

*A summary of*

# “Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor $\alpha$ Inhibition”

*Mark C. Genovese, MD, Jean-Claude Becker, MD, Michael Schiff, MD, et al.*

— *N Engl J Med.* 2005;353:1114–1123.

*With a managed care analysis of the article by Jaan Sidorov, MD,  
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# Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor $\alpha$ Inhibition

**A study in the *New England Journal of Medicine* provides clinical evidence of a new treatment for rheumatoid arthritis. The agent is the first to offer an option for patients who have had an inadequate response to anti-TNF- $\alpha$  therapy.**

**G**enovesse and colleagues report the results of the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN), a 6-month, randomized, double-blind, placebo-controlled trial enrolling adults who had responded inadequately to anti-TNF- $\alpha$  treatment for rheumatoid arthritis (RA). Adalimumab was not in widespread use at the time the study began, in December 2002, and thus most subjects were current or former users of infliximab or etanercept.

ORENCIA<sup>®</sup> (abatacept),\* a selective costimulation modulator, is the first member of a new class of drugs for treating patients with RA. It is a recombinant fusion protein consisting of a fragment of the Fc domain of human IgG1 and the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). A naturally occurring inhibitory molecule induced on the surface of T cells, CTLA-4 binds with CD80 and CD86 on the surface of antigen-presenting cells and down-regulates T-cell activity. In the normal immune response, interaction of CD80 and CD86 with CD28 provides a costimulatory signal that is necessary for full activation of T cells. Abatacept acts by binding to CD80 and CD86, blocking their interaction with CD28 on T cells, thereby preventing full T-cell activation.

ATTAIN enrolled adults (female, 77.1 percent in the abatacept arm and 79.7 percent in the placebo arm; white, 96.1 percent in the abatacept arm and 93.2 percent in the placebo arm; baseline number of tender and swollen joints, 31.2 and 22.3 in the abatacept arm and 32.8 and 22.0 in the placebo arm respectively; baseline HAQ disability index score, 1.8 for each treatment group) with RA of at least 1 year's duration (mean, 12.2 years in the abatacept arm and 11.4 years in the placebo arm) who had an inadequate response to  $\geq 3$  months of anti-TNF- $\alpha$  treatment but were receiving

background therapy with disease-modifying antirheumatic drugs (DMARDs) (Table 1). Patients were randomized to abatacept or placebo in a 2:1 ratio. They also were stratified as former or current users of anti-TNF- $\alpha$  treatment. Patients received a fixed dose of abatacept according to body weight (Table 2, back page), administered via 30-minute intravenous infusions.

Prior to randomization, current users of infliximab or etanercept underwent a washout period of 60 or 28

*Continued on back page*

**TABLE 1 Selected baseline characteristics**

	<b>Inclusion criterion</b>	<b>Abatacept (N=258)</b>	<b>Placebo (N=133)</b>
Age	$\geq 18$ years	53.4 years	52.7 years
Disease duration	$\geq 1$ year	12.2 years	11.4 years
Anti-TNF therapy user status			
Current		38%	41%
Former (discontinuation of etanercept or infliximab prior to enrollment)		62%	59%
Anti-TNF therapy used			
Infliximab		68%	60%
Etanercept		32%	40%
Adalimumab		2%	2%
Most commonly used medications at baseline			
Methotrexate		76%	82%
NSAIDs		70%	71%
Corticosteroids		70%	65%
Swollen joints, number (66 assessed)	$\geq 10$	22.3	22.0
Tender joints, number (68 assessed)	$\geq 12$	31.2	32.8
C-reactive protein level	$\geq 1$ mg/dL	4.6 mg/dL	4.0 mg/dL
Physical function score (HAQ)		1.8	1.8
Pain score (100 mm VAS)		70.8	69.9
Patient's global assessment of disease activity (100 mm VAS)		69.2	69.7
Physician's global assessment of disease activity (100 mm VAS)		68.8	67.3

NSAIDs=nonsteroidal anti-inflammatory drugs, VAS=visual-analogue scale.  
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\* On Dec. 23, 2005, the U.S. Food and Drug Administration approved abatacept (Orencia<sup>®</sup>) for the treatment of adults with moderately to severely active rheumatoid arthritis who have responded inadequately to one or more DMARDs or TNF antagonists.

## Managed Care Considerations: A Treatment Option With a Novel Mechanism of Action For Patients With Rheumatoid Arthritis

By Jaan Sidorov, MD

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The treatment of rheumatoid arthritis (RA) has been revolutionized by the advent of disease-modifying antirheumatic drugs (DMARDs) and biologic inhibitors of inflammatory cytokines. Unfortunately, a significant fraction of RA patients may not benefit from them.<sup>1</sup> In the prestigious *New England Journal of Medicine*, Genovese et al reported in 2005 on the efficacy of a novel treatment option for these individuals.

Abatacept is a fusion protein that, unlike other biologic agents for RA, inhibits T-cell activation. In their prospectively conducted, double-blinded, randomized trial, Genovese et al reported that approximately half the study subjects receiving abatacept versus approximately 20 percent receiving placebo had a clinically and statistically significant reduction in the signs and symptoms of RA as measured by an ACR 20 response over a period of 6 months. This was accompanied by improvements in physical function and degree of disability.

At this time, we do not understand the effects of abatacept on clinical outcomes beyond 3 years.<sup>2</sup> We also need to learn more about its role in preserving joint integrity beyond 12 months<sup>2</sup> as well as its comparative value using standardized metrics, such as dollars per quality-adjusted life years. Hope-

fully, additional studies will answer these questions in time.

Managed care organizations (MCOs) will need to consider how to include abatacept in their benefit programs. This may mean relying on precertification with a precise clinical definition of what



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constitutes inadequate response of, or intolerance to, DMARDs or biologic agents. While this clinical trial lasted 6 months, and clinical improvement has been maintained up to 3 years from other clinical trials of inadequate responders to methotrexate,<sup>2</sup> MCOs also will need to determine criteria for prolonged coverage of this treatment.

Patients receiving this agent who did not experience a significant improvement are likely to have considerable health care needs, and MCOs must assess what resources are available to these patients. This may include careful review and application of the covered benefit (e.g.: Are rehabilitation services being used effectively?), case management (e.g.: Are family and community resources maximally available?), or disease management (e.g.: Member coaching may help patients become more active members of their health care team.).

Abatacept is an option for patients with inadequate response to DMARDs such as methotrexate or the other commonly used bio-

logic agents. Due to increased rate of infection and serious infection without enhancement of efficacy in patients taking concomitant abatacept and TNF antagonists, abatacept should not be administered concomitantly with TNF antagonists. Abatacept is not recommended for use concomitantly with anakinra.<sup>2</sup> While significant challenges are likely in making abatacept available to members, MCOs and other stakeholders now have another option for beneficiaries who are struggling with RA.

### REFERENCES

1. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med*. 2004;350:2591-2602.
2. Orenzia (abatacept) [prescribing information]. Princeton, N.J.: Bristol-Myers Squibb Co. December 2005.

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**TABLE 2 Dosing of abatacept\* in ATTAIN**

Body weight	Abatacept
<60 kg	500 mg
60–100 kg	750 mg
>100 kg	1,000 mg

\*The first three doses were administered at 2-week intervals, on days 1, 15, 29, and every 28 days thereafter via a 30-minute intravenous infusion. ADAPTED FROM GENOVESE 2005

days. According to the researchers, this could have invoked an artificial flare or worsening of disease. There was, however, no evidence of flare in patients who had a washout period and were assigned to placebo. This indicates that these patients were not benefiting from TNF- $\alpha$  inhibition and that the significant improvement observed after randomization to abatacept reflected the treatment of active baseline disease.

**Efficacy.** The two primary endpoints were the proportion of patients achieving an American College of Rheumatology response (ACR 20) and the proportion with an improvement of at least 0.3 points in the Health Assessment Questionnaire (HAQ) disability index at 6 months (exceeding the minimal clinically important change of 0.22). An ACR 20 response represents a  $\geq 20$  percent decrease in the number of tender joints and the number of swollen joints, along with an improvement of  $\geq 20$  percent in at least 3 of 5 measures (patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of pain, physical function as assessed by the HAQ disability index, and the C-reactive protein level). Secondary endpoints included ACR 50 and ACR 70 responses at 6 months.

At 6 months, statistically significantly higher ACR response rates were achieved in the abatacept group compared with the placebo group (Table 3). ACR 20, 50, and 70 response rates were achieved in 50.4 percent, 20.3 percent, and 10.2 percent of patients treated with abatacept, respectively, compared with 19.5 percent, 3.8 percent, and 1.5 percent of patients treated with placebo. A significant

ACR 20 response rate was observed on day 15 in some patients and maintained for the duration of the study.

An improvement of 0.3 points or more in the HAQ disability index was defined as a clinically meaningful improvement, and was achieved by 47.3 percent of the abatacept group and 23.3 percent of the placebo group.

Changes in health-related quality of life were assessed by the Short Form (SF-36) Health Survey at 6 months. Statistically significant and clinically meaningful improvements (increase of  $\geq 3$  points on a scale of 0 to 100) were observed in the abatacept group as compared to placebo in all eight physical and mental subscales, as well as the two summary scores of the SF-36.

**Safety.** Rates of serious adverse events were similar in the abatacept and placebo groups (10.5 and 11.3 percent, respectively), and rates of serious infections were identical (2.3 percent). The overall rates of discontinuation were 13.6 percent in the abatacept group and 25.6 percent in the placebo group. Discontinuation because of adverse events occurred in 3.5 and 3.8 percent of the abatacept and placebo groups, respectively; discontinuation because of serious adverse events occurred in 2.7 and 1.5 percent of the abatacept and placebo groups, respectively. Headache was the most frequent adverse event in the abatacept group, reported by 12.4 percent of subjects (vs. 5.3 percent in the placebo group). Rates of other adverse events were similar in the treatment and placebo groups.

Of abatacept-treated patients, 1.3 percent developed antibodies with low-level reactivity against abatacept; in one patient, the response was against the IgG portion of abatacept, and in two others the response was against the CTLA-4-binding portion.

**Conclusion.** ATTAIN provides clinical evidence that abatacept, with its novel mechanism of action, may offer a new treatment for RA, and it is the first agent to offer a therapeutic option for patients who respond inadequately to anti-TNF- $\alpha$  therapy.

#### Reference

Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor  $\alpha$  inhibition. *N Engl J Med.* 2005;353:1114–1123.

**TABLE 3 Selected endpoints**

	Abatacept	Placebo	P value
ACR 20*	50.4%	19.5%	<.001
ACR 50	20.3%	3.8%	<.001
ACR 70	10.2%	1.5%	.003
$\geq 0.3$ -point improvement in HAQ disability index*	47.3%	23.3%	<.001
SF-36 physical-component summary score (mean change from baseline) <sup>†</sup>	7	1	<.001
SF-36 mental-component summary score (mean change from baseline) <sup>†</sup>	5	2	<.01

\*Primary endpoint.

<sup>†</sup>Scores range from 0–100, with a higher score indicating better quality of life. An improvement of 3 points was considered clinically meaningful.

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