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.

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)). A second index—the Clinical Disease Activity Index (CDAI)—has been widely used to measure remission (≤ 2.8) and LDA (≤ 10.0). A third index—the Routine Assessment of Patient Index Data 3 (RAPID3)—correlates with DAS28 (CRP) and CDAI. Finally, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have established criteria that employ an index.

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 antirheumatic 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 adalimumabcomparison in biologic-naïve rheumatoid arthritis subjects with background methotrexate (AMPLE) study confirms their utility and consistency for agents with different mechanisms.
based definition, Simplified Disease Activity Index (SDAI) $\leq 3.3$, or a Boolean definition $\leq 1$, and have recommended that either definition should be selected as an outcome measure defining remission in RA clinical trials. 

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

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. 

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. 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. 

Assessments
In a post hoc analysis, patients in the intent-to-treat population were grouped according to disease duration at baseline ($\leq 6$ (early) vs $>6$ months (later disease)) for each treatment. 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 $\leq 3.2$ (tender joint counts (TJCs) and swollen joint counts (SJCs) out of 28 joints, CRP and patient global assessment (100 mm visual analogue scale (VAS))). CDAI remission was defined as $\leq 2.8$ and LDA $<10.0$ (TJC and SJC (66/68 joints), patient and physician global assessment (0–10 VAS)). SDAI remission was defined as $\leq 3.3$ and LDA $\leq 11$ (TJC and SJC, CRP, patient and physician global assessment (0–10 VAS)). RAPID3 remission was defined as $\leq 3.0$ and LDA $\leq 6.0$ (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. 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.

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).

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.

### 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 | SC abatacept +MTX | SC abatacept +MTX | SC abatacept +MTX |
|                | (n=318)           | (n=71)                  | (n=247)                  | (n=258)                  |
| Patients completing the study at year 2, n (%) | 252 (79.2) | 54 (76.1) | 198 (80.2) | 196 (76.0) |
| Median (minimum, maximum) age, years | 52 (19, 83) | 50 (19, 80) | 53 (21, 83) | 52 (19, 85) |
| Female, n (%) | 259 (81.4) | 59 (83.1) | 200 (81.0) | 219 (84.9) |
| White, n (%) | 257 (80.8) | 60 (84.5) | 197 (79.8) | 199 (77.1) |
| Geographic region, n (%) | 230 (73.2) | 67 (94.4) | 163 (66.0) | 172 (66.7) |
| North America | 235 (71.8) | 63 (90.0) | 163 (66.0) | 172 (66.7) |
| South America | 88 (27.7) | 4 (5.6) | 84 (34.0) | 86 (33.3) |
| Mean (SD) disease duration, years | 1.9 (1.4) | 0.3 (0.1) | 2.4 (1.3) | 2.2 (1.3) |

CAI, 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.

Schiff M, et al. RMD Open 2016;2:e000210. doi:10.1136/rmdopen-2015-000210
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. In patients receiving abatacept, 22.3% (71/318) had ≤ 6 months’ disease duration at baseline and 77.7% (245/318) 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.
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-naive 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

**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. *n=71 at day 365, n=71 at day 729. *n=70 at day 365, n=70 at day 729. *n=247 at day 365, n=247 at day 729. *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.
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.2–14 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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Competing interests MS is a consultant and speaker for Bristol-Myers Squibb and AbbVie. MEW received research grants from and is a consultant for Bristol-Myers Squibb, Crescendo Bioscience, UCB and Amgen; he also received consultancy fees from AbbVie, Lilly, Pfizer and Novartis. RV received clinical research support from Amgen, Amgen, Bristol-Myers Squibb, Coherus, Novartis, Pfizer, Sanofi and Sandoz. GC conducts clinical research for, and is a consultant and speaker for Bristol-Myers Squibb, Abbott, Pfizer, Roche and AstraZeneca. MM is an employee and shareholder of Bristol-Myers Squibb. EM is an investigator for Bristol-Myers Squibb, Sanofi and HGS; he received consultancy fees for UCB and honoraria from Up to Date and Springer Publications. YY is a consultant for Bristol-Myers Squibb and received research support from Bristol-Myers Squibb, Celgene and Genentech. RF is a consultant for and recipient of grants from Bristol-Myers Squibb and AbbVie.

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REFERENCES

1. Fleischmann R, van der Heijde D, Koenig AS, et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? Ann Rheum Dis 2015;74:1132–7.

2. US Food and Drug Administration (FDA). Guidance for industry. Rheumatoid arthritis: developing drug products for treatment. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM354468.pdf (accessed 23 Mar 2015).

3. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009;68:954–60.

4. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23:100–8.

5. Aletaha D, Landewe R, Karonitsch T, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. Ann Rheum Dis 2008;67:1360–4.

6. Smolen JS, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404–13.

7. Pincus T, Hines P, Bergman MJ, et al. Proposed severity and response criteria for Routine Assessment of Patient Index Data (RAPID3): results for categories of disease activity and response criteria in abatacept clinical trials. J Rheumatol 2011;38:2565–71.

8. Weinblatt ME, Schiff M, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, non-inferiority, randomized study. Arthritis Rheum 2013;65:28–38.

9. Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis 2014;73:86–94.

10. van der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER. J Rheumatol 2010;37:2237–46.

11. Tobon GJ, Saraux A, Devauchelle-Pensec V. Effect of biologic agents on radiographic progression of rheumatoid arthritis. Rep Med Imaging 2010;3:35–44.

12. Anderson JJ, Wells G, Verhoeven AC, et al. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000;43:22–9.

13. Nell VP, Machold KP, Eberl G, et al. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2004;43:906–14.

14. van der Woude D, Young A, Jayakumar K, et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large arthritis cohorts. Arthritis Rheum 2009;60:2262–71.

15. Singh JA, Furst DE, Bharat A, et al. Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625–99.

16. Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum 2011;63:2854–64.

17. Wells GA, Tugwell P, Kraag GR, et al. Minimum important difference between patients with rheumatoid arthritis: the patient’s perspective. J Rheumatol 1993;20:557–60.

18. van der Heijde DM, van Riel PL, Nuer-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036–8.

19. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.

20. Cusch JJ. Early rheumatoid arthritis—is there a window of opportunity? J Rheumatol Suppl 2007;80:1–7.