

Evaluation of abatacept in biologic-naïve patients with active rheumatoid arthritis

Michael Schiff · Louis Bessette

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Abstract This article reviews the efficacy, safety, and tolerability of abatacept plus methotrexate in patients with active rheumatoid arthritis (RA) and an inadequate response to methotrexate who are naïve to biologic disease-modifying antirheumatic drugs (DMARDs). Data from the randomized, double-blind, placebo-controlled Abatacept in Inadequate Responders to Methotrexate, Abatacept or Infliximab vs Placebo, a Trial for Tolerability, Efficacy, and Safety in Treating Rheumatoid Arthritis, and phase IIb dose-finding trials and their long-term extensions are reviewed. Abatacept plus methotrexate significantly improved clinical responses, physical function, and health-related quality of life compared with methotrexate alone. More patients receiving abatacept plus methotrexate than methotrexate monotherapy achieved a low disease activity state or remission. Radiographic progression of the disease was significantly slowed in the abatacept plus methotrexate arms. Abatacept plus methotrexate was generally well tolerated with no clinically significant safety issues identified. The beneficial effects of abatacept plus methotrexate were sustained long term in extension studies, and no new tolerability or safety issues were evident. Abatacept in combination with methotrexate is an effective, safe, and well-tolerated long-term therapy in biologic-naïve patients

with active RA and an inadequate response to methotrexate. Abatacept could be considered as a first-line biologic DMARD in the treatment of RA.

Keywords Abatacept · Disease-modifying antirheumatic drugs · Efficacy · Methotrexate · Moderate disease · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by progressive disability and joint destruction [1]. Patients with active disease are usually treated with a combination of nonpharmacologic therapies, anti-inflammatory drugs, analgesics, and nonbiologic disease-modifying antirheumatic drugs (DMARDs), most commonly methotrexate. However, many patients do not respond adequately to such treatment [2–5] and require the addition of a biologic DMARD [6, 7]. Biologic DMARDs, including tumor necrosis factor (TNF)- α antagonists (etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol) and the interleukin-1-blocking agent anakinra, are of benefit to many patients [6, 7], but not all patients respond to or tolerate them [8]. Additionally, safety concerns (e.g., infections, malignancies, and autoimmune disorders, such as lupus) have been identified with some of these agents [8, 9].

Abatacept is a soluble human fusion protein consisting of the extracellular domain of CTLA4 linked to the modified fragment crystallizable portion of human IgG1 [10–12]. Abatacept inhibits full T cell activation by binding to CD80/CD86, blocking interaction with CD28, and downregulating subsequent immune effector mechanisms (e.g., production of proinflammatory cytokines, autoanti-

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M. Schiff (✉)
University of Colorado School of Medicine,
5400 South Monaco Street,
Greenwood Village, CO 80111, USA
e-mail: Lmschiff@aol.com

L. Bessette
Centre Hospitalier Universitaire de Québec-CHUL,
Sainte-Foy, Québec, Canada

bodies, and joint-eroding enzymes) [10, 11]. The modified fragment crystallizable portion in abatacept is not active and is not associated with adverse events resulting from complement-dependent or antibody-dependent cell-mediated cytotoxicity [13].

The efficacy, safety, and tolerability of abatacept plus methotrexate in patients with active RA who have failed or are intolerant of anti-TNF- α therapy are established [14, 15]. This article reviews studies of abatacept in biologic-naïve patients with active RA despite treatment with methotrexate. MEDLINE searches were conducted using “abatacept” and “rheumatoid arthritis” as search terms. Abstracts from Annual Meetings of the European League Against Rheumatism (EULAR), the Canadian Rheumatology Association, and the American College of Rheumatology (ACR) for the years 2007–2009 were also searched. Additional references were identified from the reference lists of published articles.

Efficacy in patients with active rheumatoid arthritis despite treatment with methotrexate

Abatacept in combination with methotrexate in biologic-naïve patients with active RA and an inadequate response to methotrexate has been assessed in three multicenter, randomized, double-blind, placebo-controlled, 12-month trials: the pivotal phase III Abatacept in Inadequate Responders to Methotrexate (AIM; $n=652$) trial [16]; Abatacept or Infliximab Versus Placebo, a Trial for Tolerability, Efficacy, and Safety in Treating RA (ATTEST; $n=431$) [17]; and a smaller phase IIb dose-finding study ($n=339$) [18].

The AIM [16] and phase IIb [18] studies compared abatacept with placebo, while ATTEST [17] compared abatacept or infliximab with placebo in patients with active RA who had an inadequate response to methotrexate. All patients received background methotrexate, and stable dosages of nonsteroidal anti-inflammatory drugs and oral corticosteroids were permitted. Open-label extensions (OLEs) of these trials assessed the long-term efficacy of abatacept plus methotrexate for up to 7 years [19–25].

Placebo-controlled trials

In the phase IIB dose-finding study, patients received abatacept 2 or 10 mg/kg or placebo as an intravenous infusion (Table 1) [18]. Abatacept 10 mg/kg plus methotrexate was effective in improving signs and symptoms and physical function, decreasing disease activity, and inducing remission (Table 1). Significant improvements in health-related quality of life (HRQOL) were observed for abatacept 10 mg/kg compared with placebo [18].

Most patients randomized to abatacept 10 mg/kg (73%; 84 of 115) continued treatment in a long-term extension. After 7 years of treatment, 51.4% of patients who remained on abatacept 10 mg/kg plus methotrexate (19 of 37) had achieved an ACR 70 response; low disease activity state (LDAS) was evident in ~70% of patients, and 51.5% had achieved Disease Activity Score 28 (DAS28)-C-reactive protein (CRP) remission (observed data, reported as an abstract) [20].

Clinical efficacy in phase III clinical trials

In the AIM trial, patients received intravenous abatacept ~10 mg/kg or placebo on days 1, 15, and 29 and then every 28 days [16]. Coprimary endpoints were ACR 20 response at 6 months, clinically significant improvement in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score (≥ 0.3 units) at 1 year, and radiographic progression of joint erosion (assessed with Genant-modified Sharp score) from baseline at 1 year [16]. A significantly higher proportion of patients who received abatacept plus methotrexate achieved ACR 20 response at 6 months than placebo plus methotrexate recipients. ACR response rates improved further between 6 and 12 months in the abatacept group, but not in the placebo group (Table 1) [16]. Likewise, significantly more patients receiving abatacept plus methotrexate than those receiving placebo plus methotrexate achieved a clinically meaningful improvement in physical function at 1 year (Table 1) [16].

Disease activity assessed using DAS28 (CRP) at 6 and 12 months was reduced to a greater extent in the abatacept plus methotrexate arm than in the placebo plus methotrexate arm, and more patients in the abatacept than placebo arm achieved LDAS or DAS28 (CRP)-defined remission at 12 months (Table 1) [16].

Post hoc analyses suggested that a progressive improvement in disease activity was seen in the abatacept arm. More than 90% of the 376 patients receiving abatacept plus methotrexate who achieved a moderate disease activity state at 3 months had maintained or improved this outcome at 6 and 12 months (reported as an abstract) [26].

In ATTEST, patients received abatacept ~10 mg/kg on days 1, 15, and 29, then every 28 days, or a stable dose of infliximab 3 mg/kg on days 1, 15, 43, and 85, then every 56 days, or matching placebo [17]. At 6 months, placebo recipients were reallocated to blinded abatacept treatment (this group was excluded from the 1-year analyses of abatacept efficacy) [17]. The trial was not designed as a head-to-head comparison, but it is the only published randomized clinical trial to assess the effects of two biologic therapies in the same study.

The primary efficacy endpoint was reduction in disease activity, assessed using DAS28 based on erythrocyte

Table 1 Efficacy of intravenous ABA in combination with background MTX in randomized, double-blind, multicenter PB plus MTX-controlled, phase II and III clinical trials in biologic-naïve pts with active RA, despite treatment with MTX

Trial	Treatment regimen	No. of pts	Response rate at 6 (12) months, % of pts				Mean change in DAS28-ESR score at 6 (12) months	LDAS ^b at 6 (12) months, % of pts	DAS28-defined remission ^c at 6 (12) months, % of pts	Median change in Genant-modified sharp erosion score at 12 months
			ACR 20	ACR 50	ACR 70	Physical function ^a				
Phase IIb study										
Phase IIb dose-finding [18, 36]	ABA 2 mg/kg on days 1, 15, and 30, then monthly+MTX	105	41.9 ^d (42.0 ^e)	22.9* (23.0 ^e)	10.5* (12.0 ^e)	48.0 ^e (38.0 ^e)	30.5 (28.6)	15.0 ^d (22.0 ^e)		
	ABA 10 mg/kg on days 1, 15, and 30, then monthly+MTX	115	60.0*** ^a (62.6***)	36.5*** (41.7***)	16.5*** (20.9**)	58.3*** (49.6***)	40.0*** (44.6**)	26.1*** (34.8***)		
	PB on days 1, 15, and 30, then monthly+MTX	119	35.3 ^d (36.1)	11.8 (20.2)	1.7 (7.6)	33.6 (27.7)	19.3 (21.9)	9.2 (10.1)		
Phase III trials										
AIM [16]	ABA~10 mg/kg on days 1, 15, and 29, then every 4 weeks+MTX	433	67.9*** ^d (73.1***)	39.9*** (48.3***)	19.8*** (28.8***)	63.7*** ^e (63.7*** ^e)	38.1 (42.5)	14.8 (23.8***)	0* ^{d,f}	
	PB on days 1, 15, and 29, then every 4 weeks+MTX	219	39.7 ^a (39.7)	16.8 (18.2)	6.5 (6.1)	39.3 ^g	10.0 (9.9)	2.8 (1.9)	0.27 ^{d,f}	
ATTEST [17]	ABA~10 mg/kg on days 1, 15, and 29, then every 4 weeks+MTX	156	66.7*** (72.4 ^g)	40.4*** (45.5 ^f)	20.5* (26.3 ^g)	61.5** (57.7 ^g)	20.7 (35.3)	11.3 (18.7 ^g)		
	IFX 3 mg/kg on days 1, 15, 45, and 85, then every 8 weeks+MTX	165	59.4** (55.8)	37.0** (36.4)	24.2** (20.6)	58.8** (52.7)	25.6 (22.9)	12.8 (12.2)		
	PB on days 1, 15, and 29, then every 4 weeks+MTX ^h	110	41.8	20.0	9.1	40.9	10.8	2.9		

Abatacept (ABA), placebo (PB), and infliximab (IFX) were administered as intravenous infusions; Methotrexate (MTX) was administered according to the regimen established prior to study entry. Patients (pts) were aged ≥18 years, had been diagnosed with rheumatoid arthritis (RA) (ACR criteria) for ≥1 year, and had persistent, active disease despite treatment with MTX (10–30 mg/week [18] or ≥15 mg/week [16, 17]) for ≥3 months, with ≥12 tender and ≥10 swollen joints [16–18]

ACR American College of Rheumatology, AIM Abatacept in Inadequate Responders to Methotrexate, ATTEST Abatacept or Infliximab vs Placebo, a Trial for Tolerability, Efficacy, and Safety in Treating rheumatoid arthritis, DAS28 28-joint count Disease Activity Score, DAS28-CRP DAS28 based on C-reactive protein level, DAS28-ESR DAS28 based on erythrocyte sedimentation rate, HAQ-DI Health Assessment Questionnaire-Disability Index, LDAS low disease activity state, mHAQ modified Health Assessment Questionnaire

^a Clinically important improvement from baseline assessed using mHAQ (improvement of ≥0.22) [36] or HAQ-DI (improvement of ≥0.3) [16, 17]

^b DAS28 of <3.2; assessed using DAS28-ESR [17] or DAS28-CRP [16, 36]

^c DAS28 of <2.6; assessed using DAS28-ESR [17] or DAS28-CRP [16, 36]

^d Primary endpoint

^e Data estimated from a graph

^f Twenty-fifth and 75th percentiles for change from baseline in erosion scores with ABA+MTX were 0.0 and 1.0 and with PB+MTX 0.0 and 1.3

^g Between-group difference (95% confidence interval) for ABA+MTX vs IFX+MTX: ACR 20, 16.7% (5.5, 27.8); ACR 50, 9.1 (–2.2, 20.5); ACR 70, 5.7 (–4.2, 15.6); HAQ-DI, 5.0 (–6.5, 16.5); DAS28, –0.62 (–0.96, –0.29); DAS28-defined remission, 18.7 (–2.2, 15.2)

^h For the first 6 months only; at day 198, PB+MTX recipients were reallocated to ABA+MTX; results after reallocation are not reported

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs PB+MTX.

sedimentation rate (DAS28 [ESR]) at 6 months [17]. After 6 months of treatment, abatacept plus methotrexate significantly reduced the signs and symptoms of RA compared with placebo plus methotrexate, as measured by mean change from baseline in DAS28 (ESR) and ACR 20, ACR 50, and ACR 70 responses (Table 1). Nearly twice as many patients in the abatacept arm than in the placebo arm achieved a good EULAR response or LDAS at 6 months, and approximately four times as many patients in the abatacept arm than in the placebo arm were in DAS28 (ESR)-defined remission at 6 months (Fig. 1) [17].

A similar response to treatment at 6 months was seen when the infliximab plus methotrexate and placebo plus methotrexate regimens were compared (Table 1; Fig. 1), and there were no significant between-group differences for response to abatacept or infliximab [17].

After 12 months of treatment, improvements in ACR 20, ACR 50, and ACR 70 responses and DAS28 (ESR) scores achieved at 6 months with abatacept- or infliximab-based treatment were maintained (Table 1). However, the proportions of patients achieving a good EULAR response, LDAS, and DAS28 (ESR)-defined remission with abatacept plus methotrexate continued to increase, whereas the response to infliximab-based treatment stabilized (Fig. 1) [17]. After 12 months, a greater reduction in DAS28 (ESR) was observed with abatacept plus methotrexate than with infliximab plus methotrexate (-2.88 vs -2.25 ; estimate of difference, 95% confidence interval [CI], -0.62 , -0.96 , -0.29) [17].

An increasing magnitude of clinical response (moving from ACR 20 to ACR 50) and improvement in disease activity (moving from LDAS to remission) between 6 and 12 months was achieved with abatacept- or infliximab-based regimens, and most patients maintained or improved their disease status during this time. A numerically higher percentage of patients receiving abatacept moved from LDAS at month 6 to remission at month 12 compared with patients treated with infliximab (41.7%; 95% CI, 22.8, 63.1 vs 28.0%; 95% CI, 12.9, 49.6, respectively; reported as an abstract) [27].

A significant, clinically meaningful improvement in physical function (HAQ-DI) was seen with abatacept or infliximab plus methotrexate versus placebo plus methotrexate at 6 months (Table 1). These improvements were maintained at 1 year, and there was no significant between-group difference [17].

Health-related quality of life

HRQOL was improved to a greater extent with abatacept plus methotrexate than placebo plus methotrexate in the AIM [16, 28] and ATTEST trials [17]. A clinically meaningful improvement (increase of ≥ 3 units) from baseline in the Medical Outcomes Study Short Form-36 physical and mental component summary scores was seen at 6 months with abatacept plus methotrexate in both trials, and this differed significantly from changes with placebo plus methotrexate ($P < 0.05$). After 12 months of treatment

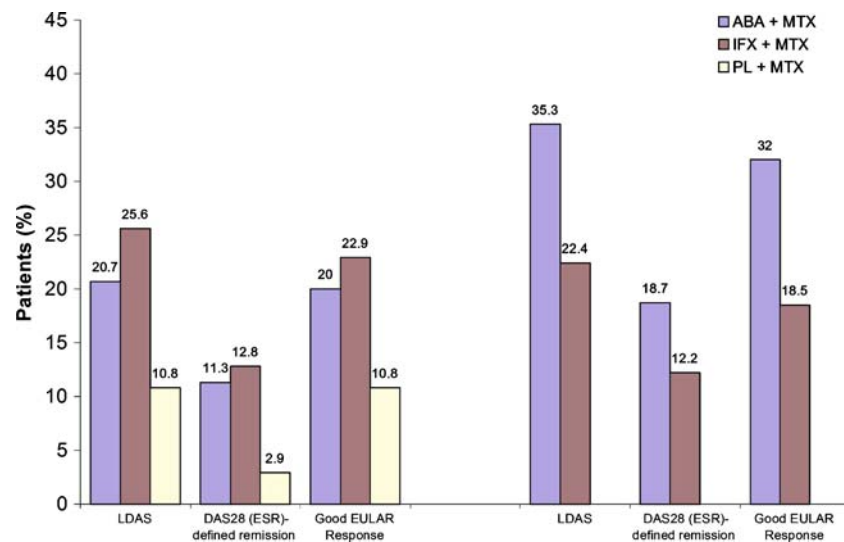


Fig. 1 Efficacy of abatacept (ABA) plus methotrexate (MTX) in patients with active rheumatoid arthritis, despite prior MTX. Proportion of patients who achieved LDAS ($DAS28 \leq 3.2$), DAS28 (ESR)-defined remission ($DAS28 < 2.6$), and a good EULAR response at 6 and 12 months with ABA ~ 10 mg/kg once every month ($n = 156$), infliximab (IFX) 3 mg/kg once every 8 weeks ($n = 165$), or matching placebo (PL; $n = 110$ [for 6 months only]), plus background MTX, in the

randomized, double-blind ATTEST trial [17]. ABA, IFX, and PL were administered as an intravenous infusion, and patients continued their previous MTX treatment regimen. ATTEST Abatacept or Infliximab vs Placebo, a Trial for Tolerability, Efficacy, and Safety in Treating rheumatoid arthritis, DAS28 28-joint count Disease Activity Score, DAS28 (ESR) DAS28 based on erythrocyte sedimentation rate, EULAR European League Against Rheumatism, LDAS low disease activity state

in the AIM trial, a significant between-group difference favoring abatacept was maintained for the physical (3.8; $P < 0.001$) and mental (1.76; $P = 0.038$) component summary scores [16].

Significant, clinically meaningful improvements in physical and mental component summary scores from baseline were also seen with infliximab plus methotrexate at 6 months compared with placebo plus methotrexate in ATTEST. However, at 12 months, the physical component score was improved to a greater extent with the abatacept regimen than with the infliximab regimen (between-group difference, 1.93; 95% CI, 0.02, 3.84) [17].

Long-term extensions

The OLE of the AIM trial included 83% of the 652 patients (abatacept, 378; placebo, 161) randomized in the double-blind trial. All patients received abatacept ~10 mg/kg plus methotrexate, with >90% (abatacept, 340; placebo, 148) completing year 1 of the extension [23] and 70% of the original abatacept recipients (266 of 378) receiving 5 years of treatment (reported as an abstract) [25]. As in the other two trials, most patients in ATTEST entered the OLE phase (86%; 372 of 431) and >90% of these patients (344 of 372) completed 2 years of treatment. Patients initially randomized to abatacept plus methotrexate continued on this combination, while those originally randomized to infliximab switched to abatacept on entering the extension at the 1-year time point (reported as abstracts) [19, 29].

ACR responses with abatacept plus methotrexate at year 1 in the AIM trial were maintained after 5 years of treatment (ACR 20, 81.9% at year 1 vs 83.6% at year 5; ACR 50, 54.0% vs 61.1%; ACR 70, 32.4% vs 39.6%) [25]. Post hoc analyses showed that DAS28 (CRP)-defined remission at year 1 (25.4%) was also sustained at year 5 (33.7%) [23, 25] and that the LDAS rate had increased by 27% at year 2 (from 44.1% at year 1 to 56.1%) [23]. Clinically meaningful improvements in physical function (HAQ-DI) and HRQOL achieved at 1 year with abatacept plus methotrexate were maintained at year 2 [23].

In the OLE of ATTEST, reduced disease activity was maintained with ongoing abatacept treatment [19]. The LDAS rate in the 132 patients who were originally randomized to abatacept plus methotrexate and continued this regimen in the extension phase was 37% at year 1 and 42% at year 2, and corresponding DAS28 (ESR)-defined remission rates were 20% and 26%. The LDAS and DAS28 (ESR)-defined remission rates at year 2 in patients who switched from infliximab plus methotrexate to abatacept plus methotrexate in the extension phase ($n = 136$) doubled and approximated those in patients receiving abatacept plus methotrexate throughout (LDAS, 23% at year 1 vs 45% at year 2; DAS28 (ESR)-defined remission, 13% vs 29%) [19].

ACR 20, ACR 50, and ACR 70 response rates achieved at the end of year 1 (72.4%, 45.5%, and 26.3%, respectively) were sustained (87%, 61%, and 41%) after 2 years of treatment with abatacept plus methotrexate [19]. In patients who switched from infliximab plus methotrexate to abatacept plus methotrexate at the end of year 1 ($n = 136$), further increases in ACR responses were evident after 1 year of treatment with abatacept plus methotrexate (ACR 20, 84% vs 55.8%; ACR 50, 71% vs 36.4%; ACR 70, 45% vs 20.6%) [19]. Further analysis showed that the majority of patients improved/maintained their disease status (based on DAS28 [CRP]) after switching to abatacept regardless of their response to infliximab treatment during the first year [29].

Radiographic response

Radiographic data were available for 92% of patients in the AIM trial [16]. Significantly greater slowing (to approximately half the rate) of structural damage progression was evident with abatacept plus methotrexate versus placebo plus methotrexate at 1 year. The median Genant-modified Sharp score for erosions (primary endpoint) with abatacept plus methotrexate was unchanged from baseline, whereas it was increased with placebo plus methotrexate (Table 1). Significant between-group differences favoring abatacept plus methotrexate were also evident for the change from baseline in median joint-space narrowing (JSN) scores (0.0 [25th and 75th percentiles, 0.0, 0.5] vs 0.0 [0.0, 1.0]; $P = 0.009$) and total scores (0.25 [0.0, 1.8] vs 0.53 [0.0, 2.5]; $P = 0.012$) [16].

Analysis of 2- [22, 23] and 5-year [24] radiographic data from AIM indicates that abatacept plus methotrexate slows structural damage progression in active RA. A 57% reduction in the radiographic progression rate with abatacept plus methotrexate, based on mean change from baseline of total score, occurred between years 1 and 2 (1.07 at year 1 vs 0.46 at year 2; $P < 0.0001$; $n = 324$) [22, 23]. There was a 66% reduction in the mean change from baseline in erosion score (0.62 vs 0.21) and a 47% reduction in the mean change from baseline in JSN score (0.45 vs 0.24).

The reduced rate of joint damage progression was maintained during years 3 to 5 ($n = 235$ – 293 ; reported as an abstract), with mean changes in total score of 0.37 between years 2 and 3 (0.23 for erosion and 0.14 for JSN scores), 0.34 between years 3 and 4 (0.23 and 0.11), and 0.26 between years 4 and 5 (0.11 and 0.14) [24].

After 2 years of treatment, 50% of patients (162 of 324) had no progression (change from baseline of ≤ 0 in total Sharp score), while 45% of patients who had some radiographic progression in year 1 of treatment (64 of 142 patients) had no progression during year 2 [22]. During

years 3 to 5, 45% to 46% of patients had no evidence of progression, and 98% of those without progression during years 1 to 4 did not progress during year 5 [24].

Pharmacoeconomic analyses

Two North American pharmacoeconomic analyses used data from abatacept trials to evaluate its cost-effectiveness as a first-line biologic therapy in patients with an inadequate response to nonbiologic DMARDs [30, 31]. An analysis from a US payer perspective (2006 costs) estimated that abatacept plus methotrexate was cost-effective versus methotrexate alone in biologic-naïve patients with active RA and an inadequate response to methotrexate. The incremental cost per quality-of-life year gained was \$US47,910 over a 10-year horizon and \$US43,041 over a lifetime horizon. At a willingness-to-pay threshold of \$US50,000 per quality-of-life year, abatacept had an 80% (10-year horizon) and 99% (lifetime horizon) probability of being cost-effective [31].

In another analysis from a Canadian payer perspective (2006 costs) using a 2-year time horizon [30], abatacept was dominant (i.e., less costly and more effective) over the sequential use of anti-TNF- α agents as a first-line biologic agent after an inadequate response to nonbiologic DMARDs. Mean cost-effectiveness ratios showed a significantly ($P < 0.001$) lower cost for achieving LDAS and DAS28-defined remission with abatacept as a first biologic

agent versus the sequential use of anti-TNF- α agents, with overall RA-related cost savings over 2 years of \$Can730 (LDAS) and \$Can504 (remission). These estimates were based on a greater probability of abatacept achieving LDAS (29.4% vs 15.6%) and DAS28-defined remission (14.8% vs 5.2%) [30].

Safety and tolerability

Abatacept was generally well tolerated in clinical trials in biologic-naïve patients with active RA (Table 2) [16–18]. The most common adverse events in the abatacept or placebo arms after 1 year of treatment in the AIM trial [16] were headache and nasopharyngitis. In the abatacept and placebo treatment groups, respectively, the occurrences of neoplasms (0.9% vs 0.9%) and serious infections (2.5% vs 0.9%), including tuberculosis (0.2% vs 0.5%), were low. In ATTEST, the incidences of serious and treatment-related serious adverse events were two to three times lower with abatacept plus methotrexate than with infliximab plus methotrexate at 6 and 12 months [17]. Serious infections were fourfold higher with infliximab-based than with abatacept-based treatment at 12 months, and five serious opportunistic infections (including two cases of tuberculosis) occurred in the infliximab arm compared with none in the abatacept arm. Autoimmune disorders and malignant neoplasms were uncommon with either biologic DMARD in this study [17]. The authors concluded that

Table 2 Summary of safety for biologic-naïve pts who received at least one dose of abatacept plus background methotrexate therapy in clinical trials

	Phase IIb dose-finding study ^a [36]	AIM ^b [16]	ATTEST ^b [17]
Patients	220	433	156
AEs/100 person-years	489.7	300.2	NA
Discontinuations due to AEs, pts (%)	18 (8.2)	19 (4.4)	5 (3.2)
SAEs/100 person-years	20.0	17.7	NA
Discontinuations due to SAEs, pts (%)	9 (4.1)	10 (2.3)	4 (2.6)
Infections/100 person-years	94.2	90.9	95.31
Serious infections/100 person-years	2.1	4.2	2.0
Deaths, pts (%)	1 (0.5)	1 (0.2)	1 (0.6)
Malignancies, pts (%)	4 (1.8)	4 (0.9) ^c	1 (0.6)
Tuberculosis, pts (%)	0 (0.0)	1 (0.2)	0 (0.0)
Opportunistic infections, pts (%)	NA	1 (0.2)	0 (0.0)
Autoimmune symptoms or disorders, pts (%)	NA	0 (0.0)	2 (1.3)

AE adverse event, AIM Abatacept in Inadequate Responders to Methotrexate, ATTEST Abatacept or Infliximab vs Placebo, a Trial for Tolerability, Efficacy, and Safety in Treating rheumatoid arthritis, NA data not available, pts patients, SAE serious AE

^a Patients received abatacept 2 mg/kg or abatacept 10 mg/kg on days 1, 15, and 30, then monthly+MTX

^b Patients received abatacept ~10 mg/kg on days 1, 15, and 29, then every 4 weeks+MTX

^c Includes all neoplasms (benign, malignant, and unspecified)

abatacept had a favorable safety profile with respect to infliximab.

Long-term data from the AIM [25] and phase IIb dose-finding studies [20, 21] showed no new safety or tolerability issues with abatacept plus methotrexate after 5 to 7 years of treatment. In the abatacept clinical development program for RA ($n=4,134$; 7 trials, 8,388 person-years of exposure), the incidence of malignancy with abatacept was 0.061 per 100 person-years, which was consistent with that in patients treated with other DMARDs ($n=41,529$) in five observational cohorts [32]. In the placebo-controlled portions of five abatacept clinical trials, more cases of lung cancer (4, 0.20%) were observed in patients receiving abatacept compared with those receiving placebo (0, 0.0%) [33]. The most recent data from the cumulative safety database show no increase in the risk of lung cancer with abatacept, with an observed incidence rate of 0.15 per 100 person-years (95% CI, 0.08–0.27) after 8,388 person-years of exposure, with no increase over time [32].

A meta-analysis of trials in patients with RA concluded that abatacept was not associated with an increased risk of serious infections compared with placebo (pooled odds ratio, 1.35; 95% CI, 0.78, 2.32) [34]. In an integrated analysis of five studies in the abatacept clinical development program (4,764 person-years of exposure) [33], the rates of serious infection were 1.9% and 3.0% for placebo and abatacept, respectively, with no increase with increased exposure to abatacept. Tuberculosis, of particular concern among patients treated with anti-TNF- α agents, occurred in two patients receiving abatacept and one placebo-treated patient. Malignancies occurred at a similar, low rate between patients receiving abatacept and placebo, and lymphoma was reported in one patient (1.4%) receiving abatacept. Systemic lupus erythematosus was reported in three patients [33].

Another cumulative safety analysis, with >10,000 person-years of exposure to abatacept, found that the incidence rate of hospitalized infections was consistent over time with increasing duration of exposure to abatacept. The incidence rate of hospitalized infections for the cumulative period was 2.73 per 100 person-years [35].

Conclusion

Clinical trial results have shown that abatacept in combination with methotrexate significantly improves signs and symptoms of RA, physical function, and HRQOL in biologic-naïve patients with active RA and an inadequate response to methotrexate. A number of these patients also achieved LDAS or DAS28-defined remission and had evidence that abatacept plus methotrexate inhibited radio-

graphic progression. Results from extension studies indicate that the beneficial effects of abatacept plus methotrexate, including reduced disease activity, slowing of disease progression, and remission rates, are sustained long term. Abatacept plus methotrexate was generally well tolerated in clinical trials, and no new safety or tolerability issues have emerged in extension studies or analyses of data from the abatacept clinical development program. The acceptability of abatacept plus methotrexate as a long-term therapy was also evident in the high rates of patient retention in the extension phases of the double-blind trials.

Although biologic DMARDs are more costly than nonbiologic DMARDs, the predicted cost-effectiveness of abatacept as a first-line biologic therapy in patients with active RA and an inadequate response to methotrexate is within the currently acceptable range, and it is dominant over sequential anti-TNF- α agents. Thus, abatacept is an effective, safe, and well-tolerated long-term therapy in biologic-naïve patients with active RA and an inadequate response to methotrexate and could be considered as a first-line biologic DMARD in the treatment of RA.

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