Comparative Overview of Safety of the Biologics in Rheumatoid Arthritis

MAJED KHRAISHI

ABSTRACT. Six biologic agents are currently available in Canada for the treatment of rheumatoid arthritis (RA): abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab. Although they are generally considered to be safe and well tolerated, concerns have been raised regarding the use of biologic therapies in the treatment of RA. The new biologic agents abatacept and rituximab have novel mechanisms of action, and may therefore offer different safety profiles. The most important safety concerns with the biologic therapies remain the increased risk of infection. An increased risk of malignancies, including lymphoma and skin cancer, has been noted in RA trials, but the extent to which each of the biologic therapies contributes to the risk of malignancy has not been clearly defined. (J Rheumatol 2009;36 Suppl 82:25-32; doi:10.3899/jrheum.090128)

Key Indexing Terms:
ANTI-TUMOR NECROSIS FACTOR- α AGENTS BIOLOGIC THERAPIES
INFECTION MALIGNANCY RHEUMATOID ARTHRITIS

Biologic therapies for the treatment of rheumatoid arthritis (RA) are disease modifying antirheumatic agents (DMARD) designed to inhibit specific components of the immune system, such as the cytokines, which play a pivotal role in either promoting or suppressing inflammation. Six biologic agents for the treatment of rheumatoid arthritis (RA) are currently available in Canada: abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab. Other biologic therapies for the treatment of RA are currently being studied in clinical trials, including golimumab and certolizumab [2 anti-tumor necrosis factor (TNF) monoclonal antibodies], and tocilizumab [an anti-interleukin 6 (IL-6) receptor monoclonal antibody].

Although the biologic therapies are generally safe and well tolerated, concerns have been raised regarding their use in the treatment of RA. This article provides a comparative review of the safety of the biologic agents for the treatment of RA.

SAFETY IMPLICATIONS OF MECHANISMS OF ACTION OF BIOLOGIC AGENTS USED TO TREAT RA

TNF is a proinflammatory cytokine that plays an important role in the pathogenesis of a variety of autoimmune diseases, including RA. Currently, 3 anti-TNF agents are approved in Canada for the treatment of RA – adalimumab, etanercept, and infliximab. The anti-TNF agents are distinguished broadly by their structures and mechanisms of action. Infliximab is a chimeric monoclonal antibody, while adalimumab is a fully human antibody. Etanercept is a recombinant molecule, produced by fusion of a human immunoglobulin G (IgG) Fc portion to two human p75 TNF-α receptors.

In addition, TNF is also an important constituent of the human immune response to infection. Released by activated macrophages, T lymphocytes, and other immune cells in response to a variety of infectious stimuli[1,2], TNF is involved in anti-tumor and anti-viral activity, and the mediation of systemic inflammatory responses to infection and sepsis. TNF also plays a critical role in immune response to a variety of infections, including those involving *Mycobacterium tuberculosis* and other intracellular pathogens[1,3]. The control and containment of intracellular pathogens are dependent on TNF, which recruits inflammatory cells to the area of infection, stimulating the formation of granulomas. In murine models, neutralization of TNF results in failure to protect against infection with *M. tuberculosis*[4-6] and bacillus Calmette–Guérin[7]. Although all 3 anti-TNF agents neutralize TNF-α activity in *vitro*, the monoclonal antibodies infliximab and adalimumab (but not etanercept) are also able to fix complement and therefore lyse cells that express surface-bound TNF-α[8]. While the full significance of this is not clear, important immune system cells, including T cells and neutrophils, express membrane-bound TNF-α, the disruption of which may result in additional immunosuppression. This may explain the higher rates of tuberculosis (TB) reactivation observed with infliximab and adalimumab than with etanercept. Another mechanism could be the high avidity and irreversible binding of the monoclonal antibodies for both soluble and transmembrane TNF[9,10], whereas etanercept is only able to bind strongly to soluble TNF[9].

From the Department of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland, Canada.

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M.M. Khraishi, MB, Ch, FRCPC, Clinical Professor of Medicine.

Address reprint requests to Dr. M.M. Khraishi, Nexus Clinical Research, 1 Anderson Avenue, St. John's, NL A1B 3E1
E-mail: mkhraish@mun.ca

TNF also activates macrophages, which phagocytose and destroy mycobacteria and other pathogens via nitric oxide-dependent and nitric oxide-independent pathways[11]. Mice deficient in this signaling pathway have been shown to be highly susceptible to infection by Listeria[12,13], as well as by *Klebsiella pneumoniae* and *Streptococcus pneumoniae*, which are both frequent causes of pneumonia in humans[14,15]. The use of anti-TNF agents to treat RA may therefore compromise the normal immune responses against infectious disease.

One of the newer biologic agents, abatacept, is the first in a new class of agents that prevents the activation of naïve T cells by inhibiting the second signal required for their costimulation. This signal is mediated by CD80 and CD86, expressed on antigen-presenting cells, and CD28, which is expressed on T cells. Abatacept may also reduce the activation of memory T cells (although to a lesser extent than for naïve T cells)[16], consistent with a reduced response against tetanus toxoid[17]. Inhibiting the CD80/CD86:CD28 costimulatory signal may also potentially prevent the T cell from inducing optimal differentiation of CD80/CD86-expressing B cells into plasma cells, which ultimately secrete antibodies. Abatacept is therefore thought to primarily affect adaptive immunity or antigen-specific immunity, with less effect on innate immunity (primary defense against pathogens). This differential mechanism of action could explain the lower rates of opportunistic infections and TB reactivation observed in the clinical trials with abatacept.

SAFETY CONCERNS WITH THE BIOLOGIC THERAPIES FOR RA

Infection. In general, the most important safety issues with the biologics are an increased risk of infections, including upper respiratory tract infections, opportunistic infections, and reactivation of TB. In a metaanalysis of randomized, controlled trials of the anti-TNF agents infliximab and adalimumab, serious infections were reported in 126 of 3,493 patients in the treatment groups (3.6%) and 26 of 1,512 patients in the control groups (1.7%) (OR 2.0, 95% CI 1.3-3.1)[18].

In particular, screening for TB is recommended for all patients prescribed a biologic therapy[19] (Figure 1). Using data from 2 observational registers, the Nijmegen inception cohort of early RA and the Dutch Rheumatoid Arthritis Anti-TNF alpha Monitoring (DREAM) register, Kievit, *et al* evaluated whether the risk of serious infection is increased with the anti-TNF agents compared with the conventional DMARD in patients with RA[20]. Infections were classified as serious when they led to hospitalization or death. The most frequently reported infections were pneumonia, serious skin infections, and septic arthritis. The rates of serious infection were 2.7 per 100 patient-years among patients who received an anti-TNF agent and 1.6 per 100 patient-years among those who received a conventional DMARD.

In a national longitudinal observational study of biologic therapies in rheumatic diseases, Dixon, *et al* com-

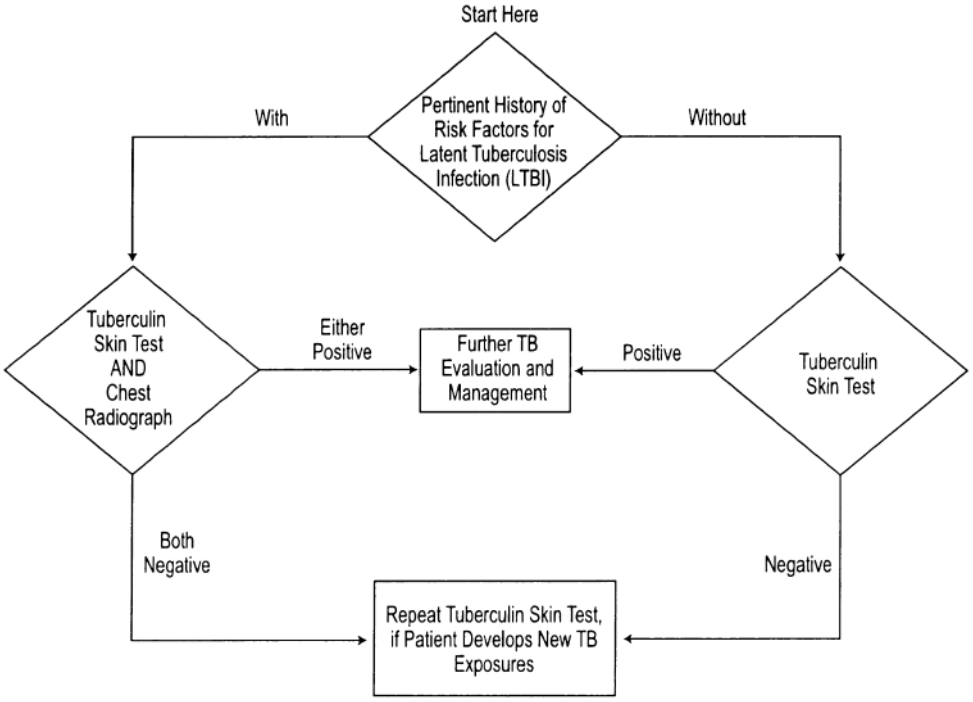

Figure 1. ACR recommendations for screening for tuberculosis (TB) among patients with RA being considered for biologic disease-modifying antirheumatic drugs[19]. Reprinted from Arthritis Rheum 2008;59:762-84, with permission.

pared rates of serious infection among 7,664 patients treated with an anti-TNF agent with rates of serious infection among a comparison population of 1,354 patients treated with traditional DMARD[21]. They also examined differences in the severity of serious infections between the cohorts, and in the rates of serious infection among the 3 anti-TNF agents. After adjusting for baseline risk factors, patients treated with anti-TNF agents were not found to be at increased risk of serious adverse events (AE) compared with those treated with traditional DMARD. Further, rates of serious infection were similar among the 3 anti-TNF agents. There was, however, an increased risk of skin and soft tissue infection, including an increased risk of bacterial intracellular infections.

Infusion/injection reactions. Among the most common AE with the anti-TNF agents are infusion/injection site reactions. A recent systematic review and metaanalysis of randomized, controlled trials assessed the safety of anti-TNF agents in the treatment of RA[22]. Patients treated with infliximab were more likely to discontinue treatment because of side effects and to suffer from severe side effects, infections, and infusion reactions. Infusion reactions are generally characterized by headache, pruritus, urticaria, flushing, hypertension, or injection site erythema[23]. Patients receiving adalimumab were also more likely to discontinue treatment because of side effects and to suffer injection site reactions[22]. However, these injection site reactions tend to be mild and self-limiting.

Malignancy. A number of studies have evaluated the incidence of lymphoma in populations of patients with RA[24-28]. These trials have found an overall increased incidence of lymphoma and lung cancer, and a decrease in breast and colon cancer in RA patients, although the extent to which different biologics are associated with different types of malignancies has not been clearly defined. Using the US National Databank for Rheumatic Diseases, Wolfe, *et al* examined incident cases of malignancy among 13,001 subjects participating in a study of RA outcomes during 49,000 patient-years of observation and 13 semiannual assessments in the years 1998 to 2005[29]. Biologic therapy was not associated with major cancers, including lung cancer (odds ratio 1.1) and lymphoma (odds ratio 1.0). However, melanoma and other skin cancers occurred more frequently among patients treated with biologic therapies.

Other safety concerns. Other potential AE associated with the biologics include lupus-like syndrome, demyelinating syndrome, effects on vaccination, and the development of blocking antibodies. The use of biologics in pregnancy and in patients with congestive heart failure and other cardiovascular diseases remains questionable[23].

SAFETY OF AVAILABLE BIOLOGIC THERAPIES FOR TREATMENT OF RA

Based on their different mechanisms of action, the different biologic therapies are associated with different AE profiles.

Safety of the anti-TNF agents. The safety of adalimumab has been assessed in patients with RA involved in global clinical trials, comprising 10,050 patients and representing 12,506 patient-years of adalimumab exposure, as well as in postmarketing surveillance, representing an estimated 78,522 patient-years of exposure to adalimumab[30]. Serious infections occurred in the clinical trials at a rate of 5.1 per 100 patient-years, which was comparable with published reports of RA populations naïve to anti-TNF therapy[31,32]. TB infection occurred in 34 patients in clinical trials and in 17 patients followed during postmarketing surveillance. However, the risk of TB was observed to decline following implementation of TB screening in clinical trials (Figure 2). The standardized incidence ratio for lymphoma was 3.19 (95% CI 1.78 to 5.26), which is consistent with the increased incidence observed in the general RA population[33].

The longterm safety of the anti-TNF agent etanercept has been evaluated in 2,054 patients with RA in North America and Europe, representing 6,654 patient-years of exposure[34]. All patients participating in the RA trials of etanercept were eligible to enroll in open-label extension studies. Lebwohl, *et al*[34] tracked the incidence of malignancies and infections requiring hospitalization or intravenous antibiotics. The incidence of malignancies was similar to that described in projections from the Surveillance, Epidemiology, and End Results (SEER) database (57 observed vs 55 predicted). The frequency of infections requiring hospitalization or intravenous antibiotics was 4 per 100 patient-years in the total population (6,654 patient-years), which is comparable to the rate seen in longterm, population-based studies[31,32].

Several reports indicate that the risk of TB is lower with etanercept, which is a soluble anti-TNF agent, than with the monoclonal antibodies infliximab and adalimumab. A comprehensive literature search of studies published between 1966 and 2004 was conducted to evaluate the role of TNF in normal and disease states and mechanisms of action of anti-TNF agents[35]. The rate of TB was found to be almost twice as high with infliximab (54 per 100,000 patients treated) as with etanercept (28 per 100,000 patients treated).

Patients with RA who fail to respond adequately to treatment with an anti-TNF agent, or who develop adverse effects forcing them to discontinue treatment, are often switched to another anti-TNF agent. This has been shown to be a safe and effective strategy[36-40]. In the open-label Research in Active RA: Adalimumab Trial

(ReACT), patients with RA were stratified according to prior anti-TNF therapy and treated with adalimumab 40 mg subcutaneously every other week for 12 weeks, in addition to their current DMARD (with the exception of anti-TNF therapies)[41]. Of the 6,610 patients enrolled in ReACT, 899 had received prior treatment with etanercept and/or infliximab. Withdrawals due to AE were similar between the 2 groups, regardless of whether patients had a history of anti-TNF therapy.

In the randomized, double-blind, placebo-controlled GO-AFTER trial, patients with active RA despite previous treatment with an anti-TNF therapy were treated with the new anti-TNF agent golimumab[42]. A total of 461 patients were randomly assigned to treatment with golimumab 50 mg, golimumab 100 mg, or placebo. Golimumab was generally well tolerated. No serious or severe reactions were reported, and none led to discontinuation.

SAFETY OF THE NON-ANTI-TNF BIOLOGIC AGENTS

Abatacept. The safety of abatacept has been assessed in 5 placebo-controlled trials and open-label extension studies, involving 2,688 patients and representing 3,827 person-years of exposure[43,44]. Three phase III studies have been completed to date: the Abatacept in Inadequate responders to Methotrexate (AIM) trial (n = 652)[45]; the Abatacept Trial in Treatment of Anti-TNF INadequate Responders (ATTAIN; n = 391)[46]; and the Abatacept Study of Safety in Use with other Rheumatoid arthritis therapies (ASSURE; n = 1,441)[47]. In addition, 2 phase II studies have examined the efficacy and safety of abatacept – one in patients with inadequate response to methotrexate (MTX; n = 339)[48], and one in combination with etanercept (n = 121)[49]. Overall, the rates of AE and serious AE in these clinical trials have been similar between abatacept and placebo[50]. The most commonly reported AE associated with abatacept were headache and nasopharyngitis. Serious infections and infestation were reported in significantly more abatacept-treated patients (3%) than placebo-treated patients (1.9%). The rates of malignancy and death were similar between the abatacept- and placebo-treated patients[50]. Acute infusion-related events were more common in abatacept-treated patients than placebo patients in the phase III studies (AIM, ATTAIN, ASSURE) (8.9% vs 5.5%). The most frequently reported events were dizziness (2.1% vs 1.3%), headache (1.8% vs 1.2%), and hypertension (1.2% vs 0.4%)[51].

Recently, the Abatacept Rheumatoid Arthritis Clinical Development Program has accumulated safety data for more than 10,000 person-years of exposure[52,53]. The incidences of serious infection (defined as hospitalized infection or any medically significant infectious event reported by the investigator), hospitalized infection (a subset of serious infection), and total malignancy (excluding non-melanoma skin cancer) were calculated in subjects who received abatacept or placebo in the double-blind and cumulative (double-blind and open-label) periods through December 2007. Incidence rates in the cumulative experience were also computed by annual intervals. In the cumulative clinical trial experience, 4,150 patients were exposed to abatacept, accounting for 10,365 person-years of exposure. Rates of malignancy and infection were comparable between the abatacept groups and the placebo groups, and remained stable over 6 years of the study. Two cases of presumed TB were reported with abatacept during the double-blind phase of the trials, and one case during the open-label phase[54].

These data suggest that longterm treatment with abatacept is generally safe and well tolerated in patients with RA. Infections account for the AE that most frequently require clinical intervention, such as interruption or discontinuation of abatacept[50]. Abatacept has not been

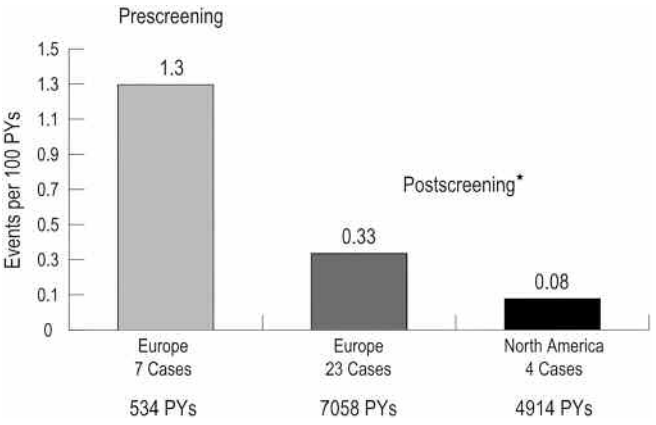

Figure 2. Rates of tuberculosis (TB) in trials of adalimumab. *Rates after implementation of TB screening procedures[30]. PY: patient-year. Reprinted from Ann Rheum Dis 2006;65:889-94, with permission.

studied in patients who have tested positive for TB, and the safety of abatacept in individuals with latent TB infection is unknown. Patients should be screened for TB and, if positive, should be treated with standard medical treatment prior to therapy with abatacept.

Rituximab. The safety and efficacy of rituximab for the treatment of RA, when given in combination with MTX, has been studied in 3 double-blind, placebo-controlled clinical trials (one phase III trial and 2 phase II trials). The Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) trial was a double-blind comparative study comprising 520 patients with severe, active RA who had experienced an inadequate response or intolerance to one or more TNF inhibitors[39]. The Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA (DANCER) trial study was a randomized, double-blind, double-dummy, controlled, 3 × 3 multifactorial study that compared 2 different dose levels of rituximab (2 × 1000 mg or 2 × 500 mg) given with or without one of 2 corticosteroid infusion regimens in combination with weekly MTX. Patients enrolled in DANCER had RA that had failed to respond to one or more DMARD and with a current inadequate response to MTX[55]. The third study was a double-blind, double-dummy, controlled study comparing rituximab monotherapy with rituximab plus either cyclophosphamide or MTX in patients with active RA who had not responded to one or more prior DMARD and with partial clinical response to MTX monotherapy[56].

AE and serious AE were comparable between the rituximab-treated groups and the placebo groups. The most frequent adverse reactions attributed to rituximab in the phase II and III studies were acute infusion reactions, which occurred in 15% of rituximab-treated patients following the first infusion compared with 5% in placebo patients[57]. Infusion reactions decreased to 2% following the second infusion in both the rituximab-treated and placebo groups. Symptoms suggestive of an acute infusion reaction include pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic edema, throat irritation, cough, and bronchospasm.

The overall infection rate in patients treated with rituximab was about 40%, and consisted primarily of lower respiratory tract infections and urinary tract infections. Serious infections occurred in 2% of rituximab-treated patients. Upper abdominal pain, muscle spasms, asthenia, and anxiety were also reported at a greater frequency in rituximab-treated patients.

In a recent exploratory analysis of 2,578 RA patients, the use of other biologic therapies in those who had previously been treated with rituximab was not associated with an increase in the rate of serious infections[58].

SAFETY OF NEW BIOLOGICS

Golimumab. The safety of the new anti-TNF monoclonal antibody golimumab was evaluated in the GO-AFTER trial, which enrolled 461 patients with active RA who had previously been treated with an anti-TNF agent[42]. Among patients randomly assigned to golimumab 50 mg, golimumab 100 mg, or placebo, serious AE were observed in 7.2%, 4.6%, and 9.7%, respectively. Serious infections occurred in 3.3%, 0.7%, and 3.2%, respectively.

Tocilizumab. Tocilizumab is a humanized anti-IL-6 receptor antibody that inhibits the function of the cytokine IL-6, which is critical to the acute-phase response and is raised in patients with RA. In a randomized, controlled trial of 306 patients with active RA assigned to tocilizumab or conventional DMARD for one year, treatment-emergent AE occurred in 96% of patients in the tocilizumab group and 87% in the group that received traditional DMARD[59]. Serious AE occurred at rates of 19% and 13%, respectively. The most frequently reported infectious event was nasopharyngitis. Mild transient increases in liver function tests were observed in both groups. Elevated lipid levels were reported predominantly in the tocilizumab-treated group, but the mean cholesterol level stabilized at around the normal upper limit. No occurrences of TB were observed in this study.

In the CHARISMA study, 359 patients with active RA and an inadequate response to MTX underwent a 4-week stabilization period on a fixed dose of MTX and were then randomly assigned to one of 7 treatment arms: tocilizumab 2 mg, 4 mg, or 8 mg either as monotherapy or in combination with MTX, or MTX plus a placebo infusion[60]. Mild nonfasting elevations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were observed. Liver enzyme elevations [mainly alanine aminotransferase (ALT)] were mild, transient, and reversible. There was no evidence of clinical hepatitis in any patients with elevated ALT. The periodicity of elevations coincided with the frequency of tocilizumab administration (monthly infusions), particularly at the initiation of treatment. There was no change in the atherogenic index, and no clear temporal association with increases in ALT levels. Temporal changes were found to be related to levels of C-reactive protein. Patients receiving tocilizumab monotherapy experienced fewer ALT elevations versus the group receiving tocilizumab in combination with MTX (2% vs 11%). Three percent of patients in the combination therapy group withdrew due to elevated ALT levels.

In a multicenter, double-blind, placebo-controlled study performed in Japan, 164 patients with refractory RA were randomly assigned to treatment with tocilizumab or placebo[61]. Laboratory abnormalities were observed in

57% and 76% of patients who received tocilizumab 4 mg and 8 mg, respectively, compared with 41% in the placebo group. Lipid metabolism-related reactions such as increases in total cholesterol, triglycerides, and high-density lipoprotein cholesterol were common in the tocilizumab groups, with 44.0% of patients exhibiting increased serum cholesterol levels.

In the recently completed Research on Actemra Determining effIcacy after Anti-TNF failurEs (RADIATE) study, 499 RA patients with an inadequate response to anti-TNF agents were given tocilizumab 8 mg or 4 mg plus MTX or placebo plus MTX[62]. AE occurred in 84.0%, 87.1%, and 80.6% of patients in the 8 mg, 4 mg, and control groups, respectively. Common AE included diarrhea, upper abdominal pain, rash, and dizziness. Serious AE occurred in 6.3%, 7.4%, and 11.3% of the 3 groups, respectively, and serious infections occurred in 4.6%, 1.8%, and 3.1%, respectively.

CONCLUSIONS

The biologic therapies are generally safe and well tolerated for the treatment of RA. The most important safety concerns with the biologic therapies are the increased risk of infection. As a result, physicians should exercise caution when considering the use of biologic therapies in patients with a history of recurrent infections or underlying conditions that may predispose them to infections. With the recent implementation of screening programs prior to treatment with biologic therapies, the risk of TB has declined among RA patients treated with these therapies.

An increased risk of malignancies, including lymphoma and skin cancer, has been noted in RA trials, but the extent to which each of the biologic therapies contributes to the risk of malignancy has not been clearly defined. Longer followup may be necessary to determine the association between biologic therapy and malignancy.

The newer biologic therapies, such as abatacept and rituximab, have unique modes of action and may offer more favorable safety profiles. However, the bulk of the safety data have come from clinical trials, and postmarketing surveillance data are awaited to add to the safety information for these agents.

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