

Abatacept in the treatment of rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory arthritis affecting 1% of the population. The immunologic dysfunction underlying this immune disorder is complex and intricate with the involvement of various immune cells as well as cytokines and surface molecules. While inhibition of TNF- α has changed the outlook of patients with this disorder, it regulates only one aspect of the inflammatory cascade associated with RA. This is corroborated by experience in the clinic, where a significant proportion of the patients do not have clinical benefit with such therapies. Furthermore, a number of patients experience blunting of the initial therapeutic benefits of TNF- α -targeted therapies. Thus, a different approach to regulate the immune dysfunction associated with RA is necessary. T cells are considered important in the pathogenesis of RA and abatacept, a fusion protein, was developed to abolish the activation of the T cell by blocking its interaction with the antigen-presenting cell. Abatacept has demonstrated promising clinical improvements in patients with RA. Although clinical experience with this new drug is limited and its mechanism of action remains to be understood, the data on the safety profile are reassuring.

KEYWORDS: abatacept • biologic therapy • CTLA4Ig • rheumatoid arthritis • T cell

Rheumatoid arthritis (RA) is a chronic, destructive, inflammatory disorder, characterized by polyarticular arthritis primarily involving small joints of the hands and feet. The synovitis, cartilage damage and bone erosion that typifies RA is characterized by infiltration of leukocytes and activation of osteoclasts. Although the precise mechanism leading up to the immune dysfunction remains unknown, both T and B cells are involved in its pathogenesis. Several pathways involving a complex network of cellular, as well as cytokine, events underlying the self-perpetuating immune dysfunction have been characterized. Current therapeutic options are aimed at targeting these immune events with a goal of halting the ongoing inflammation and bone damage, and resetting the immune imbalance.

Drug therapy is the mainstay of the treatment plan for RA. The commonly used traditional small-molecule disease-modifying antirheumatic drugs (DMARDs) include hydroxychloroquine, sulfasalazine, methotrexate (MTX) and leflunomide. The introduction of biologic DMARDs has significantly changed the outlook of patients with RA. However, a significant proportion of patients remain resistant to TNF- α -neutralizing therapies, and even those who have an initial

therapeutic response may develop blunting of such response with time. Abatacept (Orencia®, BristolMyersSquibb [NY, USA]) has been approved for the management of RA in the USA within the past 2–3 years.

Introduction to abatacept (CTLA4Ig)

T cells play a fundamental role in the pathogenesis of RA [1]. In the rheumatoid joint, the T cells express markers of activation, such as CD28 and cytotoxic T lymphocyte antigen 4 (CTLA4) [2], and are present along with several other cell types, including dendritic cells, macrophages, fibroblast-like synoviocytes and osteoclasts. Studies in animal models of RA as well as in humans have demonstrated that IL-17-secreting T cells, the Th17 cell, are important in the pathogenesis of RA. IL-17 has robust and widespread inflammatory effects on other cells of the joint. The IL-17 receptor is ubiquitously expressed on monocytes, macrophages, chondrocytes, osteoblasts and fibroblasts and induces the production of IL-1 β , IL-6, TNF- α , chemokines and matrix metalloproteinases. The inflammatory cytokines not only perpetuate synovial inflammation but also induce further Th17 cell development. Th17 cells also express RANKL and can

induce osteoclastogenesis, resulting in bone erosions [3]. Thus, IL-17-secreting T cells are important in enhancing inflammation, cellular infiltration and bone and cartilage destruction observed in RA.

In the peripheral blood, T cells are present in a naive state and must be fully activated in order to reach their full functional potential. Activation of the naive T cells requires two signals, one from the engagement of the T-cell antigen receptor with an antigen–MHC conjugate on antigen-presenting cells (APCs), and the second from the ligation of CD28 on T cells with CD80/86 on APCs. This dual activating signal into the naive T cells results in the generation of an activated phenotype of T cell manifested by the secretion of various inflammatory cytokines and upregulation of several surface molecules, as well as proliferation and survival [4–6]. Stimulation of the naive T cell by cognate antigen in the absence of the costimulatory signal results in anergy, and ligation of costimulatory molecules on the T cell in the absence of cognate antigen has no effects on the T cell.

One of the surface molecules that are upregulated on the activated T cell, following antigen recognition in the presence of costimulation, is CTLA4. CTLA4 binds to CD80/86 on APCs with higher avidity than CD28. While both CD28 and CTLA4 can bind to CD80 and CD86, studies have demonstrated that CD28 primarily binds to CD86 and CTLA4 primarily binds to CD80 [7–10]. The binding of CTLA4 with CD80/86 not only interferes with the activating signal via CD28, but also sends inhibitory signals into the newly activated T cell, via CTLA4, thus limiting T-cell activation [11,12].

The discovery of the two signal pathways that are necessary for T-cell activation and the generation of T-cell anergy in the absence of costimulatory signals led to the development of CTLA4Ig as a therapeutic intervention for diseases associated with T-cell activation, such as RA and transplant rejection. CTLA4Ig is a soluble molecule comprised of the extracellular domain of human CTLA4, in conjunction with the heavy-chain constant region of human IgG1. CTLA4Ig binds to both CD80 and CD86 and thereby prevents CD28 on T cells from binding to CD80 or CD86 on APCs. This blocks the second activating signal into the T cell and interferes with full T-cell activation. CTLA4Ig was shown to ameliorate collagen-induced arthritis, a murine model of RA [13], and also showed promise in several clinical trials in RA. CTLA4Ig was approved as a therapeutic agent for RA in 2005.

Mechanism of action of CTLA4Ig (abatacept)

Although abatacept was developed to block the ‘second signal’ necessary for full activation of the T cell, data from animal models of disease and *in vitro* studies in humans suggest that abatacept can modulate several other aspects of the immune system.

The *in vitro* effect of induction of anergy in T cells in the presence of CTLA4Ig, via interference with the second signal, has not been demonstrated to occur *in vivo* [14]. *In vivo* studies in animal models of transplantation have demonstrated that blockade of the costimulatory signal results in cell death and reduction in the number of antigen-specific T cells, leading up

to induction of tolerance in T cells [15–17]. It remains to be seen if such mechanisms of action account for the therapeutic effect of abatacept in RA.

In addition, some of the immunologic effects of abatacept are probably secondary to its effects on APCs. IL-6 is important in RA and animals models of RA and ligation of CD28 on T cells with CD80 on APCs induces the secretion of IL-6 by APCs [18]. Thus, binding of CTLA4Ig to CD80/86, could interfere with the CD80/28-induced secretion of IL-6 by APCs. Consistent with this hypothesis, IL-6 was reduced in the serum of patients with RA receiving abatacept [19]. This finding is particularly interesting since IL-6 is one of the key cytokines that is necessary for the generation and maintenance of Th17 cells, a T-cell phenotype recently associated with autoimmunity.

Furthermore, ligation of CD80/86 on APCs with CTLA4 on T cells leads to the induction of indoleamine dioxygenase (IDO) in APCs. IDO is thought to be critical in inducing anergy in T cells [20,21]. Since CTLA4Ig binds to CD80/86 on APCs, it is possible that CTLA4Ig induces anergy in T cells via induction of IDO in APCs. CTLA4Ig therapy has been shown to induce transplant tolerance in the murine pancreatic islet transplant model via induction of IDO [22]. However, generation of IDO may not be the only mechanism underlying CTLA4Ig-mediated tolerance. In studies in the rat bone marrow transplant and heart allograft models, tolerance developed in mice treated with CTLA4Ig, even in the absence of IDO [23,24]. Furthermore, it has been demonstrated that T cells from the inflamed rheumatoid synovium are resistant to regulation by IDO [25]. In addition, unlike unmodified CTLA4Ig, the Fc portion of abatacept is modified such that it does not bind to Fc receptors and hence does not mediate complement-dependent or antibody-dependent cytotoxicity, at least *in vitro* [26].

While the mechanism of action of abatacept (CTLA4Ig) in RA remains to be understood, administration of CTLA4Ig in patients with psoriasis, which has several immunologic parameters in common with RA, is associated with a decrease in the number of T cells in the plaques [27]. CTLA4Ig can also abrogate the paracrine stimulation between T cells. The phenomenon of paracrine activation of naive T cells by other activated T cells is thought to be important in mediating the self-perpetuating inflammation characteristic of the rheumatoid synovium. T cells express CD80/86 after activation through CD3 and CD28. CD80/86 expressed on activated T cells has been shown to activate other T cells via ligation with CD28 [28]. Synovial T cells in RA express class II MHC and CD80, in addition to CD28 [2,29]. Thus, it is possible that CTLA4Ig may block the paracrine stimulation between T cells of the rheumatoid synovium by binding to CD80/86 on T cells.

Although the CD28 and CD80/86 pathway is important for the stimulation of naive T cells, there is some controversy regarding the usage of this pathway by memory T cells, which are the predominant subtype of T cells in RA. While some studies have demonstrated that memory T cells are independent of CD80/86 for activation of their recall responses [30,31], CTLA4Ig has been shown to inhibit the recall function and homing capabilities of memory CD4⁺ T cells and CD80/86 expressed on B cells are

required for the activation of autoreactive T cells in a murine model of autoimmune arthritis [32,33]. This is complicated further by the finding that T cells in patients with RA have reduced expression of CD28 [34]. In addition, T cells in the rheumatoid synovium have been shown to express and utilize NKG2D, CX3CR1 and KIRS2D2, instead of CD28. The ligands for these receptors are abundantly expressed on nonhematopoietic tissue cells in the rheumatoid synovium and can induce secretion of various inflammatory cytokines, such as IFN- γ and TNF- α [35–37]. Thus, it is possible that CTLA4Ig can have distinct effects on T cells, depending on the activation status and the tissue distribution of those cells.

In addition, CTLA4Ig has been shown to modulate the number and function of Tregs and to reduce induction of reactive oxygen species. The significance of these findings pertaining to the clinical response in patients with RA remains to be evaluated [38–40]. Thus, CTLA4-based intervention has a much broader effect on the immune system, beyond blockade of the CD28 and CD80/86 interaction between T cells and APCs. The immunologic mechanism underlying clinical response in RA is open to investigation.

Clinical studies of abatacept in RA

Abatacept has been shown to have significant therapeutic responses in several trials involving RA and is currently licensed for its treatment. A summary of the clinical trials is shown in TABLE 1.

A double-blind, placebo-controlled, Phase I clinical trial of abatacept in RA showed American College of Rheumatology (ACR)-20 responses in 50% of patients without any significant adverse effects [41]. Following this, a Phase IIa trial involving 339 patients with active disease despite MTX 10–30 mg, was performed. Patients received either abatacept 2 mg or 10 mg/kg plus MTX or placebo plus MTX, for 6 months [42]. Infliximab or leflunomide was discontinued 60 days prior to enrollment. Patients were allowed to continue on stable doses of MTX, prednisone and NSAIDs. Following randomization, 119 patients received placebo plus MTX, 105 patients received abatacept 2 mg/kg plus MTX and 115 patients received abatacept 10 mg/kg plus MTX. The ACR20/50/70 responses were 60, 36 and 16% in the abatacept 10 mg/kg plus MTX arm, 42, 23 and 10% in the abatacept 2 mg/kg plus MTX arm and 25, 12 and 2% in the placebo plus MTX arm, respectively. Although, patients on abatacept 10 mg/kg had better clinical responses than patients receiving 2 mg/kg, such differences did not reach statistical significance.

Sustainability of response was further demonstrated by a Phase IIb extension study to 12 months on the same cohort of patients as in the Phase IIa study [43]. Although this was a completer analysis, ACR20 responses at 12 months for patients receiving abatacept 10 mg/kg plus MTX remained at approximately 60%, whereas the percentage of patients achieving ACR50 responses increased to 41.7 from 36% at 6 months, and the percentage of patients achieving ACR70 responses at 12 months increased to 20.9 from 16% at 6 months.

In this 12-month extension trial, assessment of physical function was carried out using the modified health-assessment questionnaire (M-HAQ). Patients receiving abatacept 10 mg/kg

demonstrated clinically significant improvement compared with placebo, in terms of both mean percentage improvement in physical activity and M-HAQ. Initial response in these patients was demonstrated as early as 30 days, with sustained benefit demonstrated at both 6 and 12 months of study (abatacept 10 mg/kg plus MTX: 58.3% at 6 months, 49.6% at 1 year; placebo plus MTX: 33.6% at 6 months, 27.7% at 1 year). Additionally, 34.8% of patients receiving abatacept 10 mg/kg plus MTX achieved disease activity score (DAS)-28 scores under 2.6 (characteristic of remission) compared with 10.1% on placebo plus MTX.

The encouraging data from the previous studies prompted inquiry into whether abatacept would be efficacious in patients who continue to have active disease despite being on anti-TNF therapies. The Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN), a 6-month, randomized, double-blind, Phase III trial in patients with RA for at least 1 year, was designed to answer this question [44]. Those with inadequate response to etanercept, infliximab, or both at approved doses for at least 3 months of treatment were included in the study. Adalimumab use was not considered in the study secondary to lack of widespread use during the time period involved. In addition to patients who had suboptimal clinical response to anti-TNF agents, patients experiencing adverse events to anti-TNF therapy were also included. All patients were on an oral DMARD or anakinra for at least 3 months, with a stable dosage for at least 28 days. Oral corticosteroid use was allowed at stable doses less than 10 mg/day (also for at least 28 days). For those receiving TNF-antagonist therapy at screening, a washout period of 28 days for etanercept and 60 days for infliximab prior to randomization was required. A total of 391 patients were randomized into either the abatacept-treatment arm or a placebo-treatment arm (in a 2:1 ratio). Those treated with abatacept received an approximated dose based on calculation of 10 mg/kg bodyweight; subjects less than 60 kg received 500 mg, those 60–100 kg received 750 mg and those greater than 100 kg received 1000 mg, via intravenous route over 30 min on days 1, 15, 29 and every 28 days thereafter, up to and including day 141.

In total, 50% of patients treated with abatacept achieved ACR20 responses at 6 months, whereas only 19.5% of patients in the placebo arm achieved such responses. Patients receiving abatacept also had greater improvements in their HAQ disability index (0.45 in the abatacept arm vs 0.11 in the placebo arm). ACR50 responses were observed in 20.3% of patients receiving abatacept compared with 3.8% receiving placebo, and ACR70 responses were observed in 10.2% of patients on abatacept compared with 1.5% on placebo.

The significant improvement in clinical efficacy that was observed at 6 months in the ATTAIN trial led to an open-label extension of another 18 months [45]. This study included 317 patients who completed the initial 6-month protocol, receiving approximately abatacept 10 mg/kg. Individuals receiving placebo were switched to abatacept at doses similar to the treatment arm. ACR20/50/70, DAS28, HAQ-Disability Index (DI), pain via visual analog scale (VAS), health-related questionnaire and fatigue via VAS were evaluated throughout the study as

measures of response to therapy. Of the initial 317 patients enrolled, 222 completed the long-term extension (LTE) for the additional 18 months. Patients receiving abatacept in the blinded phase continued to receive consistent doses of supportive DMARD/DMARD combinations throughout the entire 2-year observation period. Patients continued on abatacept through the LTE maintained ACR20/50/70 responses throughout the observation period. Patients who were switched to abatacept after 6 months of placebo, demonstrated similar ACR20/50/70 responses to the abatacept-treatment arm, when adjusted for duration of therapy.

Patients receiving abatacept for the entire duration (24 months) of the study had a reduction of 1.99 and 2.66, at 6 months and 2 years, respectively, in their DAS28 scores. At 6 months, 18.3 and 11.1% of patients achieved low disease activity score (LDAS) (DAS28 < 3.2) and remission (DAS28 < 2.6), respectively. The clinical responses continued to improve with 32 and 20.3% achieving LDAS and remission, respectively, at 2 years.

Health Assessment Questionnaire Disability Index (HAQ-DI) remained relatively stable over the 2 years in the original abatacept-treatment arm (54% at 6 months, 47.9% at 2 years). Patients who were switched from the placebo arm to the abatacept arm, during the open-label extension, achieved comparable response in

the HAQ-DI scores (46.5%) at 2 years. Significant improvement in VAS scores (defined as >10 mm change for pain and fatigue and >6 mm for sleep) was observed in both groups, showing more than -30, -25 and -11 changes in respective categories at 2 years.

Methotrexate is the mainstay of treatment for RA and is often the anchor of combination therapy. Therefore, the Abatacept in Inadequate Responders to Methotrexate (AIM) trial was designed to evaluate the safety and efficacy of abatacept in patients who have active disease despite being on maximum doses of MTX [46]. This trial design was similar to previous trials by Kremer and colleagues; however, in addition to evaluating efficacy of the drug versus placebo with regards to ACR20/50/70 responses, DAS28 and HAQ-DI scores over the course of 1 year, the effect of radiographic progression of disease was studied using the Genant-modified Sharp score. In total, 652 patients were randomly assigned to abatacept/MTX or placebo/MTX in a 2:1 ratio, respectively, with those treated with study drug receiving 10 mg/kg (approximate dosage) of abatacept on days 1, 15, 29 and every 28 days up to and including day 337 of the study. Radiographs of the hands and feet were taken at baseline and at 1 year for 586 patients. As in prior studies, the percentage of patients achieving ACR20/50/70 responses were significantly higher in the abatacept-treatment group at 6 and 12 months. With continued therapy over the course of 1 year,

Table 1. Percentage of patients achieving American College of Rheumatology 20, 50 and 70 responses during clinical trials with abatacept.

Study	Protocol	Patients (n)	Duration (months)	ACR20 (%)	ACR50 (%)	ACR70 (%)	Ref.
Kremer <i>et al.</i> (2003)*	MTX + abatacept 2 mg/kg	105	6	42	23	10	[42]
	MTX + abatacept 10 mg/kg	115	6	60	36	16	
	MTX + placebo	119	6	25	12	2	
Kremer <i>et al.</i> (2005)	MTX + abatacept 10 mg/kg	99	12	62.6	41.7	20.2	[43]
	MTX + placebo	78	12	36.1	20.2	7.6	
AIM (Kremer <i>et al.</i> 2006)†	MTX + abatacept 10 mg/kg	433	6	67.9	39.9	19.8	[46]
			12	73.1	48.3	28.8	
			6	39.7	16.8	6.5	
ATTAIN (TNF nonresponders)‡	DMARD + abatacept 10 mg/kg	258	6	50.4	20.3	10.2	[44]
			12	39.7	18.2	6.1	
			12	39.7	18.2	6.1	
ATTAIN (18-month extension)¶	DMARD + abatacept 10 mg/kg	218	18	54.8	34.1	17.1	[45]
			24	56.2	33.2	16.1	
ATTAIN (TNF nonresponders)	DMARD + placebo	133	6	19.5	10.2	1.5	[44]
ATTAIN (18-month extension)	DMARD + abatacept 10 mg/kg (switched from placebo at 6 months)	99	18	57.6	31.3	11.1	[45]
			24	51.5	32.3	13.1	

*Also included Modified Health Assessment Questionnaire (M-HAQ) findings: abatacept 10 mg/kg plus MTX, 6 months: 58.3%, 12 months: 49.6%; placebo plus MTX, 6 months: 33.6%, 12 months 27.7%.

†Also included the following findings: significant HAQ-DI improvement, MTX plus abatacept 10 mg/kg, 12 months: 63.7%; MTX plus placebo, 12 months: 39.3%; low disease activity score (LDAS) (DAS28 < 3.2), MTX plus abatacept 10 mg/kg, 6 months: 30.1%, 12 months: 42.5%; remission (DAS < 2.6), MTX plus abatacept 10 mg/kg, 6 months: 14.8%, 12 months: 23.8%; Genant-modified Sharp Score, MTX plus abatacept 10 mg/kg, 50% reduction in change from baseline at 12 months.

‡Also included Health Assessment Questionnaire Disability Index (HAQ-DI) findings (at 6 months): DMARD plus abatacept 10 mg/kg: 0.45, DMARD plus placebo: 0.11.

¶Also included the following findings: DAS28, DMARD plus abatacept 10 mg/kg, 6 months: -1.99, 24 months: -2.66; LDAS (DAS28 < 3.2), 6 months: 18.3%, 24 months: 32%; remission (DAS < 2.6), 6 months: 11.1%, 24 months: 20.3%; significant HAQ-DI improvement, 6 months: 54%, 24 months: 47.9%, (placebo switched to abatacept at 6 months) 24 months: 46.5%.

ACR: American College of Rheumatology; AIM: Abatacept in inadequate responders to methotrexate; ATTAIN: Abatacept trial I treatment of anti-TNF inadequate responders; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate.

particular improvement was demonstrated in the latter 6 months with the ACR20 response increasing to 73.1% at 12 months, from 67.9% at 6 months, in the abatacept arm. This pattern held true for ACR50 and ACR70 responses, with improvement to 48.3 and 28.8% after 1 year, respectively, from 6-month values of 39.9 and 19.8%. HAQ-DI scores of 1.7 in both abatacept- and placebo-treatment arms reflected considerable physical impairment prior to therapy with more statistically significant improvement observed in patients receiving abatacept for 1 year.

Radiographically, both treatment arms demonstrated similar erosion, joint space narrowing and total scores at baseline; however, at 1 year, abatacept-treated patients demonstrated statistically significant slowing of progression of joint damage and approximately 50% reduction in Genant-modified Sharp scores compared with patients treated with placebo.

Open-label LTE for an additional year beyond the initial 12-month study of the AIM trial showed continued efficacy and safety, in addition to slowing of radiographic progression [47,48]. ACR20/50/70 findings in this trial were very consistent with those generated in the ATTAIn trial, with near identical numbers at the end of year 1 and 2 of the study. The LDAS (DAS28 < 3.2) responders in the abatacept arm increased from 44.1% of patients at year 1 to 56.1% at year 2. This correlated with DAS28 (C reactive protein [CRP])-defined remission (DAS28 < 2.6) responders increasing from 25.4% of patients at year 1 to 30.9% at year 2.

There was a 50% reduction in radiographic progression among abatacept-treated patients compared with placebo at year 1, with continued improvement during year 2 of treatment (total score reduction by an additional 57% during year 2 vs year 1). In addition, patients treated for 2 years with abatacept versus patients in the placebo arm switched to abatacept after year 1 had significantly slower progression of disease, including total score, erosion score and joint-space narrowing. Median change in Genant-modified Sharp scores from year 1 to year 2 of the abatacept arm was 0.46 versus 0.51 for the placebo group switched to abatacept after year 1.

Finally, the Abatacept or Infliximab Versus Placebo Trial for Tolerability, Efficacy and Safety in Treating Rheumatoid Arthritis (ATTEST) was performed to quantify the treatment effect of abatacept versus infliximab versus placebo over a 12-month study period [49]. A total of 431 patients with active RA on adequate doses of MTX were randomized in a 3:3:2 ratio using an approximated weight-based dose of abatacept 10 mg/kg, infliximab 3 mg/kg or placebo. MTX was continued in all patients. During the first 6 months of the study, there were three arms: abatacept versus infliximab versus placebo. Patients receiving placebo during the first 6 months were then switched to abatacept for the remaining 6 months. Changes in background medications were allowed after the first 6 months of the study. Patients in the abatacept or infliximab arms had significant improvement in the LDAS, European League Against Rheumatism (EULAR) response and DAS28 (erythrocyte sedimentation rate [ESR])-defined remission, with slightly better results in the infliximab arm. However, at the end of the second 6 months, there were greater reductions in DAS28 (-2.88 with abatacept vs -2.25 with

infliximab), EULAR response (32% with abatacept vs 18.5% with infliximab), LDAS (35.3 vs 22.4%) and DAS28 (ESR)-defined remission (18.7 vs 12.2%) in the abatacept arm versus the infliximab arm. The data suggest that, although patients receiving abatacept had a slower onset of initial clinical improvement in comparison with patients receiving infliximab, patients in the abatacept arm continued to have a steady improvement in their clinical response during the second 6 months, eventually exceeding the clinical improvement observed in the infliximab arm at the end of year 1. In terms of HAQ-DI, both abatacept- and infliximab-treatment groups demonstrated improvements in physical function (61.5 and 58.8%, respectively).

In a recent study conducted by Buch *et al.*, MRI of affected joints and synovial biopsy were performed prior to starting and 4 months after treatment with abatacept [50]. Although there was only a small reduction in the cellular infiltration of the synovium, the expression of IFN- γ as well as other proinflammatory cytokines, such as IL-1 β , IL-6 and matrix metalloproteinases, were reduced significantly. Furthermore, the reduction in IFN- γ correlated with improvements in MRI scores. This study also evaluated the expression of RANK, RANKL and osteoprotegerin (OPG). RANK/RANKL interaction is associated with osteoclast differentiation, activation and bone resorption, whereas OPG interferes with this interaction, thereby preventing osteoclast activation and bone resorption. In the aforementioned study by Buch *et al.*, there was a trend in the reduction of expression of RANK/RANKL and upregulation of OPG in the synovium of patients receiving abatacept. These findings are interesting and may explain the immunologic mechanisms underlying improvement in bone and cartilage damage with the use of abatacept.

Safety

In terms of safety, relatively similar results were demonstrated across all of the aforementioned studies. Abatacept was tolerated well with few, if any, deaths, malignancy or opportunistic/atypical infections reported in the groups observed. Adverse events in most cases included nasopharyngitis, nausea, upper respiratory tract infections and headache; however, certain studies had higher incidences in placebo-treated patients. When abatacept 10 mg/kg was utilized and compared with a lower dosage (2 mg/kg), no increases in adverse events or discontinuations in treatment were noted. From an immunologic standpoint, antibodies to CTLA4Ig developed in some patients; however, the clinical significance of such findings remains unknown.

In the aforementioned studies, abatacept was administered along with MTX and had a favorable safety profile. However, in clinical practice, patients often receive other DMARDs, such as sulfasalazine, leflunomide or hydroxychloroquine, either as monotherapy or as combination therapy. Similarly to combination DMARD therapy, biologics are often utilized in combination with DMARDs. The Abatacept Study of Safety in Use with other RA Therapies (ASSURE) trial was designed to evaluate the safety of abatacept use in patients receiving DMARDs, as well as biologics [51]. In total, 1441 patients were enrolled in this double-blind, placebo-controlled trial lasting for 1 year. Patients who had active disease,

characterized by VAS measurement of at least 20 mm despite treatment with a biologic and/or nonbiologic DMARD, for at least 3 months were included. Patients with stable comorbid medical conditions, including congestive heart failure, asthma, chronic obstructive pulmonary disease and diabetes mellitus, were included in this study. However patients who had unstable or uncontrolled chronic conditions were excluded.

As in other studies, randomized patients were divided in a 2:1 ratio favoring the abatacept-treatment arm compared with placebo, with treated patients receiving abatacept 10 mg/kg per standards stated previously in other studies based on weight in kilograms. Approved DMARDs include MTX, hydroxychloroquine, leflunomide, gold, azathioprine, anakinra, etanercept, infliximab and adalimumab. Drug regimens including combination DMARD therapies could not be adjusted until after month 3 of the study. Fewer patients in the abatacept arm required additional nonbiologic DMARDs than those in the placebo arm (4.3 vs 7.7%, respectively) for the duration of the study.

Few adverse events (AEs), serious AEs (SAEs) or very-severe AEs were reported in either abatacept- or placebo-treated patients. Patients receiving abatacept in addition to biologic therapy developed more AEs in comparison to those receiving abatacept in conjunction with nonbiologic DMARDs. The most common AE was headache (20.4% in abatacept vs 15.6% in placebo), with only a slightly higher percentage of infection (56 vs 54.1%, respectively), represented mostly by upper respiratory tract infections and nasopharyngitis. Although the numbers were small, a higher proportion of SAEs were observed in patients receiving abatacept in combination with leflunomide. In these patients, there was no specific trend to any particular organ system or SAE type. In addition, more AEs and SAEs were demonstrated in abatacept-treated patients with chronic obstructive pulmonary disease (COPD), warranting possible caution of use in the setting of RA and pre-existing COPD. AEs were also mostly infectious, including upper/lower respiratory tract infection, bronchitis, sinusitis, influenza and herpes zoster virus. SAEs included intestinal ischemia, colon adenoma, COPD exacerbation, squamous cell carcinoma of the skin, bronchitis, basal cell carcinoma, cellulitis, cataracts and events resulting in a need for eye surgery. However, no deaths occurred in this subgroup of patients with comorbid COPD. This study, despite demonstrating that serious infections do not occur in higher frequency when abatacept use is combined with nonbiologic DMARD therapy or combinations of such, contrastingly, confirmed a higher rate of serious infections when abatacept was used with other biologic therapies.

Another study performed by Weinblatt *et al.* evaluated the safety of abatacept in combination with etanercept [52]. This multicenter, randomized, double-blind, placebo-controlled, open-label, LTE Phase II trial to 3 years total therapy included 121 patients maintained on etanercept 25 mg every 2 weeks. In the treatment arm, abatacept 2 mg/kg was administered in addition to etanercept. Following the initial 6 months of double-blind therapy, addition of other DMARDs was allowed, including plaquenil, sulfasalazine, leflunomide or MTX, with patients completing 1 year of double-blind therapy eligible for LTE for an additional 2 years. LTE included fixed-dose abatacept approximating 10 mg/kg as in

other studies with adjustment accordingly (increase or decrease) of steroids, etanercept and NSAIDs, according to RA status. In total, 80 patients eventually completed the first 2 years of the study, all eventually participating in LTE, and 61 patients completed the full 3 years of the study. Combination therapy with abatacept and etanercept did not result in significant clinical response, as measured by percentage of patients achieving ACR20 responses, over etanercept plus placebo, at 6 months. Increase in the dosage of abatacept to 10 mg/kg weight-approximated doses, as in other studies, during the open-label LTE, did not lead to any additional improvement in clinical response, beyond that observed during the first 2 years. The incidence of AEs was relatively low, however, because the combination of etanercept and abatacept demonstrated an increase in AEs, therapy-related AEs and serious infections. These findings provide additional suggestion to the findings in the ASSURE trial, which reflect a less-favorable safety profile for the combination of abatacept with biologic agents compared with standard combination of abatacept with nonbiologic DMARDs.

Expert commentary

Abatacept is a fusion protein composed of the extracellular portion of the human CTLA4 and the heavy chain of human IgG1. Immunologically, it does not deplete T cells and probably works by immunomodulation. It has been shown to induce improvements in signs and symptoms of RA in combination with MTX. It has also been demonstrated to be beneficial in patients whose disease is unresponsive to TNF- α -targeted therapies. The slowing of radiographic progression is indeed impressive and important, since patients with RA not only have signs and symptoms of synovial inflammation but also have cartilage damage and bone erosions. It is possible, although more evidence is needed, that the immunologic mechanism of action of abatacept can target both aspects of joint disease.

Abatacept infusions are well tolerated and the molecule itself is not considered immunogenic. Abatacept scores very well in terms of its safety profile and clinical studies have not demonstrated an increased incidence of infection to date. Long-term safety in terms of risk of malignancy remains an open question and will be answered in the future. Although murine studies suggest the relative safety of this drug in tuberculosis [53], the safety of this drug in patients with positive skin tests for purified protein derivative of mycobacteria remains to be resolved.

As with previous studies involving biologics in RA, a significant number of patients do not achieve ACR50/70 responses, or even ACR20 responses, over the study period. This raises the question of how long we should wait before switching patients to another therapeutic agent. Furthermore, the concern with blunting of the initial therapeutic response, as observed with TNF-targeted therapies, remains an open question.

Five-year view

Abatacept is the first T-cell-targeted therapy approved for patients with RA. It modulates the immune system without depleting the T cells and is associated with a favorable clinical outcome and safety profile. All this makes abatacept a unique and attractive

therapeutic option for RA. Furthermore, this provides the proof of concept that interventions targeting surface molecules or T cells are a viable modality of treatment in RA. Another therapeutic option in RA, targeted towards a specific immune cell, is rituximab. Rituximab targets B cells and is currently used in patients who have failed anti-TNF agents. It is probable that, with more clinical experience, abatacept and rituximab will be used as first-line biologic therapies in RA.

We now have several biologic agents (infliximab, etanercept, adalimumab, abatacept and rituximab) approved for the treatment of RA. Currently, several biologic agents are in Phase II and III clinical trials and will possibly be approved for treatment, and several others are currently under development and will join the pipeline soon. The necessity for newer drugs in RA cannot be overemphasized; however, well-designed translational

studies evaluating the immunologic mechanisms underlying clinical response, as well as adverse events associated with biologic therapy, must be undertaken. Such studies will not only advance our understanding of the immunologic dysfunction underlying RA and lead to further drug discoveries but, more importantly, provide the foundation for selecting the appropriate biologic therapy for our patients.

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Key issues

- Abatacept has shown clinical improvements in signs and symptoms of rheumatoid arthritis (RA) in combination with methotrexate.
- Abatacept is efficacious in patients with RA who are naive to TNF-neutralizing therapies, as well as those who have failed previous treatment with such therapies.
- Although abatacept is generally well tolerated, the long-term safety data are unavailable at this time.

References

- Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N. Engl. J. Med.* 344(12), 907–916 (2001).
- Verwilghen J, Lovis R, De Boer M *et al.* Expression of functional B7 and CTLA4 on rheumatoid synovial T cells. *J. Immunol.* 153(3), 1378–1385 (1994).
- Tesmer LA, Lundy SK, Sarkar S, Fox DA. Th17 cells in human disease. *Immunol. Rev.* 223, 87–113 (2008).
- Linsley PS, Brady W, Grosmaire L, Aruffo A, Damle NK, Ledbetter JA. Binding of the B cell activation antigen B7 to CD28 costimulates T cell proliferation and interleukin 2 mRNA accumulation. *J. Exp. Med.* 173(3), 721–730 (1991).
- Young JW, Koulova L, Soergel SA, Clark EA, Steinman RM, Dupont B. The B7/BB1 antigen provides one of several costimulatory signals for the activation of CD4⁺ T lymphocytes by human blood dendritic cells *in vitro*. *J. Clin. Invest.* 90(1), 229–237 (1992).
- Koulova L, Clark EA, Shu G, Dupont B. The CD28 ligand B7/BB1 provides costimulatory signal for alloactivation of CD4⁺ T cells. *J. Exp. Med.* 173(3), 759–762 (1991).
- Peach RJ, Bajorath J, Brady W *et al.* Complementarity determining region 1 (CDR1)- and CDR3-analogous regions in CTLA-4 and CD28 determine the binding to B7-1. *J. Exp. Med.* 180(6), 2049–2058 (1994).
- Linsley PS, Greene JL, Brady W, Bajorath J, Ledbetter JA, Peach R. Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors. *Immunity* 1(9), 793–801 (1994).
- Linsley PS, Brady W, Urnes M, Grosmaire LS, Damle NK, Ledbetter JA. CTLA-4 is a second receptor for the B cell activation antigen B7. *J. Exp. Med.* 174(3), 561–569 (1991).
- Greene JL, Leytze GM, Emswiler J *et al.* Covalent dimerization of CD28/CTLA-4 and oligomerization of CD80/CD86 regulate T cell costimulatory interactions. *J. Biol. Chem.* 271(43), 26762–26771 (1996).
- Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *J. Exp. Med.* 182(2), 459–465 (1995).
- Walunas TL, Lenschow DJ, Bakker CY *et al.* CTLA-4 can function as a negative regulator of T cell activation. *Immunity* 1(5), 405–413 (1994).
- Webb LM, Walmsley MJ, Feldmann M. Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2. *Eur. J. Immunol.* 26(10), 2320–2328 (1996).
- Szot GL, Zhou P, Sharpe AH *et al.* Absence of host B7 expression is sufficient for long-term murine vascularized heart allograft survival. *Transplantation* 69(5), 904–909 (2000).
- Lakkis FG, Konieczny BT, Saleem S *et al.* Blocking the CD28-B7 T cell costimulation pathway induces long term cardiac allograft acceptance in the absence of IL-4. *J. Immunol.* 158(5), 2443–2448 (1997).
- Li Y, Li XC, Zheng XX, Wells AD, Turka LA, Strom TB. Blocking both signal 1 and signal 2 of T-cell activation prevents apoptosis of alloreactive T cells and induction of peripheral allograft tolerance. *Nat. Med.* 5(11), 1298–1302 (1999).
- Wells AD, Li XC, Li Y *et al.* Requirement for T-cell apoptosis in the induction of peripheral transplantation tolerance. *Nat. Med.* 5(11), 1303–1307 (1999).
- Orabona C, Grohmann U, Belladonna ML *et al.* CD28 induces immunostimulatory signals in dendritic cells via CD80 and CD86. *Nat. Immunol.* 5(11), 1134–1142 (2004).
- Weisman MH, Durez P, Hallegua D *et al.* Reduction of inflammatory biomarker response by abatacept in treatment of rheumatoid arthritis. *J. Rheumatol.* 33(11), 2162–2166 (2006).
- Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. *Nat. Rev. Immunol.* 4(10), 762–774 (2004).
- Munn DH, Sharma MD, Mellor AL. Ligation of B7-1/B7-2 by human CD4⁺ T cells triggers indoleamine 2,3-

- dioxygenase activity in dendritic cells. *J. Immunol.* 172(7), 4100–4110 (2004).
- 22 Grohmann U, Orabona C, Fallarino F *et al.* CTLA-4-Ig regulates tryptophan catabolism *in vivo*. *Nat. Immunol.* 3(11), 1097–1101 (2002).
 - 23 Hill M, Zagani R, Voisine C, Usal C, Anegón I. Nitric oxide and indoleamine 2,3-dioxygenase mediate CTLA4Ig-induced survival in heart allografts in rats. *Transplantation* 84(8), 1060–1063 (2007).
 - 24 Pree I, Bigenzahn S, Fuchs D *et al.* CTLA4Ig promotes the induction of hematopoietic chimerism and tolerance independently of indoleamine-2,3-dioxygenase. *Transplantation* 83(5), 663–667 (2007).
 - 25 Zhu L, Ji F, Wang Y *et al.* Synovial autoreactive T cells in rheumatoid arthritis resist IDO-mediated inhibition. *J. Immunol.* 177(11), 8226–8233 (2006).
 - 26 Davis PM, Abraham R, Xu L, Nadler SG, Suchard SJ. Abatacept binds to the Fc receptor CD64 but does not mediate complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity. *J. Rheumatol.* 34(11), 2204–2210 (2007).
 - 27 Abrams JR, Kelley SL, Hayes E *et al.* Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *J. Exp. Med.* 192(5), 681–694 (2000).
 - 28 Sun ZW, Qiu YH, Shi YJ *et al.* Time courses of B7 family molecules expressed on activated T-cells and their biological significance. *Cell. Immunol.* 236(1–2), 146–153 (2005).
 - 29 Thomas R, McIlraith M, Davis L, Lipsky P. Rheumatoid synovial T cells are functionally active and can contribute to the pathogenesis of rheumatoid arthritis: comment on the article by Matthews *et al.* *Arthritis Rheum.* 37(3), 445–446 (1994).
 - 30 Croft M, Bradley LM, Swain SL. Naive versus memory CD4 T cell response to antigen. Memory cells are less dependent on accessory cell costimulation and can respond to many antigen-presenting cell types including resting B cells. *J. Immunol.* 152(6), 2675–2685 (1994).
 - 31 London CA, Lodge MP, Abbas AK. Functional responses and costimulator dependence of memory CD4⁺ T cells. *J. Immunol.* 164(1), 265–272 (2000).
 - 32 Ndejembu MP, Teijaro JR, Patke DS *et al.* Control of memory CD4 T cell recall by the CD28/B7 costimulatory pathway. *J. Immunol.* 177(11), 7698–7706 (2006).
 - 33 O'Neill SK, Cao Y, Hamel KM, Doodes PD, Hutas G, Finnegan A. Expression of CD80/86 on B cells is essential for autoreactive T cell activation and the development of arthritis. *J. Immunol.* 179(8), 5109–5116 (2007).
 - 34 Warrington KJ, Takemura S, Goronzy JJ, Weyand CM. CD4⁺CD28⁺ T cells in rheumatoid arthritis patients combine features of the innate and adaptive immune systems. *Arthritis Rheum.* 44(1), 13–20 (2001).
 - 35 Sawai H, Park YW, Roberson J, Imai T, Goronzy JJ, Weyand CM. T cell costimulation by fractalkine-expressing synoviocytes in rheumatoid arthritis. *Arthritis Rheum.* 52(5), 1392–1401 (2005).
 - 36 Yen JH, Moore BE, Nakajima T *et al.* Major histocompatibility complex class I-recognizing receptors are disease risk genes in rheumatoid arthritis. *J. Exp. Med.* 193(10), 1159–1167 (2001).
 - 37 Groh V, Bruhl A, El-Gabalawy H, Nelson JL, Spies T. Stimulation of T cell autoreactivity by anomalous expression of NKG2D and its MIC ligands in rheumatoid arthritis. *Proc. Natl Acad. Sci. USA* 100(16), 9452–9457 (2003).
 - 38 Tang Q, Henriksen KJ, Boden EK *et al.* Cutting edge: CD28 controls peripheral homeostasis of CD4⁺CD25⁺ regulatory T cells. *J. Immunol.* 171(7), 3348–3352 (2003).
 - 39 Wei L, Wei-Min L, Cheng G, Bao-Guo Z. Upregulation of CD4⁺CD25⁺ T lymphocyte by adenovirus-mediated gene transfer of CTLA4Ig fusion protein in experimental autoimmune myocarditis. *Autoimmunity* 39(4), 289–298 (2006).
 - 40 Remans PH, Wijbrandts CA, Sanders ME *et al.* CTLA-4Ig suppresses reactive oxygen species by preventing synovial adherent cell-induced inactivation of Rap1, a Ras family GTPase mediator of oxidative stress in rheumatoid arthritis T cells. *Arthritis Rheum.* 54(10), 3135–3143 (2006).
 - 41 Moreland LW, Alten R, Van den Bosch F *et al.* Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum.* 46(6), 1470–1479 (2002).
 - 42 Kremer JM, Westhovens R, Leon M *et al.* Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N. Engl. J. Med.* 349(20), 1907–1915 (2003).
 - 43 Kremer JM, Dougados M, Emery P *et al.* Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a Phase IIb, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 52(8), 2263–2271 (2005).
 - 44 Genovese MC, Becker JC, Schiff M *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. *N. Engl. J. Med.* 353(11), 1114–1123 (2005).
 - 45 Genovese MC, Schiff M, Luggen M *et al.* Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. *Ann. Rheum. Dis.* 67(4), 547–554 (2008).
 - 46 Kremer JM, Genant HK, Moreland LW *et al.* Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* 144(12), 865–876 (2006).
 - 47 Genant HK, Peterfy CG, Westhovens R *et al.* Abatacept inhibits progression of structural damage in rheumatoid arthritis: results from the long-term extension of the AIM trial. *Ann. Rheum. Dis.* 67(8), 1084–1089 (2008).
 - 48 Kremer JM, Genant HK, Moreland LW *et al.* Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum.* 58(4), 953–963 (2008).
 - 49 Schiff M, Keiserman M, Coddling C *et al.* Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a Phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann. Rheum. Dis.* 67(8), 1096–1103 (2008).
 - 50 Buch MH, Boyle DL, Rosengren S *et al.* Mode of action of abatacept in rheumatoid arthritis patients having failed TNF blockade: a histological, gene expression and dynamic MRI pilot study. *Ann. Rheum. Dis.* DOI: 10.1136/ard.2008.091876 (2008) (Epub ahead of print).
 - 51 Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety

- of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum.* 54(9), 2807–2816 (2006).
- 52 Weinblatt M, Schiff M, Goldman A *et al.* Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. *Ann. Rheum. Dis.* 66(2), 228–234 (2007).
- 53 Bigbee CL, Gonchoroff DG, Vratsanos G, Nadler SG, Haggerty HG, Flynn JL. Abatacept treatment does not exacerbate chronic *Mycobacterium tuberculosis* infection in mice. *Arthritis Rheum.* 56(8), 2557–2565 (2007).
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