A batacept is a selective T-cell co-stimulation blocker. It blocks the activation of T cells by interrupting the interaction between the CD28 ligand on the T cell and the CD80/86 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 as in infusion. 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. Data regarding the efficacy and safety of abatacept has been reviewed previously.

This article will review the peer reviewed publications and abstracts relating to Abatacept that were published from 2010 to 2011.

Sub-cutaneous Abatacept
A sub-cutaneous preparation of abatacept will likely be available in the fall of 2011. It is dosed at 125 mg weekly, without dose stratification based on weight. In a phase IIIB clinical trial the sub-cutaneous 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. It is unclear if the IV loading will be required for this product when released.

An additional study of the sub-cutaneous product studied the effect of a 3 month interruption of therapy on both efficacy and safety. Patients who responded to open-label abatacept were randomized to receive either drug (group 1) or placebo (group 2) for a 12-week period. The patients in whom abatacept was withdrawn were then retreated with abatacept either with (group 2A) or without (group 2B) a loading dose. There was no significant difference in outcome between groups 2A and 2B and patients who had initially responded to abatacept responded well when the drug was re-introduced. In the few patients who had demonstrable antibodies to abatacept, efficacy on reintroduction of the drug did not differ from those patients who lacked antibodies.

Other Indications for Abatacept
Psoriatic Arthritis
In a 6-month multicenter, randomized, double-blind, 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

Ankylosing Spondylitis
In an open label, 24-week pilot study,6 abatacept failed to produce a major clinical response in a group of TNF naïve patients (group 1) as well as a group of TNF inadequate responders (Group 2) with active ankylosing spondylitis. Dosing was given as 10 mg/kg with a loading dose at weeks 0, 2, and 4 followed by monthly infusions. An ASAS40 was achieved by 13% of group 1 and 0% of group 2. ASAS20 was seen in 27% and 20%. There was no change in the Bath Ankylosing Spondylitis Disease Activity Index score, patient global assessment, or C-reactive protein. The drug was well tolerated and there were no significant adverse reactions.

Lupus
In a 12-month, multi-center, phase IIB, randomized, double-blind, placebo-controlled trial,7 patients with non-life threatening manifestations of SLE (polyarthritis, pleurisy/pericarditis, discoid lesions) were randomized to receive either abatacept at 10 mg/kg or placebo. All patients received 1 month of prednisone at 30 mg/day followed by tapering. The primary endpoints were patients with a new flare determined by BILAG score after steroid taper. While the study failed to show differences in the primary endpoints between the abatacept and placebo groups, subgroup analysis showed a trend toward improvement in the polyarthritis group.

Comparative Efficacy and Safety Compared to Other Biologic Agents
In a study performed through the CORRONA registry,8 abatacept was comparable to anti-TNF agents in both efficacy and persistence. The percentage of patients remaining on abatacept therapy at 6, 12, and 24 months was 84, 72, and 56 compared with 81, 67, and 55 for anti-TNF agents.6

In study performed through the DANBIO registry,9 150 patients treated with abatacept were compared to 178 patients treated with tocilizumab. Ninety percent of these patients were anti-TNF failures. At weeks 24 and 48 the remission rates were 19%/39% and 26%/58%. EULAR good or moderate responses were 70%/88% and 77%/84%. The decline in DAS-28 was similar over time for both agents although the CRP declined more rapidly with tocilizumab.

Miscellaneous
A dramatic reduction in the serologic response to influenza vaccine was seen in patients treated with abatacept.10 When compared with a control group on no therapy and a group of patients with RA on methotrexate, sero-protection was achieved in only 9% versus 58% in the methotrexate group and 70% of the healthy controls. Based upon this study, patients should be vaccinated against influenza prior to starting therapy. Further studies are needed to assess whether a series of vaccinations might be more effective. Given the need to vaccinate annually for the current strain of influenza, further studies are needed to develop a rational strategy for influenza vaccinations in patients on biologic therapy.

Abatacept therapy in RA patients resulted in a decrease in the number of T regulator cells but also showed a significant enhancement in the function of these cells.11 This phenomena requires further study and validation and might provide a basis for assessing response to abatacept.

Conclusions
T-cell based therapy for rheumatoid arthritis, as well as other forms of arthritis, continues to be promising. It is likely that abatacept will prove to be effective therapy for psoriatic arthritis and may be effective for musculoskeletal manifestations of SLE. It is unlikely that abatacept will be an effective agent for ankylosing spondylitis.

Registry data suggests that the efficacy and safety of abatacept is comparable to other biologic agents. The availability of a subcutaneous version of the drug will offer a new treatment option to patients and physicians. For some patients, initial treatment with abatacept rather than an anti-TNF agent would be reasonable.

The data on influenza vaccine poses a significant clinical dilemma for physicians and data driven strategies need to be developed. The study suggesting that abatacept therapy can be interrupted for 3 months and then resumed without loss of efficacy or increase in immunogenicity suggests a possible strategy for vaccinating high-risk individuals.

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. The availability of subcutaneous abatacept in the near future would make this strategy appropriate for those patients who prefer self-injected medications to those that are infused. Given the availability of effective and safe agents that work via unique mechanisms of action, it no longer makes sense to cycle TNF-inadequate responders through three or more anti-TNF agents.

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.

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