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The Use of Biologics in Rheumatoid Arthritis: Current and Emerging Paradigms of Care

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Abstract

Background—Rheumatoid arthritis (RA) is a common inflammatory autoimmune disease that places a substantial burden on health care systems. Although there is currently no cure for RA, improved understanding of RA disease pathogenesis in recent years has led to the development of new biologic treatments designed to target specific elements of the RA inflammatory response.

Objective—To provide individuals responsible for decision making within managed care environments, including pharmacists, physicians, and other healthcare professionals, with a review of biologic therapies currently used for the treatment of RA. Investigational treatments for RA are also discussed.

Methods—A narrative review of the peer-reviewed, published literature on biologic therapies in the treatment of RA was performed.

Results—The treatment of RA is aimed at achieving the lowest possible disease activity and ideally remission. Biologic agents that target specific components of the immune response are highly effective in reducing RA symptoms, slowing the rate of disease progression, and improving physical function and quality of life measures in patients with moderate to severe RA. Dosing schedules and routes of administration vary depending on the biologic used, and these factors influence the cost of therapy and patient and physician preference.

Conclusion—The treatment of RA has been transformed in the last decade with the introduction of several targeted biologic agents. Although biologic agents are more costly in the short term than conventional disease-modifying antirheumatic drugs, drug-specific costs may be offset by significant improvements in RA symptoms, slowed disease progression, and improved physical function and quality of life for patients.

Keywords

biologic; disease progression; effectiveness; physical function; quality of life; rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting 1.3 million people in the United States.[1] Patients experience persistent joint inflammation manifesting as joint pain, stiffness, and swelling, resulting in progressive destruction of cartilage and bone in multiple joints.[2] If inadequately treated, RA can lead to permanent joint damage and deformity. Systemic symptoms, including fatigue, anemia, and low-grade fever are common; other extra-articular manifestations and complications (eg, pericarditis, myocarditis, vasculitis, and pulmonary fibrosis) are sometimes present and are generally associated with more severe clinical disease.[3] Overall, the disease is associated with substantial disability, reduced quality of life, and loss of work capacity. Within 2 years of disease onset, approximately 20% of patients are work disabled, and almost half are unable to work after 10 years.[4] Importantly, patients with severe RA have a higher risk of premature mortality than age-matched counterparts without RA, and have enjoyed none of the increase in life expectancy experienced by the general population over the last 4 decades.[5] In fact, life expectancy is reduced on average by 5–10 years.[6] Thus, RA places a significant burden on patients and healthcare systems.

Although there is currently no cure for RA, the availability of new biologic treatments that directly target components of the RA inflammatory cascade has transformed management of this disease over the past 10 years. Pharmacists and other healthcare professionals play a vital role in caring for RA patients. As the availability of new treatments for RA increases, it is important that healthcare professionals maintain awareness of the cost of treatment and of treatment-switching patterns. The aim of this review is to provide pharmacists and individuals responsible for decision making within managed care environments with a comprehensive review of biologic therapies currently used for the treatment of RA.

METHODS

A narrative review of the literature on biologic therapies in the treatment of RA was performed. Peer-reviewed, published literature was searched and relevant articles formed the basis of this review.

OVERVIEW OF RA TREATMENTS

Conventional Treatments

Traditional pharmacologic approaches have relied on combinations of non-steroidal anti-inflammatory drugs (NSAIDs; eg, aspirin, ibuprofen), analgesics, glucocorticoids (eg, prednisone, methylprednisone), and disease-modifying anti-rheumatic drugs (DMARDs).[7,8] NSAIDs and glucocorticoids act rapidly to suppress inflammation, thereby reducing pain and swelling. They may be useful as a ‘bridging therapy’, to control symptoms in the first few weeks after diagnosis while slower-acting DMARDs take effect. As long-term glucocorticoids are associated with significant dose-dependent toxicity, with an odds ratio of an adverse event of 32.3 (95% confidence interval [CI]: 4.6, 220) for doses of 10–15 mg/day and 4.5 (95% CI: 2.1, 9.6) for doses of 5–10 mg/day,[9] use of the lowest possible dose is important.

Conventional DMARDs (eg, methotrexate [MTX], hydroxychloroquine, and sulfasalazine) have long been the mainstay of treatment, and are still widely used in newly diagnosed RA patients;[7,10] another DMARD, leflunomide (approved 1998), is also used in patients with RA. Other DMARDs, now used less frequently than the former agents, include gold salts, azathioprine, cyclosporine, and tetracyclines (eg, minocycline).[11–13] All DMARDs have a relatively slow onset of action, ranging from several weeks to months. Importantly, to

satisfy the definition of a DMARD, an agent must slow clinical and radiographic progression of the disease.[14] Thus, RA treatment strategies have moved towards early initiation of DMARDs to prevent structural joint damage and disability.[10,15] Because of its long-term effectiveness, low cost, and acceptable safety profile, oral MTX is the most widely used conventional DMARD, and is the standard against which other DMARDs and newer RA therapies are compared.[7,16] Monitoring patients for potential adverse events associated with MTX treatment (eg, liver transaminase elevations, alopecia, oral ulcers, cytopenias, and interstitial pneumonitis) should be undertaken.

The American College of Rheumatology (ACR) has issued recommendations regarding safety monitoring for MTX and other DMARDS (Table I).[14] Patients with renal dysfunction may be at particular risk, and the ACR Task Force Panel recommends regular monitoring of serum creatinine levels at baseline, after starting treatment or after a dose increase, every 2–4 weeks for the first 3 months, every 8–12 weeks from 3–6 months, and every 12 weeks thereafter, for RA patients receiving MTX, leflunomide, or sulfasalazine. MTX is not recommended in patients with an estimated creatinine clearance <30 mL/min.[14] The use of MTX in combination with other conventional DMARDs is increasing, as studies have shown that this strategy may be more effective than DMARD monotherapy in patients with early active RA. The mean change per year in Sharp score was significantly lower for combination DMARDs than sulfasalazine monotherapy (5.6 vs 8.6; p=0.033),[17] and in another study, 37% of patients achieved remission at 2 years with combination DMARDs, compared with 18% of patients who received monotherapy (p=0.003).[18] Unfortunately, some patients fail to respond adequately to DMARD therapy and many do not maintain a response;[19] thus, newer biologic treatments have provided valuable clinical alternatives.

Biologics

Improved understanding of the pathogenesis of RA led to the development of several classes of biologic treatment. Biologic agents are engineered drugs that target specific inflammatory cells, cellular interactions, and cytokines that mediate RA-related tissue damage. Such agents are designed to reduce the signs and symptoms of RA and slow disease progression. The first targeted biologic for RA — a tumor necrosis factor (TNF)-antagonist, etanercept (Enbrel®, Wyeth Pharmaceuticals)[20] — was approved by the US Food and Drug Administration (FDA) in 1998. Since then, several agents have become commercially available: the TNF antagonists infliximab (Remicade®, Centocor/Schering-Plough)[21] and adalimumab (Humira®, Abbott Laboratories)[22]; the interleukin (IL)-1 inhibitor anakinra (Kineret®, Amgen Inc.)[23]; the T-cell co-stimulation blocker abatacept (Orencia®, Bristol-Myers Squibb)[24]; and the B-cell depleting agent rituximab (Rituxan®, Biogen Idec/Genentech [U.S.]; Mabthera®, Roche [EU]).[25]

Recently, two new TNF antagonists have entered the US market: certolizumab pegol (Cimzia®; UCB, Inc.),[26] and golimumab (Simponi®; Centocor).[27]

Biologic Therapy: Efficacy and Safety

Licensed biologics for RA are shown in Table II.[20–27] These drugs, except denosumab, are approved to treat moderate to severe RA that has not responded to conventional DMARDs. The rate of biologic use in clinical practice is rising as more agents become available; a recent analysis of US prescribing patterns reported an increase in biologic use from 3% of patients in 1999 to 26% in 2006.[28]

Although the cause(s) of RA remain unknown, various cells and cytokines are involved in development and amplification of the inflammatory response.[29,30] TNF antagonists act by inhibiting the binding of TNF-α (a proinflammatory cytokine) to its receptor.[31] Etanercept

is a synthetic TNF-receptor immunoglobulin (IgG1) fusion protein that binds specifically to TNF-α and TNF-β (lymphotoxin); infliximab, adalimumab, and golimumab are monoclonal antibodies (MAbs) directed against TNF-α. Certolizumab pegol is a humanized monoclonal anti-TNF-α antibody Fab' fragment that is conjugated with a polyethylene glycol chain to extend the plasma half-life.[26]

Anakinra is a recombinant protein with a similar amino acid sequence to an endogenous IL-1 inhibitor. Anakinra binds to IL-1 type-1 receptors and prevents IL-1–mediated signal transduction in target cells.[32] Abatacept is a CTLA-4 IgG1 fusion protein that prevents the co-stimulatory signal required for T-cell activation, an important component of the RA inflammatory response.[33] This agent acts 'upstream' in the inflammatory cascade compared with other biologic agents. Rituximab is a MAb that binds to CD20, a cell marker expressed on mature B-cells and pre-B-cells (but not plasma cells), resulting in selective depletion of CD20+ B-cells via several proposed mechanisms.[34]

The half-lives and dosing intervals of available biologic treatments are summarized in Table II. These factors are important because they affect treatment frequency, cost of therapy, and patient and physician treatment preference. For example, adalimumab has one of the longer half-lives of the TNF antagonists, at approximately 14 days, and requires dosing once every 2 weeks,[22] whereas etanercept has a half-life of 4 days and requires twice-weekly or once-weekly dosing.[20] Anakinra has the shortest half-life of the available biologics (4–6 hours) and requires daily administration.[22] The route of administration of biologics can also influence patient and physician preference and cost of therapy (see below). Etanercept, adalimumab, anakinra, certolizumab pegol, and golimumab are administered by subcutaneous (SC) injection.[20,22,23,26,27] In contrast, infliximab, abatacept, and rituximab require intravenous (IV) infusion.[21,24,25] Unlike abatacept, which is given once monthly, or infliximab, which is administered on an ongoing basis every 8 weeks, patients may prefer the rituximab infusion schedule of 2 infusions 2 weeks apart, with no further treatment generally for ≥6 months. Premedication with IV methylprednisolone (100 mg or equivalent) is recommended before administration of rituximab to prevent serious infusion reactions.[25]

Efficacy—Overall, biologics are highly effective in reducing RA symptoms, slowing disease progression, and improving indices of physical function and quality of life.[30,35] Clinical responses are often rapid: most patients experience improvements within a few weeks of starting treatment;[36–39] and TNF antagonists may provide benefit as early as a few days after the first dose.[40]

In RA trials, drug efficacy is frequently evaluated using ACR20, ACR50, and ACR70 responses, which indicate a 20%, 50%, and 70% improvement from baseline in most of a set of disease criteria defined by the ACR.[41] Large clinical trials with TNF antagonists demonstrated high efficacy in RA patients with established disease who had failed traditional non-biologic DMARDs such as MTX. Significantly greater proportions of patients treated with infliximab, etanercept, or adalimumab achieved ACR20, ACR50, or ACR70 responses than control patients in these studies (Table III).[38,39,42–45] Infliximab should be used in combination with MTX.[21] Of note, development of antibodies to infliximab may be associated with reduced efficacy.[46] Etanercept may be used in combination with MTX or as monotherapy.[20] However, combination therapy is superior in terms of clinical and radiographic benefit: ACR20 responses were achieved in 85% of patients receiving combination etanercept and MTX therapy, compared with 76% of patients receiving etanercept alone (p=0.0151); and the mean change in total Sharp score (TSS) was –0.54 for combination therapy, compared with 0.52 for etanercept alone (p=0.0006).[43] Adalimumab may be used in combination with MTX or other DMARDs, or as monotherapy.[22] Although combination therapy with adalimumab 20 mg weekly plus MTX

demonstrated a slightly greater ACR20 response than corresponding adalimumab monotherapy, albeit in separate clinical trials (61%[44] vs 39%[45]), a direct comparison has not been reported in the literature.

A direct head-to-head evaluation of anti-TNF therapies was not identified in a review of the current literature. However, results from clinical trials to date suggest that efficacy of these treatments is broadly comparable. Anti-TNF plus MTX combination therapy is highly effective when used in the early stages of RA (Table III).[47–50] Indeed, recently published data from the COMET trial,[49] which compared etanercept plus MTX with MTX monotherapy in patients with moderate to severe, active, early RA, showed that half the patients on combination therapy achieved clinical remission after 1 year compared with only 28% of patients receiving MTX alone ($p<0.0001$). Similar rates of remission at 1 year were observed with adalimumab plus MTX in the PREMIER trial, in which 43% of patients receiving combination therapy achieved clinical remission, compared with 23% of patients receiving adalimumab alone, and 21% of patients receiving MTX alone ($p<0.001$ for the combination vs both monotherapies).[47]

Abatacept and rituximab (given in combination with MTX) may be useful alternatives in patients with long-standing RA who have an inadequate response to TNF antagonists (Table III); in clinical trials, patients had improvements in RA signs and symptoms, physical function, health status, and progression of joint damage.[30,36,37] Unlike rituximab, abatacept is licensed in the US for use as the first biologic agent (ie, before TNF-antagonist therapy); however, some patients respond to abatacept more slowly than to TNF antagonists, so abatacept is not as widely used as TNF antagonists as a first-line biologic agent. Although the unique mechanism of abatacept action might suggest the possibility of use in combination with a TNF-antagonist, there appears to be no incremental benefit when abatacept and etanercept are used together.[51] Moreover, combination therapy with abatacept plus another biologic is associated with an increase in serious adverse events, including serious infections, and is therefore not recommended.[52] Published data on anakinra suggest that this agent is less effective than TNF antagonists (Table III);[53,54] anakinra is therefore rarely used in clinical practice.

Two new TNF antagonists, certolizumab pegol (Cimzia®) and golimumab (Simponi®), were approved in the United States in 2009 for the treatment of moderate to severe, active RA in adults.[26,27] Both these agents are administered as subcutaneous injections: certolizumab pegol is administered every 2 weeks, or once monthly, as a lyophilized solution or in a pre-filled syringe; and golimumab is administered once monthly. Phase III trials demonstrated the efficacy of certolizumab pegol, both as an adjunct to MTX (RAPID 1 and RAPID 2 studies)[55,56] and as a monotherapy (FAST4WARD study),[57] in patients with active RA who had failed previous DMARD therapy (Table III). The golimumab phase III program, which included the GO-BEFORE,[58] GO-AFTER,[59] and GO-FORWARD[60] trials, showed that golimumab effectively reduced the signs and symptoms of RA and improved physical function in various populations, including patients who had previously discontinued one or more TNF antagonists[59] or MTX (Table III).[60]

Safety—Biologics have been generally well tolerated by patients in clinical trials. Some of the most commonly reported adverse events (occurring in ≥10% of patients) associated with subcutaneously administered anti-TNF agents are injection-site reactions such as burning and stinging (Table IV). [36–39,42–45,47–51,53–57,59–61]

An erythematous rash, which typically resolves over time, may also develop at the injection site.[20–22]

Long-term follow-up and postmarketing studies have highlighted several safety concerns associated with TNF-blockade, including increased risks for serious infections (including tuberculosis [TB]) and malignancy. Although several trials of etanercept, adalimumab, and infliximab failed to demonstrate differences in serious infection rates between drug-treatment and control arms,[38,39,42] 2 trials[44,48] did report a statistically significant difference. Further, one meta-analysis of randomized, placebo-controlled trials of infliximab and adalimumab demonstrated an increased risk of serious infections (odds ratio 2.0 [95% CI: 1.3, 3.1]).[62] Data from some population-based registries and administrative databases suggest a moderately increased risk of serious infections associated with TNF antagonists. The relative risk compared to conventional treatment was 2.2 (95% CI: 0.9, 5.4) for etanercept and 2.1 (95%CI: 0.8, 5.5) for infliximab in the German biologics register.[63] Data from Swedish registers demonstrated that the relative risk for anti-TNF users versus controls was 1.43 (95% CI: 1.18, 1.73) in the first year, and decreased to 1.15 (95% CI: 0.88, 1.51) in the second year, and to 0.82 (95% CI: 0.62, 1.08) beyond 2 years of treatment.[64]

Similarly, a retrospective cohort study in the US found that the risk of serious bacterial infections in the first 6 months of anti-TNF therapy was 4.2 (95% CI: 2.0, 8.8), with an overall risk of 1.9 (95% CI: 1.3, 2.8) over a median 17 months follow-up.[65] Further analysis showed that there was no significantly increased risk beyond 6 months after starting etanercept (adjusted incidence rate ratio 1.37 [95% CI: 0.74, 2.53]) or infliximab (1.14 [95% CI: 0.55, 2.24]).[8] Thus, the risk of serious infections appears to be highest in the early stages of treatment with anti-TNF biologics. However, other observational studies showed no overall increased risk of serious infections compared with DMARD treatment.[66,67] The British Society for Rheumatology Biologics Register showed no overall increased risk of infections among users of anti-TNFs versus DMARDs (adjusted incidence rate ratio 1.03 [95% CI: 0.68, 1.57]),[66] although additional analyses showed that risk early in the course of treatment was increased (hazard ratio 4.6 during the first 90 days [95% CI: 1.8, 11.9]).[68] A US study based on administrative claims data found no increased risk of serious infections in elderly patients starting anti-TNFs versus MTX (relative risk 1.0 [95% CI: 0.6, 1.7]).[67]

A recent meta-analysis of published clinical trials showed no significant increase in the risk of serious infections for rituximab (odds ratio 1.45 [95% CI: 0.56, 3.73]) or abatacept (odds ratio 1.35 [95% CI: 0.78, 2.32]) compared with placebo in RA patients, but showed an increased risk for anakinra at doses ≥100 mg daily (odds ratio 3.40 [95% CI: 1.11, 10.46]).[69] A comparative study of infliximab versus abatacept (conducted for regulatory purposes, and without formal statistical testing of relative risk) found a lower risk of infection and other serious adverse events among the abatacept users.[61] A very rare infection, JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), has been reported in patients receiving rituximab.[25,70] This infection is very uncommon, and the rate of PML associated with RA has been estimated at 0.4 per 100,000 hospitalizations in the United States.[71]

The risk of malignancies among patients treated with TNF antagonists has yet to be definitively established, especially in view of the pre-existing association of lymphoma with severe RA. A meta-analysis of infliximab and adalimumab data revealed an increased risk of malignancy in anti-TNF-treated RA patients compared with placebo (pooled odds ratio 3.3 [95% CI: 1.2, 9.1]).[62] However, data from RA registries do not support a higher malignancy risk in patients on TNF antagonists.[72–74] The risk for anti-TNF users compared with controls was 1.1 (95% CI: 0.6, 2.1) for lymphomas in the Swedish Cancer Register,[72] 1.37 (95%CI: 0.71, 2.65) for hematologic malignancies and 0.91 (95% CI: 0.65, 1.26) for solid tumors in a US and Canadian cohort,[73] and 1.0 (95% CI: 0.6, 1.8) for lymphomas in the US National Databank for Rheumatic Diseases.[74]

In terms of safety of the newer biologic agents certolizumab and golimumab, pivotal trials showed that, overall, adverse event profiles were generally consistent with those for other TNF antagonists (Table IV), [36–39,42–45,47–51,53–57,59–61] although ongoing studies will provide valuable information about long-term safety of the newer agents. Both product labels carry warnings about serious infection (Table V).[75]

COSTS OF BIOLOGICS IN RA

The treatment of RA places a substantial financial burden on healthcare systems and individual patients. Indeed, a major problem associated with the use of biologics is cost: $1,200–1,400 per month ($14,400–16,800 per year).[24,76] Estimates show that the introduction of biologics has increased the total annual direct cost of treating a patient with RA 3-fold.[77] However, the overall costs of biologics should take into account the benefit of reducing the impact of RA disease. To date, few cost-benefit analyses have evaluated the cost of treating RA patients with biologics. A recent analysis compared costs and quality-adjusted life-years (QALYs) for infliximab, etanercept, adalimumab, and anakinra in the US Medicare population.[78] In this study, infliximab was the most costly therapy. Assuming a maximum willingness to pay of $50,000/QALY, the probability that infliximab was cost-effective was <1%. Anakinra was the least costly, but also the least effective, generating approximately 0.2 QALYs less than the anti-TNFs (statistical comparison was not made).[77] A complementary analysis was conducted using administrative claims data from privately insured RA patients in the US.[79] This study showed that 12-month costs were significantly lower for adalimumab (217 patients) than infliximab (234 patients): TNF-antagonist therapy cost, $12,853 vs $17,299 ($P$=0.002); and total RA-related healthcare cost, $14,764 vs $20,566 ($P$=0.002). In the same study, 12-month costs for adalimumab were comparable with those for etanercept. The authors acknowledged that the greater RA-related costs for infliximab than adalimumab and etanercept may have reflected higher rates of infliximab dose escalation.[79]

In a retrospective study of US health plan costs related to RA, etanercept was associated with lower drug and outpatient costs than infliximab and adalimumab.[80] Infliximab and adalimuab had RA-related monthly total healthcare costs that were 1.55 times (95% CI: 1.47, 1.64) and 1.12 times (95% CI: 1.04, 1.21) greater, respectively, than corresponding costs for etanercept. The study also observed a greater difference between start- and end-dispensing doses of infliximab (+17% over 10 months) than adalimumab (+11%) and etanercept (+4%).

In an economic evaluation of TNF-antagonist use in the UK, incremental cost-effectiveness ratios (ICERs) were £30,000 per QALY in early RA versus £50,000 per QALY in late RA.[81] TNF antagonists were most cost-effective when used as the third-line agent in a sequence of DMARDs: ICERs were £24,000 per QALY for etanercept; £30,000 per QALY for adalimumab; and £38,000 per QALY for infliximab.[81] Importantly, the cost-effectiveness of these agents is likely to be comparatively better than in the United States, where biologic use in patients with mild to moderate disease is more common in clinical practice.

Estimated costs for infliximab are up to $30,287 per year, depending on the dose schedule used, and substantial dose escalation of infliximab is common.[82] The recommended dose is an induction regimen of 3 mg/kg IV (at intervals of 0, 2, and 6 weeks), followed by maintenance dosing every 8 weeks.[21] However, for patients with an incomplete response, the infliximab dose may be adjusted up to 10 mg/kg, and/or the dosing interval can be reduced to as short as 4 weeks, which may increase treatment costs. A systematic review of published observational studies showed that more than half of all infliximab-treated patients

(n=5862) underwent dose escalation: 44% experienced a dose increase, and 8% had an increase in dose frequency.[83] A meta-analysis of infliximab dosage regimens used in randomized, controlled clinical trials showed that the higher infliximab dose (10 mg/kg) in combination with MTX was more effective than the standard 3 mg/kg dose, especially in severe RA: p=0.05 for patients reaching an ACR20 and ACR50 with the 10 mg/kg versus 3 mg/kg dose; the difference was not significant for ACR70.[84] The dose of adalimumab (self-administered subcutaneously) can be increased from 40 mg every 2 weeks, up to 40 mg weekly, if necessary,[22] thus effectively doubling the cost of treatment. In practice, however, dose escalation with adalimumab occurs less frequently than with infliximab. For example, one US claims data analysis showed that 18% of adalimumab-treated patients had dose increases, whereas almost 40% of infliximab-treated patients had infusion frequency or dose increases.[85] Dose escalation of etanercept is uncommon and is not recommended due to the lack of incremental benefit observed.[86]

A recent review, with cost-effectiveness defined as ICERs below US$50,000-$100,000 per QALY, revealed that DMARDs are cost-effective at the onset of RA, anti-TNFs are cost-effective if DMARDs fail, and rituximab or abatacept is cost-effective if anti-TNF therapy fails, which is in line with EULAR recommendations.[87] One study estimated that rituximab is cost-effective by European standards with a QALY/cost ICER of €23,696 after one year.[88] A UK cost-utility model estimated that introduction of rituximab in patients who had failed anti-TNFs would result in an ICER of £11,601, which is below local thresholds.[89] US models predict that abatacept and rituximab in combination with methotrexate are more cost-effective than methotrexate alone: the ICER was $47,191 (95% CI: $44,810–49,920) per QALY gained for abatacept/methotrexate, and $54,891 (95% CI: $52,274–58,073) per QALY gained for rituximab/methotrexate; however, from a third-party payer perspective (ie, acceptability threshold of $50,000 per QALY), the probability of cost-effectiveness was 90% for abatacept and 0% for rituximab.[90] Direct head-to-head comparisons and long-term observational studies are required to fully assess differences in cost-effectiveness between the currently available biologics.

The choice of biologic treatment for RA depends on several factors, including patient and physician preference,[91] which in turn may be influenced by reimbursement criteria set by insurance companies and state-funded healthcare systems.[92–94] In the US, there is a strong financial incentive for Medicare patients to receive infusion-based products (eg, infliximab, abatacept, and rituximab) administered at a hospital or outpatient center. The costs of these agents are reimbursed directly to the physician under Medicare Part B, and the patient is responsible for a co-payment, often 20%. Although self-administered injectables (eg, etanercept and adalimumab) are now subsidized by the Medicare Part D program, introduced in 2006 as part of the Medicare Modernization Act, most Part D insurance plans have coverage gaps, in which the enrollee is responsible for 100% of the drug cost, until the higher level of coverage comes into effect: the so-called ‘donut hole’. Thus, use of injectable biologics is prohibitively expensive for many Medicare patients once they reach this coverage gap, which typically occurs in the second month of treatment each year.

CURRENT GUIDELINES FOR BIOLOGIC USE IN RA

In 2008, the ACR developed recommendations for biologic use in RA patients (Table VI).[14] The ACR Task Force Panel recommendations assumed a background of optimal and appropriate use of non-medical therapies, such as physical and occupational therapies. The recommendations focused primarily on TNF antagonists, abatacept, and rituximab; anakinra was not recommended for patients starting or resuming treatment with DMARDs. Patients with RA who do not meet the criteria in Table VI should be treated with conventional DMARDs. As increased susceptibility to TB has been associated with TNF antagonists, the

Task Force Panel recommended that all patients be screened for latent TB before starting anti-TNF treatment. Periodic pneumococcal vaccinations and annual influenza vaccinations were recommended for all patients receiving biologics, and completion of a hepatitis B vaccination series was advised if risk factors were present. Live vaccinations (eg, herpes zoster) should be avoided during biologic therapy. The ACR guidelines are currently undergoing revision, and new recommendations are expected in 2011.

In the United Kingdom in 2008, the National Institute for Health and Clinical Excellence (NICE) published guidelines for the management of RA.; these guidelines were updated in February 2009 (Table VII).[95] NICE also acknowledged an important evidence gap in deciding on the optimal biologic for RA patients after a first TNF antagonist failure.

FOCUS ON REMISSION: EARLY AGGRESSIVE TREATMENT AND OPTIMAL SWITCHING PATTERNS

Treatment of RA should be aimed at achieving the lowest possible disease activity and, ideally, disease remission. Although clinicians have typically reserved biologics for patients with severe disease who have failed other therapies, there is now a shift towards biologic use in selected patients with early RA and high disease activity.[14] Clinical and radiographic data consistently show that early, aggressive treatment can improve the potential for superior clinical responses and remission compared with later treatment of established RA. These data suggest the existence of a ‘window of opportunity’, during which the natural disease course may be altered.[96] However, formulary restrictions often require RA patients to wait ≥6 months after starting DMARD therapy before allowing the use of biologic agents, which for some patients may result in irreversible joint damage. Importantly, improving outcomes with early treatment strategies may reduce healthcare costs and morbidity (eg, need for joint replacement, premature disability) in the long term, thereby offsetting the relatively high direct treatment costs associated with biologics.

Although the introduction of biologics has undoubtedly improved prognosis for many RA patients, there remains a significant unmet need for new, clinically effective therapies. Presently, even with early aggressive combination therapy, only about one-third of patients meet the criteria for clinical remission of RA.[97] To date, attempts to identify patients most likely to benefit from long-term treatment with a particular biologic or DMARD/biologic combination have been unsuccessful. Pharmacogenetics or biomarkers offer great promise in identifying suitable patients for specific therapies, but such markers have not yet emerged. Moreover, some RA patients taking biologics respond initially, but then lose response over time, while approximately 40% of RA patients with high disease activity never respond adequately (ie, withdraw from treatment because of efficacy, safety, or elective reasons, and/or do not achieve at least an ACR50 response) to TNF antagonists.[98] Switching biologics is typically considered in patients with an inadequate response to initial treatment, although selection of the subsequent biologic is empiric at best. Perhaps not surprisingly, a second TNF-antagonist may be less effective than other alternatives for people in whom a first TNF-antagonist failed due to lack of efficacy.[99] However, it remains unclear whether switching to a biologic with a different mechanism of action (eg, abatacept or rituximab), rather than to another TNF-antagonist, is preferable.

NICE initially recommended that physicians should not treat patients with TNF-antagonist failure with other TNF antagonists.[95] However, data from the British Society for Rheumatology Biologic Register indicated that TNF antagonist switching was prevalent in the UK, despite this guidance.[100] The NICE update acknowledges that a second TNF antagonist may be effective, even after a first TNF antagonist fails for reasons of efficacy.

ASSESSMENT OF RA DISEASE ACTIVITY

In terms of assessing clinical response to therapy, there is no universally accepted tool for monitoring RA disease activity in daily practice.[101,102] While ACR criteria are used extensively to evaluate responses in randomized, controlled clinical trials, these criteria are difficult to apply to routine-care settings and have not been widely adopted. The Disease Activity Score (DAS) and its popular derivative DAS28 (which includes a 28-joint count) are widely used in clinical trials. DAS provides an absolute score for current disease activity (as opposed to a change score; eg, ACR20) and is calculated from a complex formula. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) have been developed to provide physicians and patients with more simplified tools.[102] Unlike other composite measures, the CDAI does not require an acute-phase reactant test and is a simple calculation that can be performed at each patient visit. The Routine Assessment of Patient Index Data (RAPID3) is comparable to DAS28 and CDAI, with the advantage of a much faster assessment time,[103] thus suggesting that it may be the simplest tool to use in a clinical setting. As managed-care and insurance companies place increasing pressure on clinicians to provide evidence of responses to treatment, it seems likely that identification and standardization of an objective assessment tool for RA will assume greater importance in future. At present, however, most rheumatologists do not routinely measure or record RA disease activity. Although several factors may underlie this unwillingness, it may be partly related to concern that measuring disease activity will allow payers to restrict biologic use only to patients who meet particular disease activity criteria, as in the United Kingdom.

UNMET NEEDS: NEWLY APPROVED AND INVESTIGATIONAL TREATMENTS

Besides the biologics described above, there are other agents that are newly approved or in late-stage clinical development for the treatment of RA. As outlined in Table II, tocilizumab (Actemra®; Roche) is a new, once-monthly, IV IL-6–receptor antagonist that is approved in the US for moderate or severe RA patients who have failed at least one anti-TNF agent. Further information about this agent is not provided, since a focused review is forthcoming. Enhanced understanding of the pathophysiology of RA is also providing opportunities for other treatments with novel modes of action. Denosumab (Prolia®; Amgen), an antibody directed at receptor-activator of nuclear factor kappa B (NF-κB) ligand (RANKL) inhibits osteoclast activation and bone destruction. This agent has been used successfully in the treatment of postmenopausal osteoporosis,[104] and may also be useful as an adjunctive therapy in RA. In a phase II clinical study,[105] addition of twice-yearly injections of denosumab to ongoing MTX therapy significantly reduced structural damage in patients with RA (mean change in MRI erosion score was 0.06 [p=0.007 vs placebo]), but had no effect on clinical signs and symptoms of RA.

Pharmacologic inhibition of intracellular signaling pathways may provide novel therapeutic possibilities. For example, an orally active inhibitor of janus-kinase (JAK3) showed promising efficacy in a phase II trial: ACR20 response rates were 70.5%, 81.2%, and 76.8% with 5 mg, 15 mg, and 30 mg twice-daily doses, respectively (P<0.001 vs placebo).[106] Despite somewhat suboptimal results in RA with anakinra, alternative IL-1–targeted agents, including antibodies to IL-1β (Novartis) and the IL-1 receptor (Amgen), are in early-stage clinical development. Several new B-cell–directed agents are also under investigation.[107] Other targets of interest in RA include various cytokines (eg, IL-15, IL-17, IL-18, and IL-32), chemokine receptors, and Toll-like–receptor pathways.[29,108,109]

DISCUSSION

The introduction of biologics in 1998 has transformed the treatment of RA, and many patients have clinical responses to these agents. Patients typically experience improvements within a few weeks, and many do so after the first or second dose. According to recent ACR recommendations, RA patients who may be candidates for biologics (eg, infliximab, etanercept, adalimumab) include patients with high disease activity, and those who have previously failed to respond adequately to conventional DMARD therapy. Two new TNF antagonists, certolizumab pegol and golimumab, were approved in the US in 2009. Abatacept and rituximab may be useful alternatives in patients with long-standing RA who have an inadequate response to combination therapy with TNF antagonists plus MTX. In addition, several new treatments for RA with novel mechanisms of action are at different stages of development. Although the introduction of biologics has improved disease outcomes for many RA patients, only about one-third of established RA patients meet the criteria for clinical remission; thus, there remains a significant unmet need for new, clinically effective treatments. Several promising new treatments have emerged, including tocilizumab, a humanized anti-IL-6–receptor monoclonal antibody that was recently approved in the US. Finally, although biologics are more costly in the short term than conventional DMARDs, cost will clearly be influenced by factors such as dosing intervals and routes of administration, which vary between agents.

This review, although extensive, has certain limitations. Firstly, it was not performed as a systematic review with pre-defined search criteria; therefore, some relevant studies may not have been included. Nevertheless, the studies presented cover the range of biologics currently available for the treatment of RA in the US. Secondly, the studies included were randomized, controlled trials with strict inclusion and exclusion criteria, which may not represent the patient population in a clinical setting. Thirdly, long-term monitoring of patients and postmarketing surveillance may reveal a different picture, and pharmacists and other healthcare professionals involved in the treatment of RA should remain aware and educated in this area.

CONCLUSION

The use of biologics in the treatment of RA demonstrates significant benefits in terms of outcomes for patients. Evidence suggests that although biologics are costly, they remain cost-effective because of the major clinical benefits patients may experience with these therapies.

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Table I

ACR 2008 recommendations for optimal follow-up laboratory monitoring intervals[a] for complete blood count, liver transaminase levels, and serum creatinine levels for RA patients receiving non-biologic DMARDs.[14]

	Monitoring interval based on duration of treatment		
Agent	**<3 Months**	**3–6 Months**	**>6 Months**
Hydroxychloroquine	None after baseline	None	None
Leflunomide	2–4 weeks	8–12 weeks	12 weeks
Methotrexate	2–4 weeks	8–12 weeks	12 weeks
Minocycline	None after baseline	None	None
Sulfasalazine	2–4 weeks	8–12 weeks	12 weeks

[a]More frequent monitoring is recommended within the first 3 months of therapy or after increasing the dose.

ACR = American College of Rheumatology; DMARDs = disease-modifying antirheumatic drugs; RA = rheumatoid arthritis.

Table II

Overview of biologics used in the treatment of RA.

Drug class	Drug (US FDA approval date)	Structure	Mode of action	Dose and route of administration	Half-life	Acquisition cost[a]
Currently available treatments						
TNF antagonist	Etanercept (1998)[20]	Soluble fusion protein (dimer) of 2 recombinant p75 TNF-α receptor proteins, with each molecule linked to the Fc portion of human IgG1	Prevent binding of TNF-α to its receptor	SC injection of 25 mg twice weekly or 50 mg once weekly (self-administered)	4 days	$1,664
	Infliximab + MTX (1999)[21]	Chimeric MAB with Fc region of human IgG1 joined to variable region of mouse anti-TNF-α antibody		IV infusion of 3 mg/kg over 2 hours at weeks 0, 2, 6, then every 8 weeks, with dose adjustment up to 10 mg/kg if necessary	8–10 days	$1,109–$5,435
	Adalimumab (2002)[22]	Recombinant human IgG1 MAb to TNF-α		SC injection of 40 mg every 2 weeks (self-administered)	14 days	$1,633
	Certolizumab pegol (2009)[26]	Pegylated humanized monoclonal anti-TNF Fab' fragment		SC (liquid or lyophilized) injections of 400 mg at weeks 0, 2, and 4, followed by 200 mg every other week (or 400 mg every 4 weeks)	14 days	$1,567
	Golimumab + MTX (2009)[27]	Human anti-TNF receptor MAb		SC injection of 50 mg once a month	~14 days	$1,575
IL-1 inhibitor	Anakinra (2001)[23]	Recombinant IL-1 inhibitor	Prevents IL-1 from binding to its receptor	SC injection of 100 mg daily	4–6 hours	$1,363
T-cell co-stimulation blocker	Abatacept (2005)[24]	Recombinant fusion protein consisting of the extracellular domain of human CTLA-4 and part of the Fc domain of human IgG1	Prevents the costimulatory signal required for T-cell activation	IV infusion of 500–1000 mg over 30 minutes, depending on bodyweight, at weeks 0, 2, and 4, then every 4 weeks	17 days	$1,056–$2,112
B-cell targeted therapy	Rituximab + MTX (2006)[25]	Chimeric human/mouse anti-CD20 MAb	Binds to CD20, a cell marker expressed on mature- and pre-B cells, but not on other cells, including plasma cells; leads to selective depletion of CD20+ B cells via several mechanisms	Two separate 1000-mg IV infusions, 2 weeks apart (IV methylprednisolone 100 mg or equivalent is recommended 30 minutes before rituximab to prevent serious reaction)	19 days	$1,845
Biologics newly approved in the US						
IL-6 inhibitor	Tocilizumab (approved 2010)	Humanized anti-IL-6 receptor MAb	Prevents IL-6 from binding to both membrane-expressed	IV infusions of 4 mg/kg or 8 mg/kg every 4 weeks as		

Drug class	Drug (US FDA approval date)	Structure	Mode of action	Dose and route of administration	Half-life	Acquisition cost[a]
			and soluble IL-6 receptors	monotherapy or in combination with DMARDs		
RANKL inhibitor	Denosumab (phase II)[b]	Human anti-RANKL MAb	Binds RANKL and inhibits RANKL action	SC twice-yearly injections of denosumab plus MTX		

[a]Estimated based on vial prices 11/11/2009 and WAC from First Data Bank in US dollars.[110] The following assumptions were made: dosing based on FDA-approved labels; proprietary concessions not considered; 1 month = 30 days; average infliximab patient weighs 80 kg; maintenance dosing (not loading dose) was used; for products dosed <1× per month, monthly cost = 1/12 × annual cost; infliximab upper bound cost = 10 mg every 4 weeks; rituximab readministered at 6 months; does not include cost of concurrent medication such as MTX or infusion supplies.

[b]Denosumab is approved in the US for the treatment of postmenopausal osteoporosis (approved June 2010) but is not currently indicated for the treatment of rheumatoid arthritis.

DMARDs = disease-modifying antirheumatic drugs; IgG = immunoglobulin; IL = interleukin; IV = intravenous; MAb = monoclonal antibody; MTX = methotrexate; RA = rheumatoid arthritis; RANKL = receptor-activator of NF-κB ligand; SC = subcutaneous; TNF = tumor necrosis factor; US FDA = United States Food and Drug Administration; WAC = wholesale acquisition cost

Table III

Summary of biologic efficacy in randomized, double-blind, phase 3 trials.

Study	Study design	Relevant inclusion/exclu-sion criteria	Treatment groups	Relevant demographics	Efficacy summary – primary end point(s)	Efficacy summary –selected secondary end points
Anti-TNFs:						
Weinblatt et al. (2003); ARMADA[39]	r, db, pc, 24 wk	• Active RA • MTX-IR, and IR to 1–4 other DMARDs	Pbo Q2wks + MTX n=62 ADA 20 mg Q2wks + MTX n=69 ADA 40 mg Q2wks + MTX n=67 ADA 80 mg Q2wks + MTX n=73	• Mean age 55.5 yrs • Mean disease duration 12.3 yrs • Mean number previous DMARDs ≈ 3 • 74.6–82.3% female	**ACR20**: 47.8%, 67.2%, and 65.8% of pts in the ADA 20mg, 40mg, and 80mg gps (*P*<0.001 for all vs pbo)	**ACR50**: 31.9%, 55.2%, and 42.5% of pts in the ADA 20mg, 40mg, and 80mg gps (*P*=0.003, 20mg; *P*<0.001, 40mg and 80mg vs pbo) **ACR70**: 10.1%, 26.9%, and 19.2% of pts in the ADA 20mg, 40mg, and 80mg gps (*P*=NS, 20mg; *P*<0.001 40mg; *P*=0.02 80mg vs pbo)
Keystone et al. (2004)[44]	r, db, pc, 52 wk (24-wk data shown)	• Active RA • Stable MTX 12.5–25 mg/wk • No previous anti-CD4 antibody or TNFi therapy	Pbo Q1wk + MTX n=200 ADA 20 mg Q1wk + MTX n=212 ADA 40mg Q2wks + pbo alternate wks + MTX n=207	• Mean age 56–57 yrs • Mean disease duration 10.9 yrs • Mean number previous DMARDs 2.4 • 73–76% female	**ACR20 at 24 weeks**: ADA 20 mg, 60.8%; ADA 40 mg, 63.3% (*P*≤0.001 for both vs pbo)	**ACR50 at 24 weeks:** ADA 20 mg, 41.0%; ADA 40 mg, 39.1% (*P*≤0.001 for both vs pbo) **ACR70 at 24 weeks:** ADA 20 mg, 17.5%; ADA 40 mg, 20.8% (*P*≤0.001 for both vs pbo)
Van de Putte et al. (2004)[45]	r, db, pc, 26 wk	• Active RA • DMARD-IR	Pbo Q1wk n=110 ADA 20 mg Q2wks + pbo on alternate weeks n=106 ADA 20 mg Q1wk n=112 ADA 40 mg Q2wks + pbo on alternate weeks n=113 ADA 40 mg Q1wk n=103	• Mean age 53 yrs • Mean disease duration 11 yrs • Mean number previous DMARDs 3.7 • 77% female	**ACR20:** 35.8%, 39.3%, 46.0%, and 53.4% for ADA 20 mg Q2wks, ADA 20 mg Q1wk, ADA 40 mg Q2wks, and ADA 40 mg Q1wk (*P*≤ 0.01 vs pbo)	**ACR50**: 18.9%, 20.5%, 22.1%, and 35.0% for ADA 20 mg Q2wks, ADA 20 mg Q1wk, ADA 40 mg Q2wks, and ADA 40 mg Q1wk (*P*≤ 0.05 vs pbo) **ACR70**: 8.5%, 9.8%, 12.4%, and 18.4% for ADA 20 mg Q2wks, ADA 20 mg Q1wk, ADA 40 mg Q2wks, and ADA 40 mg Q1wk (*P*≤ 0.05 vs pbo)
Breedveld et al. (2006); PREMIER[47]	r, db, 2 yr (1-yrs data shown)	• RA <3 yrs • Not received MTX, cyclophosphamide, cyclosporine, azathioprine or >2 other DMARDs	Pbo Q2wks + MTX (MTX gp) n=257 ADA 40 mg Q2wks + MTX (combo gp) n=268 ADA 40 mg Q2wks + pbo (ADA gp) n=274	• Mean age 52 yrs • Mean disease duration 0.7–0.8 yrs • 32–33% of pts had received previous DMARDs	**ACR50 at 1 yr**: 62% (combo gp) vs 41% (ADA gp) vs 46% (MTX gp) [*P*<0.001 for combo vs both] **Mean change in mTSS at 1 yr**: +1.3 (combo gp) vs +3.0 (ADA gp) vs	**ACR20:** 73% (combo gp) vs 54% (ADA gp) vs 63% (MTX gp) [*P*≤0.022 for both vs combo; *P*=0.043 MTX vs ADA] **ACR70:** 46% (combo gp) vs 26% (ADA gp) vs 28% (MTX gp) [*P*<0.001 for both vs combo]

Study	Study design	Relevant inclusion/exclu-sion criteria	Treatment groups	Relevant demographics	Efficacy summary – primary end point(s)	Efficacy summary –selected secondary end points
				• 72–77% female	+5.7 (MTX gp) [$P \leq 0.002$ for combo vs both]	**DAS28 remission:** 43% (combo gp) vs 23% (ADA gp) vs 21% (MTX gp) [$P < 0.001$ for both vs combo]
Maini et al. (1999); ATTRACT[42]	r, db, pc, 30 wk	• Active RA • MTX-IR	Pbo + MTX n=88 IFX 3mg/kg Q8wk + MTX n=86 IFX 3mg/kg Q4wk + MTX n=86 IFX 10mg/kg Q8wk + MTX n=87 IFX 10mg/kg Q4wk + MTX n=81	• Median age 51–56 yrs • Median disease duration 7.2–9.0 yrs • Mean number previous DMARDs (excluding MTX) = 2.5–2.8 • 73–81% female	**ACR20**: 50–60% of IFX +MTX-treated pts ($P < 0.001$ vs pbo+MTX)	**ACR50:** 26–31% of IFX +MTX-treated pts ($P < 0.001$ vs pbo+MTX) **ACR70:** 8–18% of IFX +MTX-treated pts ($P \leq 0.007$ vs pbo+MTX)
St Clair et al. (2004)[48]	r, db, pc, 54 wk	• RA ≤3 yrs • MTX and TNFi-naïve (or ≤3 previous MTX doses) • No other DMARDs within 4 wks of baseline	MTX Q1wk + pbo at wks 0, 2, 6 and Q8wks thereafter n=282 MTX Q1wk + IFX 3mg/kg at wks 0, 2, 6 and Q8wks thereafter n=359 MTX Q1wk + IFX 6mg/kg at wks 0, 2, 6 and Q8wks thereafter n=363	• Mean age 50–51 yrs • Mean disease duration 0.8–0.9 yrs • 65–71% of pts were DMARD-naïve • 68–75% female	**ACR-N improvement**: 38.9% (IFX 3 mg/kg + MTX gp), and 46.7% (IFX 6 mg/kg + MTX gp) [both $P < 0.001$ vs pbo +MTX]	**ACR20**: 62.4% (IFX 3mg/kg + MTX; $P = 0.024$ vs pbo), and 66.2% (IFX 6mg/kg + MTX; $P = 0.001$ vs pbo) **ACR50:** 45.6% (IFX 3mg/kg + MTX), and 50.4% (IFX 6mg/kg + MTX) [both $P < 0.001$ vs pbo]
Schiff et al. (2006); ATTEST[61]	r, db, pc, 1 yr (6-mo data shown)	• RA ≥1 yr • MTX-IR • No previous ABA or anti-TNFs	Pbo+MTX n=110 IFX 3 mg/kg on days 1, 15, 43, 85 and Q8wks thereafter + MTX n=165 ABA ~10 mg/kg on days 1, 15, 29 and Q4wks thereafter + MTX n=156	• Mean age 49 yrs • Mean disease duration 7.3–8.4 yrs • 82–87% female	**Reduction in DAS28 at 6 mos:** −2.53 (ABA+ MTX), and −2.25 (IFX +MTX) [both $P < 0.001$ vs pbo+MTX]	**ACR20 at 6 mos:** 66.7% (ABA+MTX; $P < 0.001$ vs pbo +MTX), and 59.4% (IFX +MTX; $P = 0.006$ vs pbo +MTX) **ACR50 at 6 mos:** 40.4% (ABA+MTX; $P < 0.001$ vs pbo +MTX), and 37.0% (IFX +MTX; $P = 0.004$ vs pbo +MTX) **ACR70 at 6 mos:** 20.5% (ABA+MTX; $P = 0.019$ vs pbo +MTX), and 24.2% (IFX +MTX; $P = 0.002$ vs pbo +MTX)
Moreland et al. (1999)[38]	r, db, pc, 6 mos	• Active RA • DMARD-IR	Pbo bw n=80 ETN 10 mg bw n=76 ETN 25 mg bw n=78	• Mean age 52 yrs • Mean disease duration 12 yrs	**ACR20**: 51% (ETN 10 mg), and 59% (ETN 25 mg) [both $P < 0.001$ vs pbo] **ACR50**: 24% (ETN 10 mg), and 40% (ETN 25	**ACR70**: 9% (ETN 10 mg), and 15% (ETN 25 mg) [$P = 0.031$ for 10 mg vs pbo; $P = 0.001$ for 25 mg vs pbo]

Study	Study design	Relevant inclusion/exclu-sion criteria	Treatment groups	Relevant demographics	Efficacy summary – primary end point(s)	Efficacy summary –selected secondary end points
				• Mean number previous DMARDs 3.0–3.4 • 78% female	mg) [both P<0.001 vs pbo]	
Bathon et al. (2000)[50]	r, pc, 12 mos	• RA <3 yrs • MTX-naive	MTX 7.5–20 mg Q1wk n=217 ETN 10 mg bw n=208 ETN 25 mg bw n=207	• Mean age 49–51 yrs • Mean disease duration 11–12 mos • Mean number previous DMARDs 0.5–0.6 • 74–75% female	**AUC for ACR-N**: Significantly greater in the ETN 25 mg gp vs MTX at 3, 6, 9, and 12 mos (P<0.05)	**ACR20, ACR50 and ACR70:** Significantly higher % pts treated with ETN 25 mg vs MTX achieved responses in the first 4–6 mos (P<0.05), with NS difference thereafter. At 12 mos, ACR20 was 72% vs 65% (NS)
Klareskog et al. (2004); TEMPO[43]	r, db, 52 wk	• Active RA • IR to ≥1 DMARD (except MTX) • No MTX 6 mo before baseline	MTX Q1wk n=228 ETN 25 mg bw n=223 ETN+MTX (combo) n=231	• Mean age 53 yrs • Mean disease duration 6.3–6.8 yrs • Mean number previous DMARDs 2.3 • Mean DAS 5.5–5.7 • 74–79% female	**Mean difference in ACR-N AUC at 24 wks:** 6.1 for combo vs MTX (P<0.0001); 2.5 for ETN vs MTX (P=0.0034)	**ACR20**: 85% for combo vs 75% for MTX (P=0.0091) and vs 76% for ETN (P=0.0151) **ACR50**: 69% for combo vs 43% for MTX (P<0.0001), and vs 48% for ETN (P<0.0001) **ACR70**: 43% for combo vs 19% for MTX (P<0.0001), and vs 24% for ETN (P<0.0001) **DAS28 remission**: 35% for combo vs 13% for MTX (P<0.0001), and 16% for ETN (P<0.0001)
Weinblatt et al. (2007)[51]	r, db, pc, 1 yr	• Active RA • Received ETN ≥3 mos	ETN 25 mg bw + pbo n=36 ETN 25 mg bw + ABA 2 mg/kg on days 1, 15, 30, and Q4wk thereafter n=85	• Mean age 50–54 yrs • Mean disease duration 13 yrs • 76% female	**ACR20 at 6 mos:** 48.2% (ETN+ABA gp) vs 30.6% (ETN+pbo gp) [NS]	**ACR20 at 1 yr:** 48.2% (ETN +ABA gp) vs 30.6% (ETN +pbo gp) [NS] **ACR50 at 1 yr:** 28.2% (ETN +ABA gp) vs 16.7% (ETN +pbo gp) [NS] **ACR70 at 1 yr:** 9.4% (ETN +ABA gp) vs 5.6% (ETN +pbo gp) [NS]
Emery et al. (2008); COMET[49]	r, db, 52 wks	• RA <2 yrs • MTX and TNFi-naïve (no other DMARDs within 4 wks of baseline)	Pbo + MTX Q1wk n=263 ETN 50 mg + MTX Q1wk n=265	• Mean age 51.4 yrs • Mean disease duration 9 mos	**DAS28 remission**: 50% of pts in ETN+MTX gp vs 28% in MTX gp (P<0.0001) **No radiographic progression** (change in	**ACR20/50/70**: 86%/71%/ 48% for ETN+MTX vs 67%/ 49%/28% for Pbo+MTX (P<0.0001)

Study	Study design	Relevant inclusion/exclu-sion criteria	Treatment groups	Relevant demographics	Efficacy summary – primary end point(s)	Efficacy summary –selected secondary end points
				• 21% of pts received previous DMARDs • 73% female	mTSS ≤0.5): 80% of pts in ETN+MTX gp vs 59% in MTX gp (*P*<0.0001)	
Fleischmann et al. (2008); FAST4WARD[57]	r, db, pc, 24 wks	• Active RA • IR to ≥1 DMARD • No biologic within 6 mos • No previous anti-TNFs	Pbo Q4wks n=109 CTZ 400 mg Q4wks n=111	• Mean age 53–55 yrs • Mean disease duration 8.7–10.4 yrs • Mean number previous DMARDs 2 • 78–89% female	**ACR20**: 45.5% for CTZ gp (*P*<0.001 vs pbo)	**ACR50**: 22.7% for CTZ gp (*P*<0.001 vs pbo) **ACR70**: 5.5% for CTZ gp (*P*<0.05 vs pbo)
Keystone et al. (2008); RAPID-1[55]	r, db, pc, 52 wks (24-wk data shown)	• Active RA • MTX-IR • Not anti-TNF-IR • No biologic within 6 mos of baseline	Pbo Q2wks + MTX n=199 CTZ 200 mg Q2wks + MTX n=393 CTZ 400 mg Q2wks + MTX n=390	• Mean age 51–52 yrs • Mean disease duration 6.1–6.2 yrs • Mean number previous DMARDs 1.3–1.4 • 82–84% female	**ACR20 at wk 24**: 58.8% for the CTZ 200mg + MTX gp, and 60.8% for the CTZ 400mg + MTX gp (both *P*<0.001 vs pbo +MTX) **Mean change in mTSS at wk 52**: +0.4 for the CTZ 200 mg + MTX gp, and +0.2 for the CTZ 400 mg + MTX gp (both *P*<0.001 vs pbo+MTX)	**ACR50 at wk 24**: 37.1% for the CTZ 200 mg + MTX gp, and 39.9% for the CTZ 400mg + MTX gp (both *P*<0.001 vs pbo+MTX) **ACR70 at wk 24**: 21.4% for the CTZ 200 mg + MTX gp, and 20.6% for the CTZ 400 mg + MTX gp (both *P*<0.001 vs pbo+MTX)
Smolen et al. (2009); RAPID-2[56]	r, db, pc, 24 wks	• Active RA • MTX-IR • Not anti-TNF-IR • No biologic within 3–6 mos before baseline	Pbo Q2wks + MTX n=127 CTZ 200 mg Q2wks + MTX n=246 CTZ 400 mg Q2wks + MTX n=246	• Mean age 52 yrs • Mean disease duration 5.6–6.5 yrs • Mean number previous DMARDs (excluding MTX) = 1.2–1.3 • 78–84% female	**ACR20**: 57.3% in the CTZ 200 mg + MTX gp, and 57.6% in the CTZ 400 mg + MTX gp (both *P*<0.001 vs pbo+MTX)	**ACR50**: 32.5% in the CTZ 200 mg + MTX gp, and 33.1% in the CTZ 400 mg + MTX gp (both *P*<0.001 vs pbo+MTX) **ACR70**: 15.9% in the CTZ 200 mg + MTX gp, and 10.6% in the CTZ 400 mg + MTX gp (both *P*≤0.01 vs pbo +MTX)
Keystone et al. (2009); GO-FORWARD[60]	r, db, pc, 52 wks	• Active RA • MTX-IR (stable 15–25 mg/wk) • Anti-TNF naïve	Pbo Q4wks + MTX n=133 GOL 100 mg Q4wks + PBO n= 133	• Mean age 50–52 yrs • Mean disease duration 4.5–6.7 yrs	**ACR20 at wk 14**: 44.4%, 55.1%, and 56.2% for the GOL 100 mg + pbo, GOL 50 mg + MTX, and GOL 100 mg + MTX gps, respectively	**ACR20 at wk 24**: 35.3%, 59.6%, and 59.6% for the GOL 100 mg + pbo, GOL 50 mg + MTX, and GOL 100 mg + MTX gps, respectively

Study	Study design	Relevant inclusion/exclu-sion criteria	Treatment groups	Relevant demographics	Efficacy summary – primary end point(s)	Efficacy summary –selected secondary end points
		• No biologic or DMARDs (except MTX) within 4 wks of baseline	GOL 50 mg Q4wks + MTX n=89 GOL 100 mg Q4wks + MTX n=89	• 71–79% of pts had previous DMARDs (excluding MTX) • 79–82% female	(NS, *P*=0.001, and *P*<0.001 vs pbo+MTX) **HAQ-DI change from baseline to wk 24**: –0.13, –0.38, and –0.50 for the GOL 100 mg + pbo, GOL 50 mg + MTX, and GOL 100 mg + MTX gps, respectively (NS, *P*<0.001, and *P*<0.001 vs pbo+MTX)	(NS, *P*<0.001, and *P*<0.001 vs pbo+MTX) **ACR50 at wk 24**: 19.5%, 37.1%, and 32.6% for the GOL 100mg + pbo, GOL 50 mg + MTX, and GOL 100 mg + MTX gps, respectively (NS, *P*<0.001, and *P*<0.001 vs pbo+MTX) **ACR70 at wk 24**: 11.3%, 20.2%, and 14.6% for the GOL 100 mg + pbo, GOL 50 mg + MTX, and GOL 100 mg + MTX gps, respectively (NS, *P*<0.001, and *P*=0.017 vs pbo+MTX) **DAS28 remission at wk 24**: 12.0%, 20.2%, and 22.5% for the GOL 100 mg + pbo, GOL 50 mg + MTX, and GOL 100 mg + MTX gps, respectively (NS, *P*=0.001, and *P*<0.001 vs pbo+MTX)
Smolen et al. (2009); GO-AFTER[59]	r, db, 24 wk	• Active RA • Previously received ≥1 anti-TNF • Concomitant, stable DMARDs permitted but not required	GOL 50 mg Q4wks GOL 100 mg Q4wks Pbo Q4wks	• Median age 54–55 yrs • Median disease duration 8.7–9.8 yrs • 66–67% received MTX • 74–85% female	**ACR20 at wk 14**: 35% and 38% for the GOL 50 mg, and GOL 100 mg gps (*P*=0.0006, and *P*=0.0001 vs pbo)	**ACR20 at wk 24**: 34% and 44% for the GOL 50 mg and GOL 100 mg gps (*P*=0.0005, and *P*<0.0001 vs pbo) **ACR50 at wk 24**: 18% and 20% for the GOL 50 mg and GOL 100 mg gps (*P*=0.0003, and *P*=0.0001 vs pbo) **ACR 70 at wk 24**: 12% and 10% for the GOL 50 mg and GOL 100 mg gps (*P*=0.0041, and *P*=0.0107 vs pbo)
IL-1 receptor inhibitor:						
Bresnihan et al. (1998)[54]	r, db, pc, 24 wks	• Active RA >6 months and <8 yrs • DMARDs discontinued ≥6 wks previously	Pbo n=121 ANA 30 mg od n=119 ANA 75 mg od n=116 ANA 150 mg od n=116	• Mean age 52–54 yrs • Mean disease duration 3.7–4.3 yrs • Previous DMARDs 66–81% of pts • 70–79% female	**ACR composite criteria (% pts improved):** 39%, 34%, and 43% for the ANA 30 mg, 75 mg, and 150 mg gps, respectively (*P*=0.054, *P*= 0.258, *P*=0.014 vs pbo)	ACR20/50/70 responses not reported
Cohen et al. (2002)[53]	r, db, pc, 24 wks	• Active RA >6 mos and <12 yrs MTX-IR	Pbo+MTX n=74	• Mean age 53–54 yrs	**ACR20 at wk 12:** 38% with ANA 2mg/kg (*P*=0.007 vs pbo)	**ACR20 at wk 24:** 35% with ANA 2mg/kg (*P*=0.143 vs pbo)

Study	Study design	Relevant inclusion/exclu-sion criteria	Treatment groups	Relevant demographics	Efficacy summary – primary end point(s)	Efficacy summary –selected secondary end points
			ANA 2 mg/kg (only highest dose of dose-ranging study shown) + MTX n=72	• Mean disease duration 8 yrs • Mean number previous DMARDs (excluding MTX) 2 • 63–85% female		**ACR50 at wk 24:** 17% with ANA 2mg/kg (*P* not shown) **ACR70 at wk 24:** 7% with ANA 2mg/kg (*P* not shown)
T-cell co-stimulation inhibitor:						
Genovese et al. (2005)[37]	r, db, pc, 6 mo	• RA ≥1 yr • TNFi-IR	Pbo on days 1, 15, 29, and Q4wks thereafter n=133 ABA ~10mg/kg on days 1, 15, 29, and Q4wks thereafter n=258	• Mean age 53 yrs • Mean disease duration 11.4–12.2 yrs • Current TNFi 38–41% • Former TNFi 59–62% • 77–80% female	**ACR20:** 50.4% in ABA gp vs 19.5% in pbo gp (*P*<0.001) **HAQ-DI improvement ≥0.3:** 47.3% in ABA gp vs 23.3% in pbo gp (*P*<0.001)	**ACR50:** 20.3% in ABA gp vs 3.8% in pbo gp (*P*<0.001) **ACR70:** 10.2% in ABA gp vs 1.5% in pbo gp (*P*=0.003) **DAS28 remission:** 10.0% in ABA gp vs 0.8% in pbo gp (*P*<0.001)
B-cell CD20 antigen:						
Cohen et al. (2006); REFLEX[36]	r, db, pc, 24 wks	• RA ≥6 mos • Stable MTX 10–25 mg/wk • TNFi-IR	Pbo wk 1 and 15 + MTX Q1wk n=209 RTX wk 1 and 15 + MTX Q1wk n=308	• Mean age 52–53 yrs • Mean disease duration 12 yrs • Mean number previous DMARDs (excluding MTX) 2.4–2.6 • 81% female	**ACR20**: 51% (RTX +MTX) vs 18% (pbo +MTX) [*P*<0.0001]	**ACR50**: 27% (RTX+MTX; *P*<0.0001 vs pbo+MTX) **ACR70**: 12% (RTX+MTX; *P*<0.0001 vs pbo+MTX) **SF-36**: Mean increase from baseline in mental and physical summary scores 4.7 and 5.8 for RTX+MTX (*P*=0.0002 vs pbo+MTX) **Joint space narrowing (JSN) score**: change +0.2 (RTX+MTX; *P*=0.016 vs pbo +MTX)

ABA = abatacept; ADA = adalimumab; ANA = anakinra; anti-TNF = tumor necrosis factor inhibitor; AUC = area under the curve; bw = twice weekly; CTX = certolizumab pegol; db = double-blind; DMARD = disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; gp = group; HAQ-DI = Health Assessment Questionnaire-Disability Index; IFX = infliximab; IR = inadequate response; mTSS = modified total Sharp score; MTX = methotrexate; mo = month; NS = not significant; od = once daily; pbo = placebo; pc = placebo-controlled; pts = patients; Q1wk = every week; Q2wks = every 2 weeks, etc.; r = randomized; RTX = rituximab; SF-36 = Short Form-36; TNFi = tumor necrosis factor inhibitor; wk = week; yrs = years.

Table IV

Summary of major adverse events in randomized, controlled, phase 3 trials of biologics.

Study	Length of study	Summary of treatment	Injection-site reactions[a]	Serious infections[a]	Malignancies[a]
Anti-TNFs:					
Weinblatt et al. (2003); ARMADA[39]	24 wks	ADA 20, 40, or 80 mg, or pbo, Q2wks	15.3 (all ADA gps combined) ADA 80 mg: 11.0 ($P \leq 0.05$ vs pbo)	1.0 (all ADA gps combined)	0.5 (all ADA gps combined)
Keystone et al. (2004)[44]	52 wks	ADA 20 mg Q1wk, or 40 mg Q2wks, or pbo, + MTX	24.1	3.8 ($P \leq 0.02$ vs pbo)	0.1
Van de Putte et al. (2004)[45]	26 wks	ADA 20 or 40 mg Q2wks or Q1wk, or pbo	10.6 ($P \leq 0.05$ vs pbo)	2.3 (NS vs pbo)	0.9 (NS vs pbo)
Breedveld et al. (2006); PREMIER[47]	2 yrs	ADA 40 mg Q2wks, ADA 40mg Q2wks + MTX, or MTX	NR	ADA: 0.7[b] MTX: 1.6[b] ADA+MTX: 2.9[b] ($P<0.05$ vs ADA)	ADA: 0.9[b] MTX: 0.9[b] ADA+MTX: 0.4[b]
Maini et al. (1999);[42] ATTRACT	30 wks	IFX 3mg/kg or 10 mg/kg Q4wks or Q8wks, or pbo, + MTX	IFX + MTX: 16–20[c] Pbo + MTX:10[c]	4.1 (all IFX + MTX gps combined; NS vs pbo)	0.9 (all IFX + MTX gps combined; however, all 3 cases in IFX 10 mg/kg Q4wks gp)
St Clair et al. (2004)[48]	54 wks	IFX 3 or 6 mg/kg, or pbo (at 0, 2, and 6 wks, then Q8wks), + MTX	IFX 3 mg/kg: 21[c] IFX 6 mg/kg: 15[c] Pbo: 7[c]	IFX 3 mg/kg: 5.6 ($P=0.02$ vs pbo) IFX 6 mg/kg: 5.0 ($P=0.04$ vs pbo)	1.1 (4 pts in IFX 6 mg/kg)
Schiff et al. (2008); ATTEST[61]	1 yr	IFX 3 mg/kg Q8wks, or ABA ~10 mg/kg Q4wks, or pbo Q4wks, + MTX	NA (IV)	IFX: 8.5 ABA: 1.9	IFX: 1.2 ABA: 0.6
Moreland et al. (1999)[38]	6 mos	ETN 10 or 25 mg bw, or pbo	ETN 10 mg: 43 ($P<0.001$ vs pbo) ETN 25 mg: 49 ($P<0.001$ vs pbo)	NR	NR
Bathon et al. (2000)[50]	12 mos	ETN 10 or 25 mg bw, or MTX Q1wk	ETN 10 mg: 30 ($P<0.05$ vs MTX) ETN 25 mg: 37 ($P<0.001$ vs MTX)	<3 (in each gp)	ETN 10 mg: 1.0 ETN 25 mg: 1.4
Klareskog et al. (2004); TEMPO[43]	52 wks	ETN 25 mg bw, MTX alone, or ETN 25 mg bw + MTX	ETN: 21 ($P<0.0001$ vs MTX) ETN + MTX: 10 ($P=0.0002$ vs MTX) MTX: 2	4 (for each gp)	ETN: 1.8 ETN + MTX: 0.4 MTX: 0.4
Weinblatt et al. (2007)[51]	1 yr	ETN 25 mg bw + ABA 2mg/kg Q4wks, or ETN 25 mg bw + pbo	NR	ETN + ABA: 3.5 ETN + pbo: 0.0	NR
Emery et al. (2008); COMET[49]	52 wks	ETN 50 mg Q1wk, or pbo, + MTX	NR	ETN + MTX: 1.8 MTX: 3.0	ETN+MTX: 1 MTX: 1
Fleischmann et al. (2008); FAST4WARD[57]	24 wks	CTZ 400 mg, or pbo, Q4wks	CTZ: 4.5 Pbo: 13.8	CTZ: 1.8 Pbo: 0	CTZ: 0 Pbo: 0
Keystone et al. (2008);[55] RAPID-1	52 wks	CTZ 200 or 400 mg Q2wks, or pbo, + MTX	CTZ 200 mg + MTX: 2.3 CTZ 400 mg + MTX: 0.8 Pbo + MTX: 0	CTZ 200 mg + MTX: 5.3[b] CTZ 400 mg + MTX: 7.3[b] Pbo + MTX: 2.2[b]	CTZ 200 mg + MTX: 1.8 CTZ 400 mg + MTX: 1.0 Pbo + MTX: 0.5

Study	Length of study	Summary of treatment	Injection-site reactions[a]	Serious infections[a]	Malignancies[a]
Smolen et al. (2008); RAPID-2[56]	24 wks	CTZ 200 or 400 mg Q2wks, or pbo, + MTX	CTZ 200 mg + MTX: 1.2 CTZ 400 mg + MTX: 2.0	CTZ 200 mg + MTX: 3.2 CTZ 400 mg + MTX: 2.4 Pbo + MTX: 0.8	CTZ 200 mg + MTX: 0.4 CTZ 400 mg + MTX: 0.4 Pbo + MTX: 0.8
Keystone et al. (2009); GO-FORWARD[60]	52 wks (24-wk data presented)	GOL 100 mg Q4wks; GOL 50 or 100 mg Q4wks + MTX; or pbo + MTX	GOL 50 mg + MTX: 2.4 GOL 100 mg + MTX: 4.8 GOL 100 mg: 7.5 Pbo + MTX: 3.0	GOL 50 mg + MTX: 0.9 GOL 100 mg + MTX: 4.8 GOL 100 mg: 3.0 Pbo + MTX: 0.7	GOL 50 mg + MTX: 0.0 GOL 100 mg + MTX: 1.0 GOL 100 mg: 1.5 Pbo + MTX: 0.7
Smolen et al. (2009); GO-AFTER[59]	24 wks	GOL 50 or 100mg, or pbo, Q4wks	GOL 50 mg: 4.0 GOL 100 mg: 11.0 Pbo: 3.0	GOL 50 mg: 2.0 GOL 100 mg: 1.0 Pbo: 2.0	GOL 50 mg: 1.0 GOL 100 mg: 1.0 Pbo: 0.0
IL-1 inhibitor:					
Bresnihan et al. (1998)[54]	24 wks	ANA 30, 75, or 150 mg od, or pbo	ANA 30 mg: 50 ANA 75 mg: 73 ANA 150 mg: 81 Pbo: 25	ANA 75 mg: 0.9 ANA 150 mg: 3.4 Pbo: 0.8	NR
Cohen et al. (2002)[53]	24 wks	ANA 0.04–2 mg/kg od (2 mg/kg data shown), or pbo	ANA 2 mg/kg: 63 Pbo: 28	ANA 2 mg/kg: 0.0 Pbo: 0.0	ANA 2 mg/kg: 1.4 Pbo: 1.4
T-cell co-stimulation inhibitor:					
Genovese et al. (2005)[37]	6 mos	ABA ~10mg/kg, or pbo, + DMARDs	ABA: 5.0[c] Pbo: 3.0[c]	2.3 (in each gp)	NR
B-cell CD20 antigen:					
Cohen et al. (2006); REFLEX[36]	24 wks	RTX (2 × 1000 mg), or pbo, + MTX	RTX: 23[c,d] Pbo: 18[c,d]	RTX + MTX: 1.4 Pbo + MTX: 2.3	NR

[a]Data shown as percent of pts unless stated otherwise. Statistical significance is shown where available.

[b]Number of events per 100 pt-yrs.

[c]% pts with infusion reactions.

[d]Occurring within 24 hours of first infusion.

ABA = abatacept; ADA = adalimumab; ANA = anakinra; bw = twice weekly; CTZ = certolizumab pegol; DMARD = disease-modifying antirheumatic drug; ETN = etanercept; GOL = golimumab; gp = group; IFX = infliximab; mos = months; MTX = methotrexate; NA = not applicable; NR = not reported; NS = not significant; od = once daily; pbo = placebo; pts = patients; Q1wk = every week; Q2wks = every 2 weeks; r = randomized; RTX = rituximab; wks = weeks; yrs = years.

Table V

Summary of FDA-imposed boxed warnings about infections with TNF antagonists.[75]

• Increased risk of serious infections that may lead to hospitalization or death
• Treatment should be discontinued in the case of serious infections or sepsis
• Risk of active TB, including reactivation of latent TB. Latent TB should be treated before starting TNF antagonists
• Risk of invasive fungal infections (including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis)
• Risk of infection (bacterial and viral) with opportunistic pathogens
• Monitor patients for infections, including TB, even when an initial test for latent TB was negative

Table VI

Summary of 2008 ACR guidelines about biologic use in RA patients.[14]

RA disease duration	RA disease activity	Previous treatments failed	Recommendation
<6 months	High for 3–6 months	–	TNF antagonist plus MTX
	High for <3 months, plus features of poor prognosis,[a] and no cost or insurance coverage limitations		
≥6 months	High	MTX monotherapy	TNF antagonist
	Moderate, plus features of poor prognosis		
≥6 months	High	MTX combination therapy	With features of poor prognosis: TNF antagonists, abatacept, or rituximab (the latter only if disease activity is high)
	Moderate	Sequential administration of other nonbiologic DMARDs	Without features of poor prognosis: nonbiologic DMARD or TNF-antagonist

[a]Features of poor prognosis include functional limitation (defined using standard measurement scales such as Health Assessment Questionnaire score), extra-articular disease (eg, presence of rheumatoid nodules, secondary Sjögren's syndrome, RA vasculitis, Felty's syndrome, and RA lung disease), rheumatoid factor positivity, positive anti-cyclic citrullinated peptide antibodies, or bony erosions on radiography.

ACR = American College of Rheumatology; DMARDs = disease-modifying anti-rheumatic drugs; MTX = methotrexate; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

Table VII

Summary of 2009 UK NICE guidelines about biologic use in adults with RA.[95]

Biologic	RA disease activity	Previous treatments failed	Recommendation
Rituximab	Severe, active	DMARDs and at least 1 TNF-antagonist	Combination with MTX
			Treatment should only be continued if there is an adequate response[a]
Abatacept	NA	NA	Not recommended for the treatment of RA
Adalimumab, infliximab, and etanercept	Active (DAS28 >5.1)	2 DMARDs including MTX (unless contraindicated) of ≥6 months duration	Combination with MTX (unless inappropriate, or patient intolerant)
			Treatment should be continued only if there is an adequate response[a]
			Should be monitored (DAS28) at least every 6 months and discontinued if adequate response[a] is not maintained

[a]Improvement in DAS28 score ≥1.2 points.

DAS28 = Disease Activity Score based on 28 joints; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; RA = rheumatoid arthritis.