Updates from B Cell Trials: Efficacy

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ABSTRACT. Recent reports of data from ongoing trials have contributed substantially to our growing understanding of the potential effectiveness and safety of B cell targeted therapy in the treatment of rheumatic diseases. In addition, the results have addressed practical questions regarding the administration of specific agents. Phase II trials of rituximab (RTX) have provided data supporting efficacy in rheumatoid arthritis (RA), including more clearly defining the role of glucocorticoids in the treatment and exploring the doses necessary to improve the signs and symptoms of RA. The Phase IIb Dose-Ranging Assessment International Clinical Evaluation of Rituximab in RA (DANCER) trial demonstrated that a significant percentage of patients achieved clinical improvement when treated with different doses of RTX as compared with those given placebo. The Phase III Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) trial demonstrated efficacy of RTX in patients with a history of nonresponse to tumor necrosis factor inhibitors. Preliminary results of a small cohort of patients receiving RTX retreatment demonstrated efficacy with repeat administration. Phase II results of another B cell targeted therapy, anti-B lymphocyte stimulator protein, demonstrated efficacy. The efficacy of the agent, belimumab, resulted in an ACR20 response that was significantly higher in patients treated with belimumab versus placebo and in patients with RA. These findings support the hypothesis that B cells play an integral role in the pathogenesis of RA, and this report will review the efficacy results of clinical trials targeting B cells. (J Rheumatol 2006;33 Suppl 77:12-17)

Key Indexing Terms:
RHEUMATOID ARTHRITIS B CELLS TREATMENT EFFICACY
ADVERSE EFFECTS ANTI-B LYMPHOCYTE STIMULATOR

INTRODUCTION

As pathogenic elements in the development of rheumatoid arthritis (RA), B cells have become the focus of new therapeutics. Cell-surface proteins on B cells are potential targets for treatments currently being investigated in clinical trials. Rituximab (RTX), a chimeric monoclonal antibody to CD20, is being evaluated in Phase II and III trials for the treatment of RA. More than 370,000 patients have been treated with RTX in the oncology setting, where it has been available for more than 7 years for the treatment of non-Hodgkin's lymphoma[1]. Belimumab, a human monoclonal antibody to the anti-B lymphocyte stimulator (BLyS) protein, is presently being studied in Phase II trials, and the first peer-reviewed data were presented at the 2005 American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) Annual Scientific Meeting in San Diego, CA, USA. Clinical trial data regarding an anti-CD22 agent, epratuzumab, have been presented for lupus and Sjögren's syndrome, but to date no results have been reported for RA. Additionally, preclinical and Phase I studies are investigating TACI-Ig and Br3-Fc (2 fusion proteins utilizing the extracellular domain of the receptors for BLyS) as treatments for RA.

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RITUXIMAB

The B cell lineage antigen CD20 is not expressed on stem cells, early pre-B cells, dendritic cells, or plasma cells[2,3]. As such, anti-CD20 treatments could reduce inflammatory processes with a minimum impact on immune response. RTX is a chimeric human/murine monoclonal antibody that targets CD20[4-7]. RTX in RA is administered as a single course of 2 infusions on Day 1 and Day 15. Studies in patients with RA have shown that the mean half-life after a second 1000-mg infusion of RTX is 19 to 22 days. B cell depletion generally endures for 6 to 18 months[7]. It is hypothesized that RTX selectively depletes B cells bearing the CD20 surface marker via multiple mechanisms that include antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity, and apoptosis. Animal studies using RTX as an anti-tumor agent have shown evidence of a significant reduction in the drug's efficacy in FcγRIII-deficient mice, suggesting that ADCC is the major pathway utilized by RTX in B cell depletion[8].

RITUXIMAB CLINICAL TRIALS

To date, 3 clinical trials (2 Phase II, one Phase III) have evaluated the role of RTX in the treatment of RA. These trials were designed to evaluate the safety and efficacy of RTX monotherapy and combination therapy with disease modifying antirheumatic drugs (DMARD) [methotrexate (MTX) and cyclophosphamide (CYC)] in patients who were inadequate responders to either MTX (Phase IIa and Phase IIb) or anti-TNF agents (Phase III). In addition, one of these Phase II trials evaluated the role of glucocorticoids as part of a RTX regimen in patients with RA. Patients in all the studies were eligible to enter an extension study evaluating the longterm safety and efficacy of retreatment with RTX.

Rituximab: PHASE IIa. Results of the 48-week RTX Phase IIa trial were published in *The New England Journal of Medicine* in 2004[9]. One hundred sixty-one patients with active disease despite MTX treatment were randomly assigned to MTX (n = 40; MTX, 10 mg/wk), RTX (n = 40; RTX, 1 g x 2), RTX plus CYC (n = 41; RTX, 1 g x 2; CYC, 750 mg x 2), or RTX plus MTX (n = 40; RTX, 1 g x 2; MTX, ≥ 10 mg/wk). In addition, all patients received preinfusion methylprednisolone (100 mg) and oral prednisone on Days 2 to 7 (60 mg) and Days 8 to 14 (30 mg). All patients had failed multiple DMARD, had long-standing disease, and were all rheumatoid factor-positive (RF+) because it was originally theorized that RF+ patients would receive greater therapeutic benefit than RF-negative (RF–) patients. The primary endpoint of the study was the ACR50 response at 24 weeks, and 13% (MTX), 33% (RTX), 41% (RTX + CYC), and 43% (RTX + MTX) = of patients achieved an ACR50 response. All the RTX treatment groups were statistically superior to the placebo group continuing MTX; ACR20 and ACR70 responses were similar. The 48-week analyses also demonstrated that the patients who received the combination of RTX plus MTX continued to have significant improvement in signs and symptoms of disease as measured by ACR response: ACR20, 65%; ACR50, 35%; ACR70, 15%[9].

All 3 RTX groups had rapid and sustained B cell depletion that occurred shortly after the first infusion. B cell depletion persisted through Week 24 and showed a slow return toward the lower limit of normal at 48 weeks. The placebo group showed no change in peripheral B cell counts except for an early steroid-associated increase that rapidly returned to baseline[9,10].

Preliminary data presented by Paul Emery at the 2004 ACR/ARHP Annual Scientific Meeting addressed the question of the duration of the response to a single course of RTX. Eighteen of 40 patients (33%) who originally received RTX plus MTX continued to demonstrate an ACR20 response at Week 104, which is numerically superior to the other treatment cohorts[11] (Figure 1).

The results of this trial clearly demonstrated that RTX is effective for the treatment of RA and that CYC was not necessary to obtain a response to RTX. Based on these results, subsequent RTX trials utilized the combination of RTX plus MTX[9].

Rituximab: Phase IIb (DANCER). The DANCER study was designed to evaluate RTX dosing in combination with MTX and to evaluate the role of glucocorticoids in patients with active RA despite ongoing treatment with MTX. Initial results were presented at the 2004 European League Against Rheumatism (EULAR) Annual Congress in Vienna, Austria. More recent results were reported at the 2005 ACR/ARHP Annual Scientific Meeting.

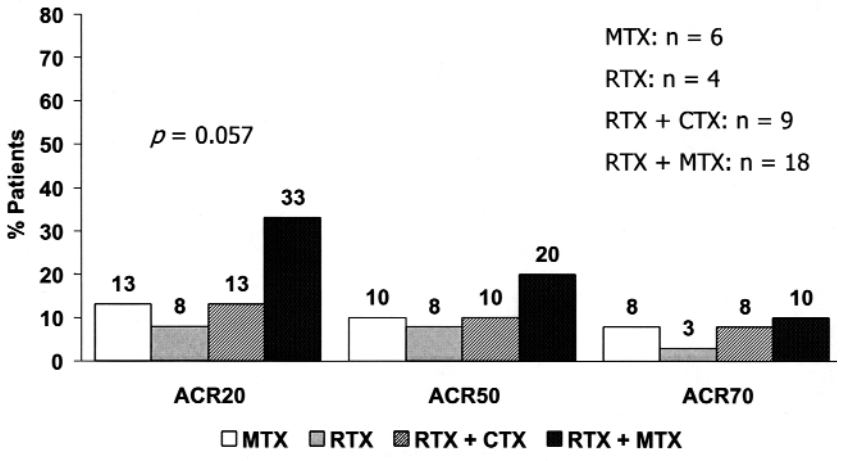

Figure 1. Rituximab in Phase IIa study; ACR responses at 104 weeks. MTX: methotrexate; CTX: cyclophosphamide; RTX: rituximab.

DANCER utilized a multifactor study design of 9 cohorts that varied by RTX and steroid combination. The objectives of this study were to look at RTX 500 mg and 1000 mg in combination with MTX and to evaluate the role of glucocorticoids in patients with active RA despite MTX treatment. The primary endpoint was an ACR20 response at Week 24 in RF+ patients, whereas secondary endpoints were the change in Disease Activity Score (DAS) and EULAR response at Week 24[12,13]. Four hundred sixty-five patients (RF+, n = 367; RF–, n = 84) were randomly assigned to placebo/placebo RTX (n = 149), RTX 500 mg (a course is equivalent to 2 doses, or 2 x 500 mg; n = 124), or RTX 1000 mg (2 x 1000 mg; n = 192) and either placebo steroids, intravenous (IV) premedication with 100 mg methylprednisolone, or IV premedication plus oral steroids (540 mg) (Table 1). All patients had long-standing disease (mean duration 10.4 yrs) that was active [mean swollen joint count/tender joint count (SJC/TJC), 21/33] despite background MTX (mean MTX dose 15.5 mg/wk). All patients had failed multiple DMARD (mean 2.4), and almost one-third (32%) had received prior treatment with biologic agents[12,13].

Of the 465 patients enrolled, 91% (n = 113) of patients who received RTX 2 x 500 mg and 86% (n = 165) of patients who received RTX 2 x 1000 mg completed 24 weeks, as compared with 65% (n = 97) of patients in the placebo group. Rescue treatment was available for patients who reported no clinical response at Week 16; thus, most patients in the placebo group exited at this point[12]. Compared with placebo, both RTX groups showed significantly superior improvement as measured by ACR response and change in DAS. ACR responses for RTX (2 x 500 mg/2 x 1000 mg) were ACR20 (55%/54%), ACR50 (33%/34%), and ACR70 (13%/20%) compared with placebo (ACR20, 28%; ACR50, 13%; ACR70, 5%; $p \leq 0.0001$ placebo vs RTX) (Figure 2). There was no significant difference in ACR responses between RTX 2 x 500 mg and RTX 2 x 1000 mg. DAS28 improved significantly in patients who received RTX (RTX, 2 x 500 mg, –1.79; RTX, 2 x 1000 mg, –2.05), with the placebo group demonstrating minimal improvement (–0.67)[12]. Additionally, all groups initially showed some clinically significant improvement in health assessment scores at Week 4; however, the RTX groups showed greater improvement than the placebo group at Week 8, and the difference was both clinically and statistically significant at Week 24[13]. With respect to the glucocorticoids, there was no effect on efficacy[12,13].

Overall, the results from this trial showed that RTX plus MTX was significantly more effective than MTX alone ($p < 0.001$) in patients with long-standing RA. There was no significant difference in response between RTX 2 x 500 mg and RTX 2 x 1000 mg. Based on these results, both doses of RTX will be evaluated in future clinical trials. Additionally, the concomitant steroids had no influence on efficacy, and only preinfusional glucocorticoids will be administered to reduce the risk of infusion reactions.

Rituximab retreatment. In an effort to gain insight into the efficacy and safety of retreatment with RTX, 192 patients from different Phase II studies as of September 2004 [Phase IIa, n = 111; Phase IIb (DANCER), n = 81] enrolled in an open-label extension study. These patients had all shown a clinical response to RTX at Week 16 or later (> 20% reduction in SJC and TJC at the same visit) and had completed at least 24 weeks of the original study[14]. Placebo responders could also enroll in the study. Retreatment was administered at least 16 weeks after the

Table 1. DANCER Study randomization and stratification of trial medication.

Treatment Groups	Rituximab Dose	No. of Patients RF+ (n=367)	No. of Patients RF– (n=84)	Glucocorticoid Dose
A	Placebo	41	21	Placebo
B		39	0	IV premedication only*
C		42	0	IV premedication plus oral**
D	500 mg, Days 1 and 15	41	0	Placebo
E		41	0	IV premedication only
F		41	0	IV premedication plus oral
G	1000 mg, Days 1 and 15	41	22	Placebo
H		41	19	IV premedication only
I		40	22	IV premedication plus oral

RF+ population: primary intention-to-treat efficacy population.
*Methylprednisolone 100 mg IV on Days 1 and 15. **Methylprednisolone 100 mg on Days 1 and 15 plus oral prednisone 60 mg on Days 2–7 and 30 mg on Days 8–14 (total oral prednisone dose = 570 mg).

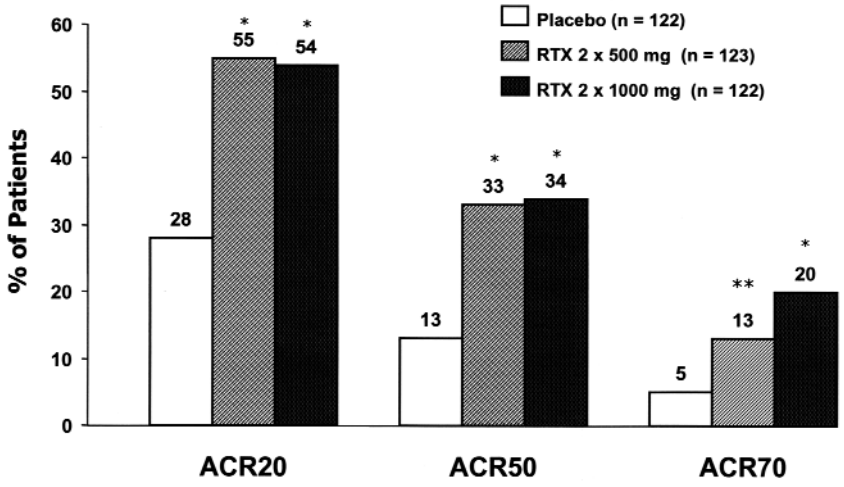

Figure 2. DANCER study ACR responses at 24 weeks. *p ≤ 0.0001 RTX versus placebo [logistic regression: contrast test in RF-positive patients (intention-to-treat population)]; **p = 0.029. Withdrawals or patients with insufficient data to calculate ACR score were classed as nonresponders.

last RTX infusion. At entry into the retreatment, patients had to demonstrate a return of active disease as reflected by a minimum of 8 swollen and 8 tender joints. All patients received premedication with IV methylprednisolone and also received oral prednisone for the first 2 weeks (total oral dose, 540 mg)[12]. The majority of patients were female, in their early 50s, with an average disease duration of 10 years, and had previously received treatment with 2 to 3 DMARD. The number of withdrawals during the first 24 weeks was very low, with only 6 patients (3.7%) ending their participation in the trial[14].

Of the patients who completed the Phase IIa study, 82 were receiving a first retreatment, 25 were receiving a second retreatment, and one was receiving a third retreatment. All 59 patients who completed the Phase IIb study were receiving a first retreatment with RTX. Results have been presented only on those patients who had completed 24 weeks' followup after retreatment.

An interesting finding was that 17% of patients had CD19+ counts below the lower limit of normal prior to the first infusion; 66% prior to the second infusion; and 52% prior to the third infusion. This implies that measuring peripheral B cells may not be an effective method for monitoring response to RTX. Some patients may flare when their B cell counts are low, and some flare when B cell levels are recovering[14].

At 24 weeks of followup, results suggest that patients continued to respond to repeated courses of RTX. ACR responses (20/50/70) were similar for the first retreatment (71%/35%/12% of patients), second retreatment (60%/30%/12% of patients), and third retreatment (63%/37%/16% of patients). Median CD19+ levels over the same period were similar: a rapid, sustained depletion, followed by a slow recovery to the lower limits of normal by Week 48[14].

Although this extension study is continuing, not all eligible patients have entered the study. They remain on their initial Phase II protocol until they require retreatment[14].

Rituximab: Phase III (REFLEX). The most recently completed trial, REFLEX, was a Phase III, randomized, placebo-controlled, double-blind, multicenter study to evaluate the safety and efficacy of RTX in combination with MTX in patients with active RA who had an inadequate response (including inadequate efficacy or toxicity) to anti-TNF therapies. The trial consisted of 114 centers in 11 countries worldwide (68 centers were in the United States, with 508 patients enrolled)[15].

The primary endpoint for this study was ACR20 response at Week 24. At Week 24, significantly more ($p < 0.0001$) RTX-treated patients than placebo-treated patients demonstrated an ACR20 (51% vs 18%), ACR 50 (27% vs 5%), and ACR70 (12% vs 1%). Similar improvements were seen in DAS28, EULAR response, and the individual components of the ACR core set[15].

Improvements in patient-reported quality-of-life outcomes at 24 weeks were clinically important and significantly better in patients who received RTX compared with the placebo group (RTX/placebo): Health Assessment Questionnaire Disability Index (HAQ-DI) –26.9/–6.5 ($p < 0.0001$); Functional Assessment for Chronic Illness Therapy-Fatigue (FACIT-F), –9.1/–0.5 ($p < 0.0001$); Medical Outcome Study Short Form-36 (SF-36) MHS (Mental Health Score) 4.7/1.3 ($p < 0.002$); SF-36 PHS (Physical Health Score) 5.8/0.9 ($p < 0.0001$)[16]. The improvement in SF-36 MHS is particularly interesting, as that degree of improvement has not traditionally been seen with other therapies.

BELIMUMAB

Belimumab, a human monoclonal antibody, specifically binds to and inhibits the biologic activity of BLyS, which is essential for B cell survival. Preclinical and clinical results to date show that belimumab can reduce the levels of circulating CD20+ B cells[17].

Results of a Phase II, multicenter, double-blind, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, and efficacy of belimumab in 283 patients with active moderate-to-severe RA were reported at the 2005 ACR/ARHP Annual Scientific Meeting. Patients were randomly assigned to receive belimumab 1 mg/kg, 4 mg/kg, or 10 mg/kg or placebo in addition to standard therapy. Patients enrolled had a mean of 11 years of disease, had failed a mean of 2.2 DMARD, and 38% had failed at least one TNF inhibitor. Patients were allowed to take concomitant DMARD, and MTX was the most common. Belimumab was administered by IV infusion on Days 0, 14, and 28, and then every 28 days for 24 weeks. The primary efficacy endpoint was ACR20 response at 24 weeks[18].

Results from this dose-ranging trial showed that ACR20 response was higher in patients with moderate-to-severe active RA treated with any dose of belimumab (29%) compared with placebo (16%; $p = 0.02$), and the ACR20 response was 35% in patients who received belimumab 1 mg/kg compared with 16% of placebo patients ($p < 0.01$) (Figure 3). B cell depletion was in the range of 20%, which is less than reported with RTX. It is unclear if belimumab will continue into Phase 3 for rheumatoid arthritis[18].

CONCLUSION

Several options for B cell depletion or modulation are currently under investigation. Compared with other B cell-targeted therapies, RTX presently has more published Phase II and Phase III trial results. As a result of these studies, some important clinical questions about RTX treatment are beginning to be answered. The combination of RTX and MTX has been shown to be effective in patients with RA who have shown inadequate response to MTX and to anti-TNF agents. The use of glucocorticoids was found to have no effect on the efficacy of RTX treatment. The duration of clinical efficacy following a single course may be as long as 104 weeks in up to 33% of patients.

Other questions remain about the effect of B cell depletion on efficacy. Does Fcγ polymorphism have a role in treatment response, as it does in patients with cancer and possibly patients with lupus? Would a fixed schedule for retreatment be advisable rather than withholding treatment until disease flare? Can treatment induce a state of B cell tolerance, and would that support utilization of B cell-modulating therapy in early RA disease? These questions should be answered in continuing and planned clinical trials.

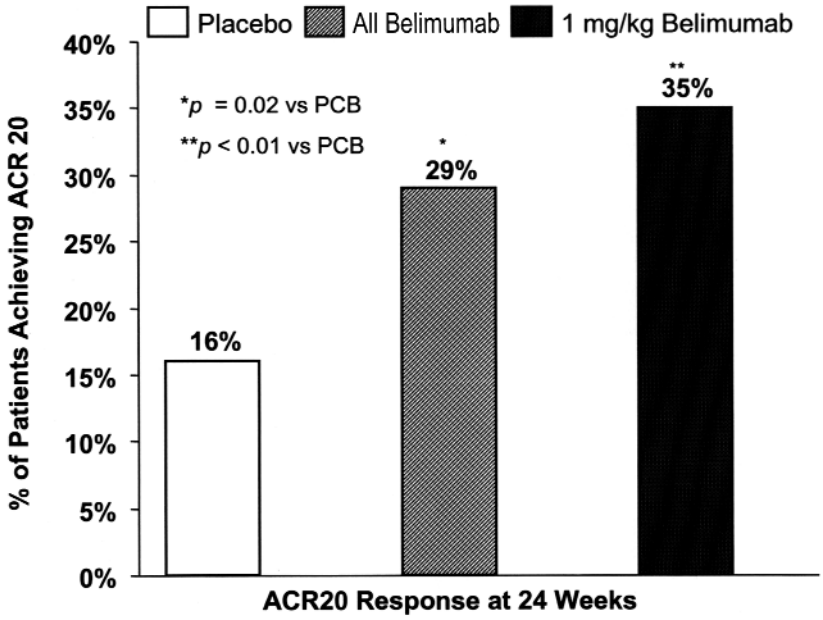

Figure 3. Belimumab in Phase II study; ACR20 response at 24 weeks.

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