

Selective modulation of T-cell co-stimulation: a novel mode of action for the treatment of rheumatoid arthritis

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ABSTRACT

Disease-modifying antirheumatic drug therapy, including biological treatments that act via tumour necrosis factor (TNF)- α blockade, have benefited numerous patients suffering from rheumatoid arthritis (RA). However, a portion of the patient population is unresponsive to initial therapy, experience a decline in response over time or may develop side effects to treatment. These factors illustrate the requirement for additional therapy options, with novel modes of action, in order to treat this chronic and disabling disease. Activated T cells predominate in the disease processes of RA. Therefore, one rational approach to therapy is to modulate or target T cells. Abatacept is a first-in-class agent that targets T-cell modulation via the co-stimulatory CD80/CD86:CD28 pathway. Preclinical studies and clinical trials have demonstrated both the rationale and efficacy of using T-cell modulation as a therapeutic approach and, as a result, abatacept is currently approved in the European Union for the treatment of RA in adults with moderately to severely active disease who have not responded to TNF- α antagonist therapy. This review will highlight abatacept as an important treatment option in the therapeutic repertoire for RA that selectively modulates T-cell co-stimulation.

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease. The complex nature of the disease process and the inherent heterogeneity of the patient population, results in varying responses to treatments (1, 2). Many patients with RA have benefited from first-line monotherapy treatment with non-biological disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX). However, the

efficacy of DMARD therapy is not universal for all patients. Discontinuations due to inefficacy or adverse events (AEs) can be high in some populations; for most patients, the discontinuation of DMARD treatment occurs within 3–5 years (3–9). The deficiency of a durable response to non-biological DMARD therapy is evidenced by one study, which reported that a proportion of patients receiving long-term non-biological DMARDs over a 20-year period experienced a deterioration in physical function. At Year 20, 35% of patients had died and 19% had severe disability compared with 14% of patients at baseline (10); this decrease in physical function was reflected in increasing joint destruction over time, as observed with radiographic imaging (10).

The introduction of biological DMARDs in the late 1990s, namely tumour necrosis factor (TNF- α) antagonists, has provided effective treatment options to many patients who do not respond adequately to non-biological DMARD therapy (11–13). However, clinical experience with TNF- α antagonists has shown that these therapies may not be suitable for all patients due to a lack of response to initial treatment or decline in response over time, and also owing to the occurrence of serious adverse reactions in some patients, such as infections or worsening of co-morbidities (13–20). These issues highlight the importance of developing alternative therapies for RA with modes of action distinct from the TNF- α antagonists. One such agent is the biological DMARD abatacept (ORENCIA[®], Bristol-Myers Squibb, Princeton, NJ) (21), which selectively modulates T-cell activation. Abatacept is approved in the European Union (EU) for the treatment of adults with moderately to severely active RA who have not responded to TNF- α antagonist therapy (21).

Conflict of interest: Dr E.H. Choy has received honoraria and served on the advisory board of Bristol-Myers Squibb.

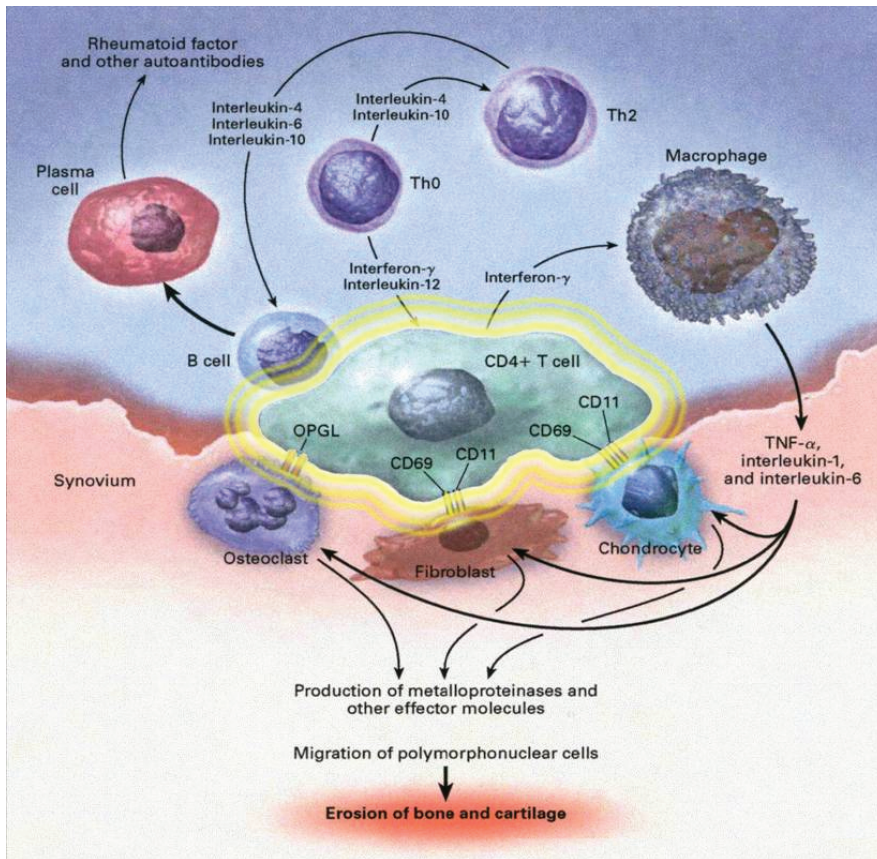


Fig. 1. The immunopathology of rheumatoid arthritis.

Th: T helper cell; OPGL: osteoprotegerin; TNF: tumour necrosis factor.

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This review will describe the central role of the activated T cell in the immunopathogenesis of RA, providing the rationale for selective modulation of T-cell co-stimulation as a viable therapeutic intervention. Evidence for the effectiveness of this approach, as demonstrated by the clinical experience to date with abatacept, will also be discussed.

The immunopathology of rheumatoid arthritis

RA is a chronic, complex, systemic inflammatory autoimmune disease, involving multiple pathways and cell types (Fig. 1) (22-24).

Following the initiation event in the pathogenesis of RA, the synovium typically demonstrates hyperplasia and increased vascularity, with high numbers of infiltrating inflammatory cells (22, 25). The synovial pathology differs between individual patients with some

presenting diffuse infiltrates in the RA synovium (25), while in other patients this is presented as aggregates (consisting of T cells, B cells and dendritic cells) or lymphoid aggregates resembling germinal cells that are rich in T cells and B cells (25). Activated T cells play an integral part in the immunopathology and disease development in the RA synovium, mediating B-cell and macrophage activation plus cytokine production that, ultimately, leads to inflammation and joint destruction (22-24).

T-cell activation consists of a two-signal process. Firstly, peptide antigen is processed by antigen-presenting cells (APCs) via the major histocompatibility complex (MHC) (26). In the case of RA this autoantigen remains unidentified (27), although citrullinated protein (22, 28), human cartilage glycoprotein 39 or the heavy-chain-binding protein (29) have all been proposed as possible candidates. The processed MHC-anti-

gen complex is then recognized by T cells via interaction with the T-cell receptor (27). The second signal involves interaction between co-stimulatory ligands on the APC and receptors on the T-cell surface, and is required to facilitate full T-cell activation, proliferation, survival and cytokine production (30). The importance of this secondary signal is demonstrated by the T-cell inactivation or anergy that is observed in the absence of the second signal (27).

Following T-cell activation, an inflammatory cascade ensues in which pro-inflammatory cytokines are secreted, such as interferon- γ and interleukin (IL)-12, which stimulate monocytes, macrophages and synovial fibroblasts to produce the cytokines IL-1, IL-5, IL-6, IL-10, IL-15, IL-18 and TNF- α (22) through cell-surface signalling and the release of soluble mediators, such as CD69, CD11, interferon-gamma and IL-17 (31). B cells are also stimulated by cell-surface interactions with activated T cells to produce autoantibodies, such as rheumatoid factor (RF) and the cytokines IL-6 and IL-10 (22). The release of these cytokines, in particular TNF- α , IL-1 and IL-6, causes the typical synovial inflammation observed in RA (22). Further inflammation and joint damage is induced by IL-1, IL-17 and TNF- α , as these cytokines increase the recruitment of neutrophils to the joints. The release of elastase and proteases by these recruited neutrophils then causes degradation of the proteoglycan in the superficial layers of cartilage, thereby exposing chondrocytes (32). Further damage to the joint is exacerbated by IL-1, TNF- α and activated T cells, stimulating osteoclasts, fibroblasts and chondrocytes to secrete matrix metalloproteinases (MMPs) that degrade the connective tissue matrix. Matrix metalloproteinases, in particular stromelysin and collagenases, are thought to be the main driver of joint damage (22). This destructive process is accelerated further by IL-1 and TNF- α as these cytokines block the production of MMP inhibitors, which are normally produced by fibroblasts (33). Along with the release of soluble mediators, activated T cells express the receptor activator of the nuclear factor

kappaB ligand (RANKL), which binds to RANK on the surface of monocytes inducing osteoclastogenesis (34). The relevance of RANKL was demonstrated in an animal model of inflammatory arthritis, whereby joint damage in RANKL knockout mice was greatly reduced compared with that seen in controls (35).

Targeting the immunopathology of rheumatoid arthritis – modes of action

In the EU, biological DMARDs that target specific pro-inflammatory cytokines involved with the immunopathology of RA (Fig. 2), including the TNF- α antagonists, are currently used for the treatment of moderate or severe RA in patients who have not responded to other DMARD treatments. These agents can be used either with concomitant MTX treatment, or in some exceptions as a monotherapy (36-38). The TNF- α antagonists include: etanercept (ENBREL[®]; Amgen, Thousand Oaks, CA), a recombinant human TNF- α -receptor fusion protein (36); adalimumab (HUMIRA[®]; Abbott Laboratories, Chicago, IL), a humanized monoclonal anti-TNF- α antibody (37); and infliximab (REMICADE[®]; Centocor, Malvern, PA), a mouse-human chimeric monoclonal anti-TNF- α antibody (38). While these treatments have provided notable clinical benefits to many patients with RA (11-13, 15), in some patients these agents fail to provide adequate benefits (13-16) or may be intolerable and increase the risk of infections (15, 17-19, 39). One alternative anti-cytokine therapy is anakinra, which is approved in the EU for the treatment of patients with RA in combination with MTX or in patients with an inadequate response to MTX alone (40). Anakinra is a recombinant, non-glycosylated synthetic form of the human IL-1 receptor antagonist (41), which downregulates the biological effects of IL-1 (Fig. 2). However, the benefits of anakinra are limited; moderate clinical improvements, together with the requirement of frequent dosing, limit its overall use as a therapy for the treatment of RA (22). Patients who have not responded adequately to available cytokine antag-

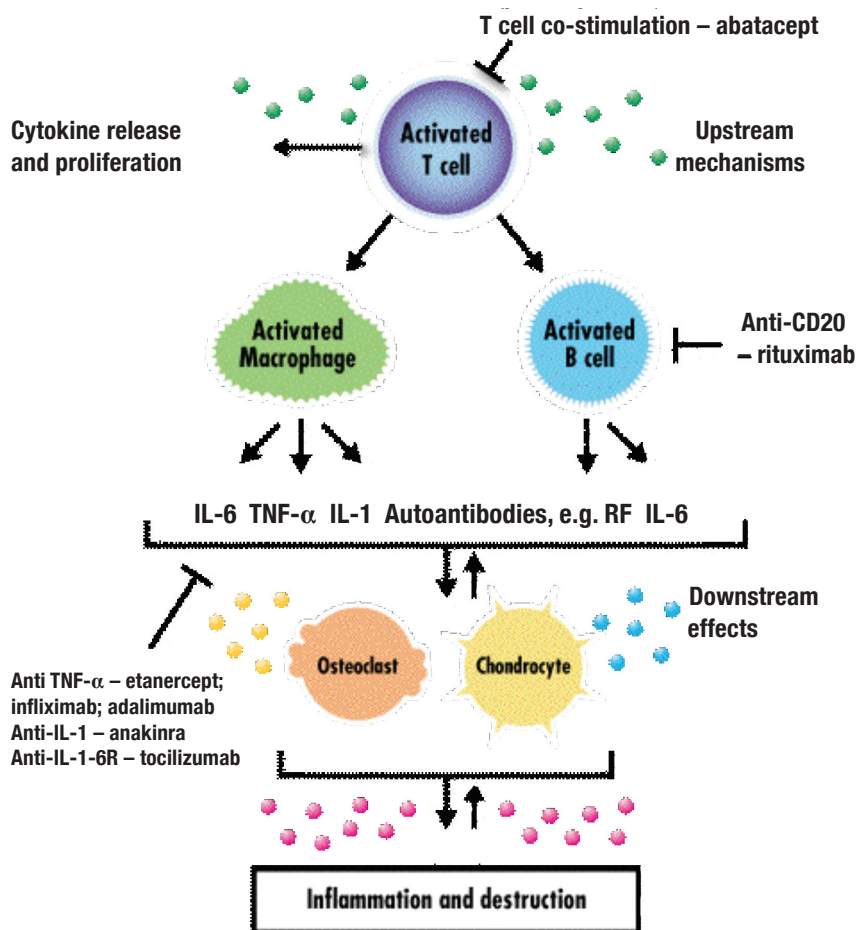


Fig. 2. Therapeutic targets in the immune cascade of rheumatoid arthritis. IL: interleukin; TNF: tumour necrosis factor; RF: rheumatoid factor; IL-6R: interleukin 6 receptor. Reproduced with permission from Cohen M: Abatacept in focus. *The Internet Journal of Rheumatology* 2007; 3(1).

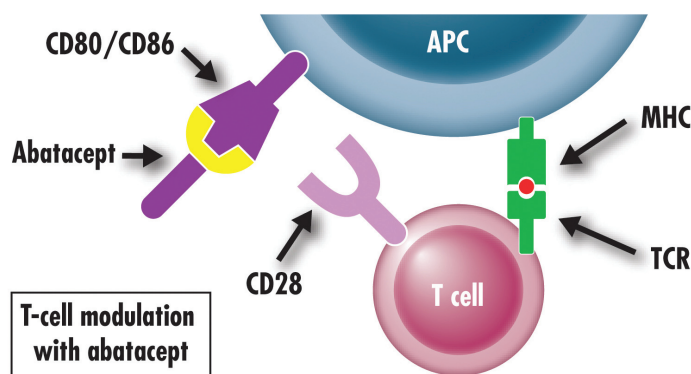


Fig. 3. Abatacept, a selective co-stimulation modulator. APC: antigen presenting cell; MHC: major histocompatibility complex; TCR: T-cell receptor.

onist therapy have limited treatment options open to them (42). This unmet need has driven the development of novel biological agents with alternative mechanisms of action. Two such agents have been approved in the EU for the treatment of RA and are described below.

Novel biological agents targeting specific cell types

Two biological therapies that target specific cell types, as opposed to pro-inflammatory cytokines, have been developed: rituximab (MABTHERA[®]; F. Hoffman Roche Ltd, Basel, Switzerland) (43) and abatacept (ORENCIA[®];

Table I. Mean serum levels of rheumatoid arthritis biomarkers at baseline and Year 1 (52).

Reproduced with permission from Weisman MH *et al.* Reduction of inflammatory biomarker response by abatacept in treatment of rheumatoid arthritis. *J Rheumatol* 2006; 33: 2162-6.

Biomarker	Mean levels at baseline (SE)			Mean levels at Year 1 (SE)			Normal range
	Abatacept 10 mg/kg (n=115)	Abatacept 2 mg/kg (n=105)	Placebo (n=119)	Abatacept 10 mg/kg (n=115)	Abatacept 2 mg/kg (n=105)	Placebo (n=119)	
CRP, mg/dL	3.0 (0.2)	3.2 (0.2)	3.2 (0.2)	1.5 (0.2)*	2.1 (0.3)	3.0 (0.3)	0–0.4
RF, IU/L	290.1 (29.9)	276 (31.2)	223.5 (29.4)	159 (32.0)	261.2 (34.3)	225.2 (32.9)	0–20.0
sIL-2R, pg/mL	1426.4 (63.8)	1413.1 (66.6)	1483.6 (62.6)	1228.3 (69.0)*	1441.5 (74.2)†	1697.1 (72.0)	676.0–2132.0
IL-6, pg/mL	27.3 (2.9)	33.8 (3.1)	26.3 (2.8)	7.3 (3.7)†	15.8 (4.0)	19.9 (4.1)	0.3–14.8
Soluble E-selectin, ng/mL	68.4 (3.3)	69.1 (3.5)	68.2 (3.3)	58.5 (3.5)‡	71.6 (3.7)	72.7 (3.7)	29.1–63.4
sICAM-1, ng/mL	403.4 (14.2)	397.6 (14.8)	393.5 (14.0)	351.0 (15.1)‡	394.1 (16.0)	408.9 (15.7)	115–306.0
TNF- α , pg/mL	11.7 (1.5)	9.0 (1.5)	11.4 (1.4)	7.4 (1.9)	7.8 (2.1)	10.3 (2.1)	1.2–8.0

* $p < 0.0001$; † $p < 0.05$; ‡ $p < 0.01$, all versus placebo; based on a longitudinal mixed-model analysis (analysis assumes that data were missing at random and not dependent on current or future response); SE: standard error; CRP: C-reactive protein; RF: rheumatoid factor; sIL-2R: soluble interleukin-2 receptor; IL: interleukin; sICAM-1: soluble intercellular adhesion molecule-1; TNF: tumour necrosis factor.

Bristol-Myers Squibb, Princeton, NJ) (21). Rituximab is a genetically engineered, chimeric human-murine anti-CD20 monoclonal antibody, which selectively depletes CD20+ B cells (Fig. 2) (43). Rituximab, prescribed with concomitant MTX, has been approved in the EU for the treatment of adult patients with severely active RA who have had an inadequate response or intolerance to other DMARDs, including one or more TNF- α antagonists (43). Outside the EU, rituximab has been indicated for the treatment of moderate-to-severe RA in patients who have experienced an inadequate response to one or more TNF- α antagonists (44).

Abatacept is a soluble, human, recombinant fusion protein that selectively modulates the co-stimulatory signal required for full T-cell activation (Fig. 2). In the EU, abatacept, in combination with MTX, is indicated for the treatment of adults with moderately to severely active RA who have an insufficient response or intolerance to other DMARDs, including at least one TNF- α antagonist (21). In several countries outside the EU, including the United States, abatacept is additionally indicated as a monotherapy (or in combination with MTX) in patients with moderately to severely active RA, including those patients with a prior history of intolerance to MTX or other DMARDs (45).

In the next section, the novel biological agent, abatacept, and its unique mode

of action are described. Data from clinical trials of abatacept in RA are also presented.

Abatacept, a selective T-cell co-stimulation modulator

As described above, T cells play a key role in the initiation of the immunopathology of RA and, as such, targeting T-cell activation constitutes a rational therapeutic strategy. Since T cells require two signals for their full activation, selectively modulating the second, or co-stimulatory signal, represents a targeted method of inhibiting full activation and the subsequent downstream inflammatory cascade.

Numerous co-stimulatory pathways exist, providing either upregulatory or downregulatory signals to the T cell (46, 47). One of the best-characterised positive co-stimulatory pathways involves the engagement of CD80/CD86 on the APC with CD28 on the T cell (47). In a normal immune response, the downregulation of CD28-mediated T-cell co-stimulation is mediated by increased expression of cytotoxic T-lymphocyte-associated antigen (CTLA)-4, which competes with CD28 for binding to CD80/CD86, since it has higher binding avidity than CD28 (48). Abatacept is a rationally designed human protein that utilises the homeostatic role of CTLA-4 to inhibit T-cell activation (49). The recombinant abatacept molecule comprises the extracellular domain of CTLA-4 and a

fragment of the Fc proportion of human IgG1, which has been modified to reduce complement fixation (50). By binding to CD80/CD86 on APCs, abatacept prevents the interaction of CD80/CD86 with CD28 on T cells and thus selectively modulates this positive co-stimulatory pathway whilst allowing other co-stimulatory pathways to remain largely intact (Fig. 3) (27, 51). Selective T-cell co-stimulation modulation with abatacept reduces T-cell activation and proliferation and causes a reduction in the production of pro-inflammatory cytokines and autoantibodies that occur downstream in the RA immune cascade, such as TNF- α , IL-6, IL-1 and RF (52).

Reductions in inflammatory biomarkers following abatacept treatment

Levels of inflammatory biomarkers can be used to assess disease activity, as well as to elucidate the mode of action and therapeutic effects of a disease-modifying agent. The effect of abatacept on levels of inflammatory biomarkers were investigated in a Phase IIb, 12-month, randomized, double-blind, placebo-controlled, dose-finding study in patients with active RA and an inadequate response to MTX (52). Patients were randomized to receive a fixed dose of either abatacept 2 or 10 mg/kg, or placebo, in addition to background MTX. Serum levels of the following biomarkers were evaluated: C-reactive

Table II. Overview of clinical efficacy at trial endpoint in the AIM and ATTAIN trials (53, 54, 57, 58).
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Study	ACR (% responders)			DAS28	Physical function	Inhibition of structural damage (mean change)		
	20	50	70	Remission* (%)	HAQ-DI responders (%) [†]	Erosion score	JSN score	Total score
AIM Clinical Trial								
6 months abatacept	67.9 [‡]	39.9 [‡]	19.8 [‡]	14.8 [‡]	–	–	–	–
6 months placebo	39.7	16.8	6.5	2.8	–	–	–	–
1 year abatacept	73.1 [‡]	48.3 [‡]	28.8 [‡]	23.8 [‡]	63.7 [‡]	0.63 [§]	0.58 ^{§§}	1.21 [§]
1 year placebo	39.7	18.2	6.1	1.9	39.3	1.14	1.18	2.32
2 year abatacept	80.3	55.6	34.3	56.1 [¶]	73.2	0.45 ^{**}	0.24 ^{**}	0.21 ^{**}
ATTAIN Clinical Trial								
6 months abatacept	50.4 [‡]	20.3 [‡]	10.2 ^{††}	10.0 [‡]	47.3 [‡]	–	–	–
6 months placebo	19.5	3.8	1.5	0.8	23.3	–	–	–
2 years [¶] abatacept	56.2	33.2	16.1	32.0	49.7	–	–	–

*Remission defined as DAS28 <2.6; [†]Responders were defined as an improvement of ≤ 0.3 units from baseline; [‡] $p < 0.001$; [§] $p < 0.05$; ^{§§} $p < 0.01$; [¶]Using a post-hoc as-observed analysis; ^{**}Mean change of Year 1 versus Year 2; ^{††} $p = 0.003$; ACR: American College of Rheumatology; DAS28: Disease Activity Score 28; HAQ-DI: Health Assessment Questionnaire Disability Index; JSN: joint-space narrowing; AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-Tumour Necrosis Factor INadequate responders.

tive protein (CRP), rheumatoid factor (RF), soluble interleukin-2 receptor (sIL-2R), IL-6, TNF- α , sE-selectin and soluble ICAM-1.

As expected for a population of patients with active RA, clinical biomarkers were elevated above the normal baseline range for individuals without disease, with the exception of sIL-2R (Table I). Following 1 year of treatment with abatacept at a dosage of 10 mg/kg, there were significant reductions in serum levels of IL-6, sIL-2R, CRP and sICAM-1 compared with the placebo group (Table I). Smaller (non-significant) reductions were seen in the levels of TNF- α and RF. The largest decreases in biomarkers were seen by Day 90, these reduced levels were maintained throughout the trial. These findings illustrate the mode of action of abatacept and indicate that the agent acts at the level of the T cell in the immunopathology of RA and, as such, may also affect several inflammatory cell types and cytokines that are involved in the immunopathogenesis of RA (52). Since markers of the activity of numerous inflammatory cell types were affected, the results from this study also support the rationale behind selective T-cell co-stimulation modulation as a novel treatment in patients with RA (52).

Efficacy of abatacept in methotrexate inadequate responders

The efficacy and safety of abatacept has been demonstrated in the 1-year, randomized, double-blind, placebo-controlled, Phase III trials; AIM (Abatacept in Inadequate responders to MTX) and ATTEST (A Trial for Tolerability, Efficacy and Safety in Treating RA) (53-55).

During the AIM study, patients received either abatacept approximating 10 mg/kg (according to weight range) or placebo, plus background MTX (53). Following the 1-year, double-blind period of the trial, efficacy of abatacept was examined during an open-label long-term extension (LTE) study; all patients in the LTE, regardless of their original treatment group at randomization, were treated with abatacept (~10 mg/kg according to weight range) (54). Efficacy was assessed using standard methods such as the American College of Rheumatology criteria (ACR 20, 50 and 70), the Disease Activity Score (DAS) 28 (CRP), the Health Assessment Questionnaire-Disease Index, the Short Form (SF)-36 and the Genant-modified Sharpe score).

In AIM, abatacept treatment resulted in significant improvements in the signs and symptoms of RA at Month 6 compared with placebo treatment (53).

These benefits were maintained over 2 years of abatacept treatment (Table II) (53, 54). ACR analyses were based on the intention-to-treat population, where all patients who discontinued treatment were considered as non-responders (non-responder analysis). In the abatacept group 73.1, 48.3 and 28.8% of patients achieved an ACR 20, 50 and 70 response at Year 1 (53), respectively, and these responses were maintained at Year 2 (80.3, 55.6 and 34.3%, respectively) (53, 54). Remission, as defined by DAS28 (CRP) <2.6, was achieved in 25.4% of patients in the original abatacept-treated group at Year 1 and this increased to 30.9% by Year 2 (54). Abatacept-treated patients also experienced significant improvements in health-related quality of life (HRQoL; as measured by the SF-36) throughout the trial compared with placebo-treated patients (at Month 6, physical component summary score [PCS], $p < 0.001$ and mental component summary score [MCS], $p = 0.009$; at Year 1, PCS, $p < 0.001$ and MCS, $p = 0.038$) (53). These improvements in HRQoL were sustained during the LTE period at Year 2 of treatment with abatacept (54). A significant inhibition of radiographic progression was seen in abatacept-treated patients compared with placebo-treated patients in the AIM trial at

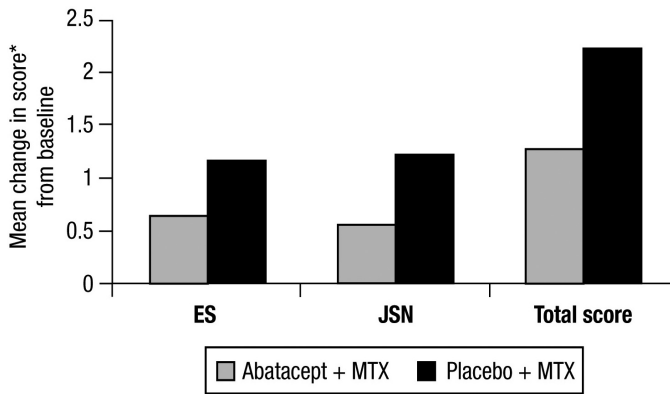


Fig. 4. Inhibition of radiographic structural damage progression at Year 1 in patients with rheumatoid arthritis and an inadequate response to methotrexate* (53).

*Measured by Genant-modified Sharp score; ES: erosion score; JSN: joint-space narrowing; MTX: methotrexate.

Year 1 (Table II), with an approximate 50% reduction in change from baseline in Genant-modified Sharp scores (56) for the abatacept- versus placebo-treated patients. The mean changes in erosion score (ES), joint space narrowing (JSN) score and total score (TS) were higher in the placebo-treated patients compared with the abatacept-treated patients at Year 1 (Table II and Fig. 4) (53). This rate of radiographic progression in the original abatacept-treated group was inhibited further in the LTE period; a 57% reduction in TS at Year 2 was observed compared with Year 1 (54). The mean changes observed in ES and JSN score in the abatacept-treated group were found to be sustained during the LTE; the mean changes from baseline to Year 1 and from Year 1-2 were similar (Table II) (54).

Patients who enrolled in the ATTEST trial, like those in the AIM trial, had previously experienced an inadequate response to MTX. Patients in the ATTEST trial were randomized to one of three treatment arms: abatacept approximating 10 mg/kg (according to weight range), infliximab 3 mg/kg or placebo, plus background MTX over 6 months. Patients were assessed for efficacy and safety (55). At Month 6, infliximab patients were switched to abatacept therapy, and blinding was maintained. At Month 6 and Year 1, patients in the original abatacept group had significant reductions in the signs and symptoms of disease, with improved physical function and HRQoL compared with the placebo group. The proportion of patients who achieved an ACR 20, 50 and 70 response at Month 6 (non-responder

analysis) was 6.7 versus 41.8%, 40.4 versus 20.0% and 20.5 versus 9.1% for the abatacept versus placebo groups, respectively. Collectively, the efficacy and safety data detailed in this study supported a relatively more acceptable risk-to-benefit profile of abatacept compared with infliximab; however, these findings must be interpreted within the constraints of the clinical trial (55).

These data demonstrate that selective T-cell co-stimulation modulation with abatacept provides significant and consistent efficacy benefits in patients with an inadequate response to MTX.

Efficacy of abatacept in tumour necrosis factor antagonist inadequate responders

The efficacy and safety of abatacept in patients with an inadequate response to TNF- α antagonist treatment has been reported in the 6-month, randomized, double-blind, placebo-controlled ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate responders) trial (57). This trial included patients receiving at least one background non-biological DMARD who had active RA despite having previously received TNF- α antagonist treatment (57). Patients in this trial received a fixed dose of abatacept, approximating 10 mg/kg according to weight range. The initial double-blind period of the ATTAIN trial was followed up by an open-label LTE study period (58). In this continued evaluation of abatacept, all patients (including those previously randomized to receive placebo) completing the double-blind phase of the trial then received abatacept ~10 mg/kg plus background

DMARDs (58). As described previously for the AIM trial, patients were assessed in terms of their disease activity, signs and symptoms of disease and efficacy of treatment using standard methods. ACR analyses were based on the intention-to-treat population, where all patients who discontinued treatment were considered as non-responders (non-responder analysis).

At Month 6, abatacept-treated patients experienced significant improvements in the signs and symptoms of their disease compared with patients receiving placebo (Table II) (57). American College of Rheumatology 20, 50 and 70 responses were met by 50.4, 20.3 and 10.2% of abatacept-treated patients compared with 19.5, 3.8 and 1.5% of the placebo-treated patients, respectively. The remission rate (DAS28 [erythrocyte sedimentation rate; ESR] <2.6) in these TNF-refractory patients was 10% in the abatacept group versus 0.8% in the placebo group (57).

Clinical benefits demonstrated at month 6 were maintained through 2 years (Table II) (58). The proportion of abatacept-treated patients achieving an ACR 20, 50 and 70 response were comparable at Month 6 and Year 2 (ACR 20, 50 and 70; 56.2, 33.2 and 16.1% at Year 2, respectively), whilst those patients switching to abatacept from placebo improved their responses over time. Furthermore, these responses were comparable with patients who had received abatacept from the beginning of the trial (ACR 20, 50 and 70; 51.5, 32.3 and 13.1% at Year 2, respectively) (58). One-fifth of the original abatacept group had achieved remission (DAS28 [ESR] <2.6) at Year 2 (58).

Patients treated with abatacept also had significantly greater improvements in HRQoL measurements at Month 6 compared with placebo-treated patients, with significant improvements in all eight subscales of the SF-36, including both the PCS and MCS ($p < 0.001$ and $p < 0.01$, respectively) (57). These significant improvements were sustained during the LTE in the abatacept arm (58). Overall, these findings in different patient populations demonstrate that selective T-cell co-stimulation modulation with abatacept provides clinical

Table III. Summary of safety events across the double-blind abatacept clinical trials.

Event	AIM 12 months		ATTAIN 6 months		ASSURE 12 months			
	Abatacept + MTX (n=433)	Placebo + MTX (n=219)	Abatacept + DMARDs (n=258)	Placebo + DMARDs (n=133)	Non-biological background therapy		Biological background therapy	
					Abatacept (n=856)	Placebo (n=418)	Abatacept (n=103)	Placebo (n=64)
AEs	378 (87.3)	184 (84.0)	205 (79.5)	95 (71.4)	786 (89.7)	360 (86.1)	98 (95.1)	57 (89.1)
SAEs	65 (15.0)	26 (11.9)	27 (10.5)	15 (11.3)	100 (11.7)	51 (12.2)	23 (22.3)	8 (12.5)
Discontinuations due to AEs	18 (4.2)	4 (1.8)	9 (3.5)	5 (3.8)	43 (5.0)	18 (4.3)	9 (8.7)	2 (3.1)
Discontinuations due to SAEs	10 (2.3)	3 (1.4)	7 (2.7)	2 (1.5)	18 (2.1)	5 (1.2)	5 (4.9)	2 (3.1)
Serious infections	11 (2.5)	2 (0.9)	6 (2.3)	3 (2.3)	22 (2.6)	7 (1.7)	6 (5.8)	1 (1.6)

All events are n, (%) unless otherwise stated; AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-tumor necrosis factor Inadequate responders; ASSURE: Abatacept Study of Safety in Use with other Rheumatoid arthritis Therapies; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug; AE: adverse event; SAE: serious adverse event.

benefits to patients who have either experienced an inadequate response to MTX or TNF- α antagonist therapy.

Safety and tolerability of abatacept in patients with rheumatoid arthritis

With any agent, particularly those that affect the immune system, it is important to evaluate the safety and tolerability following treatment.

In the AIM trial of abatacept in MTX inadequate responders, the overall frequency of AEs in biologic-naïve patients in the AIM trial was similar in the abatacept and placebo groups (Table III) (53) and consistent with those reported in the Phase II abatacept trials in a similar patient population (59, 60).

During the double-blind period of the AIM trial, serious AEs (SAEs) occurring in patients receiving abatacept treatment compared with those receiving placebo were 15.0 versus 11.9%, respectively, and types of SAE and rates of discontinuation due to SAEs were similar between treatment groups (Table III) (53, 54). In the abatacept versus the placebo group, serious infections were reported in 11 (2.5%) versus two (0.9%) patients, no major autoimmune events were reported. Neoplasms (benign, malignant and unspecified) were reported in four (0.9%) patients in the abatacept group compared with two (0.9%) patients in the placebo group. Acute infusional reactions occurring in patients receiving

abatacept treatment compared with those receiving placebo were 38 (8.8%) versus nine (4.1%), respectively.

In patients with an inadequate response to TNF- α (ATTAIN trial), the frequencies of AEs and SAEs were similar in the abatacept- and placebo-treated patients during the double-blind period (Table III) (57). Discontinuations due to AEs and SAEs were low (<4%) and were comparable between treatment groups (Table III) (57). In the abatacept versus the placebo group, serious infections were reported in six (2.3%) versus three (2.3%) patients. Acute infusional reactions were reported in 5.0% of patients compared with 3.0% of patients in the abatacept and placebo groups, respectively. During the LTE period no additional or unexpected safety issues were observed compared with the double-blind period, and the types of AEs and SAEs remained similar between the double-blind and LTE periods. A lower proportion of patients with negative anti-nuclear antibody status were randomized to the abatacept group compared with the placebo group at baseline. A subsequently lower seroconversion to ANA-positive status was reported in the abatacept group compared with the placebo group at Month 6 (7.5 and 11.3% of patients, respectively) (58).

The safety and tolerability of abatacept ~10 mg/kg was also assessed in the ASSURE (Abatacept Study of Safety in Use with other RA therapies) trial,

a 1-year, randomized, double-blind, placebo-controlled, Phase III study designed to include patients that would be encountered in routine clinical practice (61). Patients had active RA and had been receiving at least one non-biological DMARD or anti-cytokine background RA therapy for ≥ 3 months prior to study entry (61). Overall, abatacept was generally well tolerated in the ASSURE trial (Table III). A similar frequency of AEs and SAEs were observed in abatacept- and placebo-treated patients. Discontinuations due to AEs were low and also similar between treatment groups (Table III) (61). When comparing abatacept-treated patients who received background non-biological DMARDs and those who received anti-cytokine therapy, there was an increase in discontinuations, AEs and SAEs in the abatacept plus anti-cytokine subgroup (Table III) (61). This is consistent with findings from a previous trial in which patients with RA who received combined abatacept and etanercept treatment experienced an increase in AEs and SAEs with no additional clinical benefit (62). Owing to the increased risk of infections, which outweighs the clinical benefits when prescribing abatacept with an anti-cytokine agent, combination therapy is not recommended (63).

An integrated safety analysis of five randomized, placebo controlled double-blind abatacept clinical trials that encompassed a total of 1687 patient-

years of abatacept exposure analysed in December 2006, showed an acceptable safety profile in this large amalgamated patient population (64).

Conclusions

The elaborate nature of the pathophysiology of RA and the heterogeneity of both disease processes and treatment outcomes within patient populations highlights a recurring theme within RA management: the need for additional treatment options with unique modes of action. Given that T-cell activation occurs at a pivotal point in the immune cascade of RA, influencing both inflammation and joint destruction, there is a strong rationale for therapies that target T-cell activity.

By selectively modulating T-cell co-stimulation, abatacept has a novel mode of action that differs from other approved therapies for RA, such as MTX and TNF- α antagonists, providing a potential treatment option for patients who have experienced an inadequate response to these therapies. Results from a number of trials have provided support for the rationale behind the selective modulation of T-cell co-stimulation with abatacept. Firstly, abatacept-treatment has been shown to influence multiple downstream cell types as evidenced by marked reductions in the levels of RA biomarkers, such as TNF- α , CRP and RF (52). Secondly, improvements in signs and symptoms of RA have been observed in multiple Phase II and Phase III trials (53, 57-60) in patients who had experienced an inadequate response to MTX therapy and/or TNF- α antagonist. Continued evaluation during LTE open-label studies in these trials have, to date, shown that these improvements have been sustained and illustrate the durability of treatment with this agent. In addition, abatacept demonstrated consistent and acceptable safety and tolerability across these studies. Thirdly, a significant inhibition of radiographic progression has been observed in patients with an inadequate response to MTX in the Phase III AIM trial, with an approximate 50% reduction in change from baseline in Genant-modified Sharp scores at Year 1 and a progressive effect of inhibition

throughout 2 years of the LTE period. In summary, there is an ongoing need for alternative agents with different modes of action in the treatment of RA. Selective modulation of T-cell co-stimulation is one such novel target for therapy. The combined efficacy and acceptable safety observed in clinical trials of abatacept support the use of abatacept for the treatment of patients with active RA who have shown inadequate response to, or intolerance of other DMARDs, including TNF- α antagonists.

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