Using the new biologic therapies in rheumatoid arthritis: practical aspects

Joseph A Markenson
Joan and Sanford Weill Medical College of Cornell University, Hospital for Special Surgery
535 E 70th St
New York, NY 10021, USA
Tel.: +1 212 606 1261;
Fax: +1 212 535 6183;
markensonj@hss.edu

In recent years, an increase in our understanding of the inflammatory cascade in rheumatoid arthritis has led to the development of newer targeted therapies with novel mechanisms of action. This review examines the day-to-day aspects of using currently approved biologic therapies for the treatment of patients with rheumatoid arthritis and the implications of how this relates to patient management. The tolerability considerations of anti-tumor necrosis factor therapies are overviewed, and the recently-approved targeted therapies rituximab and abatacept are discussed in terms of their indication and dosing, efficacy, safety and tolerability, to assist rheumatology healthcare professionals in making optimal treatment choices for their patients.

Keywords: abatacept, B cells, biologic, co-stimulation, rheumatoid arthritis, rituximab, T cells, tumor necrosis factor

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An increased understanding of the role of immune cells, such as T and B cells, in the initiation and perpetuation of the inflammatory cascade in rheumatoid arthritis (RA) has led to the development of newer targeted therapeutic agents with novel mechanisms of action. Targeted biologic therapies, such as the tumor necrosis factor (TNF) antagonists, have provided significant benefits over traditional RA therapies and represent a considerable advancement in the treatment of RA. Even with these progressions in disease management, there are still concerns over the efficacy, safety and practical considerations of these agents. A substantial proportion of patients have no response [1–3], lose their response to treatment over time [4] or form antibodies against therapies [5–8]. Until recently, the only treatment option for these patients would be to switch to another TNF antagonist, the benefits of which have not been proven in large, randomized clinical trials. Overall, the probability of retaining a second TNF antagonist is lower than that of retaining the first [9], and patients are more likely to discontinue a second or third TNF antagonist for the same reasons as those noted for discontinuation of the first [10]. The approval of novel targeted biologic therapies, such as rituximab and abatacept, has provided valuable new options for patients not responding to their current disease-modifying antirheumatic drug (DMARD) regimen.

This review examines the day-to-day aspects of using currently approved biologic therapies for the treatment of patients with RA and the implications of how this relates to patient management.

Overview of biologic therapies for RA

Anti-cytokine therapies

The first biologic agents to be approved for RA were the TNF antagonists, etanercept [101], adalimumab [102] and infliximab [103], and the interleukin (IL)-1 antagonist, anakinra [104]. These agents, often used in combination with methotrexate (MTX), have not only helped deliver improvements in the signs and symptoms of disease, but have also led to improvements in health-related quality of life and an attenuation of radiographic progression to an extent previously considered unattainable [11]. In addition to the clinical benefits seen with these agents, there are also a number of associated efficacy and safety concerns, some of which are outlined below.

Infections with TNF antagonist therapies

Patients with active RA are reportedly at a greater risk of developing infections compared with patients without RA [12,13]. The exact cause is unknown, but this may be due to the immunomodulatory effects of RA or to the agents used in its treatment. An increased risk of infection, specifically tuberculosis, has been associated with the use of TNF antagonist therapies [14]. Serious infections, sepsis and fatalities have been reported with all three TNF antagonists. The prescribing information for etanercept features a bolded warning regarding the risk of infections [101], while the prescribing information for both adalimumab and infliximab feature boxed warnings regarding the risk of infections including tuberculosis, and it is recommended that patients with infections or those who have a history of recurrent infection should be monitored closely [102,103]. Tuberculosis has been observed

in some patients treated with etanercept [101], adalimumab [102] or infliximab [103], and for some it has been fatal [103]. In patients receiving infliximab at a dose of 3 mg/kg, insufficient clinical efficacy has been reported in some cases, and these patients may require a modification of dose, or 'dose titration' for their treatment to be efficacious. However, it should be noted that data from the Safety Trial for RA with Remicade (START) trial has highlighted that the risk of tuberculosis is increased following high-dose infliximab treatment (10 mg/kg). Therefore, the decision to prescribe higher doses of infliximab should include heightened vigilance for infection [15].

Screening for tuberculosis using the tuberculin skin test is recommended prior to starting treatment with adalimumab [102] or infliximab [103] and the author suggests that this should be extended to treatment with all TNF antagonist therapies, including etanercept. A number of different recommendations for treating patients with tuberculosis have been proposed, including using the antibiotic isoniazid prior to initiating TNF antagonist therapy [14]. The implementation of such strategies may lessen the likelihood of tuberculosis in at risk populations [14].

Although the risk of intracellular infections such as tuberculosis has been widely reported, the incidence and risk of more common serious infections is less well documented. Data from clinical trials suggest that, overall, there is an increased risk of infection following treatment with TNF antagonists [13], however, the findings from post-marketing surveillance studies (which are not controlled and limited by patient numbers) may provide a more accurate reflection of current trends. In the Antirheumatic Therapies In Sweden (ARTIS) study (a nationwide Swedish monitoring program for biologics in RA), 4160 patients with RA, who were treated with TNF antagonists, were identified between the years 1999 and 2003. The findings from this study suggest that treatment with these agents is associated with a 30% increased risk of hospitalization for infection. In addition, among patients receiving TNF antagonist therapy, pre-treatment hospitalization for infection was common (20% of patients) [16].

Malignancies with TNF antagonist therapies

Using published data from nine randomized, controlled trials, Bongartz *et al.* have also demonstrated that, along with an increased risk of infection, there is an increased risk of malignancy in patients with RA who have been treated with TNF antagonists compared with control patients [13]. In the majority of trials included in this analysis, the control group was made up of patients who were receiving placebo plus standard antirheumatic therapy (included traditional DMARDs, low-dose corticosteroids, nonsteroidal anti-inflammatory drugs and/or analgesics). Although a number of other trials, including those with data from patient registries, have shown that there is an increased risk of malignancy in patients with RA [17–19] it is uncertain to what extent the risk is attributable to TNF antagonist therapies. In the trial by Bongartz *et al.*, the pooled odds ratio for malignancy was 3.3 (95% confidence interval, 1.2–9.1) [13]. More long-term data is needed before the risk can be estimated accurately, and any future clinical recommendations must take into consideration both the risks and benefits of these agents. The US FDA has issued a statement confirming that the risk–benefit relationship for the approved indications remains favorable when used as indicated. Data from patient registries provide valuable information on RA that complement the findings from the randomized clinical trials. While the overall tumor risk was not increased in those patients treated with TNF antagonist therapies, the findings from the South Swedish Arthritis Treatment Group (SSATG) register, suggests that there is a possible increased risk for lymphoma associated with these agents. In this study, the cohort of patients treated with TNF antagonists reportedly represents a subpopulation of patients with RA who had up to a 25-fold increased risk of lymphoma due to long-standing disease activity and, as such, these results should be interpreted with some degree of caution. In addition, these findings are based on only a few cases and further studies will be needed to confirm these conclusions [19].

Additional tolerability considerations with TNF antagonist therapies

Etanercept and adalimumab should be used with caution in patients with congestive heart failure; additionally, it is advised that infliximab at doses greater than 5 mg/kg should not be used in patients with moderate-to-severe heart failure [101–103]. The use of these agents has, in rare instances, also been associated with the relapse of hepatitis B virus (HBV) infection [105]. Therefore, patients at risk for HBV infection should be evaluated for prior evidence of this infection before initiating TNF antagonist therapy and prescribers should exercise caution when prescribing TNF antagonists for patients identified as carriers of HBV.

Immunogenicity with TNF antagonist therapies

Anti-drug antibodies, which may develop in some patients treated with TNF antagonist therapies, have been associated with a loss of response to therapy [7,8,20,21]. Antibodies to the TNF-receptor portion or other protein components of etanercept were detected in approximately 6% of adult patients treated for RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis. However, these antibodies were all non-neutralizing [101]. In a 5-year trial, Klareskog *et al.* demonstrated that the development of anti-etanercept antibodies had no long-term effect on the safety and efficacy of etanercept in the treatment of patients with RA [22]. Conversely, in approximately 5% of adult patients with RA receiving adalimumab, low-titer neutralizing antibodies to adalimumab were detected at least once during treatment [102]. However, patients treated with concomitant MTX had a lower rate of antibody development than patients on adalimumab monotherapy (1 versus 12%, respectively) [102]. In a separate trial of 121 patients with RA treated with adalimumab, 17% of patients developed anti-adalimumab antibodies [7]. Of these 121 patients, significantly more efficacy nonresponders had anti-adalimumab antibodies than responders (34 vs 5%; $p = 0.032$, respectively), suggesting the production of antibodies in these patients may have a neutralizing effect. It has been estimated that approximately 30% of patients treated with infliximab do not respond to therapy and the presence of human antichimeric antibodies is negatively correlated with infliximab levels and clinical response [21]. In a landmark trial, Wolbink *et al.* demonstrated that the formation of anti-infliximab antibodies is associated with a reduced response to treatment [8]. Of the 22 patients who had detectable anti-infliximab antibodies, only eight patients (36%) were classified as responders. This is in comparison to the 29 patients who did not have detectable levels of anti-infliximab antibodies, of which 69% were classified as responders [8]. In addition, the formation of anti-infliximab antibodies has also been associated with an increased risk of infusion-related reactions [8]. The incidence of antibodies to infliximab in patients given a three-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1–2 years of infliximab treatment [103].

Long-term management

The experience gained in clinical trials with TNF antagonists in terms of efficacy and safety has generally been reflected in post-marketing surveillance [23,24], evaluating these drugs in a broader population of patients than are typically included in clinical trials. The 6-year survival-on-drug data from the Stockholm TNF Antagonist Follow-up Registry (STURE) suggest that overall survival-on-drug rates for the TNF antagonists has been less than expected: 63.2 ± 1.2% after 2 years and 43.9 ± 1.6% after 5 years, indicating that there is considerable room for improvement in terms of the long-term therapeutic management of RA [25]. Results from a 6-year observational study in southern Sweden, as reported by the SSATG, suggest that patients are also more likely to adhere to their therapy for longer if they are tolerating MTX and were started on therapy with etanercept rather than infliximab [26]. Furthermore, in patients who require continuous therapy and have failed to respond to a TNF antagonist, replacement with a different TNF antagonist may be beneficial in some cases. However, in patients registered in the BIOBADASER (a national registry of patients with arthritis who are treated with biologic agents), drug survival rates were lower for those patients treated with more than one TNF antagonist compared with patients who had been treated with only one biologic agent [9].

Recently approved agents

New therapies are looking beyond cytokines to target cell types involved in the inflammatory cascade in RA. Two therapies with different mechanisms of action to the TNF antagonists have recently been approved in the USA. Rituximab [106] – a genetically engineered chimeric anti-CD20 monoclonal antibody that depletes B cells; and abatacept [107] – a soluble human fusion protein that selectively modulates T-cell costimulation, are described below. The approval of both rituximab and abatacept for the treatment of patients with an inadequate response to TNF antagonists, provides valuable treatment choices for a population of patients who previously had very limited options. In addition, abatacept has also been approved in the USA for use in patients with an inadequate response to MTX, therefore, providing an additional treatment option for patients who have not yet been treated with a biologic therapy.

Rituximab

Indication & dosing

In the USA, rituximab, in combination with MTX, is indicated to reduce signs and symptoms in adult patients with moderately to severely active RA who have had an inadequate response

to one or more TNF antagonists [106]. Rituximab should always be used in combination with MTX [106], and is given as two 1000 mg intravenous (iv) infusions, separated by 2 weeks [106]. The rate of the infusion should be at an initial rate of 50 mg/h; if the patient tolerated the first infusion well, subsequent rituximab infusions can be administered at an initial rate of 100 mg/h, increasing by 100 mg/h increments at 30-min intervals, to a maximum of 400 mg/h as tolerated [106]. Glucocorticoids, such as methylprednisolone 100 mg or its equivalent, administered intravenously 30 min prior to each infusion are recommended to reduce the incidence and severity of infusion reactions [106]. In addition, antihistamines and acetaminophen may also be used prior to each infusion.

Clinical efficacy

The efficacy and safety of rituximab in the treatment of patients with RA have been demonstrated in several trials [27–32]. Of these trials, the key studies are the Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA (DANCER) trial in patients with an inadequate response to MTX [29] and the Randomized Evaluation of Long-term Efficacy of Rituximab in RA (REFLEX) trial in patients with an inadequate response to one or more TNF antagonists [27]. Significant improvements in the signs and symptoms of RA, as assessed by American College of Rheumatology (ACR) 20, 50 and 70 response rates (**Tables 1 & 2**), were seen in the two trials described above.

Safety considerations

According to the prescribing information, infusion-associated events occur in approximately 7% of patients treated with rituximab and serious infections occur in approximately 2% of patients treated. The prescribing information for rituximab features a boxed warning regarding the incidence of fatal infusion reactions, tumor lysis syndrome and severe mucocutaneous reactions [106].

Tolerability considerations

Patients with a history of cardiopulmonary disease should also be monitored during the infusions and in the immediate post-infusion period. Because rituximab targets all $CD20^+$ B lymphocytes (malignant and non-malignant), complete blood and platelet counts should be obtained at regular intervals during rituximab therapy and more frequently in patients who develop cytopenias. Grade 3 and 4 cytopenias (including lymphopenia [40%], neutropenia [6%], leukopenia [4%], anemia [3%] and thrombocytopenia [2%]) were reported in 48% of patients treated with rituximab [106]. However, the amount of depletion of B cells may not be correlated with either efficacy or the time needed to retreat. Recent evidence suggests that peripheral blood B-cell expression does not always reflect synovial B-cell expression, and that synovial B-cell expression may possibly be a better barometer of efficacy and/or safety than peripheral expression (studies are ongoing) [30].

Table 1. Overview of efficacy observed in clinical trials with rituximab – DANCER trial.

Treatment	ACR			Δ DAS28	EULAR			Δ HAQ-DI	FACIT-F
	20	*50*	*70*		*No response*	*Moderate /good response*	*Good response*		
Rituximab 2× 500-mg doses 24 weeks	55*	33*	13‡	–1.79	28	73§	14§	–0.43	20
Rituximab 2× 1000-mg doses 24 weeks	54*	34*	20*	–2.05	34	67	28§	–0.49	28
Placebo 24 weeks	28	13	5	–0.67§	63	37	4	–0.16	4

**p < 0.001; ‡p < 0.029; §p < 0.0001.*

DANCER: Dose-ranging Assessment iNternational Clinical Evaluation of Rituximab in RA; ACR: American College of Rheumatology; DAS28: Disease Activity Score 28; EULAR: European League Against Rheumatism; HAQ-DI: Health Assessment Questionnaire Disability Index; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue subscale.

Taken from [29].

Table 2. Overview of efficacy observed in clinical trials with rituximab – REFLEX trial.

	ACR (24 weeks) [27]			Δ DAS28 (24 weeks) [27]	EULAR moderate/ good response (24 weeks) [27]	Mean change in structural damage (mean [SD] at 1 year) [33]		
	20	*50*	*70*			*Δ Erosion score*	*Δ JSN score*	*Δ Total score*
Rituximab	51*	27*	12*	–1.83*	65*	0.59 (1.85)‡	0.41 (1.33)§	1.00 (2.76)¶
Placebo	18	5	1	–0.34	22	1.32 (3.16)#	0.99 (2.57)	2.31 (5.28)

**p < 0.0001; ‡p < 0.05; §p < 0.001; ¶p < 0.005; #a proportion of placebo-treated patients also received rituximab.*
REFLEX: Randomized evaluation oF long-term efficacy of rituximab in RA; ACR: American College of Rheumatology; DAS28: Disease activity Score 28; EULAR: European League Against Rheumatism; SD: Standard deviation; JSN: Joint-space narrowing.

Recently, it was demonstrated that repeated courses of rituximab produce equivalent or improved efficacy compared with the original baseline, with no apparent cumulative toxicity, in patients with an inadequate response to DMARDs [31,32]. The long-term safety and efficacy of rituximab is still being investigated.

Regulatory affairs

Rituximab has been approved in the USA and Europe for use in patients with RA with an inadequate response to TNF antagonist therapy [106].

Abatacept

Indication & dosing

In the USA, abatacept is indicated for reducing signs and symptoms, inducing a major clinical response, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs, including both non-biologic DMARDs such as MTX and the biologic TNF antagonists. Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists or anakinra [107]. Abatacept should be administered as a 30-min iv infusion at a dose of 500 mg for patients less than 60 kg, 750 mg for patients 60–100 kg and 1 g for patients greater than 100 kg. Following the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion, and then every 4 weeks thereafter. Standard premedication is not required [107].

Clinical efficacy

The efficacy and safety of abatacept have been assessed in a number of randomized, double-blind, placebo-controlled trials in patients aged 18 years or over with active RA, diagnosed according to ACR criteria. Abatacept has demonstrated significant reductions in the signs and symptoms of RA in both the Abatacept in Inadequate responders to Methotrexate (AIM) trial of patients with an inadequate response to MTX [34] and in the Abatacept Trial in Treatment of Anti-TNF Inadequate responders (ATTAIN) trial of patients with an inadequate response to TNF antagonists (**Table 3**) [35]. In addition, abatacept also demonstrated a significant slowing of structural joint damage in the AIM trial [34].

Table 3. Overview of efficacy seen in clinical trials with abatacept – AIM [34] and ATTAIN [35] trials.

Study	ACR			DAS28	Mean change in structural damage		
	20	*50*	*70*	*Remission*	*Δ Erosion score*	*Δ JSN score*	*Δ Total score*
AIM 6 months abatacept	67.9*	39.9*	19.8*	14.8*	-	-	-
AIM 6 months placebo	39.7	16.8	6.5	2.8	-	-	-
AIM 12 months abatacept	73.1*	48.3*	28.8*	23.8*	0.63‡	0.58§	1.21¶
AIM 12 months placebo	39.7	18.2	6.1	1.9	1.14	1.18	2.32
ATTAIN 6 months abatacept	50.4*	20.3*	10.2#	10.0*	-	-	-
ATTAIN 6 months placebo	19.5	3.8	1.5	0.8	-	-	-

**p < 0.001; ‡p = 0.029; §p = 0.009; ¶p = 0.012; #p = 0.003.*
AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-TNF Inadequate responders; ACR: American College of Rheumatology; DAS28: Disease Activity Score 28; JSN: Joint-space narrowing
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Safety considerations

The safety of abatacept has been assessed in five randomized, double-blind, placebo-controlled trials involving almost 2000 patients. Acute infusion-related events (occurring within one hour of the start of the infusion) were more common with abatacept than with placebo (9% for abatacept, 6% for placebo). The most frequently reported events (1–2%) were dizziness, headache and hypertension. Acute infusion-related events that were reported in more than 0.1% and up to 1% of patients treated with abatacept included cardiopulmonary symptoms such as hypotension, increased blood pressure and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash and wheezing. The majority of these reactions were mild to moderate with fewer than 1% of abatacept-treated patients discontinuing due to an acute infusion-related event. In controlled trials, six abatacept-treated patients compared with two placebo-treated patients discontinued study treatment due to acute infusion-related events [107]. Infections were reported in 54% of abatacept-treated patients and 48% of placebo-treated patients, and serious infections were reported in 3% of patients treated with abatacept and 1.9% of patients treated with placebo [107].

Although no cases of tuberculosis are reported in the abatacept prescribing information, as with other biologic therapies, all patients should be screened for latent tuberculosis infection with a tuberculin skin test prior to initiating therapy [107]. More cases of lung cancer were observed in abatacept-treated patients compared with placebo-treated patients (four patients [0.2%] vs none, respectively) [107]. In the cumulative abatacept clinical trials (placebo-controlled and uncontrolled, open-label) a total of eight cases of lung cancer (0.21 per 100 patient-years) and four cases of lymphoma (0.10 per 100 patient-years) were observed in 2688 patients (3827 patient-years). In terms of immunogenicity, 1.7% of patients developed binding antibodies to either the entire abatacept molecule or to the cytotoxic T-lymphocyte-associated antigen-4 portion of abatacept. No relationship between immunogenicity and the efficacy or safety of abatacept was observed [107].

Tolerability considerations

Of 2688 patients treated with abatacept in the double-blind and open-label clinical trial phases, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria and dyspnea, occurred in less than 0.6% of abatacept-treated patients and generally occurred within 24 h of abatacept infusion [107].

Because an increased incidence of infection has been seen when abatacept is used in combination with another biologic therapy [36], abatacept is not recommended for use concomitantly with TNF antagonists or with anakinra. The effects of using abatacept in combination with rituximab have not been assessed [107].

Regulatory affairs

Abatacept is approved in the USA and Canada for the treatment of moderate to severe RA in patients with an inadequate response to MTX and/or TNF-antagonist therapy [107]. In Europe, approval has been restricted for use in patients with RA who have experienced an inadequate response to TNF antagonist therapy only.

Conclusion

The expanding range of biologic therapies offers greater opportunity to maximize clinical effectiveness for a broad range of patients with RA, including those with an inadequate response to TNF antagonists – a population of patients that previously had very limited treatment options. To date, the clinical experience with the most recently approved therapies, rituximab and abatacept, suggests that their safety and tolerability profiles are not dissimilar to the profiles of the TNF antagonists. The approval of rituximab in combination with MTX for the treatment of patients with an inadequate response to TNF antagonists, provides a feasible option for patients who have experienced inadequate responses to all other treatment options. Since abatacept can be used either as monotherapy or in combination with non-biologic DMARDs in patients with an inadequate response to MTX and/or TNF antagonist therapy, it provides a valuable therapeutic option with a novel mechanism of action that can be considered for use in these patient populations. However, more data are needed and several long-term data extensions are currently underway to substantiate the persistency of response and provide a continued evaluation of the safety data for both of these agents.

Future perspective

The exciting findings with abatacept to date are expected to be substantiated and extended with continued long-term observations. In addition,

trials are ongoing in other patient populations, including those with early RA and juvenile RA. The mechanism of action of abatacept also suggests potential for this drug in other autoimmune disease states. The promising effects seen to date with rituximab also suggest potential for enduring efficacy; however, the long-term effects of B-cell depletion have yet to be established.

Together with more aggressive treatment strategies and revolutionary new methods of detecting an inadequate response to treatment, the arrival of the targeted therapies discussed here suggests that the future of RA will include significant, tangible improvements in patients' quality of life, with the real possibility of remission becoming an achievable goal of treatment.

Acknowledgement

The author would like to thank Leigh Prevost, BSc (Hons) Pharm, Medicus International, for editorial assistance.

Financial & competing interests disclosure

Speakers bureau and advisory boards for Abbott, Bristol-Myers Squibb, Wyeth, Genentech and Novartis. Research grants from Abbott, Bristol-Myers Squibb, Wyeth, Genentech. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was utilized in the production of this manuscript. Editorial support was funded by Bristol-Myers Squibb.

Executive summary

- Tolerability challenges have been identified with tumor necrosis factor (TNF) antagonist therapy in the treatment of rheumatoid arthritis (RA), and long-term survival-on-drug data have been worse than expected.
- As such, novel therapies with alternative mechanisms of action are sought.
- Recently approved therapies include rituximab – a genetically engineered chimeric anti-CD20 monoclonal antibody that depletes B cells, and abatacept – a soluble human fusion protein that selectively modulates T-cell co-stimulation.

Rituximab

- Indication and dosing:
  - –Rituximab, in combination with methotrexate (MTX), is indicated to reduce signs and symptoms in adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonists.
  - –Rituximab should always be used in combination with MTX, and is given as two 1000 mg intravenous infusions, separated by 2 weeks.
- Clinical efficacy:
  - –Clinical trials have shown significant improvements in the signs and symptoms of RA, as assessed by American College of Rheumatology 20, 50 and 70 response rates.
- Safety:
  - –Infusion-associated events occur in approximately 7% of patients treated with rituximab, and serious infections occur in approximately 2% of patients treated with this agent.
  - –The prescribing information for rituximab features a boxed warning regarding the incidence of fatal infusion reactions, tumor lysis syndrome and severe mucocutaneous reactions.

Abatacept

- Indication and dosing:
  - –Abatacept is indicated for reducing the signs and symptoms, inducing a major clinical response, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active RA who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs), including both non-biologic DMARDs such as MTX and the biologic TNF antagonists.
  - –Abatacept should be administered as a 30-min intravenous infusion at a fixed dose based on a patient's body weight (500 mg for patients <60 kg, 750 mg for patients 60–100 kg and 1g for patients >100 kg). Following the initial infusion, it is recommended that the second infusion should be given two weeks after the first infusion and the third, 4 weeks after the first infusion. Any additional infusions should be given every four weeks thereafter.
- Clinical efficacy:
  - –Abatacept has demonstrated significant improvements in the signs and symptoms of RA both in patients with an inadequate response to MTX and in those with an inadequate response to TNF antagonist therapy.
- Safety:
  - –Acute infusion-related events were more common with abatacept than with placebo (9% for abatacept, 6% for placebo).
  - –Serious infections were reported in 3% of patients treated with abatacept and 1.9% of patients treated with placebo.
  - –An increased incidence of infection has been reported when abatacept is used in combination with other biologic agents.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Weinblatt ME, Keystone EC, DE Furst *et al.*: Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 48, 35–45 (2003).
2. Weinblatt ME, Kremer JM, Bankhurst AD *et al.*: A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N. Engl. J. Med.* 340, 253–259 (1999).
3. Lipsky PE, van der Heijde DM, St Clair EW *et al.*: Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N. Engl. J. Med.* 343, 1594–1602 (2000).
4. Buch MH, Bingham SJ, Bryer D, Emery P: Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. *Rheumatology (Oxford)* 46, 1153–1156 (2007).
5. Criscione LG, St Clair EW: Tumor necrosis factor-alpha antagonists for the treatment of rheumatic diseases. *Curr. Opin. Rheumatol.* 14, 204–211 (2002).
6. Maini R, St Clair EW, Breedveld F *et al.*: Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 354, 1932–1939 (1999).
7. Bartelds GM, Wijbrandts CA, Nurmohamed MT *et al.*: Clinical response to adalimumab: The relationship with anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann. Rheum. Dis.* 66(7), 921–927 (2007).
8. Wolbink GJ, Vis M, Lems W *et al.*: Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum.* 54, 711–715 (2006).
9. Gomez-Reino JJ, Carmona L: Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Res. Ther.* 8, R29 (2006).
10. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ: Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum.* 56, 13–20 (2007).
11. Keystone EC, Kavanaugh A: What to do with TNF failures. *Expert Opin. Drug Saf.* 4, 149–155 (2005).
12. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE: Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum.* 46, 2287–2293 (2002).
13. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V: Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 295, 2275–2285 (2006).
14. Carmona L, Gomez-Reino JJ, Rodriguez Valverde V *et al.*: Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 52, 1766–1772 (2005).
15. Westhovens R, Yocum D, Han J *et al.*: The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum.* 54, 1075–1086 (2006).
16. Askling J: TNF antagonist treatment and risk of hospitalisation for infection. Results from the national swedish monitoring program for biologics in RA (ARTIS). Presented at: *The American College of Rheumatology Annual Meeting*. Washington DC, USA (2006).
17. Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH: Rheumatoid arthritis and cancer risk. *Eur. J. Cancer* 32A, 1753–1757 (1996).
18. Thomas E, Brewster DH, Black RJ, Macfarlane GJ: Risk of malignancy among patients with rheumatic conditions. *Int. J Cancer* 88, 497–502 (2000).
19. Geborek P, Bladstrom A, Turesson C *et al.*: Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann. Rheum. Dis.* 64, 699–703 (2005).
20. Klareskog L, van der Heijde D, de Jager JP *et al.*: Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 363, 675–681 (2004).
21. van der Laken CJ, Voskuyl AE, Roos JC *et al.*: Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. *Ann. Rheum. Dis.* 66, 253–256 (2007).
22. Klareskog L, Wajdula J, Yeh P, Fatenejad S: Low autoantibody and anti-etanercept antibody formation and lack of impact on clinical outcomes following 5 years of treatment with enbrel in patients with rheumatoid arthritis [Abstract from ACR]. *Arthritis Rheum.* 52, S348 (2005).
23. Geborek P, Crnkic M, Petersson IF, Saxne T: Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann. Rheum. Dis.* 61, 793–798 (2002).
24. Schiff MH, Burmester GR, Kent JD *et al.*: Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 65, 889–894 (2006).
25. van Vollenhoven R, Cullinane C, Bratt J, Klareskog L: Six-year report of the STURE registry for biologicals in rheumatology: satisfactory overall results, but plenty of room for improvement. Presented at: *The European League Against Rheumatism Annual Meeting*. Amsterdam, The Netherlands, (2006).
26. Kristensen LE, Saxne T, Nilsson JA, Geborek P: Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. *Arthritis Res. Ther.* 8, R174 (2006).
27. Cohen SB, Emery P, Greenwald MW *et al.*: REFLEX Trial Group: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum.* 54, 2793–2806 (2006).

• **Pivotal rituximab trial in rheumatoid arthritis (RA) patients.**

28. Edwards JC, Szczepanski L, Szechinski J *et al.*: Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N. Engl. J. Med.* 350, 2572–2581 (2004).

29. Emery P, Fleischmann R, Filipowicz-Sosnowska A *et al.*: The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum.* 54, 1390–1400 (2006).
• **Pivotal rituximab trial in RA patients.**
30. Dass S, Coulthard AC, Rawston A *et al.*: B Cell Levels in Synovium Predict Efficacy of Rituximab in RA Better Than Those in Peripheral Blood. Presented at: *The American College of Rheumatology Annual Meeting*. Washington DC, USA (2006).
31. Emery P, Furst DE, Ferraccioli G *et al.*: Long-term efficacy and safety of a repeat treatment course of rituximab in RA patients with an inadequate response to disease-modifying anti-rheumatic drugs. Presented at: *The American College of Rheumatology Annual Meeting*. Washington DC, USA (2006).
32. Keystone E, Fleischmann R, Emery P *et al.*: Long-term efficacy and safety of a repeat treatment course of rituximab in rheumatoid arthritis patients with an inadequate response to one or more TNF inhibitors. Presented at: *The American College of Rheumatology Annual Meeting*. Washington DC, USA (2006).
33. Keystone E, Emery P, Peterfy CG *et al.*: Prevention of joint structural damage at 1 year with rituximab in rheumatoid arthritis patients with an inadequate response to one or more TNF inhibitors (REFLEX study). Presented at: *The American College of Rheumatology Annual Meeting*. Washington DC, USA (2006).
34. Kremer JM, Genant HK, Moreland LW *et al.*: Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* 144, 865–876 (2006).
• **Pivotal abatacept trial in RA patients.**
35. Genovese MC, Becker JC, Schiff M *et al.*: Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N. Engl. J. Med.* 353, 1114–1123 (2005).
•• **Pivotal abatacept trial in RA patients; first clinical trial of a novel RA therapy in patients with an inadequate response to TNF antagonist therapy.**
36. Weinblatt M, Combe B, Covucci A, Aranda R, Becker J-C, Keystone E: Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs. *Arthritis Rheum.* 54, 2807–2816 (2006).
• **Pivotal abatacept trial in RA patients.**

Websites

101. Wyeth: Enbrel (etanercept) for subcutaneous injection. Prescribing information. www.wyeth.com (Accessed March 1 2006).
102. Abbott: Abbott Laboratories Pharmaceutical Products Group. Humira (adalimumab). Prescribing information. www.rxabbott.com (Accessed March 1 2006).
103. Centrocor: Remicade (infliximab) for IV Injection. Prescribing information. www.remicade.com (Accessed March 1 2006).
104. Amgen: Kineret (anakinra). Prescribing information. www.kineretrx.com (Accessed March 27 2006).
105. Health Canada: www.hc-sc.gc.ca/dhp-mps/medeff/advisories avis/public/2006/anti-tnf_therapy_pc-cp_e.html (Accessed 30 June 2006.)
106. Genentech: RITUXAN (rituximab). Prescribing information. www.rituxan.com (Accessed 3 August 2006).
107. Bristol-Myers Squibb: ORENCIA (abatacept). Prescribing information. www.orencia.com (Accessed April 1 2007).

Affiliation

• *Joseph A Markenson, MD, Professor*
Joan and Sanford Weill Medical College of Cornell University, Hospital for Special Surgery
535 E 70th St
New York, NY 10021, USA
Tel.: +1 212 606 1261;
Fax: +1 212 535 6183;
markensonj@hss.edu