Abatacept In Focus
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Abstract
There have been considerable advances in the treatment of rheumatoid arthritis. However, many patients are found to be refractory to traditional disease-modifying antirheumatic drugs and the newer anti-cytokine therapies. Agents such as abatacept and rituximab now offer exciting new options for patients, including those who, until recently, had limited treatment options.

Randomized, multinational, double-blind, placebo-controlled trials have assessed the efficacy and safety of abatacept in patients with active RA, who are methotrexate (MTX) and tumor necrosis factor (TNF) antagonist inadequate responders. Results from these trials have shown that abatacept provides significant clinical and health-related quality of life benefits in both MTX and TNF antagonist inadequate responders. Abatacept also slowed the progression of structural damage compared with placebo/MTX alone. In addition to these clinical benefits, a fixed dose of abatacept has demonstrated a consistent safety and tolerability profile.

Longer-term data will be necessary to confirm the observations seen to date.

INTRODUCTION
Rheumatoid arthritis (RA) treatment is entering a new era, targeting the immunopathology of the disease with increased specificity and selectivity beyond that observed with traditional disease-modifying antirheumatic drugs (DMARDs). Several new agents have proven to be effective in many patients who previously demonstrated an inadequate or failing response to traditional DMARDs, such as methotrexate (MTX).

Of the currently approved biologic therapies, the majority target pro-inflammatory cytokines involved in the downstream processes of the RA immune cascade. These include the tumor necrosis factor (TNF) antagonists, etanercept, infliximab, and adalimumab, and the interleukin (IL)-1 antagonist, anakinra. These agents, often used in combination with the non-biologic DMARD, MTX, have helped deliver improvements in signs and symptoms of the disease, including radiographic outcomes, as well as improvements in health-related quality of life (HRQoL). Despite the efficacy of agents such as TNF antagonists, approximately 20–40% of patients may not respond to anti-cytokine therapy. Other patients may lose their response to treatment over time; in some patients, this is due to the formation of antibodies against the biologic agent. Patients who are refractory to MTX and/or anti-cytokine agents had limited options until recently. However, the investigation of earlier events in RA immunopathogenesis as potential therapeutic targets, has led to developments in the RA armamentarium.

This review will give an overview of the two newest biologic agents approved for the treatment of RA, with focus on the first-in-class therapy, abatacept.

NEW THERAPEUTIC TARGETS
Rheumatoid arthritis is a complex autoimmune disease, involving multiple immune pathways and cell types. The immunopathology of RA involves activated T cells, which mediate immune processes within the synovium, resulting in...
the release of cytokines, autoantibodies and other inflammatory mediators from macrophages, T cells and B cells. These, in turn, stimulate the downstream release of further inflammatory mediators resulting in the direct attack upon joint structures by macrophage- and fibroblast-like synoviocytes and other cells. In order to become fully activated, a T cell must not only recognize an antigen that has been processed and presented by an antigen presenting cell (APC), but also receive a co-stimulatory signal. One of the best characterized co-stimulatory pathways is the engagement of CD80/CD86 on APCs with CD28 on T cells. Another co-stimulatory pathway involves the CD40 ligand, in which T cells interact with B cells via the CD40:CD40L pathway, thereby facilitating B-cell activation and the production of autoantibodies. T-cell activation is also downregulated by co-stimulatory pathways. The CD28-mediated T-cell activation is downregulated by expression of endogenous cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which binds to CD80/CD86 with a much higher affinity than CD28.

The elucidation of RA immunopathology has led to the development of novel forms of therapy, two of which have recently been approved for the treatment of RA. These are Rituximab® (rituximab) (Genentech Incorporated, San Francisco, CA) – a genetically engineered chimeric anti-CD20 monoclonal antibody that depletes B cells, and ORENCIA® (abatacept) (Bristol-Myers Squibb, Princeton, NJ) – a soluble human fusion protein that selectively modulates T-cell co-stimulation (Figure 1).

**Figure 1**

Figure 1: Therapeutic targets of biologic therapies

Abatacept is the first RA therapy to be approved for the treatment of RA in patients with an inadequate response to either traditional DMARDs such as MTX or biologic DMARDs such as TNF antagonists. As such, the focus of this review will center on the clinical effectiveness, safety and dosing of abatacept treatments for patients in this previously limited treatment group.

**ABATACEPT**

Abatacept is the first in a new class of agents that selectively modulates the CD80/CD86:CD28 pathway of T-cell co-stimulation. It is a soluble, recombinant, fully-human fusion protein, comprising the extracellular domain of CTLA-4 linked to the Fc (hinge, CH2 and CH3 domains) portion of immunoglobulin G1.

Abatacept acts by binding to CD80/CD86 on APCs and preventing its interaction with CD28 on T cells. Whereas most RA therapies target one specific cytokine or molecule involved at the end stages of RA immunopathology, the novel mechanism of action of abatacept – acting at the level of the T cell – provides the potential to impact multiple downstream events. This has been demonstrated by reductions in multiple inflammatory biomarkers following treatment with abatacept in patients with active RA and an inadequate response to MTX or TNF antagonists. By selectively modulating the CD80/CD86:CD28 pathway, abatacept may allow other co-stimulatory pathways to remain largely intact due to the fact there are other possible co-stimulation pathways.

In the US, abatacept is indicated for reducing signs and symptoms in adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonists. It is also approved for non-Hodgkin's lymphoma. The Phase IIb DANCER (Dose-ranging Assessment iNternational Clinical Evaluation of Rituximab in RA) trial, evaluating the efficacy and safety of rituximab in RA patients, indicated that rituximab was highly effective in patients with active RA, as measured by American College of Rheumatology (ACR) 20 responses compared with placebo. Data from the REFLEX (Randomized Evaluation of Long-term Efficacy of rituXimab in RA) trial in patients with active RA and an inadequate response to one or more TNF antagonists show significant improvements in signs and symptoms of RA with rituximab treatment, as assessed via ACR 20, 50 and 70 response rates.
symptoms, inducing a major clinical response, slowing the progression of structural damage and improving physical function, in adult patients with moderate-to-severely active RA who have had an inadequate response to one or more DMARDs, such as MTX or TNF antagonists. Abatacept may be used as monotherapy or concomitantly with non-biologic DMARDs, but is not recommended for use concomitantly with TNF antagonists or anakinra.21

**EFFICACY OF ABATACEPT IN CLINICAL STUDIES**

Several randomized, multinational, double-blind, placebo-controlled trials in patients with active RA have assessed the efficacy and safety of abatacept in patients with an inadequate response to MTX22,23,24 and in those with an inadequate response to TNF antagonists (Table 1).25

A pilot, dose-finding, double-blind, placebo-controlled trial conducted in patients with RA treated unsuccessfully with at least one DMARD, demonstrated the safety and tolerability of abatacept monotherapy, and indicated a dose-dependent efficacy.26 Subsequently, a 12-month, randomized, double-blind, placebo-controlled, Phase III trial of abatacept plus MTX in patients with RA refractory to MTX therapy demonstrated significant improvements in the signs and symptoms of RA, physical function and HRQoL over 1 year.33 Across Phase III clinical trials, a fixed dose of abatacept, determined according to weight range, was administered over a 30-minute infusion at Weeks 0, 2 and 4, and then every 4 weeks thereafter.19

### Table 1: Overview of key abatacept clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Dose</th>
<th>Patient type</th>
<th>DB</th>
<th>OL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIM</strong></td>
<td>Phase III, 12-month, randomized, controlled study in patients with active RA and an inadequate response to MTX</td>
<td>10 mg/kg abatacept as a single intravenous infusion at Weeks 0, 2 and 4, and every 4 weeks thereafter</td>
<td>Patients with active RA and an inadequate response to MTX</td>
<td>Abatacept 10 mg/kg IV</td>
<td>Placebo + MTX</td>
</tr>
<tr>
<td><strong>ATTAIN</strong></td>
<td>Phase III, 12-month, randomized, controlled study in patients with active RA and an inadequate response to MTX</td>
<td>10 mg/kg abatacept as a single intravenous infusion at Weeks 0, 2 and 4, and every 4 weeks thereafter</td>
<td>Patients with active RA and an inadequate response to MTX</td>
<td>Abatacept 10 mg/kg IV</td>
<td>Placebo + MTX</td>
</tr>
<tr>
<td><strong>ASSURE</strong></td>
<td>Phase III, 12-month, randomized, controlled study in patients with active RA and an inadequate response to MTX</td>
<td>10 mg/kg abatacept as a single intravenous infusion at Weeks 0, 2 and 4, and every 4 weeks thereafter</td>
<td>Patients with active RA and an inadequate response to MTX</td>
<td>Abatacept 10 mg/kg IV</td>
<td>Placebo + MTX</td>
</tr>
</tbody>
</table>

*All patients treated with 10 mg/kg abatacept during OL phase. DB=double-blind; OL=open-label; IV=intravenous; RA=rheumatoid arthritis; DMARD=disease-modifying antirheumatic drug; N/A=not applicable; SC=subcutaneous; MTX=methotrexate; AIM=Abatacept in Inadequate responders to Methotrexate; ATTAIN=Abatacept Trial in Treatment of Anti-TNF INadequate responders; TNF=tumor necrosis factor; ASSURE=Abatacept Study of Safety in Use with other Rheumatoid arthritis therEpies

AIM (Abatacept in Inadequate responders to Methotrexate) was a 1-year, randomized, double-blind, placebo-controlled, Phase III trial that evaluated the clinical and radiographic effects of abatacept in patients with persistent, active, moderate-to-severe RA and an inadequate response to MTX therapy.23 Patients randomized to abatacept received a fixed dose, based on weight range, approximating 10 mg/kg on Days 1, 15 and 29, and every 4 weeks thereafter, and were compared with placebo over 1 year. The primary endpoints were an ACR 20 response at 6 months, the proportion of patients with clinically meaningful improvements in physical function at 1 year (≥0.3 units in the Health Assessment Questionnaire Disability Index [HAQ-DI]), and the radiographic progression of joint erosions at 1 year (assessed as change from baseline in the Genant-modified
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Sharp score. At 6 months, ACR 20 responses for abatacept versus placebo were 67.9% versus 39.7%, ACR 50 responses were 39.9% versus 16.8% and ACR 70 responses were 19.8% versus 6.5% (p<0.001 for all) (Table 2). At 1 year, responses for abatacept versus placebo increased to 73.1% versus 39.7% for ACR 20, 48.3% versus 18.2% for ACR 50 and 28.8% versus 6.1% for ACR 70 (p<0.001 for all) (Table 2).24 Clinically meaningful improvements in physical function were achieved in significantly more patients treated with abatacept than placebo (64% versus 39%; p<0.001).24 Moreover, abatacept significantly slowed the progression of structural damage compared with placebo at 1 year.24

ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate responders) was a 6-month, randomized, double-blind, placebo-controlled, Phase III trial that evaluated the efficacy and safety of abatacept in patients with active RA and an inadequate response to at least 3 months of anti-TNF therapy.25 Patients discontinued anti-TNF therapy prior to randomization and received abatacept or placebo in addition to at least one DMARD. The primary efficacy parameters were ACR 20 response and the proportion of patients demonstrating improvement in functional disability (≥0.3 units in the HAQ-DI).25 At 6 months, ACR 20 responses for abatacept versus placebo were 50.4% versus 19.5% (p<0.001), ACR 50 responses were 20.3% versus 3.8% (p<0.001) and ACR 70 responses were 10.2% versus 1.5% (p=0.003) (Table 2).25 Moreover, at 6 months, a clinically meaningful improvement in physical function was experienced by significantly more patients treated with abatacept than placebo (47.3% versus 23.3%; p<0.001).25

Eligible patients completing the double-blind periods of the AIM and ATTAIN trials were entered into the corresponding long-term extension (LTE) phase of each trial where data continue to be collected.

In addition to efficacy benefits and tolerability, one outcome that influences patients' satisfaction with treatment is quality of life.28 Patients with RA experience significant levels of fatigue, a symptom that correlates with work dysfunction and the overall health status of patients.28,30 In the AIM and ATTAIN trials,24,25 abatacept was shown to provide clinically meaningful and statistically significant improvements in HRQoL and physical function, in addition to improvements in other patient-reported measures such as fatigue.28,31 Moreover, abatacept demonstrated both clinically meaningful and statistically significant improvements in all eight subscales of the Short Form (SF)-36, in both patients with an inadequate response to MTX,25 and in those with an inadequate response to TNF antagonists.25 (Figure 2a and b)

Figure 3

Table 2: Summary of results from the AIM and ATTAIN trials

<table>
<thead>
<tr>
<th>Study</th>
<th>ACR 20</th>
<th>ACR 50</th>
<th>ACR 70</th>
<th>RAAS</th>
<th>Broader score</th>
<th>JRA score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIM</td>
<td>59.9%</td>
<td>39.9%</td>
<td>19.8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6 months</td>
<td>Abatacept</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AIM</td>
<td>39.1%</td>
<td>16.8%</td>
<td>6.6%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6 months</td>
<td>Placebo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AIM</td>
<td>23.1%</td>
<td>46.9%</td>
<td>20.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 months</td>
<td>Abatacept</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AIM</td>
<td>28.7%</td>
<td>10.2%</td>
<td>8.1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12 months</td>
<td>Placebo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ATTAIN</td>
<td>50.4%</td>
<td>36.9%</td>
<td>10.3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6 months</td>
<td>Abatacept</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ATTAIN</td>
<td>18.5%</td>
<td>3.6%</td>
<td>1.5%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*p<0.001; TNS: TNF antagonist; AIM: American College of Rheumatology, DAS28: Disease Activity Score 28; RAAS: Raxstar activity score; JRA: Joint space narrowing

CTLA-4=cytotoxic T-lymphocyte-associated antigen-4

**Figure 5**
Figure 2b: Health-related quality of life at 6 months in patients with an inadequate response to tumor necrosis factor antagonist therapy


SF-36=Short Form-36

**SAFETY AND TOLERABILITY OF ABATACEPT IN CLINICAL STUDIES**

Evidence of sustained safety and tolerability are of key importance when making treatment decisions for RA, since it is a chronic condition requiring long-term therapy. Given the structure and mechanism of action of abatacept, the rates and types of infection, in addition to evidence of immunogenicity and autoimmunity, are also of relevance.

**SAFETY CONSIDERATIONS**

An integrated assessment of safety data from five double-blind abatacept clinical trials comprising approximately 2000 patients,
 has demonstrated that abatacept is generally safe and well tolerated when combined with non-biologic background therapy.
The most commonly reported adverse events (AEs) (occurring in ≥10% of abatacept-treated patients) were headache, upper respiratory tract infection, nasopharyngitis and nausea; the most commonly reported serious AEs (SAEs) were serious infections and malignancies.

Table 3 presents AEs occurring in ≥3% of all patients and in ≥1% in abatacept-treated patients.

Infections were reported in 54% of abatacept-treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5–13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza and bronchitis. Serious infections were reported in 3% of patients treated with abatacept and 2% of patients given placebo. The most common (<1%) serious infections reported with abatacept were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis and acute pyelonephritis. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1%), bronchitis and herpes zoster (both <1%). The most frequent infections resulting in discontinuation were pneumonia, localized infection and bronchitis (all <1%).

In placebo-controlled trials (involving 1955 patients treated with abatacept for a median of 12 months), the overall frequencies of malignancies were similar in the abatacept- and placebo-treated patients (1.3% and 1.1%, respectively).

However, more cases of lung cancer were observed in abatacept-treated patients than placebo-treated patients (4 patients, <1% versus 0, respectively). In the cumulative abatacept clinical trials (placebo-controlled and uncontrolled, open-label), a total of eight cases of lung cancer (0.21 cases per 100 patient–years) and four cases of lymphoma (0.10 cases per 100 patient–years) were observed in 2688 patients (3827 patient–years).

The potential role of abatacept in the development of malignancies in humans is unknown and long-term studies will be necessary to evaluate this risk.

**Figure 6**

Table 3: Summary of adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Abatacept + background therapy</th>
<th>Placebo + background therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Cough</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Back pain</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

*Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept or infliximab); includes 124 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept or infliximab).

DMARD=drug modifying antirheumatic drug

The incidence rates of serious infection, serious pneumonia, neoplasms and malignancies did not appear to increase over the double-blind period of these studies.
TOLERABILITY CONSIDERATIONS

Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion; assessed in Phase III trials only) were more common in the abatacept-treated patients than the placebo recipients (9% vs 6%, respectively). The most frequently reported infusion-related events (1–2%) were dizziness, headache and hypertension. Less than 1% of abatacept-treated patients discontinued due to an acute infusion-related event. Of 2688 patients treated with abatacept in the double-blind and open-label clinical trial phases, there were two cases of anaphylaxis or anaphylactoid reactions.

Events potentially associated with drug hypersensitivity were reported in less than 0.6% of abatacept-treated patients and generally occurred within 24 hours of infusion.

Due to the lack of data regarding the use of biologic therapies in combination with other treatments, the ASSURE (Abatacept Study of Safety in Use with other Rheumatoid arthritis Therapies) trial assessed the safety of abatacept versus placebo treatment in combination with other biologic therapies. The trial was a Phase III, double-blind, randomized, placebo-controlled, multicenter, 1-year study in patients with active RA during 1 year of abatacept treatment added to a background of treatment with ≥1 non-biologic or biologic DMARDs in patients who may have had concurrent stable comorbid diseases. The rates of AEs and SAEs were similar in the subgroup receiving abatacept plus non-biologic background therapy and the subgroup receiving placebo plus non-biologic background therapy. However, AEs, SAEs and discontinuations were higher in patients receiving background biologic therapy. Serious infections occurred more frequently in the abatacept plus non-biologic therapy group versus abatacept plus biologic group (2.6% versus 5.8%). In the small subgroup of patients receiving background anakinra, serious infections occurred more frequently with abatacept than with placebo (7.7% versus 0%). This study concluded that abatacept should not be administered concomitantly with biologics, specifically with TNF antagonists.

CONCLUSIONS

Recent advances in the understanding of the immunopathology that underlies RA allowed the development of new therapeutic agents including the recently approved therapies abatacept and rituximab. Abatacept is approved for use in MTX and TNF antagonist inadequate responders – providing significant clinical and HRQoL benefits in both populations and slowing radiographic progression in MTX inadequate responders. From the available clinical trials, a fixed dose of abatacept has demonstrated a consistent safety and tolerability profile in patients with active RA and an inadequate response to MTX, and in those with an inadequate response to TNF antagonists. Longer-term observations will be required to confirm the data available to date.

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References

15. Genentech. Rituxan® (rituximab) for IV Injection.
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