T-Cell Agents in the Treatment of Rheumatoid Arthritis
2012 Update

Gary E. Solomon, M.D.

Abatacept is a selective T-cell co-stimulator blocker. It blocks the activation of T cells by interrupting the interaction between the CD28 ligand on the T cell and the CD80 and CD86 ligand on the antigen presenting cell. This “second” signal is necessary for T cell activation in addition to the “first signal,” which is the interaction between the T-cell receptor and the MHC-antigen complex on the antigen presenting cell. “Upstream” blockade of T cell activation has profound effects on “downstream” events including the production of the cytokines TNF, IL-1, and IL-6, and B-cell activation.

Abatacept is currently approved for reducing signs and symptoms, inducing a major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderate to severe rheumatoid arthritis. It may be used as monotherapy or in combination with non-biologic DMARDS. Currently, abatacept is available both as an infusion and as a self-administered subcutaneous injection. For the infusible form, loading doses are given on weeks 0, 2, and 4 followed by monthly dosing. The dosing is weight based with three dose stratifications for weights less than 60 kg, between 60 and 100 kg, and greater than 100 kg. The subcutaneous form is given as a fixed dose of 125 mg per week irrespective of weight. This article will review the peer reviewed publications and abstracts relating to abatacept that were published in 2011 and 2012.

Subcutaneous Abatacept

A subcutaneous preparation of abatacept was approved by the FDA in August 2011. In a phase IIIB clinical trial, the subcutaneous dose was as effective as the intravenous dose, and the safety profile was comparable. Immunogenicity was low, and injection site reactions were both rare and mild. In this study, all patients received IV loading with a single dose of 10 mg/kg. While the official approved label requires a single intravenous loading dose (based on weight), it is being widely used without the loading dose.1

The ATTUNE study evaluated the consequences of switching patients who were on long-term intravenous abatacept to subcutaneous therapy. In this study, there was no loss of efficacy following the switch; indeed in this study of 123 patients, no patients discontinued drug due to loss of efficacy following the switch. One patient discontinued secondary to an adverse reaction, and two patients had mild injection site reactions but continued therapy. There was no increase in immunogenicity seen following the switch.2

Immunogenicity was further studied in the ALLOW trial. In this study, a 3 month interruption of therapy, followed by re-introduction of drug did not result in a statistically significant difference in immunogenicity compared with a group of patients who received continuous drug therapy. There were no safety differences between the two groups, and in patients who flared following drug withdrawal, efficacy was re-established when the drug was resumed.3

Other Indications for Abatacept

Psoriatic Arthritis

In a 6 month multicenter, randomized, double blinded, placebo controlled, phase II study, 170 patients with psoriatic arthritis were treated with abatacept at doses of 3 mg/kg, 10
mg/kg, or 30 mg/kg with loading doses on days 1 and 15 followed by monthly infusion. The primary endpoint of an ACR20 was 19% in the placebo group and 33%, 48%, and 42% in the Abatacept treated groups. All groups showed an improvement in MRI, HAQ, and SF-36 with the greatest improvement seen in the 10 mg/kg group. The safety profile of the three groups was similar. This same patient population was followed in a 6 month open label extension study, and benefits were sustained throughout the treatment period.5

Axial Spondyloarthropathy
In a small open label study, abatacept given for 6 months failed to meaningfully improve disease activity, function, or other disease parameters.6 These results are consistent with a previous study that failed to demonstrate a clinical response in patients with ankylosing spondylitis.7

Type 1 Diabetes Mellitus
In a multi-center study of patients with recently diagnosed insulin dependent diabetes mellitus, patients were randomized to receive abatacept at a dose of 10 mg per kg, or placebo infusion for a 24 month period. The primary outcome measured was the baseline-adjusted geometric mean 2-h area-under-the-curve (AUC) of serum c-peptide level after a mixed-meal tolerance test at 2 year follow-up. The AUC was 59% higher (95% CI 6.1-112) with abatacept than with placebo. There was an average of 9.6 months’ delay in c-peptide reduction with abatacept. There were few infusion related reactions, and there was no increase in infection or neutropenia between the treatment and the placebo groups.8

Adult-onset Still’s Disease
In a single case report, abatacept was effective in treating adult-onset Still’s disease, with the patient in remission after 35 months of therapy.9 A second case report also documented efficacy in a patient who had failed previous treatment with anti-TNF and anti-IL-1 therapy.10

Rheumatoid Vasculitis
In a single case report, abatacept produced both clinical improvement and normalization of laboratory parameters in a patient who had failed to respond to methotrexate, TNF inhibitors, steroid, immunoabsorption, plasmapheresis, and IL-1 inhibition.11

Crohn’s Disease and Ulcerative Colitis
Four placebo-controlled trials failed to reveal any efficacy in the treatment of moderate-to-severe CD or UC.12

Comparative Efficacy and Safety Compared to Other Biologic Agents, Switching Biologic Agents
In an open label extension of the ATTEST trial, patients treated with either abatacept, infliximab, or placebos for one year were switched to abatacept for year two. Of 431 patients assigned abatacept, 79.8% remained on the drug through year 2. At years 1 and 2, 19.7% and 26.1% of abatacept treated patients achieved DAS 28 remission (< 2.6) while 13.3 and 28.6% of infliximab-to-abatacept patients achieved DAS-28 remission.13

Higher remission rates were achieved in patients with early RA treated with abatacept, compared to those with long standing RA (> 10 years). DAS28-CRP remission was seen in 35.2% of patients with early disease at year 1 vs. 19.4% of patients with long standing disease. At year 3, the results were 46.0% vs. 30.9%. This study provided support for the concept of treating biologic naïve patients with inadequate response to MTX earlier in their disease course.14

In a patient cohort (DANBIO) with > 90% TNF failures, a good-or-moderate EULAR response rate was achieved in patients treated with either abatacept or tocilizumab.15

In a head-to-head study (AMPLE) looking at 646 biologic-naïve patients with RA, abatacept was compared to adalimumab. ACR responses for the two groups were comparable at 4 weeks and 52 weeks. Both drugs exhibited a similar time course for onset of action and similar inhibition of radiographic progression. There were no significant safety differences between the two groups. An important feature of this study was the fact that in both groups, the patients were on background methotrexate.16

Basic Science, Mechanism of Action
Macrophages and cytokine stimulated T cells (Tck) were mixed in the presence of abatacept or control Ig with and without TLR ligands. Abatacept reduced production of TNF by macrophages. Tck and TLR ligands were synergistic in their induction of the production of proinflammatory cytokines by macrophages, most notably IL12p70. Production of this cytokine was reduced in the presence of abatacept. This study strongly suggests that the biologic effects of abatacept extend beyond antigen specific T cell mediated effector function.17

Further evidence of the broader effects of abatacept is provided by a study in which immunohistochemical analysis of synovium was performed in patients treated with either methotrexate or methotrexate plus abatacept. Expression of MMP-3, CD8, CD4, CD8, CD20, CD80, and CD86 was significantly decreased in the synovium of patients treated with abatacept versus the methotrexate control. These finding indicate inhibition of not only T cells, but B cells and macrophages.18

Miscellaneous
Data from a French registry (Orencia and Rheumatoid arthritis—ORA) showed that CCP positivity was associated with EULAR clinical response and with a higher abatacept retention rate at 6 months. A EULAR response was obtained
in 59.1% of the 558 patients in the registry (good 20.4% and moderate 38.7%).

In a cost-effectiveness study where the endpoint was remission or low disease activity, the use of abatacept as a second line agent following failure of a TNF agent (either etanercept, adalimumab, or infliximab) regimens that used abatacept as the second agent were more cost effective than those that use rituximab as the second agent.

Psoriasiform lesions were reported in three patients with rheumatoid arthritis who were treated with abatacept. Previously, this observation had been confined to patients receiving anti-TNF agents. The mechanism underlying this observation remains unclear.

Abatacept, methotrexate, and rituxan inhibit the antibody response to vaccination with A/H1N1. This may have clinical implications and booster vaccinations may be required for high risk individuals.

Abatacept can be safely used in patients with hepatitis B if antiviral prophylaxis for hepatitis B is given concurrently.

Conclusions

T-cell based therapy for rheumatoid arthritis, as well as other forms of arthritis, continues to be promising. Abatacept is an effective therapy for psoriatic arthritis, and may be effective for musculoskeletal manifestations of SLE. It is unlikely that ABA will be an effective agent for axial spondyloarthropathies, Crohn’s disease, or ulcerative colitis. Preliminary data suggest that it may be an effective agent if used early in Type I diabetes mellitus.

Registry data suggests that the efficacy and safety of ABA is comparable to other biologic agents. The availability of a subcutaneous version of the drug offers a new treatment option to patients and physicians who prefer injectable biologics. For some patients, initial treatment with ABA rather than an anti-TNF agent would be reasonable. The low immunogenicity of abatacept offers advantages over more immunogenic molecules for the treatment of a chronic disease like rheumatoid arthritis.

The biologic effects of abatacept seem to extend beyond inhibition of T cell effector functions and include inhibition of TNF generation as well as macrophage and B cell function.

The cumulative data regarding the efficacy and safety of abatacept strongly supports its early use in the treatment of rheumatoid arthritis. For patients who fail to have an adequate response to methotrexate, the addition of abatacept as the first biologic agent is a viable strategy. It would also be appropriate to switch a patient who had an inadequate response to an anti-TNF agent to abatacept as the second biologic agent.

Disclosure Statement

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References

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