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ORIGINAL ARTICLE

Reductions in disease activity in the AMPLE trial: clinical response by baseline disease duration

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ABSTRACT

Objectives: To evaluate clinical response by baseline disease duration using 2-year data from the AMPLE trial.

Methods: Patients were randomised to subcutaneous abatacept 125 mg weekly or adalimumab 40 mg bi-weekly, with background methotrexate. As part of a post hoc analysis, the achievement of validated definitions of remission (Clinical Disease Activity Index (CDAI) ≤2.8, Simplified Disease Activity Index (SDAI) ≤3.3, Routine Assessment of Patient Index Data 3 (RAPID3) ≤3.0, Boolean score ≤1), low disease activity (CDAI <10, SDAI <11, RAPID3 ≤6.0), Health Assessment Questionnaire-Disability Index response and American College of Rheumatology responses were evaluated by baseline disease duration (≤6 vs >6 months). Disease Activity Score 28 (C-reactive protein) <2.6 or ≤3.2 and radiographic non-progression in patients achieving remission were also evaluated.

Results: A total of 646 patients were randomised and treated (abatacept, n=318; adalimumab, n=328). In both treatment groups, comparable responses were achieved in patients with early rheumatoid arthritis (≤6 months) and in those with later disease (>6 months) across multiple clinical measures.

Conclusions: Abatacept or adalimumab with background methotrexate were associated with similar onset and sustainability of response over 2 years. Patients treated early or later in the disease course achieved comparable clinical responses.

Trial registration number: NCT00929864, Post-results.

Key messages

What is already known about this subject?

► Patients with longer disease duration have been shown to respond less well to treatment with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) than patients with rheumatoid arthritis of shorter duration.

What does this study add?

► This study demonstrates that treatment with abatacept or adalimumab and background methotrexate, whether earlier or later in the course of disease, leads to comparable clinical benefits, irrespective of the criteria used to assess disease activity.

► Data from this post hoc analysis suggest that the effect of disease duration on treatment response may be minimal if patients are treated with an effective biological DMARD and patients can achieve comparable responses whether treated early in the course of the disease or later.

How might this impact on clinical practice?

► When measuring treatment response in clinical practice, the choice of disease activity measures to be used and their interpretations presents numerous complexities.

► The use of multiple measures of clinical remission and low disease activity in this unique comparative data set from the Abatacept versus adaliMumab comParison in bioLogic-naïvE rheumatoid arthritis subjects with background methotrexate (AMPLE) study confirms their utility and consistency for agents with different mechanisms.

INTRODUCTION

Several clinical outcome measures exist to measure disease activity in patients with rheumatoid arthritis (RA). Although not validated for remission or low disease activity (LDA), one often-used measure is the Disease Activity Score 28 (C-reactive protein; DAS28 (CRP)).[1–3] A second index—the Clinical Disease Activity Index (CDAI)—has been widely used to measure remission (≤2.8) and LDA (≤10.0).[4–6] A third index—the Routine Assessment of Patient Index Data 3 (RAPID3) —correlates with DAS28 (CRP) and CDAI.[7] Finally, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have established criteria that employ an index-

based definition, Simplified Disease Activity Index (SDAI) ≤3.3, or a Boolean definition ≤1,[6] and have recommended that either definition should be selected as an outcome measure defining remission in RA clinical trials.[6]

Several studies of patients on biological disease-modifying antirheumatic drugs (bDMARDs) have shown long-term improvements in functional and radiographic outcomes following treatment,[8–11] and it has been demonstrated that early initiation of DMARDs improves clinical and structural outcomes.[12–14]

Abatacept versus adaliMumab comParison in bioLogic-naïvE rheumatoid arthritis subjects with background methotrexate (AMPLE) was the first head-to-head study powered to compare bDMARDs with different mechanisms of action on a background of methotrexate (MTX) in patients with RA who were naïve to bDMARD therapy and in whom MTX therapy had not provided adequate response. In 1-year and 2-year analyses, the efficacy and safety of abatacept and adalimumab were comparable.[8 9] Here, we summarise clinical response by baseline disease duration, using 2-year data from the AMPLE trial.

METHODS
Study design
The trial design for AMPLE (NCT00929864) has been described previously.[8] Patients were randomised to subcutaneous (SC) abatacept (Bristol-Myers Squibb, Princeton, New Jersey, USA) 125 mg weekly or SC adalimumab (Abbott Laboratories, North Chicago, Illinois, USA) 40 mg bi-weekly, in combination with a stable dose of MTX. The maximum disease duration for study entry was 5 years.[8]

Assessments
In a post hoc analysis, patients in the intent-to-treat population were grouped according to disease duration at baseline (≤6 (early) vs >6 months (later disease) for each treatment[15]). Rates of remission and LDA were assessed using several disease activity criteria. DAS28 (CRP) 'remission' was defined in the protocol as <2.6 and 'LDA' as ≤3.2 (tender joint counts (TJCs) and swollen joint counts (SJCs) out of 28 joints, CRP and patient global assessment (100 mm visual analogue scale (VAS)).[6] CDAI remission was defined as ≤2.8 and LDA <10.0 (TJC and SJC (66/68 joints), patient and physician global assessment (0–10 VAS)).[4 6] SDAI remission was defined as ≤3.3 and LDA ≤11 (TJC and SJC, CRP, patient and physician global assessment (0–10 VAS)).[6] RAPID3 remission was defined as ≤3.0 and LDA ≤6.0 (Health Assessment Questionnaire-Disability Index (HAQ-DI), patient pain score and patient global assessment (both 100 mm VAS)). Boolean remission was assessed (TJC and SJC, CRP and patient global assessment), but LDA was not determined by the Boolean definition.[6] Physical function was assessed using the HAQ-DI, and a clinically meaningful HAQ-DI response was defined as an improvement of 0.3 units from baseline.[16 17]

Plain radiographs of hands and feet were taken at baseline, years 1 and 2, and scored using the modified Sharp/van der Heijde scoring system (see online supplementary material).[18]

The proportion of patients in each group achieving an ACR 20%, 50% and 70% improvement response rate (ACR20/50/70) was assessed at 2 years.[19]

Table 1 Baseline demographics and clinical characteristics (intent-to-treat population)

Characteristic	Total population		≤6 months' disease duration		>6 months' disease duration	
	SC abatacept +MTX (n=318)	SC adalimumab +MTX (n=328)	SC abatacept +MTX (n=71)	SC adalimumab +MTX (n=70)	SC abatacept +MTX (n=247)	SC adalimumab +MTX (n=258)
Patients completing the study at year 2, n (%)	252 (79.2)	245 (74.7)	54 (76.1)	49 (70.0)	198 (80.2)	196 (76.0)
Median (minimum, maximum) age, years	52 (19, 83)	52 (19, 85)	50 (19, 80)	52 (22, 75)	53 (21, 83)	52 (19, 85)
Female, n (%)	259 (81.4)	270 (82.3)	59 (83.1)	51 (72.9)	200 (81.0)	219 (84.9)
White, n (%)	257 (80.8)	256 (78.0)	60 (84.5)	57 (81.4)	197 (79.8)	199 (77.1)
Geographic region, n (%)						
North America	230 (72.3)	235 (71.6)	67 (94.4)	63 (90.0)	163 (66.0)	172 (66.7)
South America	88 (27.7)	93 (28.4)	4 (5.6)	7 (10.0)	84 (34.0)	86 (33.3)
Mean (SD) disease duration, years	1.9 (1.4)	1.8 (1.4)	0.3 (0.1)	0.3 (0.1)	2.4 (1.3)	2.2 (1.3)
Median HAQ-DI	1.5	1.5	1.5	1.5	1.5	1.4
Median DAS28 (CRP)	5.5	5.5	5.5	5.7	5.6	5.4
Median CDAI	36.2	36.5	34.4	38.0	36.2	39.2
Median SDAI	38.1	37.6	37.0	36.3	38.3	37.4

CDAI, Clinical Disease Activity Index; DAS28 (CRP), Disease Activity Score 28 (C-reactive protein); HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; SC, subcutaneous; SDAI, Simplified Disease Activity Index.
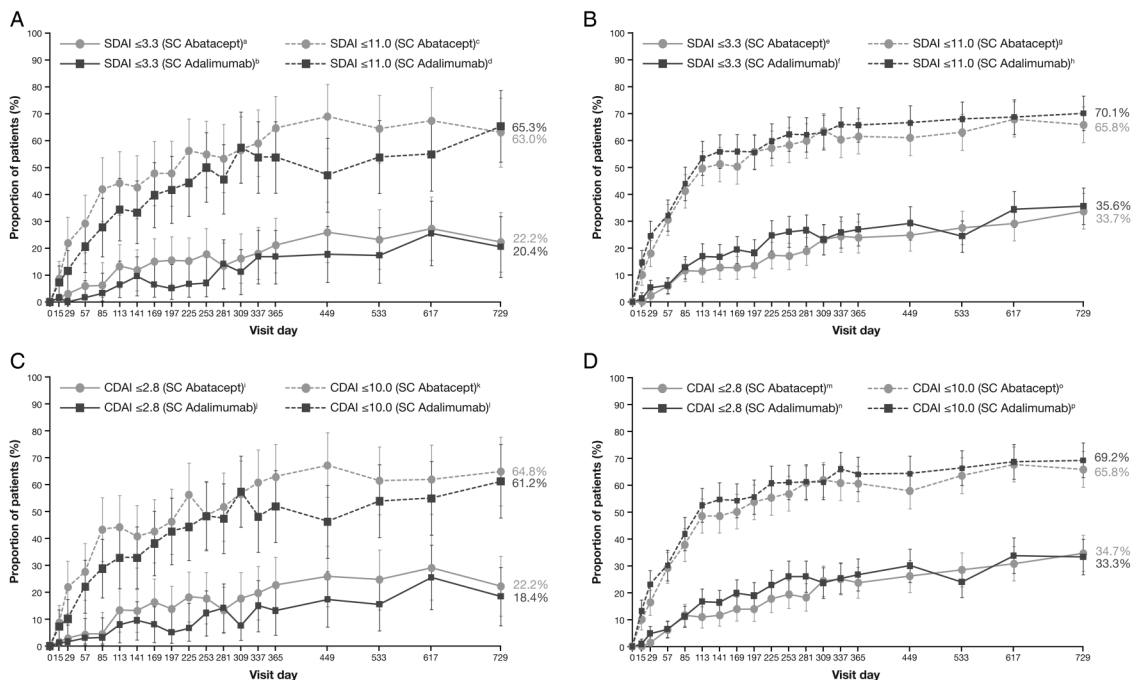
Figure 1 Proportion of patients with SDAI LDA or remission with disease duration at baseline of (A) ≤6 months or (B) >6 months; CDAI LDA or remission with disease duration at baseline of (C) ≤6 months or (D) >6 months. (A, B) Remission defined as SDAI response ≤3.3. LDA defined as SDAI response ≤11.0. (C, D) Remission defined as CDAI response ≤2.8. LDA defined as CDAI response ≤10.0. Number of randomised and treated patients with disease duration ≤6 months: SC abatacept, n=71; SC adalimumab, n=70. Number of randomised and treated patients with disease duration >6 months: SC abatacept, n=247; SC adalimumab, n=258. [a]n=62 at day 365, n=54 at day 729. [b]n=54 at day 365, n=49 at day 729. [c]n=62 at day 365, n=54 at day 729. [d]n=54 at day 365, n=49 at day 729. [e]n=213 at day 365, n=196 at day 729. [f]n=213 at day 365, n=194 at day 729. [g]n=213 at day 365, n=196 at day 729. [h]n=213 at day 365, n=194 at day 729. [i]n=62 at day 365, n=54 at day 729. [j]n=54 at day 365, n=49 at day 729. [k]n=62 at day 365, n=54 at day 729. [l]n=54 at day 365, n=49 at day 729. [m]n=215 at day 365, n=196 at day 729. [n]n=214 at day 365, n=195 at day 729. [o]n=215 at day 365, n=196 at day 729. [p]n=214 at day 365, n=195 at day 729. All error bars represent 95% CIs. CDAI, Clinical Disease Activity Index; LDA, low disease activity; SC, subcutaneous; SDAI, Simplified Disease Activity Index.

Statistical analysis

In all patients who had completed year 2 (day 729) of the study, individual measures of remission/LDA (CDAI, SDAI, RAPID3, Boolean (remission only)) were calculated using post hoc analyses of as-observed data. Mean rates of ACR20/50/70 response, mean remission/LDA (CDAI, SDAI, RAPID3, Boolean (remission only)) and HAQ-DI were calculated and compared by disease duration subgroup (≤6 and >6 months) for each treatment (see online supplementary materials). For all mean response rates, 95% CIs were calculated.

RESULTS
Patient population

Baseline demographics and clinical characteristics of the total population, and by disease duration, are shown in table 1. A total of 646 patients were randomised and treated with background MTX: 318 in the abatacept group and 328 in the adalimumab group. In total, 79.2% (252/318) of patients in the SC abatacept group and 74.7% (245/328) of patients in the adalimumab group completed year 2.[9] In patients receiving abatacept, 22.3% (71/318) had ≤6 months' disease duration at baseline and 77.7% (247/318) had >6 months' disease duration; 76.1% (54/71) of patients with ≤6 months' disease duration and 80.2% (198/247) with >6 months' disease duration completed year 2. The distribution of disease duration at baseline and those who completed year 2 for the adalimumab-treated patients was comparable to that of abatacept-treated patients (table 1).

Efficacy

Overall, in patients achieving remission or LDA at year 1, most maintained remission at 2 years irrespective of the definition used. The rates of sustained remission and DAS28 (CRP) <2.6 and ≤3.2 were comparable between the abatacept and adalimumab treatment arms (see online supplementary table S1). More than 85% of patients who achieved remission or LDA at year 2, irrespective of the definition used, had radiographic non-progression at year 2 (see online supplementary figures S1–4). There was a high correlation with improvements in physical function in patients who had achieved remission or LDA at year 2, irrespective of the criteria used

Figure 2 Proportion of patients with HAQ-DI response, by disease duration (ITT population): (A) ≤6 months or (B) >6 months. *HAQ-DI response defined as an improvement of ≥3 units from baseline. [a]n=71 at day 365, n=71 at day 729. [b]n=70 at day 365, n=70 at day 729. [c]n=247 at day 365, n=247 at day 729. [d]n=258 at day 365, n=258 at day 729. Error bars represent 95% CIs. HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; SC, subcutaneous.
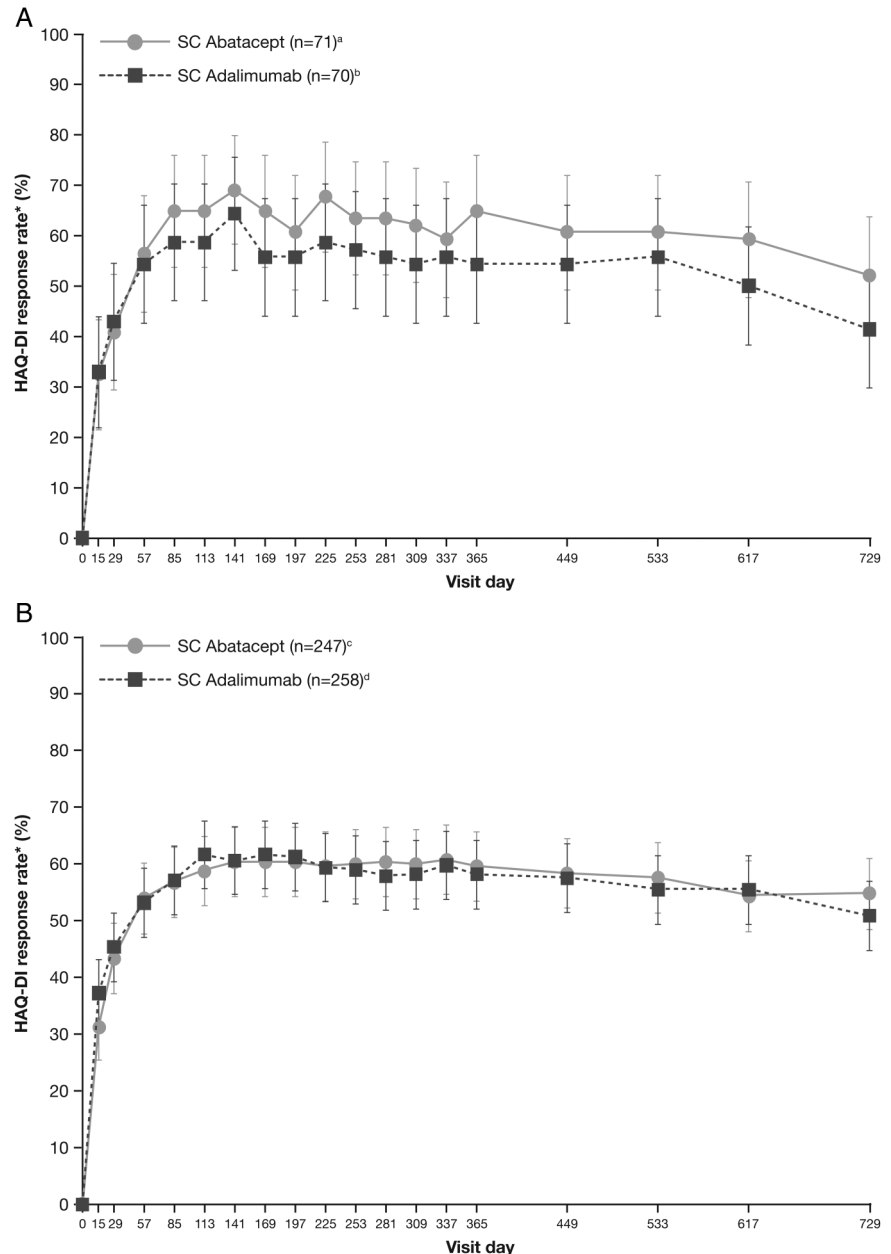
for remission and LDA (see online supplementary figure S5).

In patients with ≤6 months' disease duration, outcomes for the abatacept and adalimumab groups were comparable, regardless of LDA or remission definition (figure 1; see online supplementary figure S6). Additionally, comparable proportions of patients in both treatment groups achieved ACR20, 50 and 70 response rates, regardless of their disease duration at baseline (see online supplementary figure S7). In the ≤6 months' disease duration group, proportions of patients receiving abatacept or adalimumab who had achieved ACR responses at year 2 were 72.2% and 73.5% for ACR20, 55.6% and 51.0% for ACR50, and 37.0% and 28.6% for ACR70, respectively. The proportions of patients with >6 months' disease duration who had achieved ACR responses were 75.4% and 80.3% for

ACR20, 56.3% and 63.6% for ACR50, and 39.7% and 40.9% for ACR70, respectively.

The proportions of patients who achieved clinically meaningful HAQ-DI responses over time, by disease duration at baseline, are shown in figure 2. For patients with ≤6 months' disease duration, 52.1% on SC abatacept and 41.4% on adalimumab achieved HAQ-DI responses at year 2, while for those with >6 months' disease duration, 54.7% and 50.8% achieved HAQ-DI responses.

DISCUSSION

Biological-naïve patients treated with abatacept or adalimumab on background MTX achieved comparable responses over 2 years in terms of onset and sustainability of LDA and remission, HAQ-DI response and inhibition of radiographic progression, irrespective of the

criteria used to assess disease activity. Disease duration did not affect clinical response (reductions in disease activity as assessed by SDAI, CDAI, RAPID3, Boolean remission and HAQ-DI). In this group of patients who had a maximum disease duration of 5 years at study entry, abatacept-treated and adalimumab-treated patients with early RA (≤6 months' duration) achieved comparable responses to those with later disease (>6 months' duration) across a range of clinical measures.

Patients who achieved remission according to stringent criteria (SDAI, Boolean) were more likely to be radiographic non-progressors and achieve clinically meaningful improvements in physical function than those who achieved LDA or DAS (CRP) ≤3.2. Patients achieving CDAI-defined remission displayed similar radiographic outcomes over 2 years to those achieving SDAI remission (see online materials).

Patients with longer disease duration have been shown to respond less well to treatment with conventional synthetic DMARDs than patients with RA of shorter duration.[12–14 20] A meta-analysis of about 1400 patients with RA from 14 randomised trials using ACR20 response rates identified shorter (≤1 year) disease duration at the start of treatment to be one of the strongest predictors of response to conventional synthetic DMARD therapy.[12] However, data from the current post hoc analysis suggest that the effect of disease duration on treatment response may be minimal if patients are treated with an effective bDMARD; patients can achieve comparable responses whether treated early in the course of the disease (defined as ≤6 months in this study based on ACR criteria) or later (>6 months).[15] The disparities between the results of the present and previous studies may be linked to changes in more efficacious treatment options and differences in cut-offs used to separate disease duration cohorts.

When measuring treatment response, either in clinical studies or clinical practice, the choice of disease activity measures to be used and their interpretations presents numerous complexities. The use of multiple measures of clinical remission and LDA in this unique comparative AMPLE data set confirms their utility and consistency for agents with different mechanisms.

There are some limitations to the present study. The analyses presented here are post hoc, and additional prospective studies are needed to confirm these results. The selection of DAS28 (CRP) as a measure of disease activity is also a limitation. The criteria of DAS28 (CRP) <2.6 and ≤3.2 were defined prior to the recent guidance from the US Food and Drug Administration, which states that DAS28 (CRP) <2.6 is a measure of LDA rather than remission.[2] DAS28 (CRP) also shows no correlation with DAS28 (erythrocyte sedimentation rate), and neither corresponds well with CDAI or SDAI.[1] We did, however, utilise defined criteria of remission (CDAI, SDAI, Boolean, RAPID3) in this post hoc analysis and the results are consistent with these validated measurements.

This study demonstrates that treatment with abatacept or adalimumab and background MTX, whether earlier or later in the course of disease, leads to comparable clinical benefits at least up to 5 years' disease duration, irrespective of the criteria used to assess disease activity.

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