What Is the Place of Recently Approved T Cell-Targeted and B Cell-Targeted Therapies in the Treatment of Rheumatoid Arthritis? Lessons from Global Clinical Trials

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ABSTRACT. The recently approved therapies abatacept and rituximab have significantly improved treatment options for patients with rheumatoid arthritis, especially for patients who have an inadequate response to tumor necrosis factor inhibitors. This article reviews the latest efficacy and safety data for both abatacept and rituximab. One-year data from abatacept and rituximab clinical trials show significantly better efficacy and reduction in radiographic damage for these therapies compared with placebo. In addition, repeated courses of rituximab confer continued efficacy for patients. The safety profile of these therapies shows that infusion reactions and infections are the most commonly reported important adverse events. Premedication with corticosteroids reduces the infusion reactions to rituximab. (J Rheumatol 2007;34 Suppl 79:15-20)

Key Indexing Terms:
T CELL B CELL TARGETED THERAPIES
RHEUMATOID ARTHRITIS CLINICAL TRIALS

INTRODUCTION

Until recently the options for treating rheumatoid arthritis (RA) were a variety of traditional disease modifying antirheumatic drugs (DMARD) including methotrexate (MTX) and biologic agents, especially the widely used tumor necrosis factor (TNF) inhibitors infliximab, etanercept, and adalimumab. TNF inhibitors in combination with MTX are particularly successful in many patients. Studies have shown American College of Rheumatology 70% (ACR70) response rates with combinations of infliximab, etanercept, or adalimumab plus MTX of 37%, 43%, and 49%, respectively, with ACR20 response rates reaching 80%[1-3]. However, some patients do not respond well or have contraindications to these agents. Before the approval of abatacept and rituximab, physicians had limited options for treating a patient who had an inadequate response to a TNF inhibitor; these options were increasing the dose, shortening the dosing frequency, or switching to another TNF inhibitor. However, about 50% of patients who fail a first TNF inhibitor fail a second one, and at least one-third of those who are subsequently switched to a third TNF inhibitor discontinue the third TNF inhibitor due to lack of efficacy[4-6].

Novel biologic therapies: abatacept and rituximab

There are now 2 new biologic agents available for use in patients with RA. Abatacept, formerly known as CTLA4-Ig, interferes with T cell costimulation by binding to CD80 and CD86 on antigen-presenting cells and prevents the interaction between these costimulatory molecules and their cognate receptor on the T cell, CD28. The supposed mode of action for abatacept is the inhibition of T cell activation. An alternative new therapy, rituximab, or anti-CD20, is a chimeric monoclonal antibody that binds to CD20 expressed on most B cells but not on pro-B or plasma cells[7]. Rituximab has been shown to inhibit B cell activities by depleting B cells, reducing autoantibodies, and reducing the antigen-presenting function of B cells[8].

Abatacept clinical trials

Efficacy. The pivotal clinical trials for abatacept include the Abatacept in Inadequate Responders to Methotrexate (AIM) study, the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN), and the Abatacept Study of Safety in Use With Other RA Therapies (ASSURE).

The AIM study examined 547 patients who had an inadequate response to MTX and (in addition to continuing MTX) received a monthly infusion of either placebo or abatacept (10 mg/kg body weight) for 1 year. Kremer and colleagues recently reported the 1-year ACR responses for the AIM study[9]. Seventy-three percent of patients receiving abatacept plus MTX achieved an ACR20 improvement compared with 40% of patients receiving placebo plus MTX ($p < 0.001$). An ACR50 response was achieved by 48% of patients receiving abatacept plus MTX compared with 18% of patients receiving placebo ($p < 0.001$), and an ACR70 response was

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achieved by 29% of patients receiving abatacept plus MTX compared with 6% of patients receiving placebo ($p = 0.001$).

In addition, patients receiving abatacept plus MTX had 50% less radiographic progression compared with patients receiving placebo after 1 year. Genant-modified Sharp scores were 1.2 for the abatacept plus MTX group and 2.3 for the placebo plus MTX group ($p = 0.012$; Figure 1)[9].

The ATTAIN study examined patients who had active RA and an inadequate response to TNF inhibitors (plus MTX)[10]. Patients underwent a washout period for TNF blockers prior to receiving study drugs but continued MTX. They received abatacept (plus MTX) or placebo (plus MTX). In this trial, about 50% of the patients receiving abatacept plus MTX had an ACR20 response compared with 20% of the placebo-treated patients after 6 months ($p < 0.001$). Twenty percent of patients receiving abatacept achieved an ACR50 response compared with 4% of patients receiving placebo ($p < 0.001$), and 10% of patients reached an ACR70 response compared with 2% of the placebo-treated patients ($p < 0.003$; Figure 2)[10].

Physical function of patients receiving abatacept was measured in the AIM trial and the ATTAIN trial. In the AIM trial, about 64% of abatacept-treated patients compared with 40% of placebo-treated patients improved their Health Assessment Questionnaire Disability Index (HAQ-DI) score ($p < 0.001$)[9,11]. In the ATTAIN trial, almost 47% of patients receiving abatacept compared with less than 23% of patients receiving placebo improved their HAQ-DI by more than 0.3 ($p < 0.001$)[10].

The ASSURE trial evaluated patients who were receiving nonbiologic DMARD or TNF inhibitors and had an inadequate response. In contrast to the ATTAIN trial, they continued those therapies with the addition of either placebo or abatacept[12]. The patients receiving placebo who continued their nonbiologic DMARD had a 20% improvement in the Physician Global Assessment of disease activity (PGA) by visual analog scale (VAS) score. The PGA improved by 41% for patients receiving abatacept and nonbiologic DMARD. Patients who continued their TNF inhibitors with abatacept or placebo reported outcomes that differed much less from placebo than for patients who continued nonbiologic DMARD. Patients' global assessment of disease activity by VAS showed a 36% improvement with abatacept plus a TNF inhibitor, compared with 28% improvement with placebo plus a TNF inhibitor. These numbers were 41% versus 20% for nonbiologic DMARD. The HAQ-DI changes amounted to 22% versus 15% (combination with TNF blockers) and 30% versus 9% (combination with nonbiologic DMARD), respectively ($p < 0.001$)[12]. These results indicate that the combination of a TNF inhibitor with abatacept is not more efficacious than the combination of abatacept with a nonbiologic agent such as MTX; however, there are significant safety issues from that combination (see below).

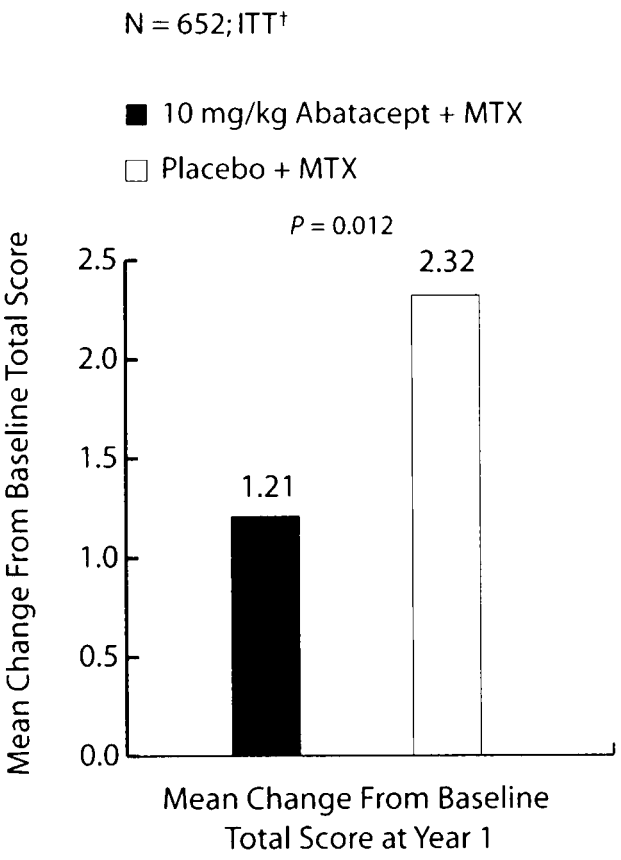

Figure 1. Radiographic progression at Year 1 in the AIM study. †547 patients completed 1 year.

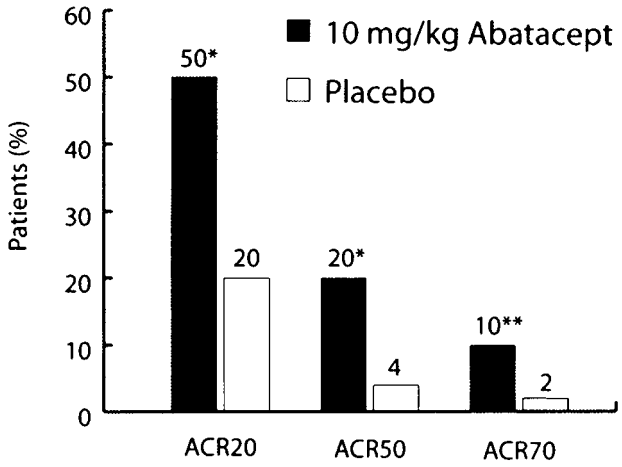

Figure 2. The ATTAIN trial: ACR responses at 6 months. *$p < 0.001$; **$p < 0.003$.

A recent study of abatacept or infliximab versus placebo was presented at the ACR Annual Meeting 2006[13]. This trial was designed to assess the efficacy and safety differences between abatacept and infliximab in a single double-blind trial. The investigators found that through 6 months, the efficacy was similar following treatment with either abatacept (10 mg/kg) or infliximab (3 mg/kg) as measured by the Disease Activity Score using 28 joint counts (DAS28), ACR response, HAQ-DI, and 36-Item Short Form General Health Survey (SF-36). At 6 months, 40.4% of patients receiving abatacept compared with 37.0% of patients receiving infliximab achieved an ACR50 response. After 1 year, 45.5% of abatacept-treated patients compared with 36.4% of infliximab-treated patients achieved an ACR50 response[13].

Safety. Infections and malignancies are the major safety concerns for a drug that interferes with T cell function. The most frequent adverse event reported by patients receiving abatacept was infusion reaction[9-11,14]. Headache, dizziness, and hypertension occurred twice as frequently in patients receiving abatacept as in patients receiving placebo. Severe infusion reactions that led to dyspnea, hypertension, urticaria, and wheezing were rare in the clinical trials[9,10,14,15].

Serious infections were reported more frequently in abatacept-treated patients than in placebo-treated patients in an analysis of 1955 patients receiving abatacept and 989 patients receiving placebo (3% vs 1.9%, respectively)[16]. These numbers are similar to the numbers cited for many immunosuppressive agents. The infections reported were mostly pneumonia, cellulitis, and diverticulitis. A recent study described that when abatacept is combined with TNF inhibitors, serious infections occurred 4 times more frequently than in the placebo group[12]. Because of these results, concurrent therapy with abatacept and a TNF inhibitor is not recommended[16].

In a number of clinical trials for abatacept, the incidence of malignancies was similar in the abatacept groups and placebo groups[14]. Lung cancers were reported more frequently in the abatacept group (n = 8 for abatacept vs n = 0 for placebo); however, this incidence was not significantly greater than expected. Lymphomas were reported in 4 patients receiving abatacept (0.1%), but this frequency was not higher than expected, as lymphoma is generally increased in patients with long-standing active RA[17]. Despite these statistics, the incidences of lung cancer and lymphoma were within the expected range in patients with RA, which is higher than for the general population (Table 1)[18].

Summary: Abatacept in combination with MTX significantly reduces inflammatory activity, slows radiographic progression, and increases functional ability and quality of life in many patients. Due to the increased risk of infections, abatacept should not be administered concomitantly with TNF inhibitors.

Table 1. Malignancies in patients receiving abatacept.

Malignancy	Abatacept	RA/DMARD Expected	General Population
Solid tumors	28	35-85	32-36
Lung cancer	11	3.5-12.3	3.7-5.0
Lymphoma	4	2.8-3.9	1.0-1.3

Rituximab clinical studies

Efficacy. The efficacy of rituximab has been demonstrated through 2 pivotal clinical trials: the Phase IIB Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER)[19] and the Phase III Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) study[20].

The DANCER study determined the appropriate treatment regimen of rituximab in combination with MTX, and that administration of glucocorticoids provided additional tolerability in patients with RA who had an inadequate response to DMARD or biologic agents. Patients (n = 465) were randomized into 9 treatment groups and received placebo (n = 149), 2 infusions of 500 mg rituximab (n = 124), or 2 infusions of 1000 mg rituximab (n = 192) with either intravenous methylprednisone premedication or intravenous methylprednisone premedication plus oral prednisone for 2 weeks. Rituximab infusions were given on Day 1 and Day 15, and all patients received MTX 10 mg/wk to 25 mg/wk[19]. This study showed that patients who received either 500 mg or 1000 mg of rituximab had an improvement in ACR50 responses at 24 weeks (33% for 500 mg or 34% for 1000 mg rituximab, as compared with 13% of placebo-treated patients; $p < 0.001$)[19]. When the potential effects of glucocorticoids on ACR response rates were examined, the investigators found no major influence on ACR response rates with the addition of glucocorticoids[19,21]. All ACR50 response rates at 6 months for patients given rituximab, with or without glucocorticoids, were significantly different from the ACR50 response rates for patients given placebo[19]. Although glucocorticoids did not influence the efficacy of rituximab treatments, they did diminish infusion reactions.

The REFLEX study was a Phase III trial of rituximab in combination with MTX in patients who had an inadequate response to TNF inhibitors (plus MTX). Figure 3 shows the ACR responses at Week 24[20] and Week 48[22] from this trial. ACR responses were significantly higher at both timepoints for patients who received rituximab plus MTX compared with patients who received placebo plus MTX ($p < 0.001$). At Week 24, 51% of patients given rituximab and MTX achieved an ACR20 response, while

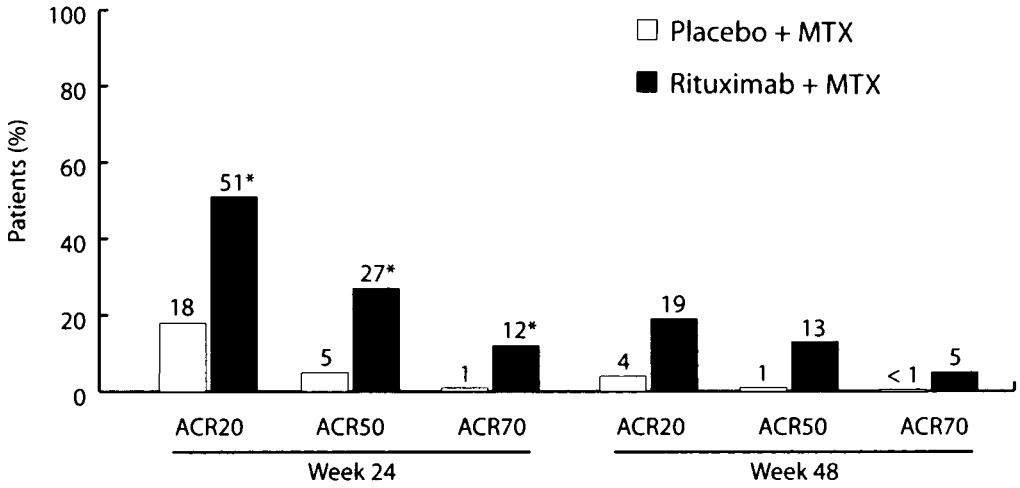

Figure 3. ACR responses at Week 24 and Week 48 for patients who received rituximab in the REFLEX trial. Placebo patients remaining in the study were those experiencing a response. Week 24: n = 201 placebo, n = 298 rituximab. Week 48: n = 24 placebo, n = 114 rituximab. *p < 0.001. Week 24 figure reprinted from Cohen SB, et al. Arthritis Rheum 2006;54:2793-806, with permission from John Wiley & Sons, Inc., a subsidiary of Wiley-Liss, Inc.

only 18% of patients achieved the same response when given placebo plus MTX (p < 0.001). Similarly, 27% and 12% of patients who received rituximab and MTX achieved an ACR50 and ACR70 response, respectively, as compared with only 5% and 1%, respectively, of patients who received MTX alone (p < 0.001).

The individual variables comprising the ACR response criteria at 24 weeks show a significant improvement in all of these measures in the patients who received rituximab compared with patients who received placebo (Table 2)[20]. Also, there was a clinically meaningful improvement in fatigue, disability, and quality of life through Week 24 for patients receiving rituximab compared with patients receiving placebo in the REFLEX trial[20].

The REFLEX trial examined patients who had an inadequate response to one or more TNF inhibitors plus MTX. A subanalysis compared patients who had failed one or more TNF inhibitors to determine any difference in the efficacy of rituximab in these patients. The results demonstrated that rituximab treatment was as successful in patients who failed multiple TNF inhibitors as it was for patients who failed one TNF inhibitor[23].

The REFLEX trial also examined the effect of rituximab on radiographic progression a year after the initiation of treatment. Radiographic data were collected 56 weeks after the first rituximab course. The results showed that patients who received at least one course of rituximab (plus MTX) had less radiographic progression after 1 year than patients who received placebo (plus MTX). Statistically significant differences were observed for total Genant-modified Sharp score (p = 0.0043), joint space narrowing (p = 0.0007), and erosion score (p = 0.0106) at Week 56 (Figure 4)[24].

Rituximab is given as a course of 2 infusions separated by 2 weeks. An important question about the repeated use of rituximab treatment is whether repeated courses of rituximab are as effective as the first one[25]. This question was addressed by Keystone and colleagues, who reported that the second course of rituximab was just as effective as the first course. In the first course, 65% of patients achieved an ACR20 response compared with 72% of patients in the second course, and similar results were observed for ACR50 and ACR70 responses[25].

An issue that arises about B cell depletion therapy is the amount of time between B cell replenishment and the time for retreatment, since rituximab does not have a fixed dosing schedule. One group has demonstrated that

Table 2. ACR Core Set at 24 weeks in the REFLEX clinical trial.

	Mean Change from Baseline		
Core Set Measure	Placebo, n = 201	Rituximab, n = 298	p
Swollen joint count (66 joints assessed)	–2.6	–10.4	<0.0001
Tender joint count (68 joints assessed)	–2.7	–14.4	<0.0001
Patient global assessment, mm, VAS	–5.3	–26.0	0.0048
Physician global assessment, mm, VAS	–6.2	–29.5	<0.0001
HAQ-DI	–0.1	–0.4	<0.0001
Pain, mm	–2.5	–23.4	0.0045
CRP, mg/d	0.0	–2.1	<0.0001
ESR, mm/h	–4.1	–18.5	<0.0001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

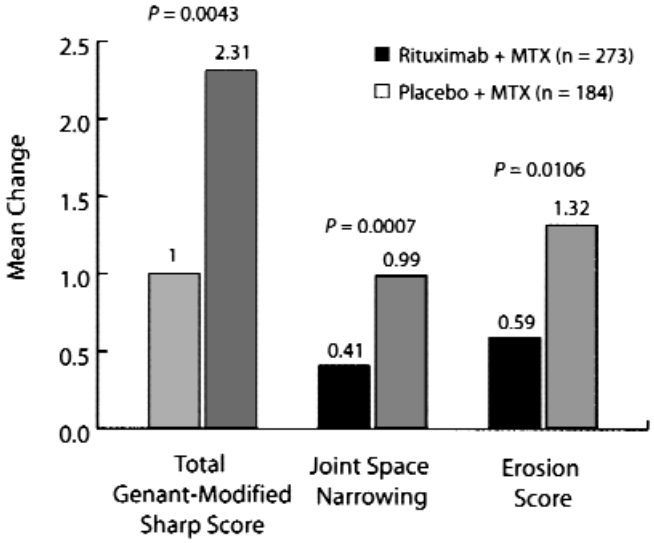

Figure 4. The REFLEX trial: radiographic progression at Week 56. Primary analysis: radiographs within time window, linear extrapolation from Week 24 for missing values.

the effect of rituximab lasted more than 30 weeks following either the first or second course of rituximab before B cells reemerged and subsequent retreatment was necessary[26]. At present, B cell counts are not routinely monitored, and most clinicians retreat with rituximab upon reemergence of symptoms.

Safety. Infusion reactions, the most frequent adverse event reported with rituximab, occur in 30% to 35% of patients with the first infusion and less frequently with subsequent infusions. These infusion reactions are generally mild to moderate[27]. Severe infusion reactions are rare, and concomitant glucocorticoid therapy reduces their frequency[19].

A pooled safety analysis of patients who were retreated with rituximab showed that there was a higher percentage of infusion reactions with the first infusion than with the second infusion in a treatment course. Additionally, patients who received more than 2 treatment courses had less risk of developing an infusion reaction[28].

One of the important outcomes from the DANCER trial was that intravenous corticosteroid premedication reduced the incidence of acute infusion reactions for patients receiving rituximab, and the addition of 2 weeks of oral prednisone did not further lower the occurrence of acute infusion reactions with the second infusion (Figure 5)[19]. It is now recommended that all patients who receive rituximab infusions be premedicated with intravenous corticosteroids[19,27].

Infections and other adverse events also were examined in detail in the rituximab clinical trials[19,20,27,29]. The rates of serious infections were higher in patients treated with rituximab compared with patients treated with placebo: 4.7 to 5.2 per 100 patient-years for rituximab compared with 3.2 to 3.7 per 100 patient-years for placebo[19,20]. In contrast to TNF inhibitors, no opportunistic infections, including tuberculosis, were observed, and the frequencies of most other adverse events were similar among placebo-treated and rituximab-treated patients. There have been no reports of malignancies to date in the rituximab-treated population.

Summary: Treatment with rituximab in combination with MTX reduces clinical disease activity, improves quality of life, and slows radiographic progression of joint damage. The duration of the response usually lasts more than 6 months for a single course, and retreatment with rituximab is effective. Adverse events reported are primarily

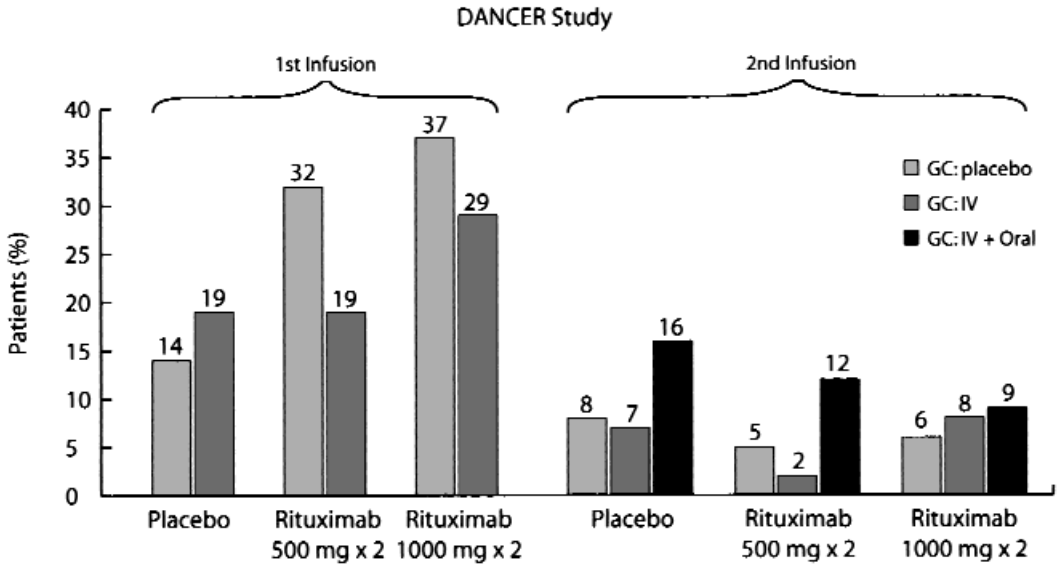

Figure 5. Intravenous glucocorticoid (GC) premedication reduces the incidence of acute infusion reaction. Reprinted from Emery P, et al. Arthritis Rheum 2006;54:1390-400, with permission from John Wiley & Sons,Inc., a subsidiary of Wiley-Liss, Inc.

infusion reactions and infections, but most are mild to moderate in severity, and the former can be minimized with corticosteroid premedication.

Clinical applications of abatacept and rituximab

Abatacept is indicated for treatment in DMARD-inadequate responders in both TNF inhibitor-naive and TNF inhibitor-inadequate responder populations[14] (in Europe only for inadequate responders to TNF blockade). Rituximab is indicated for patients who have an inadequate response to one or more TNF inhibitors[29]. Recently, a consensus statement by European and Canadian physicians for the use of rituximab in clinical practice has been published[27]. The addition of abatacept and rituximab to the current armamentarium of treatment options for RA has improved the potential for good outcomes for these patients.

REFERENCES

1. St. Clair EW, van der Heijde DMFM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432-43.
2. 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 2004;363:675-81.
3. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
4. Combe B. Switching between anti-TNF-α agents: what is the evidence? Joint Bone Spine 2004;71:169-71.
5. Finckh A, Simard JF, Gabay C, Guerne PA, for the SCQM physicians. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis 2006;65:746-52.
6. Solau-Gervais E, Laxenaire N, Cortet B, Dubucquoi S, Duquesnoy B, Flipo RM. Lack of efficacy of a third tumour necrosis factor α antagonist after failure of a soluble receptor and a monoclonal antibody. Rheumatology Oxford 2006;45:1121-24.
7. Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a human B lymphocyte-specific antigen. J Immunol 1980;125:1678-85.
8. Boye J, Elter T, Engert A. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. Ann Oncol 2003;14:520-35.
9. 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 2006;144:856-76.
10. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005;353:1114-23.
11. Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a Phase IIb, double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52:2263-71.
12. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum 2006;54:2807-16.
13. Schiff M, Keiserman M, Codding C, et al. The efficacy and safety of abatacept or infliximab in RA patients with an inadequate response to MTX: results from a 1-year double-blind, randomized, placebo-controlled trial [abstract]. Arthritis Rheum 2006;54 Suppl:L43.
14. Orencia package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2005.
15. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 2003;349:1907-15.
16. Moreland LW, Combe B, Steinfeld SD, et al. An integrated safety analysis of abatacept in the treatment of rheumatoid arthritis (RA) across patient types and background therapies [abstract OP0183]. Ann Rheum Dis 2006;65 Suppl 2:110.
17. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 2006;54:692-701.
18. Simon TA, Smitten AL, Boodhoo T, et al. Observed and expected malignancies in the abatacept clinical development program: an epidemiologic assessment [abstract SAT0132]. Ann Rheum Dis 2006;65 Suppl 2:489.
19. Emery P, Fleischmann R, Filipowicz-Sosnowski 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 2006;54:1390-400.
20. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, Phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793-806.
21. Fleischmann RM, Racewicz AJ, Schechtman J, et al. Rituximab efficacy in rheumatoid arthritis is independent of coadministration of glucocorticoids: results from the Dose-ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) study [abstract]. Arthritis Rheum 2005;52 Suppl:S130.
22. Cohen S, Emery P, Greenwald M, et al. Prolonged efficacy of rituximab in rheumatoid arthritis patients with inadequate response to one or more TNF inhibitors: 1-year follow-up of a subset of patients receiving a single course in a controlled trial (REFLEX study) [abstract THU0220]. Ann Rheum Dis 2006;65 Suppl 2:183.
23. Kremer JM, Tony H, Tak PP, et al. Efficacy of rituximab in active RA patients with an inadequate response to one or more TNF inhibitors [abstract FRI0133]. Ann Rheum Dis 2006;65 Suppl 2:326.
24. 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) [abstract OP0016]. Ann Rheum Dis 2006;65 Suppl 2:58.
25. 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 [abstract FRI0125]. Ann Rheum Dis 2006;65 Suppl 2:323.
26. van Vollenhoven RF, Cohen S, Pavelka K, et al. Response to rituximab in patients with rheumatoid arthritis is maintained by repeat therapy: results of an open-label trial [abstract SAT0197]. Ann Rheum Dis 2006;65 Suppl 2:510.
27. Smolen JS, Keystone EC, Emery P, et al. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:143-50. Epub 2006 Oct 26.
28. van Vollenhoven RF, Emery P, Bingham C, et al. Safety of rituximab in rheumatoid arthritis: results of a pooled analysis [abstract FRI0151]. Ann Rheum Dis 2006;65 Suppl 2:332.
29. Rituxan package insert. South San Francisco, CA: Biogen Idec and Genentech, Inc.; 2006.