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Abatacept

Prop INN; USAN

Treatment of Rheumatoid Arthritis
Agent for Systemic Lupus Erythematosus

BMS-188667
CTLA4-Ig
Orencia™

1-25-Oncostatin M (human precursor) fusion protein with CTLA-4 (antigen) fusion protein with immunoglobulin G1 (human heavy chain fragment)

CAS: 332348-12-6
EN: 217619

Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder resulting in joint destruction and severe disability. Despite the success of disease-modifying antirheumatic drugs (DMARDs), some patients fail to achieve a satisfactory response. Abatacept is the first in a new class of agents called selective T-cell co-stimulation blockers, and prevents the full activation of T-cells, thus preventing the production of cytokines and downstream immune responses in RA. Abatacept significantly inhibited effector function and proliferation of human T-cells *in vitro*. *In vivo*, it delayed the onset and progression of disease in a rat model of collagen-induced arthritis, with 90% inhibition of collagen-specific antibodies in these animals. In clinical studies in patients with active RA despite background treatment with methotrexate or anti-TNF therapy, ACR20 response rates were significantly higher in patients treated with abatacept for 6 months and 1 year, and the clinical response was maintained for up to 3 years. Abatacept was well tolerated in clinical studies, although a higher rate of infections has been observed in patients treated with abatacept and concomitant biological therapy. Abatacept was just recently approved by the FDA for the treatment of RA.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder characterized by symmetrical joint inflammation, often accompanied by extraarticular disease or systemic effects. It affects up to 1% of the population in many countries, with onset typically between the ages of 30 and 50 years. The progressive erosion of cartilage and bone leads to joint destruction and severe disability. Irreversible joint damage occurs early following onset of the disease, and therefore early initiation of treatment with disease-modifying antirheumatic drugs (DMARDs) is recommended by the American College of Rheumatology (ACR) (1, 2). There has been a dramatic improvement in treatments for RA, but despite the success of methotrexate, the most commonly prescribed DMARD, together with other targeted biological therapies, a proportion of patients still fail to achieve a satisfactory response according to ACR classification criteria (1).

Inflammation and joint destruction in RA are mediated by the activation of T-cells, resulting in the production of cytokines and the regulation of downstream immune responses. The activation of T-cells requires a dual signaling mechanism: the first is presentation of the major histocompatibility complex (MHC)-antigen complex by an antigen-presenting cell (APC) to an antigen-specific receptor on the T-cell, and the second is the so-called co-stimulatory signal. In the absence of this co-stimulatory signal, a state of T-cell anergy is produced in which T-cells are functionally inactivated or hyporesponsive. The most well-characterized co-stimulatory signal is that provided by CD28 binding to CD80 (B7-1) and CD86 (B7-2). A new class of agents called co-stimulation blockers prevents the second signal, thus preventing the inflammatory cascade in RA (3-5). The first agent in this class is abatacept (BMS-188667, Orencia™), a soluble fusion protein of cytotoxic T-lymphocyte-associated antigen 4 fused to the heavy-chain constant region of human IgG_1 (CTLA4-Ig) that binds CD80/CD86 with much greater affinity than CD28, thus blocking the engagement of the CD28 co-stimulatory signal required for T-cell activation (6). Abatacept was approved for use in the treatment of RA in December 2005 (7), and it is also in phase II development for systemic lupus erythematosus (SLE) (8).

Preclinical Pharmacology

Abatacept demonstrated dose-related immunosuppressive responses in mice challenged with sheep red

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blood cells (SRBCs). Following s.c. and i.v. administration of abatacept and SRBCs, complete suppression of antibody formation was observed between day 12 and day 29 regardless of the route of administration. Abatacept was more immunosuppressive following i.v. administration, as demonstrated by ED_{50} values (9, 10). Similarly, dose-related immunosuppressive activity was observed in monkeys challenged with SRBCs immediately following multiple i.v. doses of abatacept (1.0-8.7 mg/kg) (11).

Abatacept was evaluated in a rat model of collagen-induced arthritis. Rats immunized with bovine type II collagen in incomplete Freund's adjuvant were administered abatacept 1 mg/kg or control human IgG i.p. prior to immunization, then on alternate days until day 10. No paw swelling was observed in rats treated with abatacept compared with an increasing incidence of swelling in control animals up to day 21. Abatacept treatment resulted in 90% inhibition of collagen-specific antibodies and a decrease in the expression of circulating cytokines and chemokines, which were upregulated in control animals. Histological analysis on day 28 showed that abatacept significantly reduced all parameters evaluated: inflammation, pannus formation, cartilage damage and bone resorption. Immunohistochemical analysis suggested that IL-6 production in the joints was reduced. The normal appearance of the limb joints supported the protective effect of abatacept and its ability to inhibit the onset and progression of disease in an *in vivo* arthritis model (12-14).

Abatacept significantly inhibited effector function and proliferation of human T-cells in the context of a primary mixed lymphocyte reaction (MLR) using either irradiated human B-cells or monocyte-derived mature dendritic cells as APCs. Maximal inhibition was observed at concentrations between 3 and 10 μg/ml. Abatacept also inhibited cytokine production. However, abatacept had no effect on tumor necrosis factor (TNF-α) production by monocytes challenged with lipopolysaccharide (LPS) or immune complexes, indicating that innate antigen-specific immune responses were preserved (15, 16).

The effects of abatacept on renal pathology in murine lupus nephritis were also evaluated. Combined therapy with abatacept and cyclophosphamide effectively prevented the progression of renal damage, while monotherapy with abatacept slowed progression. Mice that received the combination had a decrease in proteinuria over the 4-week course of the study. The study also provided evidence that abatacept alone slowed the rate of progression of renal damage more effectively than cyclophosphamide alone, and that treatment with abatacept may reduce the need for sustained cyclophosphamide therapy in patients with lupus nephritis (17).

Pharmacokinetics and Metabolism

The pharmacokinetics of abatacept have been studied in mice, rats and monkeys.

In mice administered single s.c. doses of 0.5, 1.6 and 3.3 mg, peak plasma concentrations increased in a dose-proportional manner, whereas the increase in exposure (AUC) was less than proportional to dose; bioavailability decreased with an increase in dose, from 110% at the lowest dose to 78% at the highest dose. Absorption was prolonged, with a mean t_{max} of 9-24 h and $t_{1/2}$ values of 87-124 h (9, 10). The results from this and the following pharmacokinetic studies are summarized in Table I.

In other studies in mice, animals were administered single i.v. (0.29 mg) and s.c. (0.29 mg) doses. Following i.v. dosing, the drug was rapidly absorbed (t_{max} = 0.05 h) and distributed, but showed a prolonged elimination half-life (90 h). Absorption following s.c. dosing was prolonged, with peak serum levels being reached at 12 h, and relatively complete (bioavailability = 85%). Subsequent disposition characteristics were similar to after i.v. administration (18).

Further studies were performed in rats administered single (10, 80 or 200 mg/kg i.v. or s.c.) or repeated doses (10 mg/kg s.c. or i.v. once every other day over 13 days). Both C_{max} and AUC increased dose-proportionally after i.v. doses; clearance was dose-independent, but steady-state volume of distribution and elimination half-life increased with increasing dose. A linear but non-dose-proportional increase in C_{max} and AUC values was observed after s.c. dosing; t_{max} was prolonged and similar after all doses (36-48 h), whereas $t_{1/2}$ increased with dose (from 74.4 h on 10 mg/kg to 167 h on 200 mg/kg). The bioavailability after s.c. administration decreased with increasing dose (from 62.5% on 10 mg/kg to 41.1% on 200 mg/kg). Repeated dosing did not appear to alter the pharmacokinetics of abatacept. Anti-CTLA4-Ig antibody titers were higher following s.c. as compared to i.v. administration (19).

The pharmacokinetics of abatacept were examined in cynomolgus monkeys administered 1.0, 2.9 or 8.7 mg/kg i.v. on days 1, 4, 8, 11, 15 and 18. Steady state was reached by day 11 on all doses and pharmacokinetics were linear. No significant differences in $t_{1/2}$ values (mean = 90-160 h) were observed among the doses (11).

Safety

Safety data from the five randomized, double-blind studies comprising two 1-year phase II trials and three phase III trials of 6 or 12 months' duration were pooled and analyzed. In this population of almost 2,000 patients who received abatacept, the overall incidence of death and serious adverse events was similar between the groups. The most frequently reported adverse events were headache, upper respiratory tract infections, nausea and nasopharyngitis. There were small increases in the incidence of infection and serious infection, particularly evident in patients who received abatacept in combination with a biological DMARD (20).

Clinical Studies

In an open, single-center, mechanism of action study conducted in 12 patients with inadequate responses to at

Table I: Pharmacokinetics of abatacept (from Prous Science Integrity®).

Dose (mg or mg/kg)	AUC (g.h/l)	C_{max} (g/l)	t_{max} (h)	F (%)	Cl (ml/h or ml/h/kg*)	$t_{1/2}$ (h)	V_{ss} (ml or l/kg*)
			mice				
0.29 mg s.c. sd	7.2	0.06	12	85		77	
0.5 mg s.c. sd	15.8	0.10	24	110		87	
1.6 mg s.c. sd	45.2	0.32	12	98		124	
3.3 mg s.c. sd	73.8	0.73	9	78		97	
			rats				
10 mg/kg i.v. sd	8.9	0.24				80	0.2*
10 mg/kg i.v. 1/2d 13d		0.41				115	
80 mg/kg i.v. sd	63.2	2.16				108	0.2*
200 mg/kg i.v. sd	138.6	4.61				133	0.2*
10 mg/kg s.c. sd	5.5	0.03	48			74	
10 mg/kg s.c. 1/2d 13d		0.10				96	
80 mg/kg s.c. sd	35.2	0.13	48			132	
200 mg/kg s.c. sd	56.9	0.26	36			167	
			monkeys				
1 mg/kg i.v. 2/wk 3wk	2.8	0.03				90	
2.9 mg/kg i.v. 2/wk 3wk	8.8	0.10			0.7*	160	0.1*
8.7 mg/kg i.v. 2/wk 3wk	25.8	0.27			0.7*	135	0.1*

AUC, area under the concentration-time curve; C_{max}, peak plasma concentration; t_{max}, time to reach peak plasma concentration; F, bioavailability; Cl, plasma clearance; $t_{1/2}$, elimination half-life; V_{ss}, steady-state volume of distribution.

least 3 months of anti-TNF therapy, abatacept treatment was associated with significant decreases in synovial sublining layer infiltration by inflammatory cells. Expression of T-cell and macrophage cytokines and RANK was significantly decreased following abatacept treatment, demonstrating its global effect on a number of genes involved in inflammation (21).

The preliminary efficacy of abatacept in RA was demonstrated in a double-blind, randomized, placebo-controlled, dose-finding pilot trial in 214 patients who had been treated unsuccessfully with at least one DMARD. Abatacept or the second-generation molecule belatacept (LEA-29Y) was administered at doses of 0.5, 2 or 10 mg/kg i.v. on days 1, 15, 29 and 57. The primary efficacy endpoint of ACR criteria for 20% improvement (ACR20) on day 85 increased dose-dependently and was achieved by 23%, 44% and 53% of patients, respectively, treated at abatacept doses of 0.5, 2 and 10 mg/kg, compared with 31% of patients given placebo; respective values for belatacept were 34%, 45% and 61%. Changes in the other ACR core data set variables and in morning stiffness consistently favored the active treatments over placebo, and were more pronounced at the higher doses. The safety profile of abatacept was comparable with placebo and no drug-specific antibodies were detected at any time point (22, 23). The results from this and the following studies are summarized in Table II.

In a randomized, double-blind, placebo-controlled phase IIb trial, abatacept was evaluated in 339 patients with active RA despite methotrexate treatment. Patients were randomized to receive abatacept 10 mg/kg (n=115), abatacept 2 mg/kg (n=105) or placebo (n=119) administered i.v. on days 1, 15 and 30 and every 30 days thereafter over a 12-month period. Patients had been treated with a stable dose of methotrexate for 1 month prior to entry and continued on therapy (10-30 mg/week) for the duration of the study. The primary efficacy endpoint of an ACR20 response at 6 months was achieved in 60%, 41.9% and 35.3% of patients who received abatacept 10 mg/kg, abatacept 2 mg/kg and placebo, respectively. The ACR50 and ACR70 response rates were also significantly higher in both abatacept treatment groups compared to the placebo group at 6 months. A significantly greater proportion of patients treated with 10 mg/kg abatacept achieved an ACR20 response at 1 year (62.6% *vs*. 36.1% on placebo), but no significant differences in ACR20 responses were observed in the lower dose group relative to placebo, indicating that this dose was suboptimal. The clinical efficacy of abatacept correlated with decreases in biomarkers measured during the study, as demon-

Table II: Clinical studies of abatacept (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Abatacept, 0.5 mg/kg i.v. o.d. x 4 d (n=26) Abatacept, 2 mg/kg i.v. o.d. x 4 d (n=32) Abatacept, 10 mg/kg i.v. o.d. x 4 d (n=32) Belatacept, 0.5 mg/kg i.v. o.d. x 4 d (n=32) Belatacept, 2 mg/kg i.v. o.d. x 4 d (n=29) Belatacept, 10 mg/kg i.v. o.d. x 4 d (n=31) Placebo (n=32)	214	Abatacept and belatacept were well tolerated and effective, showing a dose-dependent response in patients with rheumatoid arthritis	22, 23
Arthritis, rheumatoid	Randomized Double-blind	Abatacept, 2 mg/kg/mo i.v. + Methotrexate x 12 m Abatacept, 10 mg/kg/mo i.v. + Methotrexate x 12 mo Placebo + Methotrexate x 12 mo	339	A monthly i.v. dose of abatacept 10 mg/kg was significantly more effective than placebo or a drug dose of 2 mg/kg in improving physical function, especially eating, hygiene, grip and walking, and quality of life evaluated using the Medical Outcomes Study Short Form-36 questionnaire in rheumatoid arthritis patients	24-34
Arthritis, rheumatoid	Open	Abatacept, 10 mg/kg i.v. 1x/mo + Methotrexate x 2 y Placebo + Methotrexate x 1 y → Abatacept, 10 mg/kg i.v. 1x/mo + Methotrexate x 1 y	84	The combination of abatacept and methotrexate demonstrated sustained clinical efficacy at 2 years in patients with rheumatoid arthritis and inadequate response to methotrexate	37, 38
Arthritis, rheumatoid	Randomized Double-blind	Abatacept, 2 mg/kg/mo i.v. + Etanercept, 25 mg 2x/wk x 6 mo (n=85) Placebo + Etanercept, 25 mg 2x/wk x 6 mo (n=36)	121	The clinical efficacy demonstrated by the combination of abatacept and etanercept in patients with rheumatoid arthiritis not responding to etanercept alone correlated with changes in biomarkers	44-47
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Abatacept, 10 mg/kg on d 1, 15 & 29 → 1x/28 d + Background therapy x 6 mo (n=256) Placebo + Background therapy x 6 mo (n=133)	391	Abatacept given for 6 months was well tolerated and significantly improved tender and swollen joint counts, patient-reported pain scores, patient-assessed disability, fatigue, sleep quality and serum C-reactive protein levels in patients with rheumatoid arthritis unresponsive to background anti-TNF therapy	50, 53, 60
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Abatacept, 10 mg/kg [approx.] on d 1, 15 & 29 → 1x/28 d + Methotrexate x 1 y (n=433) Placebo + Methotrexate x 1 y (n=219)	652	Abatacept was safe, well tolerated and effective in reducing signs, symptoms and disease progression (measured using erosion and joint space narrowing scores) in patients with active rheumatoid arthritis inadequately controlled with methotrexate	61-65, 67-71
Arthritis, rheumatoid	Randomized Double-blind Multicenter Pooled/meta-analysis	Abatacept, 10 mg/kg + Background DMARD therapy x 6 mo (n=256) Abatacept, 10 mg/kg + Background methotrexate therapy x 1 y (n=424) Placebo + Background DMARD therapy x 6 mo (n=133) Placebo + Background methotrexate therapy x 1 y (n=214)	1027	Compared to placebo, abatacept was well tolerated and significantly improved the participation in daily activities of patients with rheumatoid arthritis unresponsive to background methotrexate or anti-TNF therapy. Abatacept also decreased the serum levels of several proinflammatory mediators, T-cell activation markers and immunopathology markers	72, 73
Arthritis, rheumatoid	Randomized Double-blind	Abatacept, 10 mg/kg 1x/mo + Nonbiological DMARDs x 1 y (n=856) Abatacept, 10 mg/kg 1x/mo + Biological DMARDs x 1 y (n=103) Placebo + Nonbiological DMARDs x 1 y (n=418) Placebo + Biological DMARDs x 1 y (n=64)	1441	Abatacept was effective in improving physical function, disease activity and pain scores of patients with rheumatoid arthritis receiving background DMARD therapy, especially in those taking nonbiological *versus* biological DMARDs; safety was also superior in patients taking nonbiological DMARDs	74-76

strated by reductions in C-reactive protein (CRP), soluble IL-2 receptor (sIL-2R) and IL-6 at both 6 and 12 months. Among ACR20 responders, there was a dose-related decrease from baseline in CRP, rheumatoid factor (RF), sIL-2R, IL-6 and ICAM-1 at 6 and 12 months. There were also statistically significant and clinically meaningful benefits for abatacept in terms of improvements in physical function, as measured by the Modified Health Assessment Questionnaire (M-HAQ), and in health-related quality of life, as assessed by the Medical Outcomes 36-Item Short-Form General Health Survey (SF-36), at both 6 and 12 months. The safety profile of both doses of abatacept was similar to that of placebo over 1 year and no significant formation of neutralizing antibodies was observed (24-34). In addition, minimum serum abatacept concentrations (C_{min}) measured at predefined time points throughout the first 6 months of the study were 7-10-fold higher than the concentration shown to inhibit T-cell proliferation *in vitro* (35, 36).

Patients who completed the 1-year phase II study were eligible to enter a 1-year open-label extension phase. Patients continued to receive a fixed dose of abatacept of approximately 10 mg/kg i.v. monthly + methotrexate or placebo + methotrexate. A total of 75 patients completed 2 years of treatment. The ACR20, ACR50 and ACR70 response rates did not differ significantly at the end of 1 and 2 years; ACR20 response rates were 76% and 77% at 1 and 2 years, respectively. At 2 years, 25% of patients had achieved a major clinical response, defined by an ACR70 response for 6 consecutive months. Almost half of the patients achieved remission, as defined by a disease activity score in 28 joints (DAS28) of < 2.6 at 1 year, which was maintained to 2 years. The safety and tolerability of the combination of abatacept with methotrexate was maintained at 2 years in this study. The rates of adverse events and serious adverse events at 2 years were similar to those observed at 1 year, and there was a low rate of discontinuations due to adverse events (37-39). Patients could continue to receive abatacept for 1 further year. The results demonstrated that the efficacy and tolerability of abatacept were maintained through a total of 3 years, thus supporting its long-term use in combination with methotrexate in RA patients with an inadequate response to methotrexate (40-43).

A further randomized, double-blind, placebo-controlled phase IIb study evaluated the safety and efficacy of abatacept 2 mg/kg or placebo over 6 months in 121 patients with active RA and receiving the anti-TNF therapy etanercept (25 mg twice weekly). The modified ACR20 response rates were 48% and 28% in the abatacept and placebo groups, respectively ($p < 0.05$). Patients in the abatacept group also demonstrated significantly greater increases in the physical and mental component summaries of the SF-36 compared with placebo-treated patients. Measurement of biomarkers demonstrated a greater reduction from baseline in CRP, sIL-2R, IL-6, E-selectin, matrix metalloproteinase (MMP) and ICAM-1 at 6 months compared with placebo (44-47).

The dynamics of response to abatacept were evaluated in a randomized, placebo-controlled phase II study in 161 patients with active RA. Patients on background methotrexate received either abatacept 10 mg/kg (n=90) or placebo (n=71) for 1 year. ACR20, ACR50 and ACR70 scores were consistently higher in the abatacept group than the placebo group from day 30 onwards, as evaluated monthly to 6 months and every 2 months up to 1 year. At 1 year, ACR20 and ACR50 were achieved by 80% and 53%, respectively, of abatacept-treated patients compared with 60% and 34%, respectively, of placebo-treated patients ($p < 0.001$). Discontinuation rates for abatacept were approximately half those seen in the placebo group, and overall, the safety profile of abatacept was similar to that of placebo (48, 49).

The ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate responders) was a randomized, double-blind, placebo-controlled phase III trial in 391 patients with active RA who had an inadequate response to anti-TNF-α therapy after at least 3 months of treatment. Patients discontinued anti-TNF-α therapy before randomization and all patients continued to receive at least one DMARD at a stable dose throughout the study. Patients received either abatacept 10 mg/kg (n=258) or placebo (n=133) in a 2:1 ratio on days 1, 15 and 29, and every 28 days thereafter for 6 months. The ACR20 response rates were 50.4% in the abatacept group and 19.5% in the placebo group at 6 months ($p < 0.001$). The ACR50 and ACR70 response rates at 6 months were also significantly higher in the abatacept group than in the placebo group. The proportion of patients with an improvement of at least 0.3 from baseline in the HAQ disability index was also a primary efficacy endpoint. Significantly more patients in the abatacept group achieved this endpoint (47.3% *vs*. 23.3% in the placebo group; $p < 0.001$), thus demonstrating a clinically meaningful improvement in physical function in patients treated with abatacept. In addition, rates of remission at 6 months were significantly higher in the abatacept group than in the placebo group (10% *vs*. 0.8%; $p < 0.001$) and patients in the abatacept group had significantly greater improvements from baseline in scores for all 8 physical and mental subscales of the SF-36. Assessment of fatigue severity and sleep quality showed that abatacept was also effective in improving these parameters. The clinical benefits of abatacept were observed irrespective of disease duration, previous anti-TNF therapy (etanercept, infliximab or both), and time since discontinuation of anti-TNF therapy. The efficacy of abatacept was also maintained throughout a 1-year, open, long-term extension study of the ATTAIN trial. The incidence of adverse events or serious infections was similar in the two groups (50-60).

The AIM (Abatacept in Inadequate responders to Methotrexate) trial was a further randomized, double-blind, placebo-controlled phase III trial. Patients with active RA despite methotrexate treatment received abatacept 10 mg/kg (n=433) or placebo (n=219) on days 1, 15 and 29, and every 28 days thereafter for 1 year. ACR20 response rates at 6 months (the primary efficacy

endpoint) were 67.9% in the abatacept group *versus* 39.7% in the placebo group ($p < 0.001$). The ACR50 and ACR70 response rates at 6 months and 1 year were also significantly higher in the abatacept group than in the placebo group. Disease remission rates and clinically meaningful improvements in physical function assessed by HAQ were significantly higher in the abatacept group. The clinical responses to abatacept were observed irrespective of disease duration or baseline disability levels. Radiographic evaluation showed that abatacept significantly inhibited structural damage progression, as demonstrated by reductions in the progression of erosions and joint space narrowing. The inhibition of structural damage progression was observed in all patients irrespective of disease duration, although the greatest effect was observed in patients with recent-onset disease (2 years or less). The effect on structural damage progression was also observed in the absence of an ACR20 response at 6 months. There were clinically meaningful and statistically significant improvements in all 8 subscales of the SF-36 in abatacept-treated patients. Sleep quality was significantly improved and fatigue was reduced. Abatacept was generally safe and well tolerated in this study (40-43, 61-71).

Analysis of pooled data from the AIM and ATTAIN studies showed that abatacept was significantly more effective than placebo in improving patients' ability to participate in daily activities. Cumulative gains in the number of days on which patients were able to carry out their daily activities were 39 days over 6 months for ATTAIN and 101 days over 1 year for AIM. The data indicated that patients would potentially be able to gain approximately 3 active months per year (72). Abatacept treatment was also associated with marked reductions in the serum levels of multiple downstream inflammatory biomarkers and mediators of joint destruction, including RF, IL-6 and MMP-3 (73).

The ASSURE (Abatacept Study of Safety in Use with other Rheumatoid arthritis thErapies) was a randomized, double-blind phase III trial assessing the safety of abatacept during 1 year of add-on treatment with one or more biological or nonbiological DMARDs. A total of 1,441 patients with active RA received either abatacept 10 mg/kg or placebo. The incidence of adverse events and serious adverse events was similar in all groups, as were discontinuations due to adverse events. The overall incidence of adverse events, however, was highest in the group receiving abatacept and biological DMARDs (n=103), and the incidence of serious adverse events and prespecified infections and serious infections was also higher in this group of patients. The most frequently reported adverse events were headache, dizziness, urinary tract infections, dyspnea, peripheral edema and pharyngolaryngeal pain. There were also significant improvements from baseline in physical function (HAQ), disease activity and pain scores in patients treated with abatacept compared with placebo. The greatest differences between abatacept and placebo were observed when abatacept was combined with nonbiological DMARDs (74-76).

Source

Bristol-Myers Squibb Company (US).

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