

Abatacept and Rituximab

Two new biologic agents, abatacept (Orencia) and rituximab (Rituxan), have recently been approved for the treatment of rheumatoid arthritis. The data upon which they received approval comes from research studies that have been presented at ACR meetings, and published in the medical literature. These drugs, whose mechanisms of action differ from those of approved biologic agents, are also under study in other autoimmune conditions.

About Abatacept and Rituximab

Abatacept (CTLA-4Ig) is a recombinant fusion protein comprising the extra cellular domain of human CTLA-4 and an Fc domain of human IgG1 that has been modified to prevent complement fixation. Abatacept competitively binds with high avidity to CD80/CD86 preventing these molecules from engaging CD28 on T cells, and thereby prevents full T cell activation. Abatacept has been approved by the US FDA for use in adult patients with moderate to severe rheumatoid arthritis who have not responded adequately either to oral DMARDS (such as methotrexate) or to the TNF antagonists.

Rituximab, a chimeric anti-CD20 monoclonal antibody was approved in 1997 for non-Hodgkin's lymphoma. Rituximab depletes B cells that have CD20 on their surface (including pre-B cells through mature B cells; but not stem cells or plasma cells) by several effector mechanisms. B cells contribute to the pathophysiology of RA and other autoimmune conditions, providing the rationale for the study of rituximab. Rituximab has been approved by the US FDA for use in adult patients with moderate to severe rheumatoid arthritis who have not responded adequately to the TNF antagonists.

What is the clinical efficacy of the two drugs?

Abatacept: In a phase III study (the AIM study), abatacept was studied in patients with RA who had an inadequate response to methotrexate (MTX).¹ 652 patients were randomized in a 2:1 ratio to receive abatacept at 10mg/kg or placebo every 4 weeks, while continuing the background DMARD, most often MTX. After 12 months of treatment, ACR20, 50, and 70 response rates were significantly higher in the abatacept group than the placebo group (80% vs. 60%, 53.3 vs. 33.8, and 26.7% vs. 12% respectively, $p < .001$). In preliminary subset analysis of this study, abatacept was also demonstrated to significantly slow radiographic progression² of joint damage. Methodologic considerations prevent direct comparisons of inhibition of radiographic progression in abatacept and other drugs.

Abatacept was also studied in patients who had a partial or incomplete efficacy response to TNF antagonist or who experienced significant toxicity in the ATTAIN study.³ 293 patients were randomized in a 2:1 ratio to receive abatacept 10mg/kg or placebo. At 6 months, the abatacept group demonstrated significantly higher ACR20 responses than the placebo group (both groups were still on MTX) (50.4% vs. 19.5%, $p < .001$). Preliminary assessment of radiographs showed a non-significant trend towards inhibition of joint damage with treatment.

Rituximab: Rituximab was studied in a phase II trial of 161 patients who had seropositive active RA despite MTX⁴. Patients were allocated to one of 4 treatments: MTX alone, rituximab alone (1000 mg i.v. on days 1 and 15), rituximab plus cyclophosphamide, or rituximab plus MTX. All of the treatment groups received aggressive corticosteroids consisting of methylprednisolone 100mg intravenously before infusions of either rituximab or cyclophosphamide and 60mg per day on days 2 and days 4-7 and 30mg per day on days 8-14. At 24 weeks, the ACR20 response rate for patients only receiving MTX was 38% compared with 65% for patients receiving rituximab alone, 76% for patients receiving rituximab and cyclophosphamide, and 73% for patients receiving rituximab and MTX. ACR50 rates were 41% and 43% in the rituximab plus cyclophosphamide and rituximab plus MTX groups respectively, compared to 13% in the MTX only group. Current practice is not to use rituximab with cyclophosphamide.

Rituximab has also been studied in patients with RA who have failed therapy with a TNF antagonist. The clinical trial⁵ examining the efficacy and safety in this group of patients (the REFLEX trial) included 499 patients in the intent to treat population with 298 receiving rituximab 1000mg intravenously on days 1 and 15 with concomitant MTX as well as the full corticosteroid regimen from the initial large trial. Patients were eligible for this study if they had active RA despite prior treatment with etanercept, infliximab, or adalimumab. The preliminary report from this study showed the

ACR 20 responder rates at 24 weeks to be significantly higher in the rituximab group than the placebo group (51% vs 18%, $P < .001$). Seropositive and seronegative patients responded. The preliminary report also included significant improvements in the HAQ in the rituximab group. Final radiographic results from this study have not yet been reported.

Should either be used before TNF inhibitors? With TNF inhibitors?

Both agents have been studied and found to have clinical benefit in patients who have failed TNF inhibitors. Both agents have also been shown to be effective in RA patients who had not received previous therapy with TNF inhibitors. The decision as to whether to use abatacept prior to trying a TNF inhibitor will depend on many factors, such as individual patient characteristics such as comorbidity, patient preferences, clinician experience and others.

At present, combination therapy with a TNF inhibitor and abatacept or rituximab is not recommended. A large randomized trial⁶ investigated the safety of abatacept in 1441 patients who had active RA and were treated with abatacept 10mg/kg or placebo while receiving concomitant DMARD therapy. A total of 959 patients in this study received abatacept with one or more non-biologic DMARDs ($n=856$) or a biologic DMARD ($n=103$) vs. 482 patients who received the placebo with non-biologic DMARDs ($n=418$) or a biologic DMARD ($n=64$). In the preliminary report those patients receiving abatacept and a biologic DMARD had a higher incidence of infection and serious infection compared to those receiving placebo and a biologic DMARD (19.4% and 3.9% vs. 6.3% and 1.6%, respectively). None of the serious infections in the abatacept groups were opportunistic infections, and the only death was attributed to a serious infection in the placebo group. This data, along with previous data concerning the combination of TNF inhibitor with an IL-1 inhibitor, raises caution as regards combination biologic therapies. Administration of rituximab results in B cell depletion that lasts for more than 6 months. The safety of TNF inhibition in patients who have received rituximab has not been established.

Should abatacept and rituximab always be used with MTX?

In phase II studies, both abatacept and rituximab were assessed as monotherapy, without concomitant methotrexate. However, the bulk of the development program for both agents has assessed patients on concomitant MTX. For rituximab, in the phase II study where MTX was withdrawn and rituximab monotherapy used in 1 group⁴, it appeared that clinical responses to rituximab were not as long-lasting as in the group on combination rituximab plus MTX. With other biologic agents, combination therapy with MTX has afforded synergistic clinical efficacy and in some cases beneficial pharmacokinetic interactions. The extent to which this may be seen with newer biologic agents remains to be fully defined. For the present time, in most cases clinicians will probably use these agents in conjunction with MTX.

What about cost and administration?

Abatacept: Abatacept is administered i.v. over approximately 30 minutes with the fixed dose approximating 10mg/kg using 2, 3, or 4 250mg vials. The current Average Wholesale Price (AWP) cost is \$562.50 /vial. For a 70 kg patient (3 vials), the medication AWP cost for 1 year of maintenance therapy (13 doses) would be \$21,937.50. When therapy is initiated, doses are given at weeks 0, 2 and 4, and then every 4 weeks. Since it was introduced, abatacept has been available through a single distributor, and patients had to register. However, patients no longer need to register, and in the near future the drug will be available from multiple distributors

Rituximab: In RA, a typical course of rituximab is 1,000 mg given i.v. over about 4 hours, with a second 1,000 mg dose administered 2 weeks later. The AWP cost of rituximab for a 10mg/ml 10ml vial is \$582.19. Therefore, the medication AWP cost for a two dose course of therapy at 1,000 mg per course would be \$11,643.80. The yearly cost would depend on the number of course required in that time period.

For both agents, because they are administered as intravenous infusions, charges related to the infusions itself, and any other infusion related costs, such as concomitant medications, need to be considered in the overall costs of the drugs.

Are the adverse events comparable to those of TNF inhibitors? Do we need to screen for TB?

To date, the vast majority of safety data with both agents comes from clinical trials. Post-marketing safety data, which can provide important information not appreciated during trials, is eagerly awaited. All clinicians using these agents are strongly encouraged to report their safety experiences, for example by completing MedWatch forms.

Abatacept: In these trials, abatacept demonstrated a favorable toxicity profile. Infusion reactions occurred infrequently, and were almost all of the mild to moderate variety. The incidence of infections and serious infections were slightly

higher in those patients receiving abatacept when compared to placebo, but there were no deaths due to infections and no opportunistic infections. RA patients with COPD treated with abatacept experience more infections and serious adverse events than those given placebo. Antibodies to portions of the abatacept molecule have been reported infrequently, and in the patients with antibodies there was no evidence of increased toxicity or decreased efficacy associated with the development of these antibodies. Small numbers of malignancies were reported in patients in the trials and have been considered by the investigators to be unrelated to the study drug. More lung cancers have been seen in patients treated in studies in the abatacept group compared to the placebo group, and careful analysis of these individual cases suggests that the cancers may have been present prior to treatment in a few and occurred in high risk patients in all cases. Long term studies will be necessary to evaluate further any risk of malignancy. TB screening with subsequent appropriate treatment for positive patients is indicated before starting abatacept.

Rituximab: The preliminary reports from the later rituximab studies suggest a slight increase in infections in the rituximab groups compared to placebo. No opportunistic infections were reported. Mean immunoglobulin levels have been maintained above low limits of normal, but individual variations are possible. Interestingly, most of the patients receiving rituximab experience peripheral B cell depletion with various rates of repletion, but there was a lack of correlation between depletion and response and repletion and a flare of the underlying RA. From the preliminary studies, it appears that B cell counts will not be an effective way to predict response or relapse in RA patients treated with rituximab. An open label, very preliminary re-treatment trial suggests that retreatment might also be efficacious, but there are as yet no recommendations for when patients should be retreated. Repletion with more naïve B cell repertoire may be possible, but has not yet been proven.⁷ Human antichimeric antibodies (HACAs) were reported in all studies at about 5% after the initial course of treatment with no clear clinical relevance. Whether or not this will be more important with repeat infusions remains to be determined. TB screening is not required. However, screening for hepatitis is indicated as there have been a number of deaths due to reactivation of hepatitis B in the NHL population. The effect of rituximab on persons with previous hepatitis C infection is unclear.

Can rituximab be re-dosed? How often? When? Are corticosteroids necessary as premedication? What about using 500 X 2 instead of 1000 X 2 or 1000 X 1?

Open label, preliminary experience with re-treatment suggests that it might be efficacious and well tolerated. Studies assessing retreatment are in progress. A typical interval for retreatment has been after 6 months or longer. However, there are no specific recommendations available for when patients should be retreated.

In one study (DANCER), different doses of rituximab and regimens with and without corticosteroids were assessed.⁸ In this trial, 465 patients who had active RA despite methotrexate therapy were randomly allocated into nine treatment arms: placebo, 500mg of rituximab intravenously on days 1 and 15, or 1000mg of rituximab intravenously on days 1 and 15. Each of these three groups received one of three concomitant regimens: placebo, methylprednisolone 100mg intravenously 30 minutes before the infusion plus oral prednisone 60mg on days 2-7 and 30mg on days 8-14, or the same regimen of intravenous corticosteroids alone. Data from this trial suggests that adjunctive corticosteroid therapy had no effect on efficacy; however, pretreatment with 100mg of intravenous methylprednisolone reduced the severity and incidents of reactions from the first infusion by approximately 30%. The two doses of rituximab were not statistically different with regards to efficacy and had similar adverse events; however, there are no guidelines presently available concerning the use of doses lower than 1,000mg X 2.

Should CD19 and Ig levels be checked prior to rituximab administration?

Treatment with rituximab dramatically lowers peripheral B cells counts (typically measured as CD19 cells) in virtually all patients; levels remain low for months after treatment. There are no guidelines suggesting checking pre-treatment CD19 levels or measuring them post-treatment, although this was done in all the clinical trials of rituximab to date. Treatment with rituximab often lowers serum IgM levels, and may decrease serum IgG levels, although they may remain within the normal range. In all clinical studies of rituximab, Ig (IgG, IgA, and IgM) levels were checked pre-treatment, and individuals with levels below the lower limit of normal were excluded from studies. As with CD19 levels, there are no recommendations for when or how often to check IgG levels associated with rituximab therapy.

What about vaccination?

Abatacept: Live vaccines should not be given to patients receiving abatacept. Vaccinations to antigens like pneumococcus may be possible while on abatacept, but further study is required.

Rituximab: Immunization with live vaccines is not recommended. The ability of rituximab patients to generate a primary or anamnestic response is currently being studied.

The Bottom Line

Abatacept: As the first from a novel class of agents to block co-stimulatory molecules and T cell activation, the ultimate place for abatacept in the rheumatologist's armamentarium remains to be defined.

- Abatacept in combination with methotrexate has demonstrated efficacy and is approved for use in RA patients who are partially or poorly responsive to methotrexate or TNF antagonists.
- In studies of efficacy, abatacept in combination with methotrexate has been associated with a slight increase in infections but no opportunistic infections.
- Abatacept is infused over approximately 30 minutes and is usually associated with only mild infusion reactions.

Rituximab: Rituximab is currently approved only for patients who have failed TNF antagonists and who are receiving concomitant methotrexate. Whether or not the indications will be expanded in the future remains uncertain, and long term data regarding safety, radiographic effects, and when to re-treat will be important. It will also be important to establish in patients who receive rituximab and do not respond whether or not they can be treated with alternative agents while remaining B cell depleted.

- Rituximab in combination with methotrexate has demonstrated efficacy and is approved for RA patients who have failed or been intolerant to TNF antagonists.
- In the studies in RA patients demonstrating efficacy, rituximab has been associated with a slightly higher incidence in infections compared to placebo.
- Rituximab can be associated with infusion reactions, particularly with the initial infusion; pretreatment corticosteroids can decrease the incidence of infusion reactions by about a third. About 4 ½ hours are required for the first infusion; if the first infusion is well tolerated the second infusion may be given over a shorter time period, e.g., 3 to 4 hours.

Hotline Author: Marc D. Cohen, MD, Professor of Medicine, Chairman, Division of Rheumatology, Chairman, Department of Hospital Medicine, Associate Chair, Department of Internal Medicine, Program Director, Internal Residency Program, Mayo Clinic Jacksonville.

Hotline Editors: Arthur Kavanaugh, MD; Eric L. Matteson, MD, MPH

Disclosures: Dr. Cohen: Has been a paid consultant for BMS, Genentech, Wyeth, Amgen, Centocor and Abbott. Dr. Kavanaugh: Conducted drug studies for Genentech, Biogen-Idec and BMS; Dr. Matteson: Drug trials, and/or consultant, and/or confidential agreements and/or study and/or educational grants from Genentech, Amgen, Centocor, Biogen-Idec, Abbott, Wyeth, Regeneron, Takeda, Glaxo-Smith-Klein, Hoffmann-LaRoche, Human Genome Sciences, Immunex, Protein Design Laboratories, Natestch, Pharmacia & Upjohn, Schering.

Hotline is provided by the ACR as a service to members. This Hotline reflects the views of the authors and does not represent a position statement of the College.

1. Russell A, Shergy W, Numah I, et al. Abatacept treatment demonstrates rapid, consistent and sustained increases in ACR response rates over 1 year in patients with active rheumatoid arthritis. Presented at EULAR 2005. Vienna, Austria, June 8-11, 2005. Available at <http://www.abstracts2view.com/eular>. Accessed January 2, 2006.
2. Genant II, Peterfy C, Paire S, et al. Abatacept significantly inhibits structural damage progression as assessed by the Genant-modified Sharp scoring system in rheumatoid arthritis patients with inadequate methotrexate responses. *Ann Rheum Dis* 2005;64 (Suppl III):56.
3. Genovese MC, Becker J-C, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor inhibition. *N Engl J Med* 2005;353:1114-23.
4. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572-81.
5. Cohen SB, Greenwald M, Dougadas MR, et al. Efficacy and safety of rituximab in active RA patients who experience an inadequate response to one or more anti-TNF therapies (REFLEX Study). *Arthritis Rheum* 2005;52(suppl):S677.
6. Weinblatt M, Combe B, White A, et al. Safety of abatacept in patients with active rheumatoid arthritis receiving background non-biologic and biologic DMARDs: 1-year results of the ASSURE trial. *Ann Rheum Dis* 2005;64 (Suppl III):60.
7. Leandro MJ, Cambridge G, Ehrenstein MR, Edwards, Jonathan W, et al. Reconstitution of Peripheral Blood B Cells After Depletion With Rituximab in Patients with Rheumatoid Arthritis. *Arthritis Rheum* 2006;54:613-620
8. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh 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;54:1390-1400.