Efficacy and safety of abatacept therapy for rheumatoid arthritis in routine clinical practice

Aim: To evaluate treatment of rheumatoid arthritis with abatacept in the real-life clinic setting. **Materials & methods:** Patients who initiated abatacept at a single US clinic during an 18-month period were assessed in this observational, retrospective study. Patient retention, disease activity (Disease Activity Score 28 [DAS28] and Clinical Disease Activity Index [CDAI]: last observation carried forward analysis) and discontinuations due to adverse events were evaluated. **Results:** A total of 100 successive patients were included. At baseline, 97% had failed one or more anti-TNF therapy, mean DAS28 was 4.4 and CDAI was 32.9. At month 6, 80% remained on treatment. Seven out of 100 patients discontinued due to adverse events. For patients with available data, 44.1% (30/68) achieved Low Disease Activity State (≤3.2), 32.5% (27/83) low CDAI (≤10) and 33.8% (23/68) DAS28 remission (<2.6) at month 6. **Conclusions:** These real-world data are consistent with findings from clinical trials, and support abatacept as a therapeutic option. Further observations from larger cohorts of patients over longer treatment periods are now ongoing.

KEYWORDS: abatacept ▪ biologic disease-modifying antirheumatic drugs ▪ Clinical Disease Activity Index ▪ clinical practice ▪ Disease Activity Score 28 ▪ patient retention ▪ rheumatoid arthritis

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Treatment of rheumatoid arthritis (RA) includes both biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX) and anti-TNF therapies. Although these treatments benefit numerous patients with RA, a substantial portion do not respond to therapy, or they can lose their initial treatment response over time [1,2]. In addition, some patients are intolerant to anti-TNF agents or experience treatment-associated adverse events (AEs), and certain comorbidities can preclude their use [1,2]. A number of therapeutic options are available that target the pathogenesis of RA via alternative mechanisms of action to anti-TNF agents. One such therapy is abatacept, which modulates T-cell function by selectively targeting the CD80/CD86:CD28 signal required for full T-cell activation [3]. Data obtained from large, randomized, placebo-controlled clinical trials (RCTs) of abatacept in different RA patient populations, including MTX-naive patients [4] and those with an inadequate response to MTX [5,6] or to anti-TNF therapies [7,8], have demonstrated the sustained efficacy and acceptable safety of T-cell modulation as a therapeutic approach for the treatment of RA. These data are supported by findings from a large, Phase IIIb/IV, multicenter, open-label study of abatacept in anti-TNF therapy inadequate responders (the Abatacept Researched in RA patients with an Inadequate anti-TNF response to Validate Effectiveness [ARRIVE] trial) [9]. ARRIVE was designed to include patients likely to be excluded from RCTs and, therefore, more closely resemble those encountered in clinical practice.

Although clinical trial data are invaluable, there will always be variation between the results found in the trial setting and those seen in the real-world clinical practice setting. Multiple factors contribute to this variation, arising from numerous inherent differences between RCTs and clinical practice: clinical trials often apply restrictive patient selection criteria, for example the exclusion of elderly patients or patients with comorbidities; washout periods of prior therapies are often utilized in clinical trials, which may lead to increased disease activity immediately before study commencement; different evaluation criteria are also often used in the two settings, with RCTs generally employing measures designed specifically for clinical trial end point reporting that are not used in clinical practice. Additional variations include the use and dosage of concomitant medications, which are often restricted in the trial setting, and patient adherence to therapy, which is generally reported to be lower in clinical practice [10]. These variances may complicate the translation and interpretation of results from clinical trials into clinical practice. It is, therefore, important

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to support data from RCTs with observations from experience in the real-world clinical practice setting [11,12].

Here, real-world data from patients in a single center in the USA treated with abatacept immediately after it became commercially available are presented. The authors assess clinical efficacy and safety outcomes in a real-life setting to determine whether the benefits observed with abatacept treatment in clinical trials translate into benefits in clinical practice.

Materials & methods

Study design & patient population

This observational, single-center, retrospective cohort, longitudinal study was conducted at a single US site. All consecutive adult patients with active moderate-to-severe RA, as determined by the treating physician, who were initiated on abatacept treatment at the clinic between 26 January, 2006 (the date of the US launch of abatacept) and 23 August, 2007 (the study cut-off date) were identified and included in the study. All available data in patients' charts were extracted up to 23 August, 2007 or abatacept discontinuation, whichever occurred first. Depending on the date of abatacept initiation for each patient, follow-up duration could range from 0 to 18 months. Patients were assessed at the clinic according to routine clinical practice, and not at prespecified time points. Data were collected on standardized charts, and were coded and not connected to patients' identities. Given the nature of the study design, no investigational review board approval was required.

Abatacept (~10 mg/kg according to weight range) was administered by intravenous infusion on days 1, 15 and 29, and every 4 weeks thereafter from initiation. For patients who were switched from an anti-TNF therapy to abatacept, no washout period was required, and patients could receive abatacept on their next scheduled anti-TNF therapy dose. Concomitant therapies, such as MTX, other DMARDs and oral steroids, were permitted throughout the study, and could be adjusted as deemed necessary by the treating rheumatologist. Abatacept could be administered as monotherapy, in accordance with the prescribing information for the USA [101].

Characterization of the patient population

The patient population at the time of abatacept initiation is summarized, including demographics, such as age, gender and weight, and clinical characteristics, such as disease duration, presence of erosions and rheumatoid factor, and cyclic-citrullinated protein-antibody seropositivity. Previous treatment patterns for the patient population are also described, including prior use of conventional DMARDs, biologic therapies and corticosteroids.

Efficacy assessments

Efficacy outcome measures were reflective of those used in RCTs, and included assessment of patient retention rate and disease activity. Disease activity was assessed both by the Disease Activity Score 28 (DAS28) based on C-reactive protein (CRP), with Low Disease Activity State (LDAS) defined as a DAS28 score of 3.2 or less and DAS28-defined remission as a DAS28 score of less than 2.6 [13], and by the Clinical Disease Activity Index (CDAI), with low disease activity defined as CDAI score of 10 or less and CDAI-defined remission as a CDAI score of less than 2.8 [14]. Data are presented as proportions with 95% CI.

Safety assessments

All AEs and serious adverse events (SAEs) that resulted in discontinuation of abatacept are reported based on recorded data from patient charts. An SAE was defined as an AE that was fatal or life-threatening, resulted in prolonged hospitalization, resulted in persistent or significant disability or incapacity, was cancer, was a congenital anomaly or birth defect, or was an important medical event as determined by the treating physician.

Statistical analyses

Descriptive statistics were used for characterization of the patient population and are presented for all patients regardless of follow-up duration. Patient retention over the 18-month study period was assessed for all patients regardless of follow-up duration; the retention rate, with 95% CI, was estimated at month 6 using a Kaplan–Meier product-limit estimator; the corresponding Kaplan–Meier curve over 18 months is also presented. Patients who had not discontinued by the study cut-off date were right-censored. Disease activity at month 6 is presented for the modified intent-to-treat population, defined as patients with relevant baseline and post-baseline data who had initiated abatacept at least 6 months before the study end (23 August, 2007); patients could have dropped out during this time and were still included in the analysis. Missing data, including those for patients who discontinued treatment during the 6-month period, were handled using the last observation carried forward (LOCF) method. Efficacy data

were evaluated for the overall population, and were also stratified by prior anti-TNF experience according to the number of prior anti-TNF therapies failed (one, or two or more), the type of last anti-TNF therapy failed (infliximab, etanercept or adalimumab) and the reason for prior anti-TNF therapy failure (inefficacy and/or safety). The safety evaluations presented are based on all treated patients regardless of follow-up duration.

Results

Patient disposition

A total of 100 patients were identified from the clinic database as having initiated abatacept during the follow-up period and were included in the study. Patients had an abatacept median exposure time of 9 months during the follow-up period. Throughout this, 29 out of 100 patients discontinued abatacept treatment; 20 patients discontinued for lack of efficacy, seven due to AEs and two for other reasons. Following discontinuation of abatacept, ten out of 29 patients were switched to rituximab and 11 out of 29 patients were switched to anti-TNF therapy (infliximab, n = 3; etanercept, n = 5; adalimumab, n = 3). The remaining eight patients did not initiate further biologic treatment.

Characterization of patient population

At baseline, patients generally had long-standing disease, with moderate disease activity. Out of the 100 patients included in the study, 53% had disease duration of at least 10 years, mean DAS28 (CRP) was 4.4, mean CDAI was 32.9 and mean simplified disease activity index was 33.1 (Table 1). The majority of patients (97%) had previously failed at least one prior anti-TNF therapy, and 52% had failed two or more.

At the beginning of the study, 34, 27 or 40% of patients were receiving MTX, other DMARDs or no DMARD therapy, respectively, and 60% of patients were receiving prednisone or methylprednisolone therapy (Table 1). One patient was receiving both MTX and sulfasalazine at baseline, and was, therefore, counted in both groups. Of the 60 patients who were receiving steroids at baseline, 30 were able to discontinue steroid treatment during the study and the remaining 30 reduced their mean daily dose from 10.3 to 6.3 mg/day. Of the 100 patients, 40 were not receiving steroids at baseline; 17 of these were administered prednisone (mean dose of <5 mg/day) in addition to abatacept at some point during the study.

Table 1. Clinical characteristics and concomitant medications at baseline.

Measure	Abatacept-treated patients (n = 100)
Age, mean (SD)	54.6 (12.4)
Female, n (%)	88 (88)
Duration of RA, n (%)	
0–2 years	8 (8)
2–5 years	17 (17)
5–10 years	22 (22)
>10 years	53 (53)
Patients with erosions, n (%)	59 (59)
CCP antibody positive, n (%)	27 (27)
Rheumatoid factor positive, n (%)	64 (64)
DAS28 (CRP), mean (SD)	4.4 (1.3)
CDAI, mean (SD)	32.9 (17.1)
SDAI, mean (SD)	33.1 (17.0)
CRP mg/l, mean (SD)	1.1 (1.4)
Concomitant DMARD at start†, n (%)	
MTX	34 (34)
Other DMARD	27 (27)
None	40 (40)
Oral steroid at initiation of abatacept	
Prednisone or methylprednisolone, n (%)	60 (60)
None, n (%)	40 (40)
Oral steroid dose at initiation, mean (SD) mg/day	10.31 (6.55)

†One patient received MTX and sulfasalazine and was, therefore, included in both the MTX and the 'other DMARDs' groups.
CCP: Cyclic citrullinated protein; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score 28; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; RA: Rheumatoid arthritis; SD: Standard deviation; SDAI: Simplified Disease Activity Index.

Retention rate

The pattern of retention for the 100 patients treated with abatacept over the 18-month follow-up period is shown in the Kaplan–Meier product-limit estimator graph in Figure 1. At month 6, the retention rate was 80.0% (95% CI: 71.8–88.3), owing to 18 patients who discontinued within the first 6 months of treatment initiation.

Efficacy

Disease activity

A total of 85 out of 100 patients had initiated abatacept at least 6 months before the study cut-off date and were, therefore, eligible for inclusion in the efficacy analyses. Owing to the nature of the LOCF method, only patients with data available at baseline were analyzed; 68 patients had baseline DAS28 (CRP) assessments and 83 patients had CDAI assessments.

After 6 months of treatment, 30 out of 68 (44.1%) and 23 out of 68 (33.8%) patients had achieved LDAS and DAS28-defined remission, respectively (Figure 2A & B). Overall, 27 out of 83 (32.5%) and five out of 83 (6.0%) patients achieved low CDAI and CDAI-defined remission at month 6, respectively (Figure 3A & B).

Efficacy by number of prior anti-TNF therapy failures

Of the 68 patients included in the DAS28 analysis, 67 patients had previously failed anti-TNF therapy. Of the 31 patients who had previously failed one anti-TNF treatment, 15 (48.4%) achieved LDAS at month 6, compared with 14 out of 36 (38.9%) patients who had previously failed two or more anti-TNF therapies (Figure 2A). Furthermore, 11 out of 31 (35.5%) patients with one prior anti-TNF failure and 11 out of 36 (30.6%) with at least two prior anti-TNF failures achieved DAS28-defined remission (Figure 2B). A similar trend was seen for the CDAI analysis, which included 81 patients who had previously failed anti-TNF therapy. Of the 36 and 45 patients who had previously failed one or at least two anti-TNF therapies, respectively, 14 (38.9%) and 12 (26.7%) achieved low CDAI (Figure 3A), and three (8.3%) and two (4.4%) achieved CDAI-defined remission (Figure 3B).

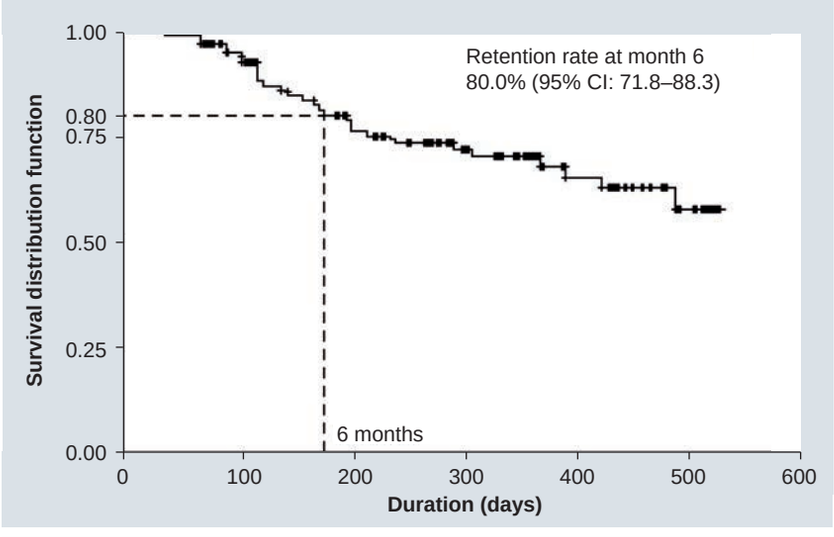

Figure 1. Kaplan–Meier plot of retention rates over 18 months of abatacept treatment. The dotted line represents the survival distribution at month 6 of abatacept treatment.

Efficacy by type of last anti-TNF therapy failure

Efficacy was further evaluated according to the type of last anti-TNF treatment received, prior to commencement of abatacept treatment. Of the 67 patients included in the DAS28 analyses who had previously failed anti-TNF therapy, 52, eight and seven patients received infliximab, etanercept and adalimumab, respectively, as their last anti-TNF therapy. At month 6, 23 out of 52 (44.2%), four out of eight (50.0%) and two out of seven (28.6%), respectively, achieved LDAS (Figure 2A), and 17 out of 52 (32.7%), three out of eight (37.5%) and two out of seven (28.6%), respectively, achieved DAS28-defined remission (Figure 2B). For the 81 patients (60, nine and 12 patients who had received infliximab, etanercept and adalimumab as their last anti-TNF therapy, respectively) included in the CDAI analyses, 20 out of 60 (33.3%), three out of nine (33.3%) and three out of 12 (25.0%), respectively, achieved low CDAI at month 6 (Figure 3A); five out of 60 (8.3%) patients previously treated with infliximab achieved CDAI-defined remission, compared with none of the patients previously treated with adalimumab or etanercept (Figure 3B).

Efficacy by reason for prior anti-TNF therapy failure

Efficacy was also assessed by the reason for prior anti-TNF therapy failure; patients could have failed for both inefficacy and safety, in which case they were included in both groups. A total of 52 and 20 patients in the DAS28 analyses failed their last anti-TNF therapy due to inefficacy and/or safety, respectively; 23 out of 52 (44.2%) and nine out of 20 (45.0%), respectively, achieved LDAS at

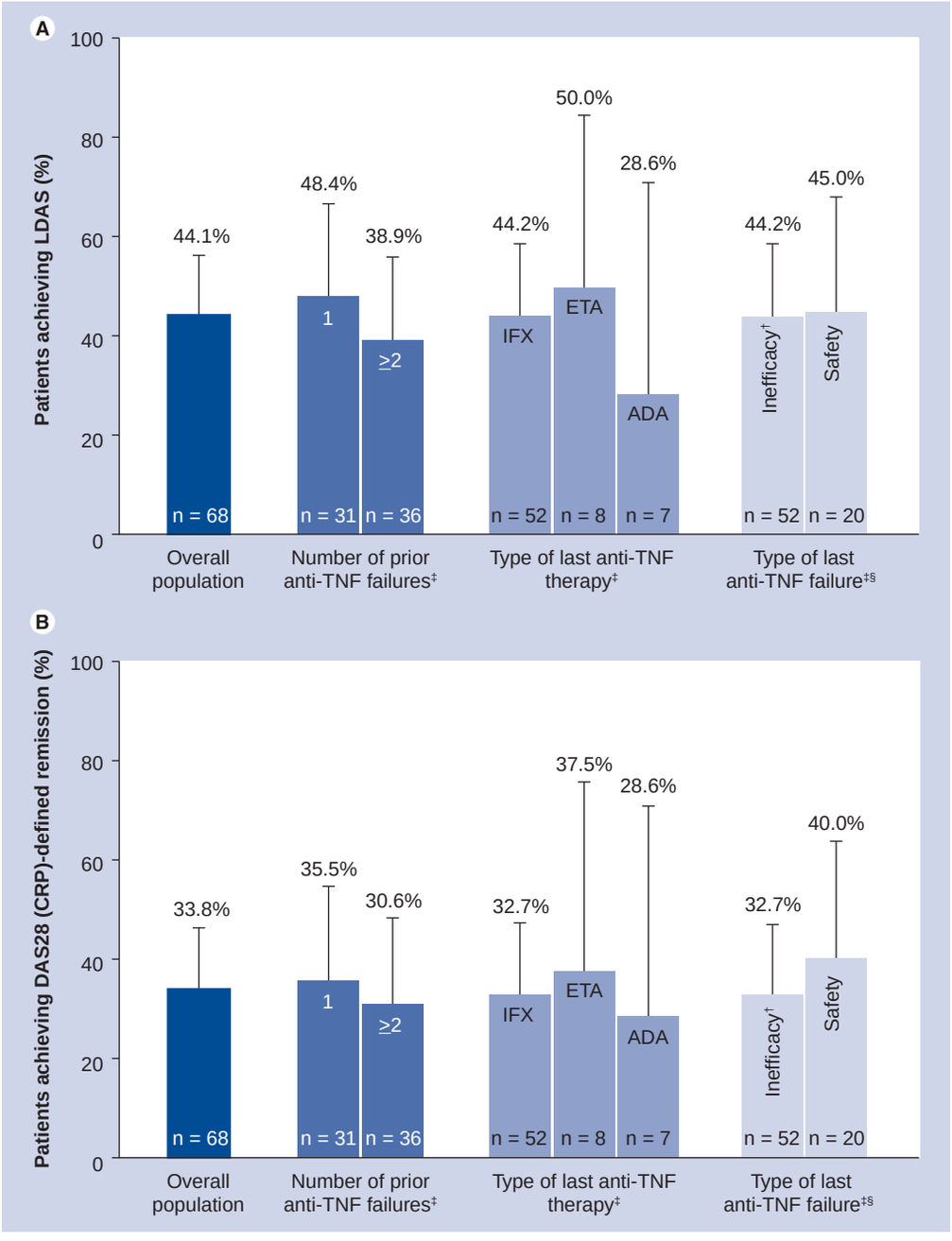

Figure 2. Low Disease Activity State (DAS28 [CRP] ≤3.2) (A) and remission (DAS28 [CRP] <2.6) (B) at month 6 (n = 68).

†Inefficacy means primary efficacy or loss of efficacy. ‡One patient did not have a history of biologic disease-modifying antirheumatic drug therapy (data not shown). §Patients could have failed for more than one reason. Analyses are based on patients who were initiated on abatacept ≥6 months before the study end point, and for whom baseline data were available (last observation carried forward analyses). Error bars represent 95% CI.

ADA: Adalimumab; CRP: C-reactive protein; DAS28: Disease Activity Score 28; ETA: Etanercept; IFX: Infliximab; LDAS: Low Disease Activity State.

month 6 (Figure 2A) and 17 out of 52 (32.7%) and eight out of 20 (40.0%), respectively, achieved DAS28-defined remission (Figure 2B). In the CDAI analyses, 65 and 22 patients who previously failed anti-TNF therapy due to inefficacy and/or safety, respectively, were included; 20 out of 65 (30.8%) versus nine out of 22 (40.9%) patients, respectively, had achieved low CDAI (Figure 3A), and five out of 65 (7.7%) and two out of 22 (9.1%) patients had achieved CDAI remission, respectively, at month 6 (Figure 3B).

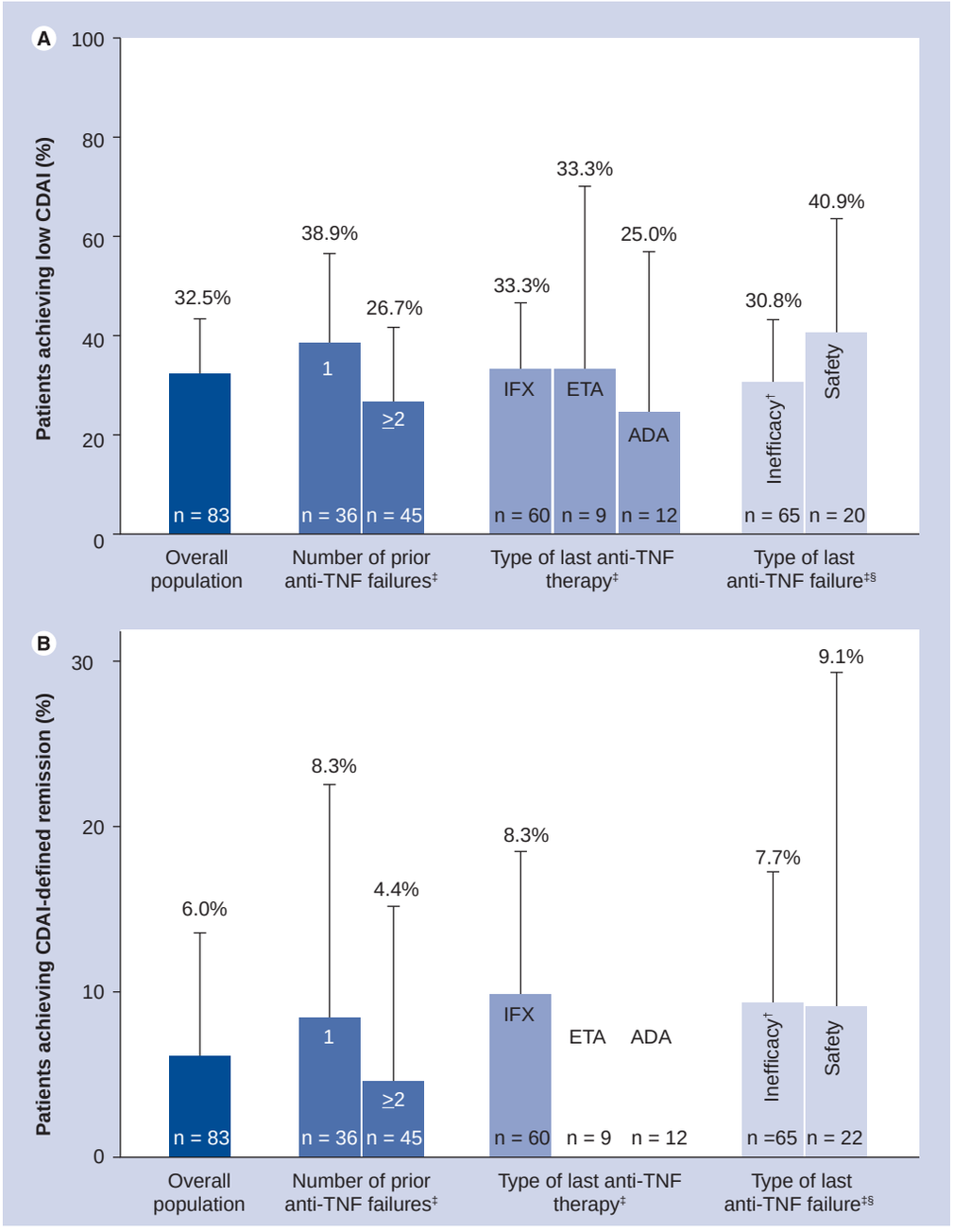

Figure 3. Low Clinical Disease Activity Index (CDAI ≤10) (A) and remission (CDAI<2.8) (B) at month 6 (n = 83).

†Inefficacy means primary efficacy or loss of efficacy. ‡Two patients did not have a history of biologic disease-modifying antirheumatic drug therapy (data not shown). §Patients could have failed for more than one reason. Analyses are based on patients who were initiated on abatacept ≥6 months before the study end point, and for whom baseline data were available (last observation carried forward analyses). Error bars represent 95% CI.

ADA: Adalimumab; CDAI: Clinical Disease Activity Index; ETA: Etanercept; IFX: Infliximab.

Safety

Throughout the 18-month study period, 7% of the 100 treated patients discontinued abatacept treatment for safety reasons. Three of these were classified as AEs (recurrent mild infection, hepatitis C and an influenza-like illness in one patient each) and four were classified as SAEs (pneumonia leading to death in one patient and malignancies in three patients). The three malignancies were lung cancer, uterine cancer and pulmonary carcinoma (in one patient each). The lung cancer was diagnosed 1 month after the patient received their first (and only) dose of abatacept; this patient died a few months later of

metastatic lung cancer, which the clinician felt was not related to abatacept use. The patients with uterine cancer and pulmonary carcinoma were diagnosed after 13 and 6 months of abatacept treatment, respectively; both patients discontinued abatacept treatment.

Discussion

Data obtained in RCTs provide crucial information regarding the efficacy and safety of RA therapies. However, owing to inherent differences between RCTs and routine clinical practice, it is important to gather information from the clinical setting to supplement and extend data obtained from clinical trials [11,12]. Here, real-world data from patients with RA, the majority of whom were refractory to anti-TNF therapy, treated with abatacept in a single clinic from the date of commercial availability in the USA are presented.

The 100 patients observed in this study had relatively long-standing RA and moderate disease at baseline. Among them, 40% received abatacept as monotherapy and 60% received concomitant medications, of which 34% received concomitant MTX. Of the 29 discontinuations reported during this study, the majority were due to lack of efficacy (20%) or safety (7%); 20% of patients had discontinued treatment within 6 months. For patients with available efficacy data (i.e., had initiated abatacept ≥6 months prior to study end and had the appropriate baseline efficacy assessments), a considerable proportion had achieved LDAS and DAS28-defined remission at month 6 (44 and 34%, respectively). Furthermore, 33% achieved low CDAI at 6 months, while 6% achieved CDAI-defined remission. In the subgroup analyses, efficacy results were generally similar regardless of number or type of prior anti-TNF agent, or reason for treatment failure.

Baseline demographics and clinical characteristics for the patients evaluated here are mostly consistent with those reported for patients in registry studies that examined the efficacy of abatacept in the clinical setting, namely the Consortium of Rheumatology Researchers of North America (CORRONA) and RHUMADATA registries [15,16]. However, these registries included higher proportions of biologic-naive patients compared with the patients assessed here, of whom the majority (97%) had failed previous treatment with anti-TNF agents; a comprehensible difference given that data from this study were collected in the clinical practice setting immediately after launch, when abatacept treatment was initiated mainly in refractory patients.

Real-life efficacy outcomes reported here are consistent with those from the CORRONA and RHUMADATA studies, in which significant improvements in disease activity and tender and swollen joint counts were observed with abatacept treatment over 6 months [15,16]. The magnitude of efficacy benefits observed overall was similar between this study and the CORRONA and RHUMADATA studies, despite differences in disease activity assessments. In the present study, disease activity was measured by means of composite indices, which are commonly used in RCTs and are more closely representative of the assessments used in clinical practice in the EU.

Similarities can be seen between the baseline demographics for the 100 patients assessed in this study and those for RA patients with an inadequate response to anti-TNF agents included in the abatacept RCTs, Abatacept Trial in Treatment of Anti-TNF Inadequate responders (ATTAIN) and ARRIVE. Age, race and gender were all similar. However, differences are also apparent. Patients in this study had moderate baseline disease activity with a mean DAS28 (CRP) score of 4.4, which was lower than that reported in ATTAIN (6.5) and ARRIVE (6.2).

Concomitant MTX use as reported here also differs from the abatacept clinical trials, during which more than 75% of patients received background MTX. However, the proportions of patients treated with corticosteroids at abatacept initiation were similar between the two settings, and ranged between 60 and 70% of patients. Interestingly, half of the patients in this study receiving steroids at baseline discontinued them during follow-up and the other half were able to reduce their dose. This suggests that abatacept treatment may allow for a reduction or cessation of concomitant steroid use in a large proportion of patients, which could be used as a surrogate marker for the clinical efficacy of abatacept in the real-world setting. In clinical practice, rheumatologists generally taper steroids as soon as a patient improves; conversely, in RCTs, background medication often remains constant as part of the study design [17].

The high retention rates observed over 6 months of abatacept treatment in this study were also similar to those reported in the ATTAIN and ARRIVE trials (82–90%) over a 6-month period [7,18]. This finding is particularly relevant given the lower expectations physicians may have for patients to remain on therapy in clinical practice compared with in clinical trials. In both this study and the ATTAIN and ARRIVE studies, lack of efficacy was the most

common reason for discontinuation; an unsurprising finding given the majority of these patients had biologic-refractory disease.

Efficacy benefits reported here are reflective of disease activity outcomes reported in abatacept RCTs for patients who have previously failed anti-TNF therapy [7,8,18]. In the ATTAIN and ARRIVE trials, 17–22% and 10–13% of patients achieved LDAS and remission, respectively, by month 6 of treatment [7,8,18], compared with 44 and 34% in this study. One important consideration, however, is that the mean baseline disease activity for patients in this study was lower than that for the RCT patients [7,8,18]. Of note, in the long-term extension of the ATTAIN study, the proportion of patients achieving LDAS and DAS28-defined remission increased from month 6 to year 2 [8]. It remains to be determined whether similar improvements in efficacy over time are experienced in clinical practice.

The subgroup analyses determined that efficacy was generally similar regardless of number or type of prior anti-TNF agent, or reason for treatment failure. These observations are supported by previous findings from the ARRIVE trial, which included a larger patient population with similar prior biologic experience [18]. The patient numbers for the subgroup efficacy analyses were low, however, and conclusions should be drawn in consideration of this.

Safety findings reported in this study are also comparable with those in the clinical trials, with 7% of patients discontinuing due to AEs over 18 months. In an integrated safety summary of five abatacept RCTs across different patient populations, 5.8 and 2.8% of patients discontinued due to AEs and SAEs, respectively, during the 6-month double-blind periods [19]. In the ARRIVE trial, 3.9 and 1.6% of patients discontinued due to AEs and SAEs, respectively [18]. Over 2 years of the ATTAIN trial in anti-TNF inadequate responders, 7.0 and 5.0% of patients discontinued due to AEs and SAEs, respectively [8].

With regard to individual safety events, the cases of hepatitis C and lung cancer are of interest given that, in many countries, hepatitis C serology and lung x-rays are mandatory before initiation of a biologic agent. In this case, however, the majority of patients had previously received biologics, and in the USA there is currently no guidance around testing for hepatitis C or lung cancer when switching biologics.

Interpretation of our findings alongside those from RCTs should be made within the context of the study, which itself faces certain limitations. The study was carried out in the routine clinical practice setting, where treatment course is determined according to clinical presentation and decisions made by the physician and patient. This means that patients have greater flexibility over their routine care and, within reason, are treated with their medication of choice. It is possible that this may impact patients' perceptions of their treatment response. Furthermore, there was no predetermined visit schedule in accordance with the observational and retrospective design, and only available data from the patient charts were collected. Together, these factors resulted in missing data for the efficacy analyses.

The patient cohort was relatively small, including just 100 individuals, which should be acknowledged when drawing conclusions from these findings. The efficacy population, which included patients who had initiated abatacept 6 months or more prior to study end, included fewer patients. However, as efficacy results are presented for a modified intent-to-treat population, with missing data handled by LOCF, thereby taking into account data from patients who discontinued therapy, and given the high retention rates for patients evaluated in this study, the authors feel the efficacy results are generally representative of the population studied, and provide accurate observations of what to expect when patients remain on therapy in clinical practice. In addition, clinical efficacy was assessed by the composite disease activity indices, DAS28 and CDAI, the latter of which can be performed in clinical practice without acute phase reactant evaluation. As the CDAI is not frequently used as an end point in RCTs it is more challenging to place our CDAI results in the context of clinical trial data. More widespread use of these types of simple and comprehensive composite measures in RCTs would facilitate comparisons between clinical trials and real-world data.

Furthermore, the data for the study were collected from patient charts, and only AEs that resulted in discontinuation were recorded. For this reason, the safety evaluation is an underestimation of AE occurrence compared with that reported for RCTs, which report all AEs regardless of outcome.

Despite these limitations, certain methodology was employed that makes comparison with RCT data more favorable than with most real-life data analyses. Efficacy results are presented for a modified intent-to-treat population, with missing data handled by LOCF, an analysis both reflective of those used in clinical trials and more

stringent and conservative than the as-observed analyses often favored in observational registry studies. Furthermore, efficacy was evaluated over a 6-month period; this duration is often used in clinical trials as the time to assess a primary end point, as it has been shown that the majority of patients will respond to biologic treatment within this timeframe.

Conclusion

In conclusion, within the limitations discussed, the data presented here from this real-world observational study corroborate the high retention rates and efficacy benefits reported with abatacept in patient registry studies [15,16], and extend the efficacy and safety findings from abatacept RCTs [7,18]. These data from the early clinical use of abatacept, presented here for the first time, support the use of abatacept as a rational therapeutic option for patients with RA, irrespective of prior anti-TNF therapy experience. Moving forwards, it will be important to evaluate the safety and efficacy of abatacept in clinical practice over longer periods of time, an undertaking now ongoing in large databases in multicenter settings with high numbers of patients. This will help determine if the benefits seen with long-term abatacept treatment in the clinical trial setting translate into routine clinical practice, and will help confirm the findings from this real-world cohort of patients with RA.

Financial & competing interests disclosure

M Schiff has received research grants and consulting fees from Bristol-Myers Squibb, and M Le Bars is an employee of Bristol-Myers Squibb and owns shares and stock options. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- There is a subset of patients with rheumatoid arthritis who do not respond to treatment with traditional disease-modifying antirheumatic drug (DMARD) therapies, such as methotrexate; in addition, there is a substantial proportion who do not respond to anti-TNF therapy.
- Abatacept is a biologic DMARD with an alternative mechanism of action to anti-TNF therapy; it modulates T-cell function by selectively targeting the CD80/CD86:CD28 signal required for full T-cell activation.
- Randomized controlled trials (RCTs) have demonstrated long-term sustained efficacy, combined with consistent safety in patients treated with abatacept who have previously failed DMARDs, including methotrexate and anti-TNF therapy.
- Given the inherent differences between the RCT setting and clinical practice, it is important to gather information from the clinical setting to supplement and extend data obtained in clinical trials, to determine whether observed benefits translate into benefits in the real world.

Materials & methods

- This is an observational, retrospective cohort, longitudinal study that followed rheumatoid arthritis patients with moderate disease treated with abatacept in a US clinic for up to 18 months, when abatacept was first released for commercial use in the USA.
- There were no inclusion criteria as per RCTs; patients were initiated and treated at the judgement of the treating rheumatologist.
- Efficacy and safety outcome measures were reflective of those used in RCTs and clinical practice; in particular, efficacy was assessed for a modified intent-to-treat population with missing data handled using the last observation carried forward.

Results

- Patients had long-standing refractory disease, with moderate disease activity; the majority of patients had failed at least one prior anti-TNF therapy.
- A high proportion of patients remained on treatment throughout the follow-up period, with an 80% retention rate at month 6.
- At month 6, 44.1 and 33.8% of patients had achieved Low Disease Activity State (LDAS) and Disease Activity Score 28 (DAS28) remission, respectively, and disease activity outcomes were generally similar regardless of the number of prior anti-TNF therapies patients had failed or reason for failure.
- Over the 18-month follow-up period, 7% of patients discontinued due to safety reasons.

Discussion

- Findings from this study confirm the high retention rates, clinical efficacy benefits and tolerability of abatacept seen in RCTs, and suggest that abatacept is a viable treatment option after prior DMARD/biologic failure in clinical practice.
- The efficacy findings presented here are supported by observations from patient registries that have shown significant improvements in disease activity with abatacept treatment.
- Further observations from larger cohorts of patients, and over longer periods of time, will be important moving forwards to further evaluate the benefits of long-term abatacept treatment in routine clinical practice.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

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4 Westhovens R, Robles M, Ximenes AC *et al.*: Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. *Ann. Rheum. Dis.* 68(12), 1870–1877 (2009).

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7 Genovese MC, Becker JC, Schiff M *et al.*: Abatacept for rheumatoid arthritis refractory to tumor necrosis factor-α inhibition. *N. Engl. J. Med.* 353(11), 1114–1123 (2005).

▪▪ **Details the 6-month safety and efficacy outcomes of the first Phase III, randomized, placebo-controlled trial (RCT) of abatacept in patients refractory to anti-TNF therapy, the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN) study, and demonstrates significant clinical and functional benefits and acceptable safety with abatacept treatment in these patients.**

8 Genovese MC, Schiff M, Luggen M *et al.*: Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. *Ann. Rheum. Dis.* 67(4), 547–554 (2008).

▪▪ **Presents data from the long-term extension of the ATTAIN study, and reports that improvements in clinical efficacy and physical function seen at month 6 are maintained throughout 2 years of long-term treatment with abatacept, and that no new safety events occurred with open-label therapy relative to treatment in the 6-month, double-blind period.**

9 Schiff M, Pritchard C, Huffstutter JE *et al.*: The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. *Ann. Rheum. Dis.* 68(11), 1708–1714 (2009).

▪▪ **The open-label Abatacept Researched in Rhematoid Arthritis Patients with an Inadequate anti-TNF response to Validate Effectiveness (ARRIVE) trial included patients likely to be excluded from RCTs, reflecting the population encountered in clinical practice. The population included patients who had switched directly from anti-TNF therapy to abatacept, had failed up to three anti-TNF agents for efficacy or safety reasons, or had a positive purified protein derivative test at entry. Safety and efficacy results from ARRIVE confirmed and extended the findings from ATTAIN, which had more stringent inclusion criteria and included only patients who had previously failed one or two anti-TNF therapies for efficacy reasons only.**

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