharp/van der Heijde score was significantly lower in patients in the combination treatment arm at both year 1 and year 2 (1.3 and 1.9 Sharp units, respectively) than in patients in the MTX arm (5.7 and 10.4 Sharp units, respectively) or the adalimumab arm (3.0 and 5.5 Sharp units, respectively). In a subanalysis of the same study, Kimel *et al.* demonstrated that combination therapy resulted in significant improvement in the physical component of the Short Form-36 questionnaire that is similar to the normal US population [32]. The 5-year open-label extension of this trial demonstrated significantly better long-term clinical, functional and radiographic outcomes with combination therapy than with adalimumab or MTX monotherapy [33].

In the ARMADA trial, 271 patients who were MTX incomplete responders were treated with 20, 40 or 80 mg of adalimumab or placebo every other week while continuing their MTX [27]. At week 24, ACR20/50/70 response rates for patients receiving 40 or 80 mg of adalimumab were significantly greater compared with the placebo group. The responses were rapid and sustained over the study duration. Similar results were observed in the DE019 trial with 200 patients per group. Despite adalimumab being a fully human antibody, anti-adalimumab antibodies have been detected in a significant

number of patients [36]. Adalimumab responses and long-term sustainability may be reduced by anti-adalimumab antibodies, but adalimumab generally has good sustainability similar to that of etanercept and generally better than infliximab.

■ Golimumab

Golimumab is a fully human IgG1 anti-TNF- α antibody that was generated and affinity matured in an *in vivo* system. It is very similar in structure to infliximab without the mouse protein. It was approved by the FDA/EMA in or soon after 2009 for the treatment of moderate-to-severe RA in combination with MTX. It is approved in its subcutaneous form 50 mg once monthly, and an intravenous formulation has also been evaluated in the GO-FURTHER trial and found to be safe and efficacious [37]. Previously, in a Phase II dose-ranging study in RA patients with an incomplete response to MTX, golimumab at a dose of 50 mg every 2 weeks and golimumab 100 mg every 2 or 4 weeks was found to be efficacious compared with placebo, with no significant differences between the treatment groups [38]. In the GO-BEFORE trial golimumab as monotherapy (100 mg) or in combination (50 and 100 mg) with MTX versus placebo plus MTX was compared in RA patients who were MTX naive [39]. In the intent-to-treat analysis, the primary end point of an ACR50 response rate superiority at 24 weeks for patients in the golimumab plus MTX groups compared with MTX alone was not achieved. Golimumab plus MTX did inhibit radiographic progression at 52 weeks and achieve secondary outcome measures significantly better than MTX alone. In the GO-FORWARD study, golimumab at 50 and 100 mg was clinically superior to placebo in RA patients with an incomplete response to MTX, although radiographic progression in all study arms was minimal, and the golimumab groups were not superior in inhibiting radiographic progression when compared with the placebo group [40]. The GO-AFTER study evaluated golimumab in patients with an incomplete response to TNF inhibitors, and demonstrated that in patients with a previous lack of efficacy to TNF inhibitors that golimumab had a significant ACR20 response rate, Disease Activity Score in 28 joints (DAS28) response change and DAS28 remission rate compared with placebo [41,42]. Importantly, this was the first double-blind, placebo-controlled, prospective trial to demonstrate the efficacy of

one TNF inhibitor in RA patients who had failed other TNF inhibitors. Golimumab has been shown to have low immunogenicity with between 0 and 7.2% of patients acquiring anti-golimumab antibodies [37]. The incidence of injection site reactions is similar to the other injectable TNF inhibitors.

■ Certolizumab

Certolizumab pegol is a humanized Fab fragment (Fc free) fused to a 40-kd polyethylene glycol (PEG) moiety. The PEGylation was intended to improve pharmacodynamics, bioavailability and possibly localization to inflamed tissues [43]. The lack of an Fc region minimizes Fc-mediated effects such as complement-dependent cytotoxicity and antibody-dependent cytotoxicity. It was FDA/EMA approved in 2009 for the treatment of moderate-to-severe RA as monotherapy or in combination with MTX. It is available in the subcutaneous form at a dose of 400 mg at 0, 2 and 4 weeks, then every 2 weeks or 400 mg every 4 weeks. In the RAPID 1 study, the ACR20 response rates at 24 weeks were 58.8 and 60.8%, for the 200 and 400 mg lyophilized doses, respectively, compared with 13.6% for placebo. Improvements in all ACR core set of disease activity measures, including physical function, were observed [44]. A *post hoc* analysis of the RAPID 1 study showed that the response at week 12 is highly predictive of achieving low disease activity at 1 year [45], again suggesting a rapid onset of action. In the RAPID 2 study, a liquid formulation was used and demonstrated similar significant improvements in ACR20 response rates, physical function, increased work productivity and inhibition of radiographic progression [46]. In the FAST4WARD study, Fleischmann *et al.* demonstrated an ACR20 response reaching 45.5% in the certolizumab monotherapy group compared with 9.3% in the placebo group ($p < 0.001$) [47]. In the REALISTIC study, certolizumab was also effective in patients who previously failed anti TNF with an ACR20 response of 51.1%, compared with 25.9% in the placebo group ($p < 0.001$) [48]. It has a low level of injection site reactions and discomfort with the injection.

Antibodies against B cells

B cells are critical to the pathogenesis of RA. Mature B cells may evolve into antibody producing plasma cells. Although the precise role of B-cell-producing autoantibodies in RA remains unclear, B cell and plasma cell infiltration into synovium has consistently been

found [49]. In addition to their role as precursors to antibody producing plasma cells, B cells may function as antigen-presenting cells and may also produce inflammatory cytokines and may costimulatory molecules important for T-cell function [49].

■ Rituximab

As rituximab is a B-cell-depleting agent, chimeric/IgG1 monoclonal antibody which binds to the CD20 cell surface marker found on several maturation stages of B lymphocytes. It gained FDA/EMA approval in 2006 for the treatment of moderate-to-severe RA in combination with MTX in patients with inadequate response to anti-TNF. Rituximab is given via the intravenous route at a dose of 1000 mg for two doses 2 weeks apart for each cycle. The first study evaluated rituximab in RA was reported by Edwards *et al.* [50]. Four treatment groups consisting of MTX monotherapy, rituximab monotherapy, rituximab plus cyclophosphamide and rituximab plus MTX were compared, and all rituximab groups had a better ACR20 response compared with MTX monotherapy, with a comparable safety profile. In the DANCER study, the efficacy of 500 and 1000 mg of rituximab versus placebo infused 15 days apart with pretreatment methylprednisolone was evaluated in RA patients who remained on MTX despite an incomplete response [51]. There were no differences between the two doses in primary clinical outcomes with both doses significantly more efficacious than placebo, but more stringent outcome measures, such as remission, favored the higher dose. Radiographic inhibition was also superior at the higher dose. The corticosteroids did not seem to contribute to efficacy, but significantly reduced the frequency of acute infusion reactions at the first infusion; 35% in the placebo group versus 25% of the glucocorticosteroid-treated group.

In the REFLEX trial, rituximab was efficacious in patients with RA who had an incomplete response to one or more TNF inhibitors [52]. Significantly more patients treated with rituximab plus MTX achieved an ACR50 response rate compared with placebo plus MTX, 27 versus 5%. All primary outcome measures were achieved in the rituximab group, which also demonstrated less radiographic progression and improved patient reported outcomes. Rituximab has also demonstrated efficacy in patients with early RA in the IMAGE trial [53], in incomplete MTX responders who were biologic-treatment naive in the SERENE trial [54], and as monotherapy with some success [55].

Retreatment with rituximab is successful, but the optimal interval for such retreatment is not clearly established. A number of treatment schedules have been used including a fixed retreatment schedule every 6 months, an as-needed schedule and a treat-to-target approach, all with some success [56,57]. The fixed dose schedule appeared to be superior to retreatment at the time of flares. The efficacy of repeated courses of rituximab seems about the same as the original course with some increase in the proportion of patients achieving remission over time. The retreatment of initial nonresponders (all seropositive) has been less successful [58]. Rituximab is significantly more efficacious in trials in seropositive patients compared with those that are seronegative [59].

Rituximab has been used in patients failing prior biologics without an increase in serious infections, compared with other biologics [51]. Moreover, other biologics have been used in rituximab-inadequate responders without an increase in serious infections [60]. Rituximab may be particularly helpful in patients who might have another connective tissue disease other than RA and in patients with lymphoma and those with multiple sclerosis.

Antibodies that interfere with IL-6 function

IL-6 is a pleiotopic cytokine produced by myriad immunologically important cells that has an important role in T-cell activation and immunoglobulin secretion [61]. It also stimulates synovial fibroblast differentiation and osteoclast activation [61]. Dysregulation of IL-6 is also, in part, responsible for many of the generalized systemic effects of RA, including anemia of chronic disease as well as the acute phase reactants seen in this disease [61].

■ Tocilizumab

Previously called MRA, tocilizumab is a humanized/IgG1 mAb directed against IL-6 receptor in its soluble and transmembrane form. It was approved by the FDA/EMA in early 2010, or slightly before, for the treatment of moderate-to-severe RA in patients with an inadequate response to DMARDs and/or anti-TNF in a monthly, intravenous dose of 4 and 8 mg/kg. A subcutaneous form of tocilizumab is currently under study. In the AMBITION trial, tocilizumab monotherapy was shown to be superior to MTX monotherapy with an ACR20 response of 69.9 versus 52.5% ($p < 0.001$), respectively [62]. The SAMURAI trial also established the efficacy

and radiographic inhibition of tocilizumab monotherapy [63]. The CHARISMA study evaluated three different doses of tocilizumab as monotherapy and in combination with MTX in patients who were incomplete MTX responders [64]. An ACR20 was achieved by 61 and 63% of patients receiving 4 and 8 mg/kg of tocilizumab as monotherapy, respectively, and by 63 and 74% of patients receiving those doses of tocilizumab plus MTX, respectively, compared with 41% of patients receiving placebo plus MTX. The OPTION trial also established the significant efficacy of tocilizumab in MTX incomplete responders [65]. In the LITHE study of MTX partial responders, efficacy as measured by ACR response rates, patient function were superior to placebo in the 4 and 8 mg tocilizumab groups, and the mean change in the radiographic total Genant-modified Sharp score was 0.29 and 0.34 with tocilizumab 8 mg/kg plus MTX and 4 mg/kg plus MTX, respectively, versus 1.13 with placebo plus MTX ($p < 0.0001$ for both comparisons) [66]. The RADIATE study demonstrated the efficacy of tocilizumab in patients who were incomplete responders to TNF inhibitors [67]. ACR20 response rates were 50, 30.4 and 10.1% of patients in the 8, 4 mg/kg and placebo groups, respectively. Patients responded regardless of failure of a TNF inhibitor or the number of failed treatments.

Patients failing to achieve an adequate response to 4 mg/kg of tocilizumab by 4 months demonstrated an improved response to the 8 mg/kg dose. Of significance, the high proportion of patients achieving a DAS 28 low-disease state or remission relative to other biologics may reflect both an anti-inflammatory effect, as well as the direct inhibition of acute phase reactants by IL-6, resulting in low composite indices.

Tocilizumab is particularly indicated for patients requiring monotherapy since it is the only biologic demonstrating superiority to MTX monotherapy in early RA. It is also indicated in patients with anemia of chronic disease since it dramatically increases hemoglobin as a consequence of reduction in hepcidin – the protein that inhibits iron utilization in RA.

Antibodies that interfere with IL-1 function

IL-1 is produced by many cell types in response to myriad inflammatory stimuli and mediates multiple immunologic and inflammatory pathways. In patients with RA, the levels of naturally produced IL-1 receptor antagonist in the synovium is thought to be insufficient to

counteract the increased levels of IL-1 produced in this disease [68].

■ Anakinra

Anakinra is the recombinant form of a human receptor antagonist (IL-1ra), and was approved by the FDA/EMA in, or slightly after, 2002 at a daily dose of 100 mg subcutaneously for moderate-to-severe RA that has been unresponsive to initial disease DMARD therapy. It has been studied in RA in several trials [69–73]. Cohen *et al.* reported an ACR20 response rate of 38% in the anakinra treated group at 24 weeks compared with 22% in the placebo group ($p < 0.001$) [71]. Genovese *et al.* reported no additional efficacy benefit but additional toxicity when combining anakinra to etanercept [73]. Anakinra is used uncommonly in RA because of its modest efficacy coupled with its intensive daily SC regimen.

Comparative efficacy studies

■ Indirect comparison of efficacy of biologics

The efficacy of biological agents from randomized controlled trials have been indirectly compared through meta-analyses, registry reviews and retrospective analyses. These types of comparisons are often controversial and may be fraught with methodological challenges, including differences in study selection, patient inclusion and exclusion criteria, differences in primary and secondary outcomes, differences in comorbidities, and the use of concomitant medications. In addition, many older RA studies had a different study population available compared with recent studies, as earlier, many more patients were biologically naive and often with longer disease duration, had many more swollen and tender joints, and often had severe erosive disease. Nevertheless, indirect comparative efforts attempt to compare the efficacy of available agents. One study comparing tocilizumab to other biologics in RA patients with an incomplete response to DMARDs suggested that tocilizumab has a comparable ACR20 response when compared with other biological agents, but a higher probability to achieve an ACR70 response than the TNF inhibitors (adalimumab, infliximab and etanercept) and abatacept in both the random and fixed effect model [74]. Another study assessing RA patients with an incomplete response to an initial TNF inhibitor used a multiple-treatment Bayesian meta-analysis to show that certolizumab had a higher probability to achieve an ACR20 response than

infliximab, adalimumab and anakinra, and equivalent or superior to that of etanercept, golimumab and tocilizumab [75]. In this study, the higher response likely reflects the use of effect size as a measure of response particularly when the placebo rate was the lowest of all trials as a consequence of a high placebo, early escape rate. A third study assessing the odds ratio of achieving an ACR50 at 6 months for RA patients with an incomplete response to a prior TNF inhibitor by Salliot *et al.* found that alternative TNF inhibitors had a higher probability than abatacept of achieving an ACR50 and rituximab had a higher probability than tocilizumab (odds ratio: 2.61; 95% CI: 1.10–6.37) [76].

■ Direct comparison of efficacy

Head-to-head, prospective trials of biologics have been rare, but increasingly utilized. In the ATTEST trial that compared MTX plus placebo to either MTX plus abatacept or infliximab in the fixed dose of 3 mg/kg every 8 weeks, the ACR20 response was similar at 6 months but significantly higher in the abatacept group than the infliximab group at 1 year [77]. The 1-year results of the AMPLE trial showed that subcutaneous abatacept was not inferior to adalimumab when combined with MTX, and different biologics may have different safety outcomes [78]. The ADACTA trial demonstrated that adalimumab monotherapy was superior to adalimumab monotherapy in patients who were intolerant of MTX or for whom continued treatment with MTX was inappropriate [79]. The result was consistent with the rather modest responses of adalimumab monotherapy observed in an early trial. Kume *et al.* demonstrated similar efficacy of tocilizumab, etanercept and adalimumab monotherapy with regards to the outcome measures DAS28 ESR, C-reactive protein, Health Assessment Questionnaire, cardio-ankle vascular index, and the aortic augmentation index normalized to a fixed heart rate of 75 bpm [80].

Comparison data from registries are now becoming available. In the 3-year prospective observational MIRAR trial, Gomez-Reino *et al.* reported that switching to rituximab after an incomplete response to a first TNF inhibitor was better than switching to adalimumab or infliximab, but not etanercept at 6 months [81]. In the DANBIO registry, infliximab, adalimumab and etanercept were compared, and adalimumab had the highest rates of treatment response and remission, followed by etanercept, while infliximab had the lowest responses [82]. Finckh *et al.* utilized the Swiss RA registry to show that, in

patients who were incomplete responders to one or more TNF inhibitors, rituximab was probably superior to another TNF inhibitor [83]. Similar results were published by Chatzidionysiou and van Vollenhoven from the Stockholm TNF follow-up registry [84]. Finally, Hishitani *et al.* reported from The Osaka University Biologics for Rheumatic Diseases registry that tocilizumab and etanercept had a higher retention than adalimumab and infliximab [85]. Comparative studies are only beginning to answer common clinical questions regarding RA treatments, particularly those involving biologic therapies including monoclonal antibody treatments. Confounders affecting the results must be carefully considered when evaluating these comparative studies.

Safety

■ Infections

Infections are the most common adverse event associated with the use of all biologics [86–99]. The risk of infection is increased in RA patients with previous infections, very active disease, significant comorbidities such as, but not limited to, diabetes mellitus and chronic lung disease, and corticosteroid use, particularly over 10 mg of prednisone equivalent daily [87]. Owing to patient selection issues, including comorbidities, differences in disease activity and differences in disease duration safety data from clinical trials may not be as clinically relevant as safety data emerging from large registries. In one review, the risk of a severe infection in a RA patient treated with infliximab relative to untreated patients was 2.0, although the overall risk of infection in all RA patients taking a TNF inhibitor is probably 1.0–2.0 [90]. Infection risks with anakinra and tocilizumab are probably similar to the TNF inhibitors, with rituximab perhaps having slightly less risk [95–99]. Infection risk may be higher with the use of increased doses of infliximab and anakinra [90,97]. The risk of infection with the TNF inhibitors seems to stabilize after the initial 6 months of use [90,94]. Respiratory tract infections are most commonly reported. Of significance, the highest infection rates are observed with steroids in combination with the biologic. It is likely that steroids generate a higher risk of infections than biologics alone. Vigilance with a high index of suspicion and the use of aggressive diagnostic procedures and prompt treatment is required for RA patients treated with biologics.

The risk of granulomatous infections, such as tuberculosis, is also increased in patients using monoclonal antibody TNF inhibitors [100–107].

With infliximab, tuberculosis reactivation was often noted after the third or fourth infusion, with two-thirds of reactivation occurring in less than 6 months, with 40% of cases being extrapulmonary [101,105]. Pretreatment screening is part of all biologic treatment guidelines [108,109] and has dramatically reduced, but not completely eliminated, the risk. Other opportunistic infections have been reported, including histoplasmosis, coccidiomycosis, listeriosis and *Pneumocystis jirovecii*. Opportunistic infections have also been reported with the use of abatacept, anakinra and tocilizumab, although the risk may not be as high as with the TNF inhibitors, and the risk with rituximab is very low [95–99]. Viral infections are also probably increased in RA patients taking TNF inhibitors, anakinra and tocilizumab [87,109], although there remains some controversy about the increased risk of herpes zoster [110–112]. Hepatitis B is a relative contraindication to the use of TNF inhibitors and an absolute contraindication to the use of rituximab in hepatitis B because of the risk of reactivation. Screening for hepatitis B before initiation of biologics is therefore imperative [108,109,113–116]. TNF inhibitors can be used in combination with antiviral agents. Screening should also include hepatitis C. The use of TNF inhibitors in the presence of this infection is much less of a concern than with hepatitis B [108,109,117]. Progressive multifocal leukoencephalopathy (PML) has been reported in RA patients treated with rituximab [118–120]. The infection is a reactivation of latent *John Cunningham polyomavirus* infection and is ultimately almost always uniformly fatal. Exposure to the virus is endemic, but PML is rare, and the role of rituximab in the pathophysiology of PML is uncertain. Patient counseling regarding the small PML risk is required with rituximab use in RA [121]. Recently, data with PML have shown no new cases in the past 3 years despite increased use of rituximab at present, thus there appears to be less concern regarding induction of PML with rituximab. Hypogammaglobulinemia does occur in some patients treated with rituximab, although any association between low immunoglobulins observed in trials and increased infection has not been consistently demonstrated [99]. Immunoglobulin levels usually return to normal as B cells reconstitute.

Although any increased postoperative infectious risk is uncertain, biologics are generally held for several half-lives before elective surgery [109,122,123]. They may be restarted when wound healing has begun 1–2 weeks postoperative.

■ Malignancies

The use of TNF inhibitors in patients with RA has not been associated with an increased risk of solid cancers, with the exception of cutaneous malignancies [124–135]. Lymphoma risk is also not obviously increased, and may be related to the level of RA disease activity rather than the biologic [124]. An unusual hepatosplenic lymphoma was reported in young patients with inflammatory bowel disease treated with infliximab and also other concomitant immunosuppressives [136]. TNF inhibitors may be associated with a small increased risk of melanoma and are clearly associated with nonmelanomatous skin cancers [137,138]. Malignancies have been reported with anakinra, tocilizumab and rituximab, but the risk does not seem higher than predicted in RA patients [95–99]. Longer-term follow-up is required to more clearly understand the risk of malignancies with these drugs.

■ Demyelinating diseases

Symptoms of demyelinating neurologic dysfunction have been associated with TNF inhibitors, including exacerbations of any pre-existing demyelinating disease [139,140]. Resolution of these symptoms with drug withdrawal is common. Peripheral neuropathic symptoms have also been described. TNF inhibitors should be withdrawn immediately if neurologic symptoms occur with use, and probably should be avoided in patients with pre-existing demyelinating symptoms [109].

■ Congestive heart failure & other cardiovascular events

Infliximab was associated with an increased mortality when it was studied as a potential treatment in heart failure, at high doses (in non-RA patients), and as a consequence the entire class of TNF inhibitors has been considered contraindicated in patients with unstable and late-stage congestive heart failure [141–143]. Studies of RA patients with mostly mild-to-moderate heart failure have not consistently demonstrated worsening and some improve [143]. Any use of these drugs in RA patients with heart failure should be carried out cautiously on an individual patient basis, if at all, with careful follow-up. Myocardial infarction does not appear to be increased in RA patients taking TNF inhibitors. In fact, cardiovascular events have recently been shown to decrease in frequency in RA patients, particularly in patients responsive to these drugs [144–147].

Lipid abnormalities have been reported with all biologics and with tocilizumab in almost 20% of patients [96,97]. Lipid levels should be monitored in RA patients receiving all biologics and particularly with tocilizumab [108,109]. Despite these lipid changes, there has been no obvious increase in cardiac events in a follow-up study at 5 years with tocilizumab. Longer-term follow-up studies are underway to determine the true cardiovascular risk profile of this medication.

■ Injection site reactions & infusion reactions

Injection site reactions with the subcutaneous TNF inhibitors tend to be mild, requiring only local treatment. More common and severe reactions have been reported with anakinra, where painful, erythematous reactions may require symptomatic treatment. These reactions, occurring in as many as 70% of patients using anakinra, are a common cause of drug discontinuation [95]. Infusion reactions with infliximab and rituximab may occur during or after drug infusion, although most occur within 2 h postinfusion [148,149]. Symptoms include flushing, urticaria, headache, fever, chills, but may be more severe with dyspnea, chest tightness and hypotension. Mild infusion reactions to infliximab are seen as commonly as 20%, and most require symptomatic treatment and slowing of the infusion. Severe reactions occur in 2–3% of patients with the requirement of more supportive care and cessation of drug. With infliximab, the presence of antichimeric antibodies is associated with a higher rate of infusion reactions. Infusion reactions with tocilizumab are rare, mild and usually early in the course of treatment [148,149]. Infusion reactions to rituximab, however, are more common, particularly with the first infusion [98,99]. Severe infusion reactions with rituximab have been reported, particularly with too rapid infusion and without corticosteroid pretreatment [98,149]. The use of concomitant corticosteroids decreases many of the infusion-related side effects [98].

■ Autoimmune syndromes

TNF inhibitors have been associated with increased production of autoantibodies, including antinuclear and antidouble-stranded DNA antibodies. Clinical manifestations, however, are rare, although mild lupus has been reported [150,151]. Worsening of psoriasis or the onset of new psoriatic lesions have been described with

the use of TNF inhibitors in RA, perhaps the result of unopposed IFN- α in certain patients [152–154]. Uveitis has very rarely been reported with etanercept use, although cause and effect remain uncertain [155,156].

■ Other safety concerns

Increases in liver function tests and cytopenias have been described with the TNF inhibitors [157,158]. Neutropenia has been reported with tocilizumab [96–97]. Monitoring of all of these medications should not only include clinical evaluation but laboratory testing, such as complete blood counts and at least transaminase levels, but the ideal frequency is unknown.

Responses to vaccinations may be abnormal with the use of biologics, and whenever possible immunizations should be administered before these drugs are initiated [159,160]. Gastrointestinal perforation has been reported with tocilizumab, and may be a complication of diverticulosis, and therefore tocilizumab should be avoided in patients with a history of diverticulosis or diverticulitis [96,97]. Tocilizumab may also block IL-6-mediated hepatic synthesis of C-reactive protein and the fever response, prohibiting a typical response to infection and other insults [96,97]. TNF inhibitors are labeled as class B, but their use during pregnancy should probably be avoided, although recent data have not shown an increase in fetal abnormalities [161–164]. Hypothetically, because it lacks an Fc fragment and is pegolated, certolizumab does not cross the placenta and might be safer than the other TNF-inhibitors. Similarly, because the TNF inhibitors are parenteral, the theoretical risk of TNF inhibition through lactation is low. Anakinra (class B), tocilizumab (class C) and rituximab (class C) should be avoided during pregnancy and lactation until more data are available.

Immunogenicity

Antidrug antibodies have been described with all TNF inhibitors to a variable extent. These antibodies may be associated with decreased drug effect or survival and both primary and secondary response failure [165–168]. These antibodies have been demonstrated more frequently with infliximab and adalimumab, and therefore more data are available for these agents. Antichimeric antibodies to infliximab, particularly with low doses or intermittent use, may block the drug's effectiveness and increase its clearance [165]. Antidrug antibodies have been shown to increase the frequency and severity of

infusion reactions. Simultaneous use of MTX or other agents have been shown to decrease antibody formation [164]. Antibodies to adalimumab are also common, with one study demonstrating such antibodies were present in 28% of patients studied [168]. The development of antibodies to adalimumab was associated with lower drug concentrations, a lower likelihood of attaining minimal disease activity and a lower likelihood of attaining remission. Although the measurement of antidrug antibodies to the TNF-inhibitors in practice is not yet readily available, such measurements could be clinically relevant, as diminishing responses in patients with antibodies might require higher doses of drug, whereas in patients without antibodies, a change of drug might be indicated. The PEGylation of certolizumab may make this drug less antigenic, but the importance of this is not established. Antibodies to tocilizumab and rituximab have been demonstrated, although they seem less likely to interfere with the efficacy of these drugs [169].

Biosimilars

Biological agents are very large, complex molecules. Producing these sophisticated drugs requires many complicated steps. Patents for many of these agents will expire soon, giving third-party companies the opportunity to develop their own biological components or biosimilars [170,171]. Biosimilars are not generic, they are similar but not identical to the original product. Reverse engineering a biological agent is a much more complex process than synthesizing a generic version of a small-molecule drug, where the chemical structure can be copied exactly. Any small alteration in the source materials or production process will lead to changes in the molecular structure of the molecule, and potentially also in its biological effects, safety and immunogenicity. Nevertheless, the introduction of these agents could substantially increase the availability of effective treatments and cost savings. These agents do not require Phase III or IV studies, only pharmacokinetic and equivalence studies (Phase I/II). The potential contribution of the biosimilars remains to be determined.

Emergency monoclonal antibodies

Many mAbs against new targets are undergoing clinical trials. IL-17 is a proinflammatory cytokine produced primarily by a subset of CD4 T cells, called Th₁₇ cells, which represent a third subset of lymphocytes in addition to the classically described Th₁ and Th₂ populations. IL-17

production has been implicated in a variety of autoimmune diseases, including RA. In a Phase I trial Genovese *et al.* demonstrated the efficacy of different doses of ixekizumab (LY2439821), a humanized, hinge-modified IgG4 mAb against IL-17A [172]. Brodalumab (AMG 827), a fully human IgG2 mAb against IL-17RA, receptor is currently in Phase II trials [173]. Tabalumab, a fully human IgG4 monoclonal antibody that neutralizes soluble and membrane-bound B-cell activating factor, has been recently withdrawn from development [174,175]. Sirukumab and BMS945429 are mAbs against soluble IL-6 rather than IL-6 receptor under Phase III and II clinical trials, respectively [176,177]. Ofatumumab is a humanized monoclonal antibody against the CD20 protein that appears to inhibit B-cell activation, and this agent has been demonstrated as efficacious in RA in early clinical trials [178].

Conclusion

Monoclonal antibodies with different mechanisms of action and route of administration are highly effective therapeutic agents in the treatment of RA with an acceptable safety profile. Choosing the appropriate treatment is a complex decision that is affected by clinical data, physician and patient preference, and payers. Almost undoubtedly, these types of agents will continue to be important agents in the rheumatologists' armamentarium. How to use these agents more selectively, particularly regarding which agents are best for which patients, hopefully will be better established in the future with new biomarkers. Prediction as to what agent to use in the right patient at the right time is clearly a research priority. Monoclonal antibodies as new agents are expensive, and the cost/benefit analysis justifying their use is also critical to practitioners. Many aspects regarding the efficacy and safety of the supposedly cheaper biosimilars need to be evaluated before they are available for widespread use, but their availability and the emergence of new agents in the future may substantially change the RA treatment landscape.

Future perspective

Many agents are now available to treat RA, and many of them are monoclonal antibodies. Several new monoclonal antibodies are currently under development and hopefully will be available as other alternatives. Hopefully in the future, studies will define how best to use all of the available agents, with cost, efficacy and safety all considered. They may ultimately be

used in aggressive induction combination protocols, with fewer or alternative agents used for maintenance. Hopefully too, some calculus of biomarkers, perhaps using proteonomics, will identify which patients to treat most aggressively and otherwise. Optimizing the timing of treatment, determining whether treatment will be continuous or intermittent, and determining which drugs are best for which patients all are issues which need to be studied in the future. The future of RA treatments appears to full of promise, although there are a variety of critical

issues that will need to be resolved with carefully designed and interpreted clinical studies.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Background: monoclonal antibodies

- Monoclonal antibodies are novel therapeutic agents used with great success in the treatment of rheumatoid arthritis (RA).
- Different parts of the immune system have been targeted by monoclonal antibodies with relatively similar efficacy profiles.

TNF inhibitors

- There are currently four monoclonal antibodies available that are directed against TNF: infliximab, adalimumab, golimumab and certolizumab.
- All of these agents are efficacious in RA, with clinical studies establishing their clinical efficacy and their radiographic inhibition. These agents are most effective in combination with methotrexate.
- There are subtle differences in the clinical studies establishing their efficacy and between the agents themselves.

Antibodies against B cells

- Rituximab is a depleting antibody directed against CD20 on the surface of B cells, which has established benefit in RA both with regards to clinical efficacy and radiographic inhibition.
- Retreatment with rituximab is beneficial, but the optimal schedule has yet to be established.

Antibodies that interfere with IL-6 function

- Tocilizumab is a monoclonal antibody directed against the IL-6 receptor that has established benefit in RA both with regards to clinical efficacy and radiographic inhibition.
- This agent has been studied in a variety of RA patients subsets as both monotherapy and in combination with methotrexate.

Antibodies that interfere with IL-1 function

- Anakinra interferes with IL-1 function and has established efficacy in RA, although its use is complicated by the need for daily injections with a high frequency of injection site reactions.

Comparable efficacy studies

- Indirect comparative efficacy studies are fraught with difficulties since duration and severity of disease, concomitant medications and illnesses, dates of studies performed, inclusion/exclusion criteria, among other variables, all may be different.
- Direct comparative efficacy studies are few, and also may have design issues, which make their interpretation difficult.

Safety

- The most serious safety issues for monoclonal antibodies include the risk of infections and malignancies.
- TNF-inhibitors have several different safety issues than rituximab, tocilizumab and anakinra, and these distinctions may be important for certain RA patients.
- The risk/benefit ratio for the different agents must be individualized and understood by rheumatologists and their patients.
- Antidrug antibodies may interfere with the efficacy of these agents.

Biosimilars

- Future therapies will hopefully include cheaper biosimilars, which have only recently become available in some countries. Their approval and use in the USA and Europe will require review, but the extent of these reviews are still uncertain.

Emerging monoclonal antibodies

- New monoclonal antibodies directed against new targets are under development, and hopefully several will emerge as alternative agents in the armamentarium against RA.

Future perspective

- Monoclonal antibodies and other new agents to treat RA will undoubtedly be available in the future.
- How best to use these agents and in which patients will require careful and critical clinical study.

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