Drug Evaluation
Future Rheumatology

Durability of therapeutic response in rheumatoid arthritis: clinical trial experience with abatacept

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The chronic, progressive nature of rheumatoid arthritis (RA) demands long-term treatment with therapies able to reduce disease activity, prevent progressive destruction of joints and restore quality of life, and also to maintain these responses over the long term. However, many established RA therapies are unable to consistently maintain initial clinical responses, highlighting the need for additional treatment options that deliver sustainable responses. Emerging clinical trial data for abatacept provides further insight into the durability of this agent; evidence from Phase III trials in biologic-naive patients and those with an inadequate response to tumor necrosis factor-α antagonists has demonstrated that abatacept provides significant and sustained benefits over 2 years across a range of clinical, radiographic and quality-of-life end points, with a consistent and acceptable safety and tolerability profile. These findings suggest that abatacept is a valuable addition to the RA treatment paradigm, and may provide durable responses for adults with moderately to severely active RA.

Rheumatoid arthritis (RA) is a progressive, debilitating autoimmune disease that is associated with increased morbidity and mortality and requires chronic treatment [1]. Unless appropriately managed, within 10 years of disease onset over half of patients with RA will be work disabled [2]. Treatment goals for RA include reduction in disease activity, prevention of the progressive destruction of joints, restoration of quality of life (QoL) and, ultimately, the achievement of sustained disease remission [3]. While many established therapies for RA offer reductions in disease signs and symptoms and have been shown to inhibit radiographic progression, a common concern is their inability to consistently provide sustained benefits. This is seen with a number of therapies, including the widely used DMARD, methotrexate (MTX) [4]. Although an effective therapy for RA, a proportion of patients prescribed MTX exhibit a decline in response over time. Additionally, despite the known efficacy of newer biologic DMARDs, such as TNF-α antagonists, a subset of patients fail to maintain their initial response over time [5]. It may be possible to manage some of these patients through dose titration, dose scheduling adjustments or concomitant use of nonbiologic DMARD therapy; however, these methods are not always sufficient to maintain adequate disease control [6], highlighting the need for new therapies that provide durable improvements.

This paper discusses the importance of defining a durable response to RA therapy, and provides an overview of the available long-term clinical trial data for abatacept (ORENCIA®; Bristol-Myers Squibb, NJ, USA) as evidence that this therapeutic option has the potential to provide clinically meaningful and, importantly, sustained improvements in patients with this chronic disease.

Durability of response in patients with rheumatoid arthritis

It is important that durability of response be defined in a clinical setting in order to ensure that a patient's disease is managed effectively. At present, there is no formal consensus of what defines a durable or, for that matter, an adequate response, the latter being to some degree a prerequisite for the former. It is the authors opinion that, firstly, patients should be made to feel better as rapidly as possible, with signs and symptoms of disease well controlled, and radiographic progression inhibited. Secondly, this initial response should be maintained over years without the chronic use of concomitant steroids. Although natural fluctuations in disease activity might contribute to changes in treatment responses, the continued requirement for modifications to a given treatment regimen, for example, by dose titration or the addition of concomitant background therapy, may also signal a lack or loss of durability of response.

It is imperative that any decline in response to treatment be quickly identified in order to prevent further, and in some cases unnecessary, progression of the disease. This can be achieved

Keywords
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through frequent assessment using consistent measures of response as part of routine clinical care. Successful evaluation of a patient's response to treatment over time should include regular assessments across multiple clinical, structural and patient-reported end points. In addition, as chronic long-term treatment for RA carries a risk of adverse events (AEs), safety concerns should also be assessed routinely, and the benefit-to-risk ratio re-evaluated over the course of treatment.

Abatacept: a brief overview

Abatacept is a first-in-class selective T-cell co-stimulation modulator, which was approved for its first indication in RA by the USA FDA in 2005. Emerging clinical trial data provide an interesting insight into the potential durability of this agent over the longer term.

Abatacept is indicated for reducing signs and symptoms, inducing a major clinical response, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active RA [101]. It is a fully human, soluble fusion protein, consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) linked to the modified Fc (hinge, CH2 and CH3 domains) portion of human immunoglobulin G1. By employing the high binding avidity of CTLA-4 (Figure 1), abatacept competitively binds to CD80/CD86 on the antigen-presenting cell and interrupts the positive costimulatory signal that is essential for T-cell activation [101]. The competitive binding event to CD80/CD86 causes T-cell modulation rather than depletion, leaving other co-stimulatory pathways intact, thereby allowing normal immune processes to continue to function.

Clinical experience with abatacept to date

Abatacept has been studied in two distinct RA patient populations: biologic-naive patients with

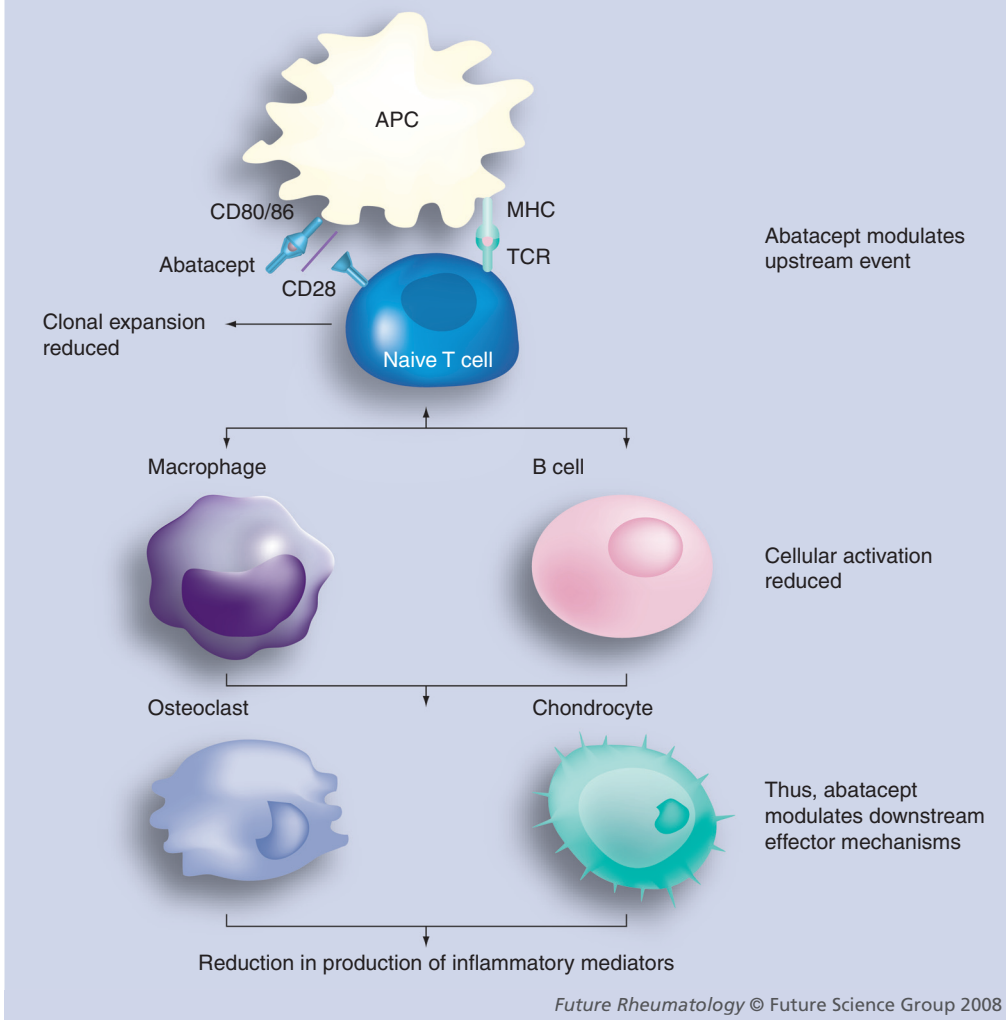


Figure 1. Abatacept mechanism of action. APC: Antigen-presenting cell; MHC: Major histocompatibility complex; TCR: T-cell receptor.

an inadequate response to MTX (Abatacept in Inadequate responders to Methotrexate trial [AIM]; a 12-month Phase IIb trial) [7,8], and those with an inadequate response to TNF-α antagonists (Abatacept Trial in Treatment of Anti-TNF-α INadequate responders [ATTAIN]) (Table 1) [9]. The Phase IIb trial has reported experience through 5 years, and is still ongoing after 7 years; this paper reviews the recently published 2-year data from the AIM and ATTAIN trials as an indicator of both durability and potential over the longer term.

Disease activity and clinical-treatment effectiveness are typically assessed using the ACR criteria, which defines durability as either a major clinical response (MCR) or an extended MCR (EMCR), whereby patients maintain a 70% reduction in ACR criteria (ACR70) or greater response for at least 6 or 9 consecutive months, respectively [10]. Disease Activity Score 28 (DAS28) can also be used to assess disease activity [11], whereby a score of less than 3.2 indicates a Low Disease Activity State (LDAS) and a score of 2.6 or less indicates clinical remission [12].

In the double-blind periods of the AIM and ATTAIN trials, a fixed dose of abatacept approximating 10 mg/kg demonstrated both statistically and clinically significant improvements in the signs and symptoms of RA, physical function and health-related quality of life (HRQoL) outcomes compared with placebo [8,9]. As early as day 15, abatacept demonstrated statistically significant improvements in ACR20 response rates compared with placebo [8,9] and, in biologic-naive patients, demonstrated a significant slowing of structural damage progression through 1 year [8].

The longer term safety and efficacy of abatacept is currently being evaluated in the open-label extensions of the AIM and ATTAIN trials (Table 1). The data indicate a consistent safety and durable efficacy profile. It should be noted that analyses of the efficacy data were performed either on the intent-to-treat population using data from all patients, with those who discontinued the study for any reason at any time being considered as nonresponders (nonresponder analysis), or using only patients with data available at the visit of interest (as-observed analysis) [13,14]. In both MTX and TNF-α antagonist inadequate responders, abatacept, at a fixed dose, maintained the initial improvements in the signs and symptoms of RA, physical function and HRQoL outcomes over 2 years of treatment and, in some cases, provided further improvements in these outcomes over time [13,14]. For example, in the ATTAIN trial, the proportion of patients receiving prednisone decreased over 2 years of abatacept use; 59.2% at baseline versus 59.6% at 6 months and 49.7% at 2 years [13].

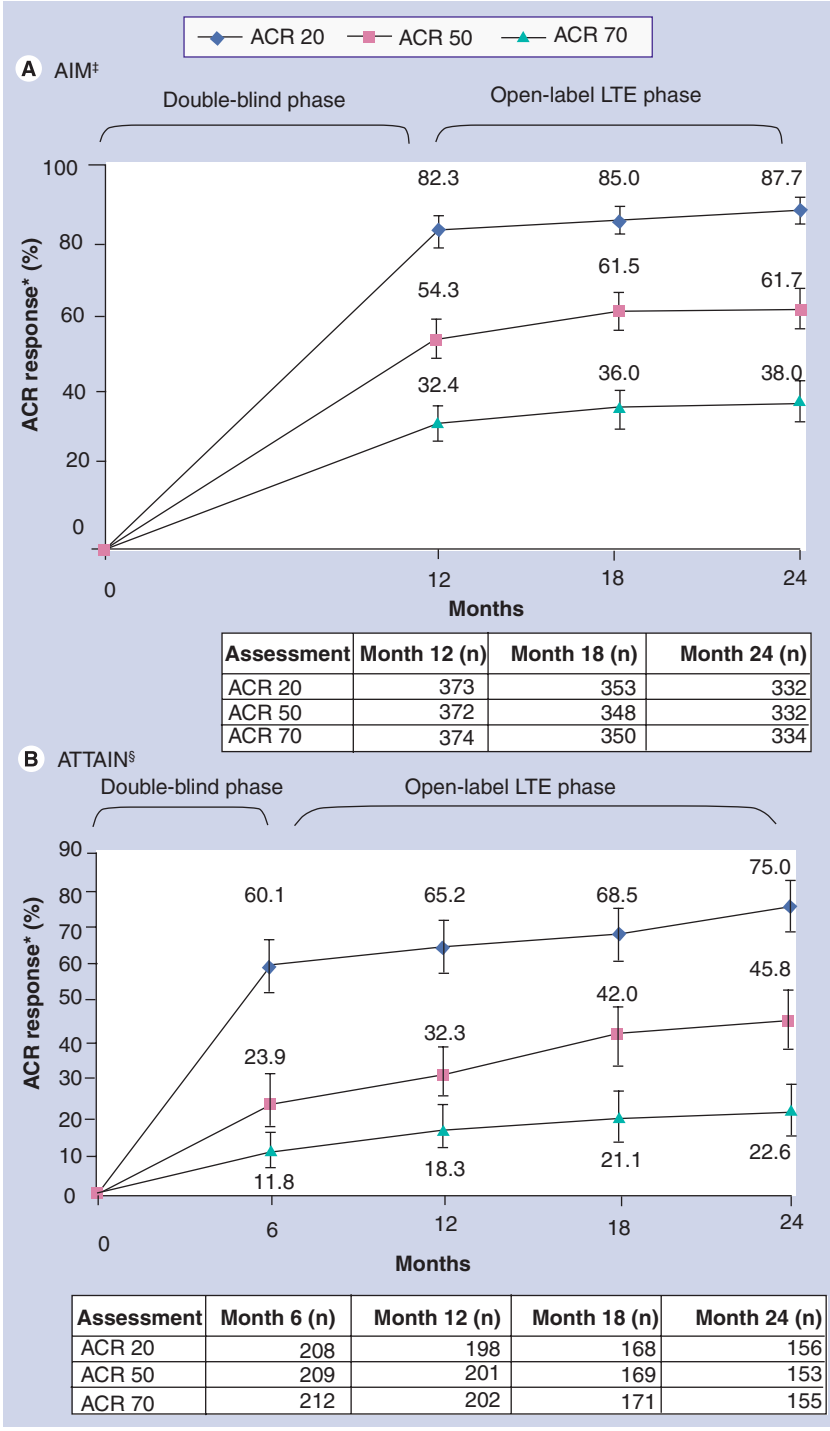
Clinical end points

Overall, the ACR responses observed at the end of the double-blind period were maintained or improved in patients with an inadequate response to MTX or TNF-α antagonists over the open-label extension periods (Figure 2). Following 1 and 2 years of treatment in MTX inadequate responders, ACR20 responses were 82.3 and 87.7%, respectively; ACR50 responses were 54.3 and 61.7%, respectively; and ACR70 responses were 32.4 and 38%, respectively (Figure 2A) [14]. Following 6 months and 2 years of treatment in TNF-α inadequate responders,

Table 1. Overview of two Phase III key abatacept clinical trials.

Study	Study design	Dose	Patient type	DB (n)	OL* (n)	Ref.
AIM	Phase III, 12-month, randomized, DB, placebo-controlled study with parallel dosing, with an OL extension	10 mg/kg abatacept as a standardized dose (500 mg for patients <60 kg, 750 mg for patients 60–100 kg and 1 g for patients >100 kg) or placebo by iv. infusion on a background of MTX	Biologic-naïve patients with active RA receiving MTX	Abatacept + MTX = 433 Placebo + MTX = 219	539	[8,14]
ATTAIN	Phase III, 6-month, randomized, DB, placebo-controlled study with parallel dosing, with an OL extension	10 mg/kg abatacept as a standardized dose (500 mg for patients <60 kg, 750 mg for patients 60–100 kg and 1 g for patients >100 kg) or placebo by iv. infusion on a background of at least one DMARD	Patients with active RA who had been treated with TNF-α antagonist therapy for ≥3 months and were designated as TNF-α antagonist therapy failures due to inadequate efficacy	Abatacept + DMARDs = 258 Placebo + DMARDs = 133	317	[9,13]

**All patients were treated with 10 mg/kg abatacept during the OL phase.*
AIM: Abatacept in inadequate responders to methotrexate trial; ATTAIN: Abatacept trial in treatment of anti-TNF-α inadequate responders; DB: Double blind; iv.: Intravenously; MTX: Methotrexate; OL: Open label.



Assessment	Month 12 (n)	Month 18 (n)	Month 24 (n)
ACR 20	373	353	332
ACR 50	372	348	332
ACR 70	374	350	334

Assessment	Month 6 (n)	Month 12 (n)	Month 18 (n)	Month 24 (n)
ACR 20	208	198	168	156
ACR 50	209	201	169	153
ACR 70	212	202	171	155

Figure 2. Summary of ACR20, 50 and 70 responses through 2 years of treatment for the abatacept arms only. (A) AIM (reproduced from [14]. Copyright [2008, John Wiley & Sons, Inc.]. Reproduced with permission of John Wiley and Sons Inc.); **(B)** ATTAIN (reproduced from [13] with permission from the BMJ Publishing Group).
*Responses are based on the as-observed population of patients with data available at the visit of interest; ‡Patients who received placebo plus MTX upon entry into the open-label extension period were switched to abatacept plus MTX on day 365; §All patients who received placebo plus DMARDs upon entry into the open-label extension period were switched to abatacept plus DMARDs on day 169.
AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-TNF-α INadequate responders; LTE: Long-term extension; MTX: Methotrexate.

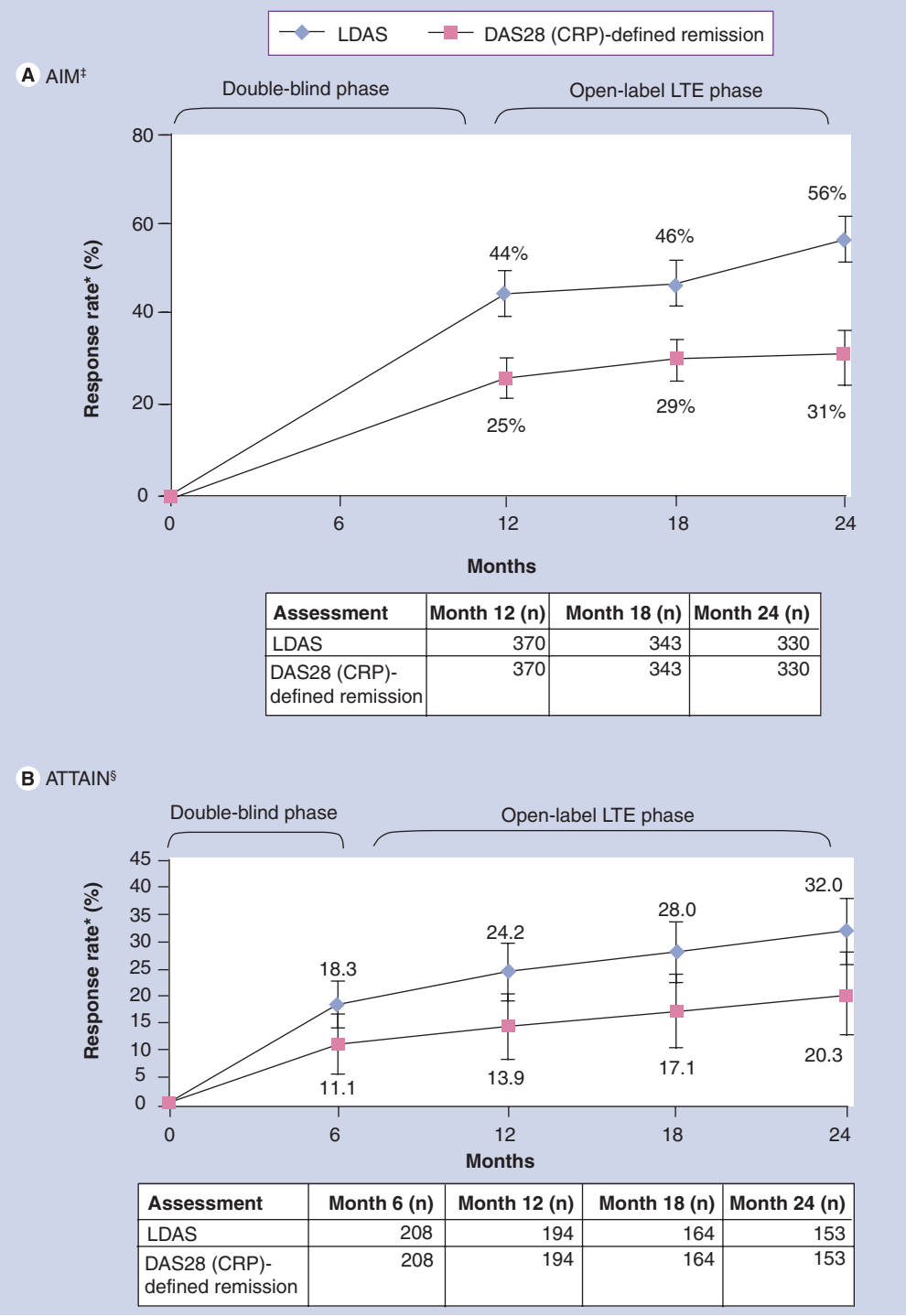
ACR20 responses were 59.4 and 56.2%, respectively; ACR50 responses were 23.5 and 33.2%, respectively; and ACR70 responses were 11.5 and 16.1%, respectively (Figure 2B) [13]. The proportion of patients achieving an MCR and an EMCR increased in the second year for both patient populations receiving abatacept; 16.0 and 9.0% of MTX inadequate responders achieved a MCR and an EMCR, respectively, at year 1, and this proportion increased to 28.2 and 19.1%, respectively, at year 2 [14]. Similar results were observed in the TNF-α antagonist inadequate responders at 2 years, with 18.9 and 10.6% achieving an MCR or an EMCR, respectively [13].

Improvements in LDAS and DAS28-defined remission were also demonstrated through 2 years of abatacept treatment in both trials (Figure 3) [13,14]. In MTX inadequate responders, the proportion of patients achieving LDAS and DAS28-defined remission increased from 44 and 25% at the end of the double-blind period to 56 and 31% at 2 years, respectively [14]. The 95% confidence intervals (95% CIs) for the proportion of patients with an LDAS did not overlap at 1 year (44.1% [95% CI: 39–49%]) versus 2 years (56.1% [95% CI: 51–61%]) (Figure 3A) [14]. In TNF-α inadequate responders, the proportion of patients (95% CI) achieving LDAS and DAS28-defined remission increased from 18.3 (95% CI: 13.0–23.5%) and 11.1% (95% CI: 6.8–15.3%) at the end of the double-blind period, to 32.0 (95% CI: 24.6–39.4%) and 20.3% (95% CI: 13.9–26.6%) at 2 years, respectively [13]. There was no overlap in the 95% CI for LDAS between the double-blind period and 2 years (Figure 3B) [13].

In addition, 3-year data from both the AIM and ATTAIN trials were presented at the annual meeting of ACR in 2007, which demonstrated that the proportion of abatacept-treated patients who were ACR responders or achieved LDAS/DAS28 (CRP)-defined remission increased through 3 years, and there was no overlap of 95% CIs from 6 months to 3 years [15].

Structural (radiographic) end points

The findings from the long-term follow-up period of the AIM trial have demonstrated that abatacept inhibits the progression of structural damage (based on Genant-modified Sharp total scores, joint-space narrowing and erosion scores), with greater effects observed at year 2 than at year 1 [16]. The mean change in Genant-modified Sharp total score was reduced from 1.07 units in year 1 to 0.46 units in year 2, with similar changes reported for joint-space narrowing and erosion scores. During the first year, 56% of abatacept-treated



Assessment	Month 12 (n)	Month 18 (n)	Month 24 (n)
LDAS	370	343	330
DAS28 (CRP)-defined remission	370	343	330

Assessment	Month 6 (n)	Month 12 (n)	Month 18 (n)	Month 24 (n)
LDAS	208	194	164	153
DAS28 (CRP)-defined remission	208	194	164	153

Figure 3. Summary of LDAS and DAS28 (CRP)-defined remission through 2 years of treatment for the abatacept arms only. (A) AIM (reproduced from [14]. Copyright [2008, John Wiley & Sons, Inc.]. Reproduced with permission of John Wiley and Sons Inc.); **(B)** ATTAIN (reproduced from [13] with permission from the BMJ Publishing Group).
*Responses are based on the as-observed population of patients with data available at the visit of interest; ‡Patients who received placebo plus MTX upon entry into the open-label extension period were switched to abatacept plus MTX on day 365; §All patients who received placebo plus DMARDs upon entry into the open-label extension period were switched to abatacept plus DMARDs on day 169.
AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-TNF-α Inadequate Responders; CRP: C-reactive protein; DAS28: Disease Activity Score 28; LDAS: Low Disease Activity State; LTE: Long-term extension; MTX: Methotrexate.

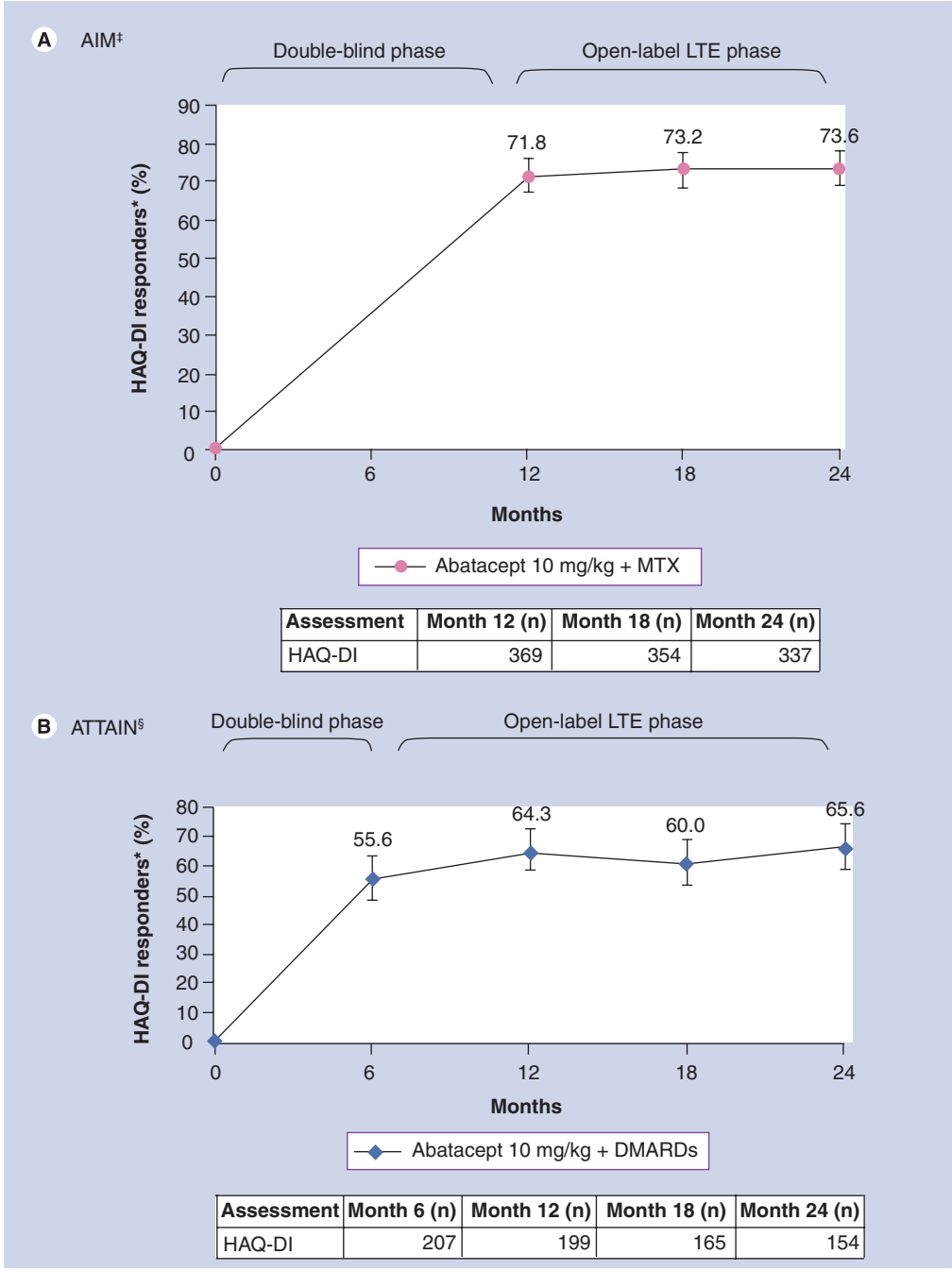


Figure 4. Proportion of patients with clinically meaningful as-observed HAQ-DI responses through 2 years of treatment for the abatacept arms only. (A) AIM (reproduced from [14]. Copyright [2008, John Wiley & Sons, Inc.]. Reproduced with permission of John Wiley and Sons Inc.); **(B)** ATTAIN (reproduced from [13] with permission from the BMJ Publishing Group).
*HAQ-DI responses (improvement of ≥0.3 units from baseline) are based on the as-observed population of patients with data available at the visit of interest; ‡Patients who received placebo plus MTX upon entry into the open-label extension period were switched to abatacept plus MTX on day 365; §All patients who received placebo plus DMARDs upon entry into the open-label extension period were switched to abatacept plus DMARDs on day 169.
AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-TNF-α INadequate responders; HAQ-DI: Health assessment questionnaire disability index; LTE: Long-term extension; MTX: Methotrexate.

patients had no progression of structural damage (defined by a change in the total score of ≤0 compared with baseline) compared with 45% of placebo-treated patients. In their second year, the proportion of abatacept-treated patients with no radiographic progression increased to 66% [16].

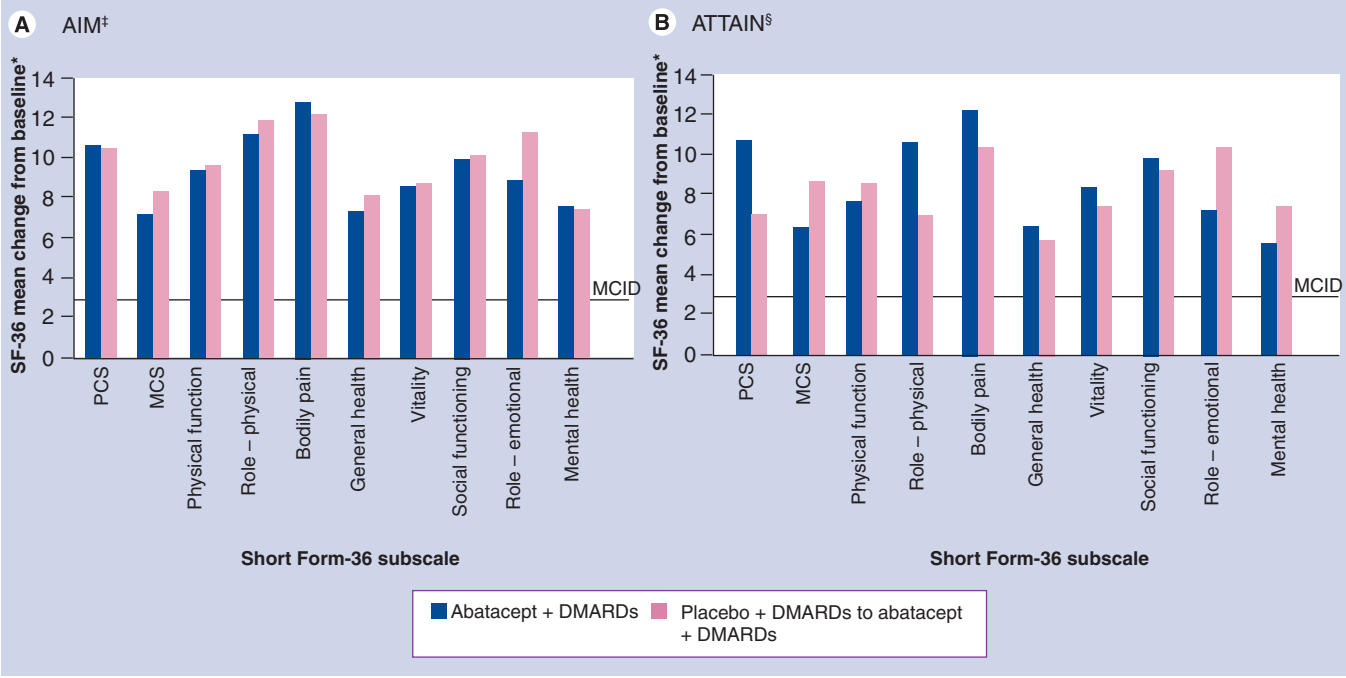


Figure 5. Improvements in health-related quality of life through 2 years of treatment. (A) AIM (reproduced from [14]. Copyright [2008, John Wiley & Sons, Inc.]. Reproduced with permission of John Wiley and Sons Inc.); **(B)** ATTAIN (reproduced from [13] with permission from the BMJ Publishing Group).
*Mean change from baseline in SF-36 subscale scores are based on the as-observed population of patients with data available at the visit of interest; ‡Patients who received placebo plus MTX upon entry into the open-label extension period were switched to abatacept plus MTX on day 365; §All patients who received placebo plus DMARDs upon entry into the open-label extension period were switched to abatacept plus DMARDs on day 169.
AIM: Abatacept in Inadequate responders to Methotrexate; ATTAIN: Abatacept Trial in Treatment of Anti-TNF-α INadequate responders; MCID: Minimal clinically important difference; MSC: Mental component summary; MTX: Methotrexate; PCS: Physical component summary; SF-36: Short Form-36.

Patient-centered outcomes

Abatacept has demonstrated significant, sustained and clinically meaningful improvements in physical function and across a wide range of HRQoL outcomes [13,14]. The proportion of patients achieving a clinically meaningful improvement (defined as a reduction in the baseline score of ≥0.3) in physical function, as assessed by the Heath Assessment Questionnaire Disability Index (HAQ-DI), was maintained through 2 years of abatacept treatment in both patient populations (Figure 4A & B) [13,14]. In MTX inadequate responders, a total of 66.8% patients treated with abatacept demonstrated a clinically meaningful improvement in physical function at 2 years as measured by HAQ-DI response, compared with 71.8% after 1 year of treatment [14]. In ATTAIN, the proportion of patients experiencing a clinically meaningful HAQ-DI response at 2 years was maintained [14].

The clinically meaningful improvements in all eight subscales of the Short Form-36 (SF-36) health survey, including mental and physical component scores (MCS and PCS), observed at the end of the double-blind period were also maintained through 2 years of abatacept treatment in both MTX and TNF-α inadequate responders (Figure 5A & B) [13,14]. The mean improvement from baseline in the SF-36 score for the MCS and PCS at 2 years was 7.2 and 10.6, respectively, for MTX inadequate responders and 6.2 and 10.3, respectively, for TNF-α inadequate responders.

Along with the physically disabling effects of RA, the mental wellbeing of patients is often impacted [17]; therefore, it is important to assess patient-reported outcome measures, such as sleep quality and fatigue, which contribute to work and relationship difficulties [1]. Using a 100 mm visual analog scale, improvements in fatigue were maintained through 2 years in both the AIM and ATTAIN studies [13,14]. In MTX inadequate responders, the mean improvement from baseline was 28.0 and 30.9 points after 1 and 2 years, respectively. Similarly, in TNF-α antagonist inadequate responders, the mean improvement from baseline was 25.0 and 28.2 points after 6 months and 2 years, respectively. Patients from both trials also experienced improvements in sleep quality, measured using

the Medical Outcomes Study-Sleep Scale, and these improvements were maintained over 2 years.

Tolerability & safety profile

The safety and tolerability findings observed during the open-label extensions of AIM and ATTAIN were consistent with the findings from the double-blind study periods, and support the use of abatacept over the longer term (Table 2) [13,14].

Administration of abatacept was associated with an overall low incidence of acute infusional events during the course of the AIM and ATTAIN trials [13,14]. In the open-label extensions of these trials, the types and incidence of the most commonly reported AEs were generally similar to those reported in the double-blind periods [13,14]. Through the double-blind and long-term follow-up periods of the abatacept-treated MTX inadequate responders, a total of 550 patients experienced AEs at an incidence of 257.7/100 patient-years, which is consistent with the rate of AEs reported for the double-blind period alone (300.2/100 patient-years) [14]. In the comparable periods of abatacept treatment in TNF-α antagonist inadequate responders, a total of 329 patients experienced AEs at an incidence of 308.7/100 patient-years, which is lower than the rate of AEs reported for the double-blind period alone (436.5/100 patient-years) [13].

During 2 years of treatment in the AIM and ATTAIN trials, there was no increase in the reported incidence of infections, serious infections or malignancies [13,14]. Overall, the rates were similar to those reported during the double-blind periods alone [13,14]. As presented at the annual meeting of ACR in 2007, no unique safety events were observed through 3 years of the AIM and ATTAIN trials, compared with the double-blind periods of these trials [15].

Table 2. Summary of cumulative safety in the AIM and ATTAIN trials.

Events	Study cumulative period (days 1–729)	
	AIM (n = 593)*	*ATTAIN (n = 357*)*
AEs/100 patient-years	257.7	308.7
SAEs/100 patient-years	16.3	23.4
Infections/100 patient-years	77.6	89.4
Serious infection/100 patient-years	4.3	5.0
Discontinuations due to infection (n)	7	5
Malignancies (n)	14	11
Autoimmune disease (n)	15	8
Deaths (n)	3	2

**All patients who were randomized to abatacept and received one dose of study medication, plus all patients who were randomized to placebo and entered the long-term extension (and subsequently received one dose of study medication).*
AE: Adverse event; AIM: Abatacept in Inadequate responders to Methotrexate trial; ATTAIN: Abatacept Trial in Treatment of Anti-TNF-α INadequate responders; SAE: Serious adverse event.

Conclusion

The chronic and progressive nature of the pathophysiology of RA underscores the importance of achieving a durable treatment response; however, consensus on what defines a durable response to therapy and how to monitor or measure such a response is required. In the future, regulatory bodies may well establish requirements for monitoring disease activity and for providing evidence that preset efficacy targets are being achieved by patients to demonstrate the value of the treatment.

The complex heterogeneity of RA, resulting in a large amount of interindividual variability in the disease pathology and treatment outcomes, emphasizes the need for a variety of durable therapeutic options with different mechanisms of action; abatacept is a class of biologic therapy for RA that fits this criteria. Evidence from key Phase III clinical trials has demonstrated that over 2 years of treatment, abatacept provides significant and sustained benefits across a wide range of clinical end points, including HRQoL, in both biologic-naive patients with an inadequate response to MTX and those with an inadequate response to TNF-α antagonists, together with a consistent and acceptable safety and tolerability profile [13,14]. Furthermore, these findings were achieved without the need for dose adjustment. The 3-year data from these studies are anticipated, and it will be interesting to monitor the evolution of the clinical profile of abatacept over the longer term.

In lieu of longer-term outcomes, the findings to date suggest that abatacept is a valuable addition to the RA treatment paradigm, and may provide durable responses for patients with an inadequate response to MTX who have not received prior biologic therapy, as well as for those who have not responded well to treatment with TNF-α antagonists.

Future perspective

In lieu of a cure for RA, it is hoped that the development of alternative RA treatments will provide more patients with an achievable durable response from their treatment, and ultimately long-term relief from the chronic and disabling effects of this disease.

Executive summary

Durability of response in patients with rheumatoid arthritis

- Rheumatoid arthritis (RA) is a progressive, debilitating autoimmune disease associated with increased morbidity and mortality that requires chronic treatment.
- Without a cure, inhibiting the destructive pathway of the disease over the long-term is the main treatment objective and highlights the need for durable therapies for RA.
- Defining both adequacy and durability of response in a clinical setting is key in the management of RA, such that alternative treatments can be quickly sought following a decline in effectiveness of current therapy.
- Multiple assessments must be carried out on a consistent and routine basis over the course of treatment, in order to appropriately evaluate adequate and continued response.

Abatacept: a brief overview

- The development of treatments with novel mechanism of actions means that rheumatologists now have more options for managing patients with RA.
- Abatacept selectively modulates the activation of T cells; T cells are believed to play a key role in the immunopathology of RA.

The Phase III clinical experience with abatacept

- Abatacept, at a fixed dose, not only maintained initial improvements in the signs and symptoms of RA, physical function and health-related quality of life outcomes over 2 years of treatment in both methotrexate (MTX) and TNF-α antagonist inadequate responders, but in some cases, also improved patient-reported outcomes.

Conclusion

- The findings to date suggest that abatacept is a valuable addition to the RA-treatment paradigm and may provide clinically meaningful and durable responses for both patients with an inadequate response to MTX who have not received prior biologic therapy, as well as those who have not responded well to treatment with TNF-α antagonists.

One such alternative therapy, abatacept, has demonstrated potential durability of response as observed during the long-term extension of clinical trials involving biologic-naive patients with RA with an inadequate response to MTX and patients who have had an inadequate response to TNF-α antagonists. Along with more traditional measures, studies with abatacept have also highlighted the importance of assessing HRQoL outcomes.

Significantly improving day-to-day living for patients with RA over the long term has become a real possibility and an achievable goal of treatment. Newer biologic therapies, such as abatacept, may serve to add to these improvements if current trends in clinical outcomes continue.

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