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Review Article

ABATACEPT IN RHEUMATOID ARTHRITIS

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ABSTRACT
Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic joint inflammation, which if left untreated leads to progressive disability and joint destruction. A combination of anti-inflammatory agents, steroids, disease-modifying antirheumatic drugs (DMARDs), and biological agents are used to treat RA. Patients who fail to respond to traditional DMARDs may receive tumor necrosis factor-α (TNF-α) antagonists. However, approximately one-third of patients fail TNF-α antagonists due to adverse effects or lack of efficacy, and there are limited treatment options available to these patients. As knowledge of the underlying immunopathology of RA evolves, new strategies for inhibiting the inflammatory process have emerged. It is well known that activated T cells play a key role in orchestrating the immunopathological mechanisms of RA. Inhibiting the full activation of T cells is a rational strategy in the treatment of RA and represents a novel method of inhibiting disease activity, distinct from inflammatory cytokine blockade. Abatacept, a soluble human fusion protein that selectively modulates the co-stimulatory signal required for full T-cell activation, is approved for the treatment of rheumatoid arthritis (RA) in the United States, Canada, and the European Union. It is approved for reducing the signs and symptoms of RA, inducing major clinical response, slowing the progression of structural damage, and improving physical function in RA patients with moderate-to-severe disease who have had an inadequate response to other disease modifying, anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) antagonists.
KEY WORDS: Abatacept, Rheumatoid Arthritis, T Cell Co-stimulation modulator, Tumor necrosis factor-α

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 vascularization. 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].

THE RATIONALE FOR MODULATING T-CELL ACTIVATION IN RA

RA is an auto inflammatory disease involving multiple cell types including dendritic cells, macrophages, monocytes, T and B cells, endothelial cells and fibroblasts which respond to genetic and environmental factors. Although the etiology of RA remains obscure, it is thought that an unknown antigen triggers a pro-inflammatory signaling cascade within the synovium. Activated T cells play a central role in this pathway by initiating this cascade with subsequent stimulation of macrophages and synovial fibroblasts to produce inflammatory cytokines including TNF-α, interleukin-2 and interferon-γ[11]. T cells are also involved in activating B cells which then produce autoantibodies such as rheumatoid factor and anti-cyclic citrullinated peptides[12,13]. In addition, activated T cells produce the receptor activator of nuclear factor-κB (RANK) ligand that in turn binds to RANK on osteoclasts. This induces bone resorption and also stimulates chondrocytes to produce matrix metalloproteinases-1 and -3 leading to cartilage destruction[14].

ABATACEPT: A SELECTIVE T-CELL CO-STIMULATION MODULATOR

Abatacept is a selective modulator of the CD80 or CD86 signal which is required for full T-cell activation. It is FDA approved for reducing the signs and symptoms of RA to slow the progression of structural damage and improving physical function in RA patients with moderate-to-severe disease who have had an inadequate response to other disease modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) antagonists.

By targeting T cells, abatacept has a fundamentally different mechanism of action in compare to other therapies for RA. Abatacept modulates T-cell activation by binding to CD80 and CD86 and thereby blocking interaction with CD28. For full activation, T cells require two distinct signals. The first occurring when major histocompatibility complex molecules on antigen-presenting cells (APCs) present a peptide to the T-cell receptor[15]. The second co-stimulatory signal is provided by further interaction between specific receptors on the APC and the T cell. If only one of the signals is transmitted, full activation of T cells does not occur. Abatacept was developed to mimic the action of an endogenous protein and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 is a transmembrane protein which acts as a negative regulator of T-cell activation. It binds to CD80/CD86 with higher affinity than CD28 and thus inhibit the positive co-stimulatory signal. Abatacept is a fully soluble human fusion protein, incorporating only the extracellular domain of human CTLA-4, which is then linked to a modified Fc portion of human immunoglobulin G1[16]. The modified Fc region helps to stabilize the fusion protein but is not therapeutically active. So, abatacept does not mediate complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity (ADCC). These latter effects (complement-dependent cytotoxicity and ADCC) lead to cell lysis, which has been linked to adverse events such as serious infusion reactions[17]. In relation to its unique selectivity of modulating T-cell co-stimulation, abatacept results in decreased proinflammatory cytokine secretion and decreased autoantibody production[18], thereby making T-cell co-stimulation modulation a rational strategy for RA therapy.

PHARMACOLOGY

Abatacept is a selective co stimulator modulator. It is a soluble fusion protein which contains the extracellular domain of human cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) which is linked to the modified Fc portion of human immunoglobulin G1. In unaltered disease, antigen-presenting cell proteins CD80 or CD86 bind to the CD28 protein on T cells, thus facilitating T-cell activation and RA disease progression. Abatacept competes with CD28 for binding to CD80 and CD86. Abatacept's greater affinity for CD80 and CD86 allows it to selectively modulate T-cell activation. The binding inhibits sustained T-cell proliferation and the production of proinflammatory cytokines[19]. Here, abatacept inhibits T-cell function, but does not deplete T cells.

Radiographic assessments demonstrated an inhibitory effect on structural damage progression at Month 6, which was maintained for 6 months following therapy cessation, with similar trends observed for MRI assessed osteitis, erosion and synovitis[20].

PHARMACOKINETICS

Healthy Adults and Adult RA

The pharmacokinetics of abatacept was studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions (Table 1). The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. In RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of Cmax and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady-state by day 60 with a mean (range) trough concentration of 24 (1 to 66) mcg/mL. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients. Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing bodyweight. Age and gender (when corrected for body weight) did not affect clearance. Concomitant methotrexate (MTX), NSAIDs, corticosteroids and TNF blocking agents did not influence abatacept clearance. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept[21].

Juvenile Idiopathic Arthritis

In patients 6 to 17 years of age, the mean (range) steady-state serum peak and trough concentrations of abatacept were 217 (57 to 700) and 11.9 (0.15 to 44.6) mcg/ml. Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept increased with baseline body weight. The estimated mean (range) clearance of abatacept in the juvenile idiopathic arthritis patients was 0.4 (0.20 to 1.12) ml/h/kg. After accounting for the effect of body weight, the clearance of abatacept was not related to age and gender. Concomitant methotrexate, corticosteroids and NSAIDs were also shown not to influence abatacept clearance[21].

PRECLINICAL DEVELOPMENT

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]. 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 modulatorof T-cell function; some degree of systemic alteration is expected.

CLINICAL DEVELOPMENT

Phase 1 (Psoriasis)

Abrams *et al.*

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. 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.*

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)

Olle *et al.*

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. 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. 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. Abatacept infusions were well tolerated at all dose levels. No notable renal, 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 2). Clinical and laboratory evaluation in this study generally demonstrated efficacy for abatacept in the treatment of signs and symptoms of RA[27].

Kremer *et al.*

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. Patients were randomly assigned to receive 10 mg/kg of abatacept, 2 mg/kg of abatacept or placebo on days 1, 15, 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[28].

Weinblatt *et al.*

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- 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. 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.* (AIM)

The first study examined the individual components of the ACR criteria over time in RA patients in AIM (Abatacept in Inadequate responders to Methotrexate) trial. This one-year, randomized, double-blind, placebo-controlled trial included 652 patients with an inadequate response to MTX. 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. Significant improvements were also observed by three months in all ACR components; these continued to increase through six and 12 months (Table 3). Radiographic evaluation showed significant reductions in the progression of erosions, joint space narrowing and total scores with abatacept compared with placebo (Table 4). Abatacept was generally safe and well tolerated in this population[30].

Genovese *et al.* (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, 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[31].

The Cochrane Review meta-analysis assessed safety across the biologic DMARDs based on withdrawals from clinical trials due to AEs . Based on this criterion, there was a trend towards a favourable safety profile of abatacept vs placebo, relative to adalimumab or infliximab[32].

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[33]. Abatacept has not been reported to lead to increased formation of ANA and anti-ds DNA antibodies, compared with placebo[34].

CONCLUSION

Abatacept is a fusion protein combining the extracellular portion of human CTLA-4 and IgG. It 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. Selective T-cell co-stimulation modulation with abatacept offers a potentially valuable therapeutic option for patients with RA who are refractory to TNF-α antagonist therapy and have progressed through the treatment paradigm and are more likely to have severe disease. Clinical trials have not shown an increase in ADEs compared with placebo. It is a novel drug in the treatment of rheumatoid arthritis, although its cost and the lack of experience with long term use should limit its use to patients who are refractory to or have had serious reactions to other treatments. Longer term data on efficacy and safety are needed to further validate T-cell co-stimulation modulation as a therapeutic approach for RA.

REFERENCES

1. Dipiro JT. Rheumatoid arthritis. In: Talbert RT, Yee GC, Matzke GR. Pharmacotherapy: A Pathophysiologic Approach, 6th ed. New York: McGraw- Hill; 2005:1671–1682.
2. Matsumoto AK, Rheumatic arthritis: Clinical presentation. Available at: www.hopkins-arthritis.som.Jhmi.edu/rheumatoid/rheum_clin_pres. html.
3. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004; 350(25): 2591–2602.
4. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001; 344: 907–916.
5. Smith JB, Haynes MK. Rheumatoid arthritis: A molecular understanding. Ann Intern Med 2002; 136: 908–922.
6. Harris ED. The clinical features of rheumatoid arthritis in Textbook of Rheumatology, 6th ed. Philadelphia: WB Saunders; 2001:967–1000.
7. Olsen NJ, Stein MC. New drugs for rheumatoid arthritis. N Engl J Med 2004; 350(21): 2167–2179.
8. Abbott JD, Moreland LW. Rheumatoid arthritis: Developing pharmacological therapies. Expert Opin Invest Drugs 2004; 13(8): 1007–1018.
9. Mariette X. Emerging biological therapies in rheumatoid arthritis. Joint Bone Spine 2004; 71(6): 470-–479.
10. Moreland L, Alten R, Bosch F. Co stimulatory blockade in patients with rheumatoid arthritis: A pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA4-Ig and LEA29Y eighty-five days after the first infusion. Arthritis Rheum 2002; 46(6): 1470–1479.
11. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001; 344: 907–916.
12. Yamada A, Salama AD, Sayegh MH. The role of novel T cell co stimulatory pathways in autoimmunity and transplantation. J Am Soc Nephrol 2002; 13: 559–575.
13. Burkhardt H, Sehnert B, Bockermann R. Humoral immune response to citrullinated collagen type II determinants in early rheumatoid arthritis. Eur J Immunol 2005; 35: 1643–1652.
14. Tanaka S, Nakamura K, Takahasi N. Role of RANKL in physiological and pathological bone resorption and therapeutics targeting the RANKL–RANK signaling system. Immunol Rev 2005; 208: 30–49.
15. Cravens PD, Lipsky PE. Dendritic cells, chemokine receptors and autoimmune inflammatory diseases. Immunol Cell Biol 2002; 80: 497–505.
16. Linsley PS, Brady W, Urnes M. CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med 1991; 174: 561–569.
17. Davis PM, Abraham R, Xu L. Abatacept binds to the Fc receptor CD64 but does not mediate complement-dependent cytotoxicitym or antibody dependent cellular cytotoxicity. J Rheumatol 2007; 34: 2204–2210.
18. Weisman MH, Durez P, Hallegua D. Reduction of inflammatory biomarker response by abatacept in treatment of rheumatoid arthritis. J Rheumatol 2006; 33: 2162–2166.
19. Emery P, Russel A, Tate G. Abatacept induces sustained improvements in health-related quality of life, sleep quality and fatigue over 3 years in rheumatoid arthritis patients with inadequate methotrexate responses. Ann Rheum Dis 2005; 64(Suppl III): 403.
20. Emery P, Durez P, Dougados M . The impact of T-cell co-stimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept. Ann Rheum Dis 2010; 69: 510–6.
21. ORENCIA® (Abatacept), Prescribing information.
22. Dumont FJ. Technology evaluation: Abatacept, Bristol-Myers Squibb. Curr Opin Molec Therapeutics 2004; 6(3): 318–330.
23. Pearson TC, Alexander DZ, Winn KJ. Transplantation tolerance induced by CTLA4-Ig. Transplantation 1994; 57(12): 1701–1706.
24. Azuma H, Chandraker A, Alkalin E. Blockade of T-cell stimulation prevents the development of experimental chronic allograft rejection. Proc Natl Acad Sci USA 1996; 93(22): 1239–1244.
25. Abrams J, Lebwohl MG, Guzzo CA. CTLA4 Ig-mediated blockade of T-cell co-stimulation in patients with psoriasis vulgaris. J Clin Invest 1999; 103(9): 1243–1252.
26. Abrams J, Guzzo CA, Hayes SL. Blockade of T lymphocyte co stimulation with cytotoxic T lymphocyte–associated antigen 4-immunoglobulin (CTLA4-Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. J Exp Med 2000; 192(5): 681–693.
27. Oelke K. Investigational Drug Data Base Meeting Report. Presented at the 65th annual meeting of the American College of Rheumatology, November 10–15, 2001.
28. Kremer J, Dougados M, Emery P. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept. Arthritis Rheum 2005; 52(8): 2263–2271.
29. Parchamazad P, Ghazvini P, Honeywell M, Treadwell P. Abatacept (CTLA4-Ig, Orencia): An Investigational Biological Compound for the Treatment of Rheumatoid Arthritis. Drug Forecast. 2005; 30(11): 633-638.
30. Steinfeld S, Moreland, L, Abud C. Rapid and significant improvements in the components of the ACR criteria in

abatacept treated rheumatoid arthritis patients in the phase III AIM (Abatacept in Inadequate responders to Methotrexate) trial. Presentation at the European League against Rheumatism meeting, June 9, 2005, Vienna, Austria.
31. Genovese M, Becker J, Schiff M. Abatacept for rheumatoid arthritis refractory to TNF-alpha inhibitors. N Engl J Med 2005; 353(11): 1114–1123.
32. Singh A, Christensen R, Wells GA . Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Syst Rev 2009; 4: CD007848.
33. FDA, September 6, 2005. Available at: www.fdaadvisorycommittee.com/FDC/ Advisory Committee/ Committees/Arthritis+Drugs/090605 OrenciaP.html.
34. EMEA, London. Abatacept: summary of product characteristics, 2010.

TABLE 1: PHARMACOKINETIC PARAMETER (MEAN, RANGE) IN HEALTHY SUBJECTS AND RA PATIENTS AFTER 10 MG/KG INTRAVENOUS INFUSION(S)

PK Parameter	Healthy Subjects(After 10mg/kg Single Dose) n=13	RA Pateints(After 10 mg/kg Multiple Doses[a]) n=14
Peak Concentration(C_{max}) [mcg/ml]	292(175-427)	295(171-398)
Terminal half life($t_{1/2}$) [days]	16.7(12-23)	13.1(8-25)
Systemic Clearnce (CL) [ml/h/kg]	0.23(0.16-0.30)	0.22(0.13-0.47)
Volume of distribution(Vss) [L/kg]	0.09(0.06-0.13)	0.07(0.02-0.13)

[a] Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter

TABLE 2: 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%)

TABLE 3: MEAN PERCENT IMPROVEMENT FROM BASELINE IN AMERICAN COLLEGE OF RADIOLOGY COMPONENTS AFTER ABATACEPT AND PLACEBO THERAPY FOR RHEUMATOID ARTHRITIS

Duration	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

TABLE 4: 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 (25th, 75th percentile)	0.63 (1.77) 0.00 (0.00, 1.02)	1.14 (2.81) 0.27 (0.00, 1.27)
Joint space narrowing score	Mean (SD) Median (25th, 75th percentile)	0.58 (1.54) 0.00 (0.00, 0.49	1.18 (2.58) 0.00 (0.00, 0.97)
Total score	Mean (SD) Median (25th, 75th percentile)	1.21 (2.94)) 0.25 (0.00, 1.78)	2.32 (5.04) 0.53 (0.00, 2.54)