

Abatacept (CTLA4-Ig, Orencia): An Investigational Biological Compound for the Treatment of Rheumatoid Arthritis



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INTRODUCTION

Rheumatoid arthritis (RA) is the most common systemic inflammatory autoimmune disease. Characterized by symmetrical joint involvement, RA can cause irreversible joint deformities and functional impairment. The estimated prevalence is 1% to 2%, and there is no racial predilection.¹ The disease appears to be two to three times greater in women.² Its onset is usually earlier in women, commonly beginning in the childbearing years.³

Chronic inflammation of the synovial tissue lining the joint capsule results in the proliferation of this tissue and synovium-lining cells, resulting in synovial hyperplasia and neovascularization. Inflammatory cells in the synovial tissue of patients with RA include macrophages, B and T lymphocytes, and plasma cells.

The proinflammatory cytokines—tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6)—are key substances in the initiation and continuation of rheumatoid inflammation.² Cytokine release in the synovium is the result of CD4+ T cells being activated by arthritogenic antigens associated with major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (APCs).⁴

The symptoms of RA usually develop insidiously over the course of several weeks to months. Prodromal symptoms include fatigue, weakness, low-grade

fever, loss of appetite, and joint pain. Stiffness and muscle aches may precede the development of joint swelling. The small joints of the hands, wrists, and feet are most commonly affected in RA. The knee can also be involved, with loss of cartilage, instability, and joint pain.^{1,5} Extra-articular involvement, including rheumatoid nodules, vasculitis, eye inflammation, neurological dysfunction, cardiopulmonary disease, lymphadenopathy, and splenomegaly, are manifestations of the disease.^{1,6}

Traditional pharmacological therapies for RA have included nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), such as gold salts, D-penicillamine, hydroxychloroquine, azathioprine, cyclosporine, sulfasalazine, and methotrexate (MTX). Recent advances in understanding the cytokine networks that are responsible for the ongoing inflammatory response in RA have led to the development of biological response modifiers (BRMs).^{7,8} BRMs that have been approved for the treatment of RA include adalimumab (Humira®, Abbott), etanercept (Enbrel®, Amgen/Wyeth), and infliximab (Remicade®, Centocor), which are inhibitors of TNF- α , and anakinra (Kineret®, Amgen), which is a recombinant IL-1 receptor antagonist.

Although DMARDs and TNF- α inhibitors can slow disease progression in RA, only two-thirds of patients respond to therapy.⁹ Nearly seven years after infliximab was introduced on the market, new hope is finally emerging with the development of biological therapies. The efficacy of these agents in RA has been demonstrated in recently published randomized, placebo-controlled trials involving a monoclonal antibody to the IL-6 receptor (MRA), a monoclonal B-cell-specific antibody to CD20 (rituximab [Rituxan®, Biogen/Genentech]),

and a cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin (CTLA4-Ig), also called abatacept. Abatacept (Orencia, Bristol-Myers Squibb) is a fusion protein in a new class of drugs called the *co-stimulation modulators*.^{9,10}

PATHOPHYSIOLOGY

The hallmark of a vertebrate immune system is the ability to discriminate between self and nonself. This property has led to the evolution of a system requiring multiple signals to achieve optimal activation of immunocompetent cells. More than 20 years ago, it was proposed that B-lymphocyte activation requires two signals. Now it is believed that all lymphocytes require both an antigen-specific signal and a nonspecific signal.^{10,11}

Pathogenic elements thought to be critical in the perpetuation of disease have become key therapeutic targets. These include:¹²

- adhesion molecules.
- chemokines.
- inflammatory cell subsets (T cells, B cells, dendritic cells, macrophages, synovial blasts).
- co-stimulatory molecules.
- cytokines.
- angiogenesis factors.
- proteolytic enzymes.
- the intracellular signal transduction cascade that generates proinflammatory molecules.

CD4+ T CELLS

T cells can be divided into two types: CD4+ and CD8+.

CD8+ cells have traditionally been known as “suppressor” or “cytotoxic” T cells. These terms reflect their ability to down-regulate the effects of CD4+ cells and to kill virally infected cells.

The CD4+ cells, the classic “helper”

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cells, are crucial, for example, for antibody production and activation of cytotoxic immune responses. They are also the dominant T cells in inflammatory infiltrates in the synovia of RA patients.¹⁰ The impact of this role is further substantiated by the fact that MHC class II is also abundantly expressed in the rheumatoid synovium; thus, T cells have the potential to become reactivated locally in the joints.¹³

In response to activation by antigen presentation, CD4+ cells initiate and regulate several cell-mediated immune processes that cause the synovial inflammation and joint destruction characteristic of RA. Activated CD4+ cells release chemical mediators such as interferon-gamma (IFN- γ) and IL-17, which stimulate the activity of other immune cells (such as B cells, monocytes, macrophages, and fibroblasts). These stimulated immune cells then release a second set of chemical mediators that induce inflammation and joint damage, including IL-1, IL-6, TNF- α , matrix metalloproteinases (MMPs), prostaglandins, nitric oxide, and other substances that destroy connective tissue.¹⁴

CD4+ T cells also activate macrophages and chondrocytes in the synovium by direct cell-to-cell interactions that are mediated by cell-surface receptor molecules.

CD4+ cells stimulate the production of antibodies, including rheumatoid factor, by B cells and promote the proliferation of bone-resorbing osteoclasts, which contribute to further bone injury.

Although T cells are the most abundant inflammatory cells in the joints of RA patients and exhibit phenotypic markers of activation, there is little or no evidence of the efficacy of anti-CD4+ T-lymphocyte strategies, and significant toxicities have been observed. However, it is possible that modulation of T-cell function, perhaps by altering the stimulatory pathway, might be beneficial. An approach in which the activity of antigen-specific T cells is controlled by targeting co-stimulatory molecules has now been developed, and several studies have shown its effectiveness in controlling the clinical signs and symptoms of RA.^{11,15}

CO-STIMULATORY ACTIVATION OF T CELLS

Two distinct signals are required for

the activation of T cells. The first is an antigen-specific interaction between the T-cell receptor and the nominal antigen presented in the context of the MHC on the surface of an APC. The second (co-stimulation) signal is delivered by the interaction between a cell-surface receptor on the T cell (CD28) with its ligands CD80 and CD86 on the APC.^{14,16} Co-stimulatory activation initiates the induction of the IL-2 cytokine, stimulates cell proliferation, activates T-cell effector functions, and triggers cell-signaling pathways that promote cell survival. In addition, co-stimulation (the second signal) results in clonal expansion of the T-cell line and initiates differentiation of some T cells into the T-cell "memory" line.

CTLA4-Ig STRUCTURE AND FUNCTION

Multiple co-stimulation pathways regulate T-cell function both positively and negatively. Among the stimulatory pathways, the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) cell-surface molecule, expressed by activated T cells, shares about 30% of the amino acid sequence that makes up CD28 and binds to the same APC ligands, CD80 and CD86, that bind to CD28.^{14,16,17}

Roughly 36 to 72 hours after initial T-cell activation, the cells or cells within the expanding population start to express endogenous CTLA4-Ig on their surface; this has a net result of decreasing the activated T-cell pool.

CTLA4-Ig is constructed by genetically fusing the external domain of human CTLA4 and a fragment of the Fc domain of human immunoglobulin G1 (IgG1), which has been modified to be non-complement-fixing. By blocking the engagement of CD28, CTLA4-Ig prevents the delivery of the second co-stimulatory signal that is required for the optimal activation of T cells.¹⁵ Blocking the second signal is a novel therapeutic concept that has led to the development of the drug abatacept.

APPROVAL STATUS AND POTENTIAL INDICATIONS

Abatacept is not yet approved for the treatment of RA in the U.S. The Biologics License Application for abatacept is

currently under review at the U.S. Food and Drug Administration (FDA). On September 6, 2005, the FDA's Arthritis Advisory Committee recommended approval of the agent for this use.¹⁸

Because some of the same medications that work for RA also relieve psoriasis, some advocacy groups would like to see an indication for this use with abatacept. A small study has been conducted on psoriasis (see Clinical Development, next column).²⁵

PRECLINICAL STUDIES Autoimmune Disease

CTLA4 shares significant sequence homology between the human and mouse (murine) versions of the molecule, so that fusion compounds containing this ligand can be effectively studied in murine models of a variety of human diseases.¹⁶ CTLA4-Ig has been used with success in animal models of autoimmune disease. It has been studied in preclinical transplant models as well as in models of systemic lupus erythematosus, experimental allergic encephalitis (a murine model of multiple sclerosis), and collagen-induced arthritis. Administering doses of CTLA4-Ig to mice delayed the onset of lupus manifestations, as measured by the development of proteinuria and histological evidence of renal disease.^{16,19} In mouse models of arthritis, CTLA4-Ig prevented the development of collagen-induced arthritis and was effective in its treatment.^{8,20,21}

The ability of abatacept to suppress deleterious immune responses has been extensively investigated in rodent models of transplant rejection. An early study demonstrated that abatacept therapy could block rejection of human pancreatic islet grafts in mice by preventing T-cell recognition.²² In several subsequent studies, abatacept prolonged the survival of diverse types of vascularized solid-organ allografts, including heart, kidney, liver, intestine, and lung.^{23,24}

Toxicity

No toxicity was observed in animal models. Abatacept was well tolerated in nonhuman primates and rodents and did not cause general immunosuppression or alterations in hematological parameters.²² However, as abatacept is a modulator of T-cell function, some degree of systemic alteration is expected.

Table 1 Adverse Drug Events Occurring up to Day 85 after Abatacept (CTLA4-Ig) Therapy for Rheumatoid Arthritis

Event	Placebo	CTLA4-Ig
Headache	1 (3.1%)	8 (8.9%)
Nausea and vomiting	2 (6.3%)	5 (5.6%)
Fatigue	1 (3.1%)	4 (4.4%)
Arthritis	3 (9.4%)	4 (4.4%)
Hypotension	2 (6.3%)	3 (3.3%)

Adapted from Moreland L, Alten R, Bosch F, et al. *Arthritis Rheum* 2002;46(6):1470-1479. Reproduced with permission from John Wiley & Sons, Inc.¹¹

hepatic, or hematological adverse drug events (ADEs) were observed during the trial. Overall, 173 of 214 patients (81%) reported ADEs during the treatment period, and 129 patients reported ADEs during the follow-up period (Table 1).¹¹ Clinical and laboratory evaluation in this study generally demonstrated efficacy for abatacept in the treatment of signs and symptoms of RA.

Kremer et al.²⁸

A double-blind, randomized, placebo-controlled investigation of the effectiveness of abatacept was performed in 339 patients with RA who had not responded to previous MTX therapy.^{15,28} Patients were randomly assigned to receive 10 mg/kg of abatacept, 2 mg/kg of abatacept, or placebo on days 1, 15, and 30, and monthly thereafter for six months. All patients continued to receive a stable dose of MTX (10-30 mg/week) and, if required, a low dose of corticosteroids (10 mg/day) and NSAIDs.

After six months, ACR 20 (20% improvement), ACR 50 (50% improvement), and ACR 70 (70% improvement) responses were significantly higher with abatacept 10 mg/kg than with placebo. Patients receiving abatacept 2 mg/kg did not demonstrate any ACR 20 responses that differed significantly from those taking placebo, but they did achieve significantly higher ACR 50 and ACR 70 responses.^{15,28}

Weinblatt et al.²⁹

Another study was conducted to evaluate the efficacy of abatacept in RA patients whose disease remained active despite treatment with etanercept. In this six-month, double-blind, placebo-

CLINICAL DEVELOPMENT

Phase I (Psoriasis)

Abrams et al.²⁵

A multicenter, open-label, dose-escalation study was conducted in 43 patients with moderate-to-severe psoriasis. The patients received four intravenous infusions of abatacept on days 1, 3, 16, and 29 and were observed for up to 26 weeks after treatment.²⁵ Overall, 46% of the treated patients achieved greater than 50% improvement in disease activity, compared with baseline values; only 4% of 23 control patients achieved this response.²⁵

Abrams et al.²⁶

Skin biopsy analyses have demonstrated that clinical improvement was associated with reduced cellular activation of T cells, keratinocytes, and vascular endothelium in the psoriatic lesions. There was also a reduction in CD80, CD86, and MHC class II expression of dendritic cells and a decrease in their numbers within the psoriatic lesions.²⁶

Although abatacept was well tolerated in this study, there have been no reports

of its use in treating psoriasis since January 2003.

Phase 2 (Rheumatoid Arthritis) Olle²⁷

In a double-blind, placebo-controlled pilot trial, abatacept was administered to 214 patients with RA whose disease had not been controlled with standard DMARDs.²⁷ Patients were given 0.5, 2, or 10 mg/kg of CTLA4-Ig as monotherapy. Infusions were administered on days 1, 15, 29, and 57. Patients were evaluated on day 85, with a follow-up period extending to day 169.²⁷

The primary efficacy endpoint was the proportion of patients meeting the American College of Rheumatology 20% improvement criteria (ACR 20). For patients who completed the study to day 85, there was a dose-dependent improvement in ACR 20 responses after abatacept treatment, reaching a response rate of 23% with 0.5 mg/kg, 44% with 2 mg/kg, 53% with 10 mg/kg, and 31% with placebo.²⁷

Abatacept infusions were well tolerated at all dose levels. No notable renal,

Table 2 Mean Percent Improvement from Baseline in American College of Radiology Components after Abatacept and Placebo Therapy for Rheumatoid Arthritis

	1 Month		3 Months		6 Months		12 Months	
	Abatacept	Placebo	Abatacept	Placebo	Abatacept	Placebo	Abatacept	Placebo
Tender joints	31.9	25.4	52.8	34.9	62.6	40.7	68.8	42.1
Swollen joints	33.5	27.2	54.7	33.2	65.0	39.5	70.5	42.4
Pain	19.8	2.9	39.5	5.2	42.5	3.5	50.5	8.0
Physical function	15.8	12.7	30.2	21.3	35.2	20.9	37.3	19.6
Patient global	21.2	2.9	39.6	16.6	42.0	13.7	48.3	19.6
Physician global	33.1	21.4	53.6	36.1	62.2	36.5	68.0	37.9

Adapted from Steinfield S, Moreland L, Abud C, et al. *Ann Rheum Dis* 2005;64:457-471. Reproduced with permission from the British Medical Journal Publishing Group.³⁰

Table 3 Joint Space Narrowing Scores and Total Scores in Placebo and Abatacept Patients with an Inadequate Response to Methotrexate (MTX)

Change from baseline		Abatacept + MTX	Placebo + MTX
Erosion score	Mean (SD) Median	0.63 (1.77)	1.14 (2.81)
	(25th, 75th percentile)	0.00 (0.00, 1.02)	0.27 (0.00, 1.27)
Joint space narrowing score	Mean (SD) Median	0.58 (1.54)	1.18 (2.58)
	(25th, 75th percentile)	0.00 (0.00, 0.49)	0.00 (0.00, 0.97)
Total score	Mean (SD) Median	1.21 (2.94)	2.32 (5.04)
	(25th, 75th percentile)	0.25 (0.00, 1.78)	0.53 (0.00, 2.54)

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controlled trial, all patients continued to receive etanercept 25 mg twice weekly in addition to once-monthly infusions of either abatacept 2 mg/kg or placebo.²⁹

A total of 48.2% of patients receiving abatacept achieved ACR 20 responses, compared with 27.8% receiving placebo. The addition of abatacept to etanercept also resulted in improved quality of life for these patients.²⁹

Phase 3

Data from two large phase 3 studies of abatacept in RA were presented at the European League Against Rheumatism (EULAR) Congress held in Vienna, Austria, in June 2005.

Steinfeld et al.³⁰ (AIM)

The first study examined the individual components of the ACR criteria over time in RA patients in the Abatacept in Inadequate responders to Methotrexate (AIM) trial. This one-year, randomized, double-blind, placebo-controlled trial included 652 patients with an inadequate response to MTX.³⁰ Patients were randomly assigned to receive either placebo or a fixed dose of abatacept 10 mg/kg while continuing their MTX therapy. At one year, 73.1% of these patients achieved ACR 20 responses, 48.3% achieved ACR 50 responses, and 28.8% achieved ACR 70 responses with the active drug. The corresponding rates for the placebo patients were 39.7%, 18.2%, and 6.1%, respectively.³⁰ Significant improvements were also observed by three months in all ACR components; these continued to increase through six and 12 months (Table 2).

Radiographic evaluation showed significant reductions in the progression of erosions, joint space narrowing, and total scores with abatacept compared with placebo (Table 3). Abatacept was generally safe and well tolerated in this population.

Genovese et al.³¹ (ATTAIN)

The Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN) evaluated the efficacy and safety of abatacept for a period of six months in patients with active RA and an inadequate response to TNF inhibitors. The patients were randomly assigned to receive abatacept 10 mg/kg or placebo on days 1, 15, and 29 and every 28 days thereafter for six months in addition to at least one DMARD. Patients discontinued anti-TNF- α therapy before randomization.

After six months of treatment, 50.4% of the patients receiving abatacept achieved ACR 20 responses, compared with 19.5% of the patients receiving placebo. In addition, 20.3% of patients in the abatacept group achieved ACR 50 responses and 10.2% achieved ACR 70 responses. By contrast, 3.8% of the patients taking placebo achieved ACR 50 responses and 1.5% reached ACR 70 responses.

Remission rates were also measured; after 24 weeks of therapy, 10% of abatacept patients achieved remission, compared with 0.8% of those receiving placebo.

In the ATTAIN trial, the incidence of adverse events was similar between abatacept and placebo. The most common adverse reactions were headache and nasopharyngitis.

ADVERSE EVENTS AND CONTRAINDICATIONS

Abatacept treatment was not associated with any major adverse effects in the clinical trials. The most frequently reported ADEs included headache, upper respiratory tract infection, musculoskeletal pain, nausea, and vomiting. These ADEs occurred at comparable rates in the abatacept and placebo groups.²²⁻²⁴ Clinically significant adverse complications of immunosuppression, such as opportunistic infections and malignancy, were not observed.

The FDA Advisory Committee plans to consider the increased risk of infection when the drug is administered concomitantly with other anti-TNF agents. The FDA also appears concerned about the increased risk for lung cancer. The number of overall malignancies has been “less than expected” in a healthy population; however, RA patients are known to have higher rates of malignancies than non-RA patients. There was a higher incidence of lung cancer and lymphoma than the rate expected.³²

CONCLUSION

Abatacept, a fusion protein combining the extracellular portion of human CTLA4 and IgG, has clearly been shown to be effective at controlling the signs and symptoms of RA, particularly at a dose of 10 mg/kg given monthly. Clinical trials have not shown an increase in ADEs compared with placebo.

Further studies are warranted to confirm the long-term safety of this therapy as a component of combination regimens

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for the treatment of RA. As a co-stimulatory modulator, abatacept represents a potentially effective new approach for the treatment and management of RA and psoriasis.

The submission for abatacept was for RA only, and the FDA approval is still pending.

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