Abatacept: the first-in-class costimulation blocker for the treatment of rheumatoid arthritis

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New, effective therapies are still needed in rheumatoid arthritis as not all patients respond sufficiently to classic disease-modifying antirheumatic drugs, such as methotrexate, even with the addition of tumor necrosis factor blockers, lose their response or have to stop treatment owing to side effects. Abatacept, a fusion protein combining the extracellular portion of human cytotoxic T-lymphocyte-associated antigen 4 and an immunoglobin G1 Fc fragment, has shown efficacy in controlling the signs and symptoms of rheumatoid arthritis patients, slows radiographic disease progression and improves functionality and health-related quality of life in all domains. To date, the lack of major side effects, including infections, infusion reactions or induction of autoimmunity, together with the efficacy profile, easy administration and easy therapy monitoring of this drug, provide the first evidence of the effectiveness of a costimulation modulator in rheumatoid arthritis.

Need for new treatments in rheumatoid arthritis
During the last decade, important progress has been made in treating rheumatoid arthritis (RA) patients. An earlier and intensified use of traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), the introduction of early intensive treatment strategies and a better understanding of the etiopathogeneic mechanisms of this potentially crippling disease has changed their outcome [1,2].

Insights into the key cytokines involved have led to powerful treatments that decrease inflammation rapidly and, to a more profound extent than in earlier years, slow x-ray progression and improve function and quality of life. Currently, tumor necrosis factor (TNF)-blocking agents are marketed mainly in combination with MTX and an interleukin (IL)-1 antagonist is also available [3]. An anti-IL-6 receptor antibody [4] and anti-IL-15 [5] treatment are under investigation.

Despite this optimism (and combined with problems in new drug evaluations because fewer patients are available for clinical trials [6]), it is clear from randomized controls trials (RCTs) [7] and reports from daily practice [8,9] that not all patients benefit optimally from these new treatments; some lose efficacy after initial response or experience side effects that force them to stop the use of these biologics.

Research has highlighted the roles played by various immune events in the pathogenesis of RA [10]. Blocking the innate immune response might be crucial for controlling the manifestations of RA. However, the adaptive immune system is also of major importance and may be an efficient target for therapy.

Following the rapid immune reactions by cells of the innate immune system, adaptive immune responses, characterized by their high specificity for antigens, play a major role with their crucial effector cells: B cells, T cells and antigen-presenting cells (APCs, such as dendritic cells, macrophages and B cells). A continuous upregulation and downregulation of this adaptive immune response occurs under normal conditions.

B cells can function as APCs, are cytokine producers and can produce antibodies such as rheumatoid factor and anticitrullin antibodies and are traditionally seen as prognostic markers that are also more or less specific to the disease. Therefore, these cells are potential therapeutic targets in RA. Rituximab targets the CD20 molecule expressed selectively on B cells and depletes these cells. The first RCTs have shown promising results [11].

T-lymphocyte-directed therapies with anti-CD4 antibodies were not successful in the past and raised concerns of CD4 depletion [12]. Nevertheless, since activated T cells are present in the synovium, T-cell-directed therapies are still attractive.

Introduction to costimulation blockade: a rational treatment strategy in RA
T cells can be divided into CD4+ and CD8+ cells, the former being crucial helper cells for antibody production and activation of cytotoxic immune response. CD4+ cells are the...
dominant T cells in inflamed RA synovium and the major histocompatibility complex (MHC) class II expression in RA synovitis (needed for antigen presentation to the T-cell receptor) is an additional argumentation for a crucial role in the reactivation of T cells [13,14].

While both naïve and activated/memory T cells traffic in the circulation, at the site of inflammation mainly activated/memory T cells are found. A naïve T cell becomes activated as it encounters an antigen presented on human leukocyte antigen (HLA) molecules of APCs. Recognition of antigen and MHC by an antigen-specific T-cell receptor is not sufficient for a naïve cell to become activated. Crucial to this action is a mechanism known as costimulation that sustains APC–T cell contact and amplifies intracellular signals in the T cell [15,16].

The best characterized costimulatory signal is that between CD28 expressed on T cells, and CD80–CD86 on APCs. Inducible costimulator (ICOS), CD134, CD27 and others are additional costimulatory molecules [17]. Blocking the costimulation of B lymphocytes by antibodies to the cell surface of the protein CD154 was successful in mice with lupus [18], but has been problematic in treating systemic lupus in humans [19].

Cytotoxic T-lymphocyte-associated antigen (CTLA)4 prevents 'classic' costimulation mediated by CD28 by its higher affinity for CD80–CD86, but leaves other costimulatory mechanisms intact (Figure 1). It is expressed in activated T cells and is an essential natural downregulator for T-cell activation. If antigen-naïve T cells receive T-cell receptor (TCR) activation (signal 1) in the absence of costimulation (signal 2), the T cells become functionally anergic and are unable to perform effector roles such as cytokine production. This is one of the primary models for the use of CTLA4–immunoglobulin (Ig) in the treatment of RA. CTLA4 knockout mice die from lymphoproliferative disease [20].

CTLA4–Ig fusion protein or abatacept (Belatacept) is a fusion protein consisting of the extracellular domain of human CTLA4 and a fragment of the Fc domain of IgG1 [21] (Figure 2). CTLA4–Ig binds with approximately fourfold less avidity to CD86 than to CD80. LEA 29Y (belatacept) is a second-generation molecule created by mutating two amino acid residues and even has an increased avidity for CD80 and CD86 than the parent molecule. It has been developed further in transplantation immunology where it has shown efficacy in renal transplantation [22]. By binding avidly to CD80 and CD86, both drugs block the interaction of CD28 with CD80 and CD86, thus preventing T cells from receiving the requisite costimulatory signal for activation and proliferation.

The use of CTLA4 fusion protein as a costimulation blocker has been studied extensively in experimental autoimmunity such as murine lupus [23] and experimental autoimmune glomerulonephritis [24]. Administration of CTLA4–Ig at the time of immunization prevented collagen-induced arthritis and administration after disease onset was also of clinical benefit [25]. When CD80–CD86 is blocked, antibody titers decrease, indicating the importance of this costimulation pathway in B-cell help.

Abatacept selectively modulates T-cell activation by the CD28/CD80–CD86 costimulatory pathway, leaving other immune pathways largely intact. As a result, T-cell activation is modulated rather than blocked, which may have consequences for the control of opportunistic infections. In the Phase I psoriasis study, in which almost half of the patients achieved greater than 50% improvement in disease activity, immune reactions against new antigens occurred after initiation of abatacept treatment [26]. CD28-deficient mice also developed normal immune functions in models of infection before and after treatment with CTLA4–Ig [27].

In addition to this competitive mechanism between CTLA4 and CD28 for binding to CD80–CD86, CTLA4 could increase the threshold for T-cell activation, either by proximal blockade at the immunologic synapse or via disruption of downstream intracellular signaling pathways. Another mechanism of action may be that ligation of CTLA4–Ig with CD80–CD86 leads to activation of the enzyme indoleamine-2,3-oxygenase (IDO) [28,29]. This enzyme modulates APC function, similar to what has been proposed after interaction of APCs with regulatory CD25+CD4+ T cells. It is speculated that CTLA4–Ig mimics a function that naturally arising regulatory T cells have on APCs, such as regulatory T cells that recently are coming into the spotlight of RA research for regulation of local inflammatory reactions [30]. Another consequence of blocking the classic costimulatory pathway by CTLA4–Ig is the inhibition of the proliferation of circulating naïve and memory T cells, reducing the number available for entry in the synovium [31].
In summary, by preventing the initial activation and eventual reactivation of T cells, abatacept could control downstream damage mediated by macrophages, fibroblasts and B cells (Figure 1) [32,33].

Efficacy of abatacept in RA

Clinical efficacy of abatacept in RA

In a 12-week, dose-ranging Phase IIa study of patients with RA, both abatacept and belatacept in monotherapy showed a dose-dependent reduction in disease activity [34]. The 10 mg/kg dose of abatacept was more effective than 2 mg/kg and there were no specific signs of side effects. While 31% of the patients withdrew before week 12 in the placebo group due to lack of efficacy, 19, 12 and 9% withdrew in the 0.5, 2 and 10 mg/kg abatacept-treated groups, respectively. This was a 214-patient trial, with perfusions of active or placebo treatments at weeks 0, 2, 4 and 8, examining rather early but severe RA patients.

Following this pilot study, a 1-year, placebo-controlled Phase IIb trial was conducted [35,36]. This explored 2 and 10 mg/kg of abatacept versus placebo at weeks 0, 2, 4 and every month thereafter in MTX-insufficient responders, continuing MTX in combination with abatacept or placebo. Patients in this trial were active RA patients with disease duration of approximately 9 years; 339 patients were studied and more placebo plus MTX-treated patients withdrew due to lack of efficacy. Primary outcome was the percentage of patients achieving American College.
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Highly significant ACR20, 50 and 70 responses were seen with 10 mg/kg abatacept plus MTX compared with placebo plus MTX (Table 1), starting from month 1 (for ACR50 and ACR70) or 2 (for ACR20) onwards. ACR50 and 70 responses in the 2 mg/kg plus MTX group were statistically significant from placebo at month 6, but the ACR20 response was not. A total of 78.3% of the patients in the 10 mg/kg plus MTX group continued the study for up to 1 year, and a Kaplan-Meier survival analysis of the time to discontinuation indicated a significant difference between the 10 mg/kg abatacept plus MTX and placebo plus MTX groups for discontinuation due to lack of efficacy, not adverse events. There is preliminary evidence in abstract form that the beneficial effect on disease activity extends for up to 3 years in a completers analysis of patients offered a treatment extension [37].

A total of 45% of the abatacept-treated patients with an ACR70 response at 1 year had this response maintained for 6 consecutive months. Efficacy was seen from week 2 onwards, especially with respect to pain and patients’ and physicians’ global assessment.

In ATTAIN, the severity of patients studied was remarkable (HAQ ± 1.8, C-reactive protein [CRP] < 40 mg/l, swollen joint count ± 32 at baseline), making the clinical efficacy scores highly relevant (Table 1). The placebo responses in this trial must be among the lowest in recent RA clinical studies probably reflecting the refractory nature of the disease in these patients. In all trials abatacept was administered via a fast infusion of 30 min after reconstitution with sterile water.

Efficacy on radiographic damage
Besides the profound and durable benefit on disease activity in the AIM trial, at 1 year a significant decrease in x-ray damage was seen with abatacept plus MTX, compared with placebo plus MTX, measured with the Genant Modified Sharp scoring method. In this scoring method, erosions are scored on an 8-point scale with 0.5 increments in each joint. Maximum achievable normalized erosion score is 145. Joint space narrowing is scored on a 9-point scale with 0.5 increments, with a maximum achievable normalized joint space narrowing score of 145.
Mean change from baseline in erosion score was 0.63 for abatacept plus MTX versus 1.14 for placebo plus MTX. Also for joint space narrowing and total score there was an approximate 50% reduction in x-ray damage compared with placebo.

Comparison of these results with the magnitude of effect achieved with the TNF blockers is difficult, as the scoring method used differs and generally comparisons between trials are not correct owing to the different patient selections. Moreover, the results of x-ray progression in year 2 of the AIM trial are awaited for a more definite conclusion. It is also important to mention that in this trial, many patients in both groups showed no x-ray progression in 1 year, reflected by a median progression of zero.

Efficacy of abatacept in improving physical function & quality of life

Improvement in physical function measured by HAQ and quality of life measured by SF36 were end points in the Phase IIb as well as the Phase III studies. In the Phase IIb trial, HAQ responders (defined as the improvement from baseline by > 0.22 units) at 6 months were 58.3 versus 33.6% in placebo, and at 1 year 49.6 versus 27.7%. A total of 15.7% of patients had a HAQ of 0 at 1 year. HAQ responses were similar in the AIM Phase III trial where mean HAQ improvement at 1 year was 0.66 units in the abatacept plus MTX group versus 0.37 in the placebo plus MTX group. Also, in the ATTAIN trial where HAQ scores at baseline were high (±1.8), the mean change in HAQ score was 0.45 from baseline to 6 months compared with 0.11 for placebo-treated patients.

All SF36 subcategories, as well the physical and mental component summaries, improved significantly and were clinically meaningful from baseline in the Phase IIb and the Phase III AIM trial. Even in ATTAIN, all SF36 subscales and summary scores showed clinically meaningful and significant improvements from baseline. Additionally, fatigue and sleep quality improved considerably compared with placebo [40]. An interesting analysis in both MTX-insufficient responders as well in TNF nonresponders shows an increased ability to work or to perform other daily activities with abatacept [41].

Safety of abatacept

The safety of abatacept as reported up to now seems excellent. Severe peri-infusional events are rare and only two cases are reported in the AIM trial. At present there are no newly appearing antinuclear antibody (ANA) and anti-DNA antibodies reported, as well as no newly induced autoimmune disorders, which is of some concern with TNF blockers.

Only approximately 1% of patients are reported to develop antibody reactivity to abatacept, while in TNF blockade, the occurrence of human antichimeric antibodies (HACAs) or human antihumanized antibodies (HAHAs) is considerably higher.

Infections reported as serious adverse events are only somewhat higher in the abatacept-treated patients compared with the placebo-treated patients in the AIM trial (3.9 vs 2.3%, respectively) and no more patients withdrew from the study due to side effects in the active treatment group.

Table 1. Summary of clinical efficacy with 10 mg/kg abatacept in rheumatoid arthritis.

<table>
<thead>
<tr>
<th>Clinical response by:</th>
<th>Phase IIb trial</th>
<th>AIM</th>
<th>ATTAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months</td>
<td>1 year</td>
<td>6 months</td>
</tr>
<tr>
<td>ACR20</td>
<td>60 (35.3)</td>
<td>62.6 (36.1)</td>
<td>67.9 (39.7)</td>
</tr>
<tr>
<td>ACR50</td>
<td>36.5 (11.8)</td>
<td>41.7 (20.2)</td>
<td>39.9 (16.8)</td>
</tr>
<tr>
<td>ACR70</td>
<td>16.5 (1.7)</td>
<td>20.9 (7.6)</td>
<td>19.8 (6.5)</td>
</tr>
<tr>
<td>DAS28 &lt; 2.6</td>
<td>26.1 (9.2)</td>
<td>34.8 (10.1)</td>
<td>14.8 (2.8)</td>
</tr>
<tr>
<td>(remission)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS28 &lt; 3.2 (low</td>
<td>40 (19.3)</td>
<td>49.6 (21.9)</td>
<td>30.1 (10)</td>
</tr>
<tr>
<td>disease activity)</td>
<td></td>
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</table>

All figures are the percentage of patients that were responders to the respective response measures. ( ) are the respective percentage of patients with a placebo response in the respective trials.

ACR: American College of Rheumatology; AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-TNF Inadequate responders; DAS: Disease activity score.
Specific opportunistic infections reported today are comparable with the occurrence of these infections in the placebo arms. As with TNF blockers, careful monitoring will be needed when abatacept is used in daily practice, as rare side effects could have been missed in clinical trials and since patients with purified protein derivative (PPD) positivity were not allowed in most of the trials. Limited data are available on the combination use of abatacept and TNF blockers; however, infectious risk seems to be increased making combination not recommended [42].

Regulatory affairs
On December 23, 2005, the US FDA approved abatacept for the treatment of RA [101,102].

Conclusions
Clinical efficacy of abatacept is seen from week 2–4 onwards, expands over the subsequent months and is sustained up to over 3 years, as reported in the literature.

The effective dose is ± 10 mg/kg at weeks 0, 2, 4 and every month thereafter. From the Phase III program, a fixed dose is used of 750 mg for patients between 60 and 100 kg of body weight (a dose of 500 mg for body weight <60 kg and 1000 mg for >100 kg). The improvements in ACR scores are generally comparable with those seen in reports with currently available biologics, although improvements are even seen between month 6 and year 1 of treatment. Head-to-head comparisons with TNF blockers are not available but the severity of patients treated in AIM and especially in ATTAIN make optimistic conclusions justified.

Slowing of x-ray progression, although significant, seems somewhat less compared with reports of TNF blockers where the onset of response is generally believed to be very fast. Year 2 x-ray results in AIM and achievements in currently conducted early RA trials should be awaited for definite conclusions.
The above-mentioned substantial benefits, completed with impressive achievements in patient-centered outcomes such as function and quality of life, as well as the very encouraging safety profile, easy administration in 30 min perfusions and easy monitoring, provide this drug with a global package that provides new therapeutic options for MTX- and TNF-insufficient responders in RA.

Future perspectives
It cannot be denied that enormous progress has been made in RA treatment in recent years. Insights into etiopathogenic mechanisms will make it possible to tackle this severe disease in many different ways in the future.

Evaluating therapy strategies in daily practice, where new drugs are used differently, will be the focus of the next 5–10 years. Disease remission is perhaps feasible for the future, especially with drugs such as abatacept that act upstream in the disease process. More insights into early disease characteristics and prognostic factors will help in achieving this ultimate goal. The mechanism of action of abatacept also makes this drug a candidate for other systemic diseases such as systemic lupus erythematosus.

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