Safety of T-cell co-stimulation modulation with abatacept in patients with rheumatoid arthritis

J. Sibilia[1], R. Westhovens[2]

[1]Rheumatology Department and Immunopathology Laboratory, Louis Pasteur University, Strasbourg, France; [2]Department of Rheumatology, KU Leuven, Leuven, Belgium.

Jean Sibilia MD, PhD;
Rene Westhovens MD, PhD.

Please address correspondence to: Professor J. Sibilia, Rheumatology Department and Immunopathology Laboratory (EA 3432), Centre Hospitalier Universitaire, Louis Pasteur University – Strasbourg, Strasbourg, France.
E-mail: Jean.Sibilia@wanadoo.fr

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ABSTRACT

Abatacept selectively modulates the CD80/CD86:CD28 co-stimulatory signal required for full T-cell activation, and has been approved for the treatment of rheumatoid arthritis (RA) in combination with methotrexate in a number of countries, including the United States, Canada, and the European Union. As with any new agent, it is important to assess the safety and tolerability of abatacept, and hence an integrated safety analysis of five randomized, placebo-controlled, double-blind core abatacept clinical trials was performed. The 2,944 patients enrolled had active RA and were receiving a variety of biologic and non-biologic background disease-modifying antirheumatic drugs. Overall, 1,955 patients were treated with abatacept during the double-blind periods, and 2,688 during the cumulative double-blind and open-label periods (yielding 4764 patient–years of exposure in total).

Overall frequencies of adverse events (AEs; 88.8% vs. 85.1%), serious AEs (SAEs14.0% vs. 12.5%) and malignancies (1.4% vs. 1.1%) were similar in abatacept- versus placebo-treated patients, respectively (regardless of the potential relationship to the study therapy). Discontinuations due to SAEs were 2.8% in the abatacept group vs. 1.6% in the placebo group. The frequency of serious infections was low overall (3.0% vs. 1.9% in abatacept- versus placebo-treated patients, respectively). Acute infusional AEs (9.8% vs. 6.7% in the abatacept versus placebo groups, respectively) were mostly mild-to-moderate in intensity. Safety data through cumulative exposure were consistent with those from the double-blind periods; there was no evidence of an increase in the incidence of serious infections or malignancies with increasing exposure to abatacept. Abatacept was associated with low levels of immunogenicity, with no detectable association between immunogenicity and safety or efficacy. Abatacept treatment did not result in a higher rate of seroconversion for antinuclear or anti-dsDNA antibodies versus placebo, and was associated with a similar frequency of autoimmune events versus placebo (1.4% vs. 1.8%, respectively). Moreover, treatment with abatacept may not markedly impair the response to vaccination in healthy volunteers or RA patients.

Overall, these findings suggest that abatacept has acceptable safety and tolerability in patients with RA. Ongoing follow-up will monitor whether these features are maintained over long-term abatacept use.

Introduction

The activation of T cells plays a key role in the development and maintenance of rheumatoid arthritis (RA), resulting in inflammation and joint destruction (1). It has long been recognized that, in addition to the presentation of antigen on the major histocompatibility complex molecules of antigen presenting cells (APCs), T cells require a second, co-stimulatory signal in order to become fully activated. One of the best characterized co-stimulatory interactions is that between CD80/CD86 on the APC and CD28 on the T cell, which promotes full T-cell activation, proliferation and survival (2). Shortly after T-cell activation (within 24–48 hours), cytotoxic T-lymphocyte-associated antigen (CTLA)-4 is expressed on the surface of activated T cells and competitively binds to CD80/CD86 on the APC with a higher avidity than does CD28, inhibiting further T-cell activation (3). Abatacept is a fully human soluble fusion protein comprising the extracellular domain of human CTLA-4 linked to a modified human immunoglobulin (Ig)G1 Fc portion (4), and binds to CD80/CD86 to prevent full T-cell activation.

During its development, the abatacept molecule was modified using directed, select mutations to inactivate the Fc region of the fusion protein. Abatacept therefore is unlikely to induce complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC) (5). Under normal circumstances, the Fc region of human IgG binds to multiple receptors (CD16, 32 and 64) that regulate various immune responses, including CDC, ADCC, B-cell proliferation, cytokine production, phagocytosis and antibody-mediated inflammation (6, 7). By interfering with the interaction between the Fc region of abatacept and Fc receptors, the mutations in the abatacept Fc region minimize the risk of inappropriate activation of complement and ADCC during abatacept treatment, and thus reduce the risk of immune cell depletion. The efficacy of abatacept has previously been demonstrated both in RA patients with an inadequate response to methotrexate (MTX) (8) and in RA patients with an inadequate response to anti-tumor necrosis factor (TNF) therapy, against a background of disease-modifying antirheumatic drugs (DMARDs) (9). Abatacept (ORENCIA®) was approved by the United States (US) Food and Drug Administration for the treatment of RA in December 2005, by Health Canada in June 2006, and by the European Agency for the Evaluation of Medicinal Products in May 2007. Here we will overview the clinical safety experience with abatacept to date, presenting published double-blind clinical trial data, with a summary of current open-label results (as yet unpublished).

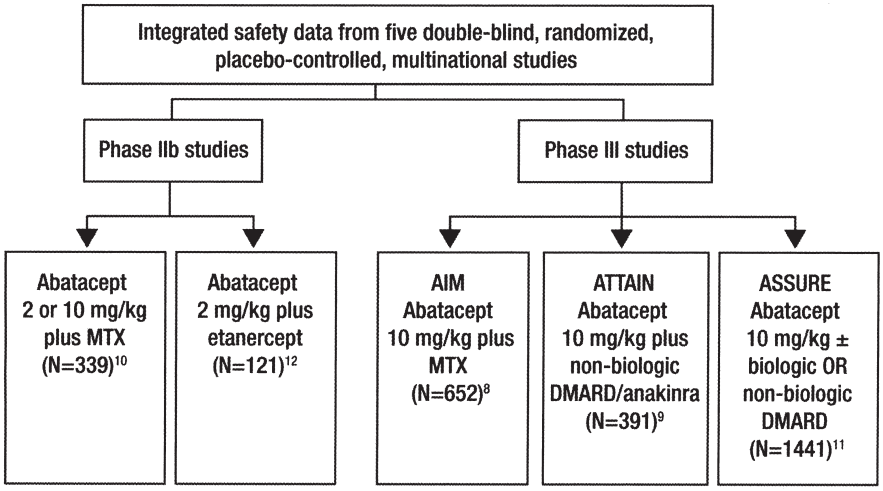

Fig. 1. Treatment information for the five core abatacept clinical trials.
MTX: methotrexate; AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-TNF Inadequate responders; DMARD: disease-modifying antirheumatic drug; ASSURE: Abatacept Study of Safety in Use with other RA therapies.

Clinical safety experience with abatacept

Integrated safety analysis of abatacept

An integrated safety analysis of abatacept in patients with RA has been performed across five randomized, placebo-controlled, double-blind core studies (8-14) (Fig. 1). These studies enrolled a total of 2,944 patients. Overall, 1,955 patients were treated with abatacept during the double-blind periods (of 6 months or 1 year), representing 1687 patient–years (p–yrs) of exposure to abatacept. The data set of all treated patients consisted of all patients who were randomized and received at least one dose of the study medication.

At randomization, patients had similar demographics and disease characteristics across the abatacept and placebo groups (Table I). Patients were largely female, with a mean age of ~52 years and a mean disease duration of ~10 years. Enrolled patients had an inadequate response to either MTX (8, 10), various biologic DMARDs (9, 12) or biologic/non-biologic DMARDs (11). All patients were receiving background therapy with one or more additional DMARDs (Fig. 1). In two studies patients were receiving background MTX (8, 10), while in another, patients received a variety of background non-biologic DMARDs (including MTX) (9). Another of the studies enrolled patients receiving background biologic therapy in the form of etanercept (12). The fifth core study (the ASSURE [**A**batacept **S**tudy of **S**afety in **U**se with other **R**A therapies] study, which is discussed in more detail below) was designed specifically to evaluate the safety of abatacept compared with placebo in patients with active RA despite background non-biologic DMARD and/or biologic therapy (11). It also assessed safety in patients with various co-morbidities in order to further define the safety profile of abatacept.

Across the five core studies, 81.9% of patients were receiving background treatment with MTX, 26.9% with other non-biologic DMARDs (most commonly chloroquine/hydroxychloroquine, leflunomide and/or sulfasalazine), 9.4% with biologic anti-TNF therapy (infliximab, adalimumab or etanercept) and 1.1% with anakinra at baseline (14). A total of 2,688 patients were treated with abatacept in the cumulative (double-blind plus open-label periods), representing 4,764 p – yrs of exposure (14).

Adverse events during the integrated safety analysis

Adverse events (AEs; defined as any unfavorable and unintended sign, symptom or disease temporally associated with the use of the study drug) were recorded for up to 2 months (56 or 60 days) after patients discontinued treatment. Overall, AEs were reported by a similar proportion of abatacept- and placebo-treated patients (88.8% versus 85.1%, respectively) during the double-blind periods, and resulted in discontinuation in 5.8% and 3.9% of patients, respectively. These AEs were considered to be at least possibly related to the study therapy in 52.2% and 46.1% of abatacept- and placebo-treated patients, respectively, leading to discontinuation in 3.4% and 2.2% of patients (14). The most frequently reported AEs in the abatacept and placebo groups, regardless of their potential relationship to the study therapy, were:

Table I. Baseline demographics and disease characteristics of patients enrolled in the five core abatacept studies.

	Background MTX n = 339 (10)	Background etanercept n = 121 (12)	AIM study, background MTX n = 652 (8)	ATTAIN study, background non-biologic DMARDs n = 391 (9)	ASSURE study, background non-biologic and biologic DMARDs n = 1441 (11)	
					Non-biologic DMARD background	Biologic DMARD background
Study type	Phase IIB	Phase II	Phase III	Phase III	Phase III	
Baseline demographics						
Age, years	54 - 56	50 - 54	50 - 51	53	52	53–55
Female, %	63–75	72 - 78	78 - 82	77–80	83–84	75–76
Baseline disease characteristics						
Disease duration, years	9–10	13	9	11–12	10	11
Number of swollen joints	20–22	20	21–22	22	–	–
Number of tender joints	28–31	29	31–32	31–33	–	–
Physical function (HAQ)	1.0*	0.9–1.0	1.7	1.8	1.5	1.5–1.6
DAS28	5.4–5.5	–	6.4	6.5	–	–
RF-positive, %	76–86	68–78	79–82	73	–	–
MTX prior to enrollment, %	98–99	–	100	76–82	80–81	56
MTX dose (mg/week)	15–16	–	16	14–15	–	–
Other non-biologic DMARDs prior to enrollment, %	17–21	–	9–12	28–31	22.1–38.0	16.2–26.9
Biologics prior to enrollment, %	–	–	0– <1	100	0	100
Corticosteroids at baseline, %	60–68	56–61 (data on file)	69–72	65–70	62–63 (data on file)	59–63 (data on file)
Median dose at baseline (mg/day)	N/A	N/A	N/A	5.0	N/A	N/A

Values are stated as means; ranges represent the spread of means across cohorts; *Modified HAQ; MTX: methotrexate; AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-TNF Inadequate responders; DMARD: disease-modifying antirheumatic drug; ASSURE: Abatacept Study of Safety in Use with other RA therapies; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score 28; RF: rheumatoid factor.

headache (18.3% *vs*. 12.7%, respectively), upper respiratory tract infection (12.7% *vs*. 12.1%), nausea (11.6% *vs*. 10.6%), nasopharyngitis (11.6% *vs*. 9.1%), diarrhea (9.9% *vs*. 10.0%) and dizziness (9.5% *vs*. 7.0%). In addition to headache, nasopharyngitis and dizziness, events reported with a frequency at least 2% higher in abatacept- versus placebo-treated patients were hypertension (6.6% *vs*. 4.6%) and dyspepsia (6.6% *vs*. 4.3%). Infections occurred in 54.1% *vs*. 48.7% of abatacept- and placebo-treated patients, respectively (13) (considered at least possibly related to study therapy in 23.2% and 19.5% of patients) (14). Infections occurring at a frequency 1% higher in abatacept- versus placebo-treated patients were nasopharyngitis (11.6% *vs*. 9.1%, respectively), urinary tract infection (5.9% *vs*. 4.7%) and rhinitis (2.7% *vs*. 1.7%) (13). The most frequent infections occurring in both groups were respiratory and urinary tract infections (13).

In the open-label periods, 88.2% of patients reported AEs. In general, the most frequently reported events were similar to those reported during the double-blind periods, and consisted of: upper respiratory tract infection (15.8%), nasopharyngitis (11.8%), headache (10.2%), back pain (9.7%), urinary tract infection (8.7%), sinusitis (8.6%), bronchitis (8.6%), diarrhea (8.3%) and cough (8.2%) (13).

Serious AEs (SAEs) were defined as any AE that was fatal, was life-threatening, resulted in or prolonged hospitalization, resulted in persistent or significant disability or incapacity, was cancer, was a congenital anomaly/birth defect, resulted in an overdose, resulted in the development of drug dependency or drug abuse, or was an important medical event. The frequency of SAEs in the abatacept and placebo groups during the double-blind periods was 14.0% and 12.5%, respectively, leading to discontinuation in 2.8% *vs*. 1.6% of patients, respectively. These were considered to be at least possibly related to the study therapy in 3.1% *vs*. 1.7% of the abatacept- and placebo-treated patients, respectively. The most frequently reported SAEs, regardless of their possible relationship to the study therapy, were RA (2% in both groups – mainly associated with RA-related surgical procedures), pneumonia (0.5% in both groups), basal cell carcinoma (abatacept: 0.6%; placebo: 0.4%), chest pain (abatacept: 0.6%; placebo: 0.4%), osteoarthritis (abatacept: 0.3%; placebo: 0.5%) and congestive heart failure (abatacept: 0.2%; placebo: 0.5%) (13). The difference in the overall frequency of SAEs between groups was largely due to differences in the frequencies of serious infections (abatacept: 3.0%; placebo: 1.9%), which are discussed in more detail below.

In the open-label periods, 20.0% of patients reported an SAE. In general, the types of event were similar to those reported during the double-blind periods

and, similar to the double-blind periods, most were reported in only one patient each (13).

Serious infections during the integrated safety analysis

Previous studies in patients with RA have shown that treatment with biologic RA therapies can be associated with an increased risk of infection (15). Across the double-blind periods of all five core studies, the frequency of serious infection was low: 3.0% and 1.9% in abatacept- and placebo-treated patients, respectively [Table II; (13)]. Serious infections considered to be at least possibly related to study therapy were reported in 1.8% and 1.0% of abatacept- and placebo-treated patients, respectively (14).

The most frequently reported serious infection in abatacept- and placebo-treated patients was pneumonia (0.5% in both groups). Other serious infections occurring at a frequency of ≥ 0.2% in the abatacept-treated patients included cellulitis, urinary tract infection, bronchitis, diverticulitis, localized infection and acute pyelonephritis (Table II) (13). There were no cases of hepatitis B or C, human immunodeficiency virus (HIV) or progressive multi-focal leukoencephalopathy (PML) reported in the abatacept-treated patients during the double-blind periods of the five core studies. One abatacept-treated patient died from pulmonary aspergillosis, considered to be possibly related to the study therapy. It is recommended that physicians exercise caution when considering the use of abatacept in patients with a history of recurrent infections or underlying conditions that may predispose them to infections.

To ascertain whether the risk of serious infection increased with the increasing duration of exposure to abatacept, the incidence rates of all serious infections, and serious pneumonia in particular, were examined at 6-month intervals (Table III) (13). No apparent increase was found in the incidence rate per 100 p–yrs of serious infections with the increased duration of abatacept exposure.

Tuberculosis (TB) is of particular concern in RA patients receiving biologic therapies such as anti-TNF agents (16-18): TNF plays a central role in inflammatory responses to mycobacterial infection through the stimulation of macrophage activity and the formation of granulomas to contain infection (19, 20). At entry to each of the abatacept studies included in the integrated safety analysis, all patients were screened for latent TB infection. Patients who tested purified protein derivative positive (PPD) or had experienced active TB within the previous 3 years were excluded from each study. There were two cases of suspected TB reported during the double-blind periods of the five core studies, one from each treatment arm and one additional case during the open-label periods (13).

Of note, pre-clinical work in mice has shown that abatacept does not appear to impair the control of *Mycobacterium tuberculosis* infection (21). In this study, chronic *M. tuberculosis* infection was

Table II. Frequency of serious infections occurring in ≥ 2 abatacept-treated patients during the double-blind periods of the five core studies (13).

Serious infection*, n (%)	Abatacept n = 1955	Placebo n = 989
Total serious infections	58 (3.0)	19 (1.9)
Pneumonia	9 (0.5)	5 (0.5)
Cellulitis	5 (0.3)	2 (0.2)
Urinary tract infection	4 (0.2)	1 (0.1)
Bronchitis	4 (0.2)	0
Diverticulitis	3 (0.2)	0
Localized infection	3 (0.2)	0
Acute pyelonephritis	3 (0.2)	0
Bronchopneumonia	2 (0.1)	0
Infected skin ulcer	2 (0.1)	0
Sinusitis	2 (0.1)	0
Subcutaneous abscess	2 (0.1)	0

*Infections recorded regardless of potential relationship to study therapy.

Table III. Incidence rates by 6-month period for serious infections and malignancies in the cumulative double-blind and open-label study periods for all abatacept-treated patients.

	Number of patients with the event (incidence rate/100 patient–years) (95% CI on incidence rate)					
	Days 1–180	Days 181–360	Days 361–540	Days 541–720	Days 721–900	Days 901–Last
Total exposure (patient–years)	1285.56	1177.04	928.37	737.13	340.97	294.74
All serious infections	50 (3.92) (2.91, 5.17)	47 (4.02) (2.96, 5.35)	32 (3.47) (2.37, 4.90)	23 (3.14) (1.99, 4.71)	10 (2.95) (1.42, 5.43)	7 (2.42) (0.97, 4.98)
Total malignancies	16 (1.25) (0.71, 2.03)	18 (1.53) (0.91, 2.42)	12 (1.30) (0.67, 2.26)	10 (1.36) (0.65, 2.50)	5 (1.47) (0.48, 3.43)	6 (2.06) (0.76, 4.48)
Solid organ malignancy	6 (0.47) (0.17, 1.02)	6 (0.51) (0.19, 1.11)	7 (0.75) (0.30, 1.55)	3 (0.41) (0.08, 1.19)	4 (1.17) (0.32, 3.01)	2 (0.68) (0.08, 2.45)
Hematologic malignancy	1 (0.08) (0, 0.43)	2 (0.17) (0.02, 0.61)	1 (0.11) (0, 0.60)	1 (0.14) (0, 0.76)	0 (0) (0, 1.08)	1 (0.34) (0.01, 1.89)

established in C57BL/6 mice. Four months later animals were treated with either abatacept, anti-murine TNF antibody or vehicle control. Following 16 weeks of treatment, 100% of animals treated with abatacept or vehicle were alive, with no changes in the mean percentage, number or activation of T cells, macrophages, neutrophils or B cells, suggesting an absence of *M. tuberculosis* infection reactivation. In contrast, 100% of animals treated with anti-murine TNF antibody had died by Week 9, with a mean survival time of 44 days. These animals had an increased bacterial load, as well as a higher infiltration of mononuclear cells in the liver and spleen, and less-organized lung granulomas, which are indicative of the reactivation and dissemination of *M. tuberculosis* infection. Acting via modulation of T-cell co-stimulation, abatacept has a fundamentally different mechanism of action from therapies targeting TNF – a feature that may explain the different pattern of TB re-activation observed here.

By affecting only certain cells of the adaptive immune response, abatacept may not impact non-antigen-dependent innate immunity, and so is unlikely to globally suppress immune function. This may, at least in part, explain some of the differences from other biologic agents in terms of treatment-associated infections.

Malignancies during the integrated safety analysis

It was important to evaluate malignancies during the abatacept RA studies, as other biologic agents have been associated with an increased risk of cancer (22). Moreover, patients with RA are known to be at increased risk of developing lymphoma (23). Anti-TNF agents appear to be associated with a 2– to 5-fold increase in the risk for lymphomas (especially non-Hodgkin's lymphomas) relative to RA patients on other drugs [see (24)]. This may be because these agents are used in patients with more severe and longstanding disease, and thus are at a higher risk of developing lymphomas. It remains to be determined whether anti-TNF agents are associated with an increased incidence/recurrence of other malignancies (24). In a mouse carcinogenicity study, an increased frequency of malignant lymphomas and mammary gland tumors was seen following abatacept treatment. This may have been associated with decreased control of murine leukemia virus and mouse mammary tumor virus, respectively, in the presence of long-term immunomodulation (14). However, there are no human equivalents of these viruses, and no clear signal has been observed in the abatacept clinical trials to date. The relevance of these findings to the clinical use of abatacept in humans, therefore, is unknown. Only long-term follow-up will determine the significance of the murine data.

In the clinical development program, the frequency of benign, malignant and unspecified tumors was 3.7% in abatacept- and 2.9% in placebo-treated patients during the double-blind periods [Table IV; (13)]. Most reported tumors were benign (46 [2.4%] abatacept- and 18 [1.8%] placebo-treated patients). The most frequently reported benign or non-malignant neoplasms in the abatacept and placebo groups were skin papillomas (0.5% *vs*. 0.4%, respectively). Malignancies were reported in 1.4% and 1.1% of patients in the abatacept and placebo groups, respectively [Table IV; (13, 14)]. The most frequently reported malignancies in the abatacept or placebo groups (excluding non-melanoma skin

Table IV. Frequency of tumors during the double-blind periods of the five core studies, and observed and expected malignancies and standardized incidence ratios during the cumulative (double-blind plus open-label) period compared with the general population (13).

Tumor, n (%)	Abatacept n = 1955	Placebo n = 989
Benign	46 (2.4)	18 (1.8)
Malignant*	27 (1.4)	11 (1.1)
Non-melanoma skin	16 (0.8)	6 (0.6)
Lung	4 (0.2)	0
Thyroid	2 (0.1)	0
Lymphoma	1† (< 0.1)	0
Breast	1 (< 0.1)	2 (0.2)
Bladder	1 (< 0.1)	0
Prostate	1 (< 0.1)	0
Renal cell carcinoma	1‡ (< 0.1)	0
Endometrial	0	2 (0.2)
Melanoma	0	1 (0.1)

Malignancy	Observed§	Expected#	SIR (95% CI)¶
Solid organ malignancies	28	37.25	0.75 (0.50, 1.09)
Lung	11	4.88	2.25 (1.12, 4.03)
Breast	4	9.66	0.41 (0.11, 1.10)
Prostate	3	3.92	0.77 (0.15, 2.24)
Colon/rectum	0	3.54	0 (0.00, 1.04)
Lymphoma	4	1.34	3.00 (0.81, 7.67)

*One abatacept-treated patient reported both a lung neoplasm and renal cell carcinoma; 3 patients in the abatacept group reported malignancies > 56 days after the final abatacept dose (one case each of bile duct cancer, squamous cell carcinoma of the cervix, and breast cancer).

†Occurred in a patient with Hashimoto's thyroiditis, a condition associated with the increased risk of lymphoma.

‡stage unspecified.

§observed number of malignancies in abatacept-treated patients in the cumulative (double-blind and open-label) clinical trials.

#Based on general population rate estimates from United States Surveillance and End Results (SEER); the number of malignancies that would have been expected in the abatacept trials if they had the same incidence rate as the general population by the method of indirect adjustment – adjusted for age and gender and taking into account duration of abatacept exposure.

¶SIR of 1.0 means the number observed in the abatacept trials is exactly the number expected in the general population.

SIR: standardized incidence ratio (observed/expected); CI: confidence interval.

cancer) were lung, breast and endometrial cancer (Table IV). One of the patients with lung cancer had a delayed pre-treatment radiograph that, upon review, suggested an abnormality prior to the commencement of study therapy. There was only one case of lymphoma reported, which occurred in a patient in the abatacept group who had a pre-existing condition (Hashimoto's thyroiditis) resulting in a predisposition to lymphoma.

Incidence rates (IRs) were computed for both the double-blind and cumulative periods. In each analysis, IRs were calculated by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Once an event occurred, the patient no longer contributed person–time for that treatment group for the purposes of determining the IR for that event. The IR (per 100 p–yrs) for an event is calculated for each group as the number of patients with an event divided by the p–yrs of exposure to that event. Overall malignancy IRs during the double-blind periods were 1.6 and 1.4 p–yrs for abatacept- and placebo-treated patients, respectively, and for solid organ malignancies the rates were 0.5 p–yrs *vs*. 0.6 p–yrs, respectively. For both overall and solid malignancies, 95% confidence intervals overlapped between the abatacept and placebo groups (13).

The effect of increasing duration of exposure on the risk of malignancy was assessed by calculating the IR of malignancy over the cumulative experience by 6-month intervals. The IRs over time remained stable for overall, solid and hematologic malignancies (Table III) (13).

In order to determine whether the observed number of malignancy cases in the abatacept cumulative clinical trial experience were similar to the number expected based on IRs of malignancies in a general population, standardized incidence ratios were computed. For this analysis, age- and sex-adjusted IR estimates from United States Surveillance and End Results (SEER) were used. The overall incidence of solid organ malignancies with abatacept during the cumulative experience was similar to that expected in a general population (Table IV) (13). Colorectal, breast and prostate cancers occurred less frequently in abatacept-treated patients than would be expected based on general population IRs (Table IV) (13). While lymphoma and lung cancer were seen more frequently among abatacept-treated RA patients than would be expected based on general population rates (Table IV) (13), a similar pattern of results was obtained upon comparing the incidence of malignancies in patients with RA from a summary of published studies with that observed in relevant general populations (13), suggesting that RA in general is associated with a higher risk of lymphoma and lung cancer. These findings have recently been confirmed through longer-term follow-up of abatacept-treated patients from the integrated safety analysis (25).

Deaths during the integrated safety analysis

A total of 16 patients died during the double-blind periods of the five core studies, 9 (0.5%) in the abatacept group and 7 (0.7%) in the placebo group. The causes of death among the abatacept-treated patients (one patient each) were: hypertensive heart disease, congestive heart failure, chest pain, coronary artery atherosclerosis, third degree burns/cardiac arrest, malignant lung neoplasm, bronchopulmonary aspergillosis, sudden death and unspecified. Only one of these (bronchopulmonary aspergillosis) was considered to be possibly related to the study therapy. One additional abatacept-treated patient died of bile duct cancer > 56 days after the last dose of the study drug, a death that was considered possibly related to study therapy.

Acute infusion reactions during the integrated safety analysis

The frequencies of acute infusion reactions (those occurring within 1 hour of the start of infusion) are available for the Phase III studies only, since only these studies noted the time post-infusion at which the event occurred. Acute infusion reactions during the double-blind periods were more frequent following abatacept than placebo administration (9.8% *vs*. 6.7% of patients, respectively) (14). Most events related to infusions were mild-to-moderate in severity, and included dizziness (2.1% *vs*. 1.3% in the abatacept versus placebo groups, respectively), headache (1.8% *vs*. 1.2%) and hypertension (1.2% *vs*. 0.4%) (13). Severe events associated with infusions occurring in ≥ 2 patients treated with abatacept included flushing (3 patients), dizziness and hypersensitivity (2 patients each). No severe acute infusional events occurred in ≥ 2 patients in the placebo group. More discontinuations due to acute infusion reactions occurred in the abatacept versus the placebo group (0.4% *vs*. 0.2%, respectively) (13).

Autoimmune events and autoantibody data during the integrated safety analysis

Autoimmune events were reported in 28 (1.4%) patients in the abatacept group and 8 (0.8%) patients in the placebo group during the double-blind periods. The most frequent autoimmune events reported in the abatacept group were psoriasis (9 patients [0.5%] *vs*. 0 placebo patients) and vasculitis (5 patients [0.3%] *vs*. 2 placebo patients [0.2%]). There were 2 cases of systemic lupus erythematosus (SLE) among patients receiving abatacept in the double-blind periods. One case was a lupus-like syndrome of moderate intensity in a patient receiving concomitant adalimumab, while the other was a moderate case of SLE which led to discontinuation (13). In addition to the 9 patients with psoriasis, one reported guttate psoriasis. Four of the psoriasis cases were new, and the remaining 6 were flares. When treatment for psoriasis was required, topical therapy was usually sufficient and the use of systemic corticosteroids was infrequent.

During the open-label periods, 1.9% of patients reported autoimmune events. The most frequent (≥ 0.3%) were psoriasis (0.7%) and vasculitis (0.3%). The overall incidence rate (per 100 p–yrs) of autoimmune events in the open-label periods did not appear to increase relative to the double-blind periods (1.43 *vs*. 1.72, respectively). Most events were mild or moderate in severity, with the exception of 2 cases of psoriasis (one severe and one very severe), and one

case each of severe SLE and multiple sclerosis, both of which were considered by the investigator to be unrelated to study therapy. All 4 patients experiencing severe autoimmune events withdrew from the study.

There was a lower proportion of abatacept-treated patients with a negative anti-nuclear antibody (ANA) status at baseline and subsequent seroconversion to ANA-positive status compared with the placebo group at both 6 months (4.1% *vs*. 6.3%, respectively) and 12 months (9.7% *vs*. 10.8%). There was also a lower proportion of abatacept-treated patients with a negative anti-dsDNA status at baseline who subsequently seroconverted to positive anti-dsDNA status versus placebo-treated patients at both 6 months (1.1% *vs*. 2.4%, respectively) and 12 months (2.7% *vs*. 4.7%) (13).

While it is important to investigate any effects of abatacept on autoimmunity, the results of clinical trials to date show that abatacept certainly demonstrates efficacy against RA, itself an autoimmune disease. It is, therefore, also relevant to evaluate the efficacy of abatacept against autoimmune diseases other than RA. In this regard, a Phase I, open-label, dose-escalation study found that >40% of patients with psoriasis who were treated with CTLA-4Ig achieved at least a 50% sustained improvement in disease activity (26). In addition, abatacept is currently being investigated in other autoimmune conditions such as inflammatory bowel disease and lupus (ClinicalTrials.gov identifiers: NCT00430677, NCT00119678, NCT00406653 and NCT00410410); results from these studies are awaited with interest.

Focus on the abatacept ASSURE safety study

One of the five core studies included in the above analysis was designed to specifically evaluate the safety of abatacept in patients with RA, and hence will receive separate consideration here. The ASSURE trial was a 1-year, multinational, randomized, double-blind, placebo-controlled clinical trial (11). Certain features of this study meant that it was perhaps more representative of real-world RA patient populations than previous RA trials, in that patients could enroll on a range of background biologic and non-biologic DMARDs, and were eligible even if they had co-morbid conditions. Patients were randomized to receive either abatacept (n = 959) or placebo (n = 482) while continuing to receive background non-biologic DMARDs (1274 patients) and/or biologic therapies (167 patients). Unlike many other studies of biologics in RA, data were also analyzed in patient subgroups according to co-morbidities, including diabetes and chronic obstructive pulmonary disease (COPD). A summary of the baseline demographics and the characteristics of the overall patient population is shown in Table I. The mean patient age was 52.3 years, with a mean disease duration of 9.7 years

Overall safety findings from the ASSURE study

Overall, the frequency of AEs in the ASSURE trial at 1 year was similar in the abatacept and placebo groups (90% and 87%, respectively). The abatacept and placebo groups were also similar in their frequencies of SAEs (12.8% and 12.2%, respectively) and severe/very severe AEs (16% and 15%, respectively). Discontinuations due to AEs were low in both the abatacept (5.4%) and placebo (4.1%) groups. Infections occurring in the abatacept- and placebo-treated groups were similar (56.0% versus 54.1%, respectively), with the most frequent being upper respiratory tract infection (15%, both groups) and nasopharyngitis (10%, both groups). Serious infections occurred in 2.9% and 1.9% of the abatacept- and placebo-treated patients, respectively (Table IV). There were no instances of TB, HIV, hepatitis B or C, PML or infection with opportunistic microorganisms.

As reported for the aforementioned across-trial safety analysis, the frequency of tumors (benign, malignant or unspecified) in the ASSURE trial was identical for the abatacept and placebo groups (3.5%) after 1 year of double-blind treatment. Neoplasms reported as SAEs occurred in 1.5% of the abatacept-treated patients versus 1.0% of the placebo-treated patients, including 15 serious malignancies: basal cell carcinoma (5 abatacept- and 3 placebo-treated patients), squamous cell carcinoma of the skin (3 abatacept-treated patients), breast cancer (one abatacept- and 2 placebo-treated patients) and lung cancer (two abatacept-treated patients) [Bristol-Myers Squibb, data on file]. No cases of lymphoma, which can be of particular concern within the context of RA, were reported in the ASSURE study.

Influence of background DMARD treatment on safety

Previous studies combining biologic RA therapies have suggested an increased risk of serious infection with no added efficacy benefits. A combination study of the interleukin-1 receptor antagonist anakinra and the anti-TNF antibody etanercept indicated that combining biologic RA therapies may increase the risk of serious infection with no added efficacy benefits (27).

Two trials have been performed to evaluate the impact of combining abatacept with other biologic therapies. In the first of these, the ASSURE trial, safety data were analyzed for patients receiving background biologic and non-biologic DMARD therapies separately (11). Of the 959 patients on the abatacept treatment arm of the ASSURE study, 89.2% received background non-biologic DMARD therapy, while 10.7% received background biologic RA therapy. In the placebo group (482 patients), 86.5% and 13.3% received background non-biologic and biologic DMARD therapy, respectively. In the subgroup of patients receiving background non-biologic DMARDs, the frequencies of AEs and SAEs were similar in the abatacept versus placebo groups (AEs: 89.7% *vs*. 86.1%, respectively; SAEs: 11.7% *vs*. 12.2%, respectively; Table V). However, when data from the subgroup of patients receiving background biologic therapy (etanercept, infliximab, adalimumab or anakinra) were analyzed, it became apparent that the frequencies of AEs and SAEs were higher in patients treated with abatacept compared with placebo (AEs: 95.1% *vs*. 89.1%; SAEs: 22.3% *vs*. 12.5%; Table V). In addition, discontinuations due to AEs were higher in the abatacept plus

biologic subgroup than in the placebo plus biologic subgroup (8.7% *vs*. 3.1%, respectively; Table V), as were discontinuations due to SAEs (4.9% *vs*. 3.1%; Table IV). In the biologic subgroup, tumors also occurred at a higher frequency in the abatacept- versus placebo-treated groups (6.8% *vs*. 1.6%, respectively; Table V).

The results of the ASSURE study are consistent with the findings of the 12-month, randomized Phase II trial of abatacept or placebo in combination with the anti-TNF agent etanercept (12). After 1 year of this study, a markedly higher percentage of patients experienced SAEs in the abatacept plus etanercept treatment arm than in the placebo plus etanercept treatment arm (16.5% *vs*. 2.8%, respectively). Moreover, no patients experienced serious infections in the placebo plus etanercept group, compared with 3.5% of patients receiving abatacept plus etanercept. Three patients in the Phase II study developed malignant tumors (basal cell carcinoma, cervical carcinoma and large B-cell lymphoma), all of whom were receiving combined etanercept and abatacept during the 2-year open-label period. The safety results of this Phase II study and the ASSURE study led to the recommendation that abatacept should not be used in combination with other biologic therapies (14, 28). When transitioning from abatacept to anti-TNF therapy, patients should be monitored closely for signs of infection (14).

Safety of abatacept in patients with co-morbidities

Unlike many other studies of biologic agents in RA, the ASSURE study also analyzed RA patients in subgroups according to background co-morbidities (11). The abatacept and placebo groups contained 65 and 31 diabetes mellitus patients, and 37 and 17 COPD patients, respectively (Table VI). Among the patients with concurrent diabetes mellitus, AEs were reported in 93.8% of the abatacept group compared with 90.3% of the placebo group (Table VI). The type and pattern of AEs occurring in diabetes mellitus patients receiving abatacept were similar to those seen in patients without diabetes mellitus receiving the same treatment. The most frequently reported class of AE in patients with diabetes mellitus was infection, which occurred at a lower frequency in the abatacept group than in the placebo group (Table VI). SAEs were higher in abatacept- versus placebo-treated diabetes mellitus patients (21.5% versus 12.9%, respectively; Table VI). The increased frequency of SAEs in the abatacept group was largely the result of SAEs classified as musculoskeletal disorders and injury.

The frequency of AEs in COPD patients was also higher in the abatacept group than in the placebo group (all AEs: 97.3% *vs*. 88.2%, respectively [Table VI] (13); AEs considered to be at least possibly related to study therapy: 51.4% versus 47.1%, respectively (14)). This included a higher frequency of AEs associated with the respiratory system (Table VI). In addition, SAEs were markedly higher in COPD patients treated with abatacept versus placebo (all SAEs: 27.0% *vs*. 5.9%, respectively [Table VI] (13); SAEs considered at least possibly related to study therapy: 5.4% *vs*. 0%, respectively (14)) although no deaths resulted from an SAE. Of the 3 cases of lung cancer in abatacept-treated patients during the ASSURE study (11), none occurred in a COPD patient (13). As in the case of AEs, SAEs included a higher frequency of respiratory-related events in abatacept- versus placebo-treated patients. As a result, it is recommended that abatacept be administered to COPD patients with caution, and that these patients be monitored for any worsening of respiratory symptoms (28).

Subgroup analyses were also performed for patients with asthma (6% of

Table V. Safety summary for the ASSURE study according to concomitant biologic rheumatoid arthritis therapy use (11).

Event*, n (%)	Non-biologic background therapy†		Biologic background therapy‡	
	Abatacept n = 856	Placebo n = 418	Abatacept n = 103	Placebo n = 64
Total adverse events	768 (89.7)	360 (86.1)	98 (95.1)	57 (89.1)
Discontinuations due to adverse events	43 (5.0)	18 (4.3)	9 (8.7)	2 (3.1)
Total serious adverse events	100 (11.7)	51 (12.2)	23 (22.3)	8 (12.5)
Discontinuations due to serious adverse events	18 (2.1)	5 (1.2)	5 (4.9)	2 (3.1)
Serious infections	22 (2.6)	7 (1.7)	6 (5.8)	1 (1.6)
Respiratory	9 (1.1)	4 (1.0)	3 (2.9)	1 (1.6)
Dermatologic	5 (0.6)	1 (0.2)	0	0
Urinary	4 (0.5)	1 (0.2)	2 (1.9)	0
Gastrointestinal	2 (0.2)	1 (0.2)	1 (1.0)	0
Gynecologic	0	1 (0.2)	0	0
Opportunistic	0	2 (0.5)	0	0
P. pneumoniae	0	1 (0.2)	0	0
Candidiasis	0	1 (0.2)	0	0
Other	3 (0.4)	0	1 (1.0)	0
Total neoplasms§	27 (3.2)	16 (3.8)	7 (6.8)	1 (1.6)
Uterine leiomyoma	4 (0.5)	1 (0.2)	0	0
Fibroadenoma of breast	4 (0.5)	0	0	0
Basal cell carcinoma	3 (0.4)	3 (0.7)	2 (1.9)	0
Deaths	5 (0.6)	4 (1.0)	0	0

*Events recorded regardless of potential relationship to study therapy.
†All patients who received a non-biologic agent at any point during the study or up to 56 days following discontinuation.
‡All patients who received a biologic agent at any point during the study or up to 56 days following discontinuation.
§Specific neoplasms listed are those occurring in > 0.2% of patients receiving abatacept plus non-biologic background therapy.
ASSURE: Abatacept Study of Safety in Use with other RA therapies; *P. pneumoniae: Pneumocystis pneumoniae*.

Table VI. Safety summary for patients with co-morbid conditions in the ASSURE trial (11).

Event*, %	Abatacept	Placebo
Chronic obstructive pulmonary disease	n = 37	n = 17
Total adverse events	97.3	88.2
Respiratory system-related	43.2	23.5
Infections	59.5	58.8
Total serious adverse events	27.0	5.9
Respiratory system-related	10.8	0
Diabetes mellitus	n = 65	n = 31
Total adverse events	93.8	90.3
Infections	50.8	58.1
Total serious adverse events	21.5	12.9

*Events recorded regardless of potential relationship to study therapy; ASSURE: Abatacept Study of Safety in Use with other RA therapies.

all patients) and congestive heart failure (1–2% of all patients). Although both subgroups were composed of too few patients for a full analysis, occurrences of SAEs and discontinuations due to AEs were similar overall for the abatacept and placebo groups.

Safety data from other abatacept clinical trials

In addition to the five core studies des cribed above, three additional trials have evaluated the safety of abatacept in patients with RA. The first – called ATTEST (**A**batacept or infliximab versus placebo, a **T**rial for **T**olerability, **E**fficacy, and **S**afety, in **T**reating RA) – was a randomized, double-blind, double-dummy, placebo-controlled, 1-year global trial, which evaluated patients with RA and an inadequate response to MTX who were randomized to receive abatacept (~10 mg/kg every 4 weeks), infliximab (3 mg/kg every 8 weeks) or placebo (every 4 weeks) on a background of MTX (29). The study was placebo-controlled for 6 months. At study end (12 months), there was a lower frequency of AEs, SAEs, serious infections, and discontinuations due to AEs and SAEs for abatacept versus infliximab (AEs, 89.1% *vs*. 93.3%, respectively; SAEs, 9.6% *vs*. 18.2%; serious infections, 1.9% *vs*. 8.5%; discontinuations due to AEs, 3.2% *vs*. 7.3%; and discontinuations due to SAEs, 2.6% *vs*. 3.6%). Two cases of TB were reported, both in patients receiving infliximab. The frequency of acute infusional events was also lower with abatacept versus infliximab (7.1% *vs*. 24.8%, respectively).

The second trial was a 6-month, randomized, double-blind withdrawal study in children and adolescents with active polyarticular juvenile idiopathic arthritis and an inadequate response to one or more DMARDs (including biologics), who had responded to abatacept treatment during a 4-month, open-label lead-in period (30). The frequency of AEs in the abatacept and placebo groups during the double-blind period was 61.7% and 54.8%, respectively, and the frequency of infections was similar in the two groups (45.0% and 43.5%, respectively). No SAEs (including infections) were reported in the abatacept group. Two patients from each treatment group experienced infusional AEs; these were all mild-to-moderate in intensity.

The third additional study – the ARRIVE (**A**batacept **R**esearched in **R**heumatoid arthritis patients with an **I**nadequate anti-TNF response to **V**alidate **E**ffectiveness) trial – was an international, 6-month, open-label, Phase IIIb study to evaluate the safety, tolerability and efficacy of abatacept with or without non-biologic DMARDs in patients with active RA and an inadequate response to at least 3 months of anti-TNF therapy. Of note, patients were not required to undergo the washout of their anti-TNF therapy and could commence abatacept on their next scheduled anti-TNF dose. In addition, patients who tested PPD positive could enroll provided they had been treated for latent TB and had a negative chest x-ray. Data from the US sub-population of 1,043 patients suggest that abatacept was generally safe and well tolerated, regardless of whether or not patients underwent a washout period for their anti-TNF therapy. No cases of TB were reported (31).

Overall, the results from all of the abatacept studies described above suggest that abatacept has acceptable safety in combination with background non-biologic DMARDs across a range of patient populations. Below, we consider some additional safety aspects of abatacept.

Safety of abatacept during pregnancy

Abatacept is currently contraindicated in pregnancy unless clearly needed (28), and it is recommended that women of child-bearing potential should use effective contraception during treatment with abatacept and up to 14 weeks after the last dose (14). However, there is currently insufficient data regarding the safety of abatacept during pregnancy; ongoing registry studies should provide further information in this area.

Abatacept is associated with a low level of immunogenicity

Several studies have evaluated the impact of selective co-stimulation modulation on the immune response. This is because recombinant biologic agents, including infliximab and adalimumab, have the potential to be immunogenic (32-36). The resulting antibody response to the agent can potentially affect pharmacokinetics and, ultimately, safety and efficacy (37-39). A decline in a drug's effectiveness due to a mounting antibody response can lead to the requirement for dose escalation, as has been reported for anti-TNF agents after long-term treatment (40).

An important and distinguishing characteristic of abatacept therefore is its low immunogenicity, as assessed in patients across multiple Phase II and III RA clinical studies (41). Of 2,237 patients with both pre- and post-baseline samples available, only 62 (2.8%) were classified as having an immune response to abatacept or CTLA-4. No ap-

parent relationship was found between immunogenicity and safety or efficacy; however, because the number of patients who seroconverted was small, further investigations are required in order to confirm this.

Abatacept may not significantly impair the response to vaccination

It is always important to evaluate the effects of agents that target any aspect of the immune system on the ability of patients to respond to vaccination. For this reason, the effect of a single 750 mg infusion of abatacept on the antibody response to intra-muscular tetanus toxin and 23-valent pneumococcal vaccine was evaluated in an open-label study of 80 healthy volunteers (42). Positive responses to the tetanus vaccination at 28 days (at least a doubling in antibody titer relative to baseline) were recorded in ≥ 60% of abatacept-treated subjects, compared with 75% of untreated controls. Likewise, > 70% of abatacept-treated subjects responded to at least 3 pneumococcal serotypes (compared with 100% of controls).

The effects of abatacept on the response to pneumococcal vaccination in patients with RA have recently been evaluated in an uncontrolled sub-study of the ARRIVE trial (43). All 21 patients in this sub-study were required to receive at least 4 doses of abatacept, with or without background non-biologic DMARDs, prior to vaccination. Serum antibody titers were evaluated prior to vaccination and ~35 days afterwards. Overall, 81% of patients mounted a response to at least one of the seven serotypes assayed, and 71% mounted a response to at least two serotypes.

In summary, therefore, abatacept treatment does not appear to significantly impair the response of healthy individuals to tetanus or pneumoccocal vaccination. Moreover, modulation of T-cell co-stimulation by abatacept in RA patients does not appear to completely inhibit the humoral response to this vaccine. It will now be important to investigate the potential effects of abatacept on vaccination response in a larger population of patients with RA, in order to ascertain whether vaccination can be recommended during abatacept treatment.

Conclusion

The treatment of RA has advanced in recent years with the advent of biologic therapies such as the anti-TNF agents adalimumab, etanercept, infliximab, the B-cell depleting agent rituximab and the T-cell co-stimulation modulator abatacept. It is always important, however, to carefully assess the safety of any new biologic RA agent given the evidence that immunosuppressants can increase the risk of serious infection and malignancy (15, 22).

Abatacept has demonstrated acceptable safety and tolerability across five core randomized clinical trials. This finding has been demonstrated in a range of RA patient populations, including those with inadequate responses to MTX or anti-TNF therapy, those on a background of non-biologic DMARDs and those with various co-morbidities. Results of two of the clinical studies, however, demonstrated that abatacept should not be co-administered with other biologic agents due to an increased risk of infection. The safety of abatacept is enhanced by the fact that this agent is associated with a low level of immunogenicity.

As with all biologic agents, long-term safety needs to be monitored. Now that abatacept has been approved in the US for almost 2 years, longer-term follow-up of abatacept clinical trials is being performed as part of an ongoing pharmacovigilance program. More recent analyses are now being performed on a total of 4,134 patients treated with abatacept, reflecting a drug exposure of 8388 p–yrs. The continuing follow-up will determine whether the safety of abatacept in patients with moderate-to-severe RA is maintained over long-term use.

Key points box

- The safety of abatacept has been assessed in an integrated analysis across five randomized, placebo-controlled, double-blind core studies, with a cumulative exposure of 4,764 patient–years through open-label treatment
- During the double-blind periods:
  – The frequency of adverse events (AEs), serious AEs and malignancies were similar in abatacept- and placebo-treated patients
  – The frequency of serious infections overall was low; there was one case of tuberculosis in each treatment group
  – Malignancies occurred at a similar frequency in abatacept- and placebo-treated patients
- The incidences of lung cancer and lymphoma during the cumulative periods were as expected for a rheumatoid arthritis (RA) population
- Studies investigating the influence of background therapies on the safety of abatacept have led to the recommendation that abatacept not be used in combination with other biologic therapies
- Abatacept was associated with low immunogenicity, and there was no apparent association between immunogenicity and safety or efficacy. Abatacept did not result in a higher frequency of autoantibodies versus placebo
- Abatacept did not markedly inhibit the responses of healthy volunteers to pneumococcal vaccination and may not completely inhibit the humoral response to this vaccine in patients with RA
- The long-term safety of abatacept continues to be monitored in an ongoing pharmacovigilence program, in order to ascertain whether this drug has similar effects with extended use

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