CONCISE REPORT

Impact of baseline anti-cyclic citrullinated peptide-2 antibody concentration on efficacy outcomes following treatment with subcutaneous abatacept or adalimumab: 2-year results from the AMPLE trial

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ABSTRACT

Objectives To examine whether baseline anti-cyclic citrullinated peptide-2 (CCP2) antibody status and concentration correlated with clinical outcomes in patients treated with abatacept or adalimumab on background methotrexate (MTX) in the 2-year AMPLE (Abatacept versus adalimumab comParison in bioLogic-naïve rheumatoid arthritis subjects with background MTX) study.

Methods In this exploratory analysis, anti-CCP2 antibody concentration was measured at baseline, and antibody-positive patients were divided into equal quartiles, Q1–Q4, representing increasing antibody concentrations. Clinical outcomes analysed by baseline anti-CCP2 status and quartile included change from baseline in disease activity and disability and remission rates.

Results Baseline characteristics were generally comparable across quartiles and treatment groups. In both treatment groups, anti-CCP2 antibody-negative patients responded less well than antibody-positive patients. At year 2, improvements in disease activity and disability and remission rates were similar across Q1–Q3, but were numerically higher in Q4 in the abatacept group; in contrast, treatment effects were similar across all quartiles in the adalimumab group.

Conclusions In AMPLE, baseline anti-CCP2 positivity was associated with a better response for abatacept and adalimumab. Patients with the highest baseline anti-CCP2 antibody concentrations had better clinical response with abatacept than patients with lower concentrations, an association that was not observed with adalimumab.

Trial registration number NCT00929864.

INTRODUCTION

The introduction of multiple biologic disease-modifying antirheumatic drugs (DMARDs) and one new targeted synthetic DMARD has significantly improved rheumatoid arthritis (RA) treatment. However, better predictors of treatment response in individual patients are still needed.

Anti-citrullinated protein antibodies (ACPA) are a sensitive and highly specific marker of RA and have been incorporated into the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) diagnostic criteria.2 ACPA are present many years prior to the onset of clinical RA in many at-risk individuals, and 70%–80% of patients with RA are ACPA positive.3 As clinical disease develops, ACPA concentration increases, the number of recognised epitopes expands and isotype usage evolves.3 5 ACPA may also predict a more severe disease course with more erosive disease6; however, the clinical relevance of ACPA concentration is unclear.7 The relationship between ACPA status/concentration and response to therapy has not been elucidated but is of interest.8

In the clinic, ACPA can be detected using anti-cyclic citrullinated peptide (CCP) ELISA, such as the CCP2 assay.9 Here, we examined whether baseline anti-CCP2 IgG status and concentration influenced clinical outcomes in patients treated with abatacept or adalimumab in the head-to-head, 2-year AMPLE (Abatacept versus adalimumab comParison in bioLogic-naïve RA subjects with background methotrexate (MTX)) study.10 11 AMPLE provided a unique opportunity to explore baseline anti-CCP2 concentration as a predictor of response to two therapies with different mechanisms of action.

METHODS

Study design AMPLE (NCT00929864) was a 2-year, phase IIIb, randomised, investigator-blinded study. Biologic-naïve patients with active RA and an inadequate response to MTX were randomised to 125 mg subcutaneous abatacept weekly or 40 mg adalimumab bi-weekly, both on background MTX.10 11

ACPA analysis Baseline anti-CCP2 antibody status (positive/negative) and concentration were determined using an anti-CCP2 IgG ELISA (Euro Diagnostica Immunoscan CCPPlus, Malmö, Sweden; obtained from IBL America). Patients with a baseline anti-CCP2 IgG concentration of ≥25 AU/mL were considered to be positive and were further divided into equal quartiles according to concentration (Q1–Q4 (highest concentration)).
Table 1 Patient demographics and baseline characteristics

| Quartile by anti-CCP2 concentration (AU/mL) | Q1, 28–235 | Q2, 236–609 | Q3, 613–1046 | Q4, 1060–4894 |
|------------------------------------------|-----------|------------|-------------|--------------|
| CCP2 negative | ABA (n=66) | ADA (n=54) | ABA (n=42) | ADA (n=55) |
| Age, years | 52.0 (24.0, 80.0) | 58.0 (21.0, 83.0) | 50.0 (22.0, 70.0) | 50.0 (19.0, 78.0) |
| Female, % | 84.8 | 85.2 | 88.1 | 83.6 |
| White, % | 92.4 | 83.3 | 88.1 | 87.3 |
| Geographic region, % | | | | |
| North America | 86.4 | 90.7 | 71.4 | 63.6 |
| South America | 13.6 | 9.3 | 28.6 | 36.4 |
| MTX dose at randomisation, mg/wk | 15.0 (7.5, 105.0) | 18.8 (7.5, 25.0) | 20.0 (10.0, 25.0) | 15.0 (7.5, 105) |
| Smoking status, % | | | | |
| Current | 27.3 | 13.0 | 21.4 | 25.5 |
| Former | 21.2 | 29.6 | 14.3 | 20.0 |
| Never | 51.5 | 57.4 | 64.3 | 54.5 |
| Disease duration, years | 1.0 (0.1, 4.6) | 1.3 (0.0, 4.7) | 1.8 (0.2, 4.5) | 1.6 (0.1, 4.5) |
| Physical function, HAQ-DI | 1.3 (0.0, 2.9) | 1.4 (0.0, 2.6) | 1.4 (0.0, 2.5) | 1.3 (0.0, 2.5) |
| CRP (mg/dL) | 0.6 (0.0, 10.4) | 0.6 (0.0, 42.2) | 0.8 (0.1, 8.4) | 0.6 (0.0, 4.8) |
| DAS28 (CRP) | 5.5 (2.5, 7.4) | 5.3 (3.0, 7.3) | 5.0 (3.1, 7.6) | 5.5 (3.1, 7.3) |
| RF positive, % | 42.4 | 51.9 | 85.7 | 92.7 |
| RF concentration, U/mL | 4.7 (0.0, 368.6) | 6.1 (0.1, 388.3) | 119.5 (1.3, 500.9) | 137.5 (0.4, 500.9) |
| Total score (X-ray) | 3.5 (0.0, 86.5) | 6.5 (0.0, 114.5) | 7.0 (0.0, 232.5) | 8.5 (0.0, 143.0) |

Data are expressed as median (min, max), unless otherwise stated.

ABA, abatacept; ADA, adalimumab; CCP2, cyclic citrullinated peptide-2; CRP, C reactive protein; DAS28, Disease Activity Score 28; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; Q, quartile; RF, rheumatoid factor.

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Outcome measures
Efficacy outcomes up to day 729 were assessed according to baseline anti-CCP2 IgG status and concentration quartile. Outcomes were adjusted mean change from baseline in Disease Activity Score 28 (C reactive protein; DAS28 (CRP)) and Health Assessment Questionnaire Disability Index (HAQ-DI) over time, percentage of patients achieving DAS28 (CRP) <2.6, ACR/EULAR remission rates defined by Clinical Disease Activity Index (CDAI; ≤2.8) or Simplified Disease Activity Index (SDAI; ≤3.3) criteria and ACR 50/70 response rates.

Statistical analyses
Analyses included all randomised and treated patients. Adjusted mean change from baseline for DAS28 (CRP) and HAQ-DI was determined for each time point using analysis of covariance (ANCOVA), with treatment and baseline DAS28 (CRP) stratification as factors and baseline values as a covariate. For comparisons between Q1–Q3 and Q4, anti-CCP2-negative and Q4, and abatacept Q4 and adalimumab Q4, the adjusted mean difference was estimated using an ANCOVA model with treatment, quartile, treatment by quartile interaction and baseline DAS28 (CRP) stratification as factors and baseline values as a covariate.

RESULTS
Patient disposition and baseline characteristics
In AMPLE, 646 patients were randomised (abatacept, n=318; adalimumab, n=328), of whom 252 (79.2%) abatacept-treated and 245 (74.7%) adalimumab-treated patients completed year 2. Serum samples were available from 508 patients at baseline: 120 (23.6%) were anti-CCP2 negative and 388 (76.4%) were anti-CCP2 positive. The number of patients per treatment group was similar in each anti-CCP2 quartile, with no consistent differences in baseline characteristics across anti-CCP2 quartiles or treatment groups (table 1 and see supplementary table S1). Quartile limits are shown in table 1.

Mean change from baseline in disease activity and disability
Although at least a ‘moderate’ EULAR response was observed in both treatment groups, improvements in DAS28 (CRP) were significantly less pronounced in patients who were anti-CCP2 negative at baseline than in those who were anti-CCP2 positive (figure 1A). The mean improvement in DAS28 (CRP) at day 729 for abatacept was significantly greater in Q4 than in Q1–Q3 combined (adjusted mean treatment difference (AMTD) (95% CI) Q1–Q3 vs Q4: –0.69 (–1.15 to –0.23); p=0.003), whereas in the adalimumab group, improvement was similar across all quartiles (AMTD (95% CI) Q1–Q3 vs Q4: –0.21 (–0.64 to 0.23); p=0.358). The AMTD (95% CI) for abatacept Q4 versus adalimumab Q4 was –0.45 (–1.00 to 0.10; p=0.112).

A similar pattern was seen for HAQ-DI: mean changes from baseline were smallest in patients who were anti-CCP2 negative at baseline in both treatment groups (figure 1B). Mean change from baseline in HAQ-DI was similar across all anti-CCP2
quartiles for adalimumab, but significantly greater in abatacept Q4 than in Q1–Q3. The AMTD (95% CI) for Q1–Q3 versus Q4 for abatacept was $-0.24 (-0.44$ to $-0.04; p=0.021$), and for anti-CCP2 negative (Neg) vs Q4. The AMTD (95% CI) for abatacept Q4 versus adalimumab Q4 was $-0.17 (-0.41$ to $0.07; p=0.173$).

Remission rates, DAS28 (CRP) <2.6 and ACR response rates

In both treatment groups, the percentage of patients achieving CDAI or SDAI remission rates for adalimumab, but significantly greater in abatacept Q4 than in Q1–Q3. The AMTD (95% CI) for Q1–Q3 versus Q4 for abatacept was $-0.24 (-0.44$ to $-0.04; p=0.021$), and for anti-CCP2 negative (Neg) vs Q4. The AMTD (95% CI) for abatacept Q4 versus adalimumab Q4 was $-0.17 (-0.41$ to $0.07; p=0.173$).

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Overall, CDAI and SDAI remission rates tended to be higher at day 729 than at day 365 regardless of treatment, anti-CCP2 status or concentration. At day 729, CDAI and SDAI remission rates were highest in the abatacept Q4 group.

**DISCUSSION**

Both adalimumab and abatacept were more effective in patients who were anti-CCP2 positive than in those who were anti-CCP2 negative at baseline. However, there were differences in the pattern of response to the two treatments when assessed by baseline antibody concentration: abatacept treatment effects were more pronounced in the highest anti-CCP2 quartile than in lower quartiles, whereas this effect was not consistently demonstrated for adalimumab. Interquartile differences for abatacept were most prominent when assessed with continuous measures such as DAS28 (CRP) and HAQ-DI versus binary response measures, possibly due to the increased sensitivity to change of continuous measures.

The improved clinical efficacy in anti-CCP2-positive versus anti-CCP2-negative patients for both adalimumab and abatacept...
suggests that ACPA status may be a relevant factor in predicting treatment response. In contrast to our results, previous studies have suggested that seropositive patients respond less well to tumour necrosis factor (TNF) inhibition than seronegative patients, or that response correlates inversely with autoantibody concentration.12–14 High baseline rheumatoid factor (RF) IgA concentration has been associated with poor response to TNF inhibitor therapy.15 The disparities between studies could be due to differences in patient populations, study setting or ACPA assay used; further study of predictive factors of treatment response in RA with standardisation of biomarker assays is warranted.

The reason for the observed differential pattern of response across quartiles for abatacept and adalimumab is unknown, but may be related to their different mechanisms of action. Abatacept selectively modulates T-cell costimulation and autoantibody production via interaction with B cells, whereasadalimumab binds directly to TNF-α. The B-cell inhibitor rituximab has also been shown to be more effective in patients with RA who are ACPA or RF seropositive versus seronegative.16 In this analysis, 90% of patients in Q4 were also RF positive at baseline; in registry and cohort studies, better abatacept efficacy and retention has been found to be associated with double-positive- or higher ACA concentration.17–20 Importantly, our analysis was a within-study comparison of two treatments, removing causes of variation inherent in cross-study comparisons.

The trend for continued improvement in remission rates, particularly in the Q4 abatacept group, may suggest that the effects of costimulatory blockade increases over time. The clinical relevance of this observation is unknown.

This exploratory analysis has some inherent limitations. Baseline serum samples were not available for all patients and there were differences in several baseline characteristics between groups (although differences were not consistent across quartiles or treatment groups). As the analysis was not preplanned, patients were not stratified by anti-CCP2 concentration at randomisation and lack of blinding in AMPLE may have influenced the patient-reported outcome measures. Additionally, there is no standard, universally accepted ACPA assay and so findings may have differed with an alternative assay. The anti-CCP2 ELISA used here demonstrated relative linearity across the assay standards and based on the distribution of measured concentrations in the anti-CCP2-positive population.

In this exploratory analysis from the AMPLE study, treatment effects for both abatacept and adalimumab were greater in patients who were anti-CCP2 positive at baseline than in those who were anti-CCP2 negative. Higher baseline anti-CCP2 concentration correlated with better DAS28 (CRP) and HAQ-DI responses and greater CDAI and SDAI remission rates with abatacept but not with adalimumab (both on background MTX). RF received grant/research support from AbbVie, Amgen, Astra, Bristol-Myers Squibb, Eli Lilly, Horizon, Johnson & Johnson, Pfizer, Roche and UCB; served on speakers bureaus for AbbVie; and received research funding from UCB. RF received grant/research support from AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Celgene, Genzyme, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi Aventis and UCB; and acted as a consultant for AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Pfizer, Roche, Sanofi-Aventis and UCB. MEW received consulting fees from Bristol-Myers Squibb, Crescendo Bioscience, UCB, AbbVie, Roche, Janssen, Pfizer, Lilly, Amgen and Novartis; and received grant support from Bristol-Myers Squibb, Crescendo Bioscience and UCB. SEC, JAM and SP are employees of and hold stock in Bristol-Myers Squibb. AJ and JZ are employees of Bristol-Myers Squibb. WHR has no conflicts of interest to report.

Ethics approval The protocol was approved by the institutional review boards and independent ethics committees at the participating sites.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement ACR response data available from authors upon request.

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### Supplementary Table 1  Additional patient demographics and baseline characteristics

| Quartile, anti-CCP2 concentration limits | CCP2 negative | Q1, 28–235 | Q2, 236–609 | Q3, 613–1046 | Q4, 1060–4894 |
|-----------------------------------------|---------------|------------|-------------|--------------|---------------|
| Characteristic                          | ABA (n=66)    | ADA (n=54) | ABA (n=42)  | ABA (n=55)   | ABA (n=46)    |
| Weight, kg                              | 82.1 (49.9, 126.3) | 84.1 (57.6, 137.0) | 80.2 (51.3, 120.7) | 76.7 (41.0, 140.2) | 73.6 (42.4, 156.5) |
| Duration of disease category, %         |               |            |             |              |                |
| <6 months                               | 27.3          | 16.7       | 11.9        | 16.4         | 19.6          |
| ≥6 months                               | 72.7          | 83.3       | 88.1        | 83.6         | 80.4          |
| Tender joint count                      | 27.5 (0.0, 64.0) | 29.0 (2.0, 67.0) | 17.0 (2.0, 67.0) | 21.0 (2.0, 68.0) | 24.0 (6.0, 65.0) |
| Swollen joint count                     | 12.5 (0.0, 52.0) | 12.0 (3.0, 48.0) | 11.5 (4.0, 55.0) | 15.0 (0.0, 47.0) | 15.0 (2.0, 48.0) |
| Subject pain assessment, VAS 100 mm     | 69.0 (12.0, 95.0) | 69.0 (4.0, 98.0) | 69.0 (22.0, 92.0) | 68.3 (15.0, 97.0) | 74.0 (7.0, 95.0) |
| Subject global assessment, VAS 100 mm   | 60.0 (9.0, 98.0) | 63.5 (6.0, 97.0) | 60.0 (11.0, 91.0) | 67.0 (11.0, 98.0) | 71.0 (1.0, 100.0) |
| Physician global assessment, VAS 100 mm | 61.5 (10.0, 95.0) | 60.5 (6.0, 94.0) | 58.5 (27.0, 91.0) | 57.0 (31.0, 96.0) | 62.0 (13.0, 97.0) |
| DAS28 (CRP) by category, %             |               |            |             |              |                |
| <3.2                                    | 6.1           | 3.7        | 3.7         | 2.4          | 1.8           |
| 3.2–5.1                                 | 34.8          | 33.3       | 50.0        | 50.0         | 32.7          |
| >5.1                                    | 59.1          | 63.0       | 47.6        | 65.5         | 68.6          |
| Joint space narrowing score             | 1.3 (0.0, 51.5) | 2.0 (0.0, 56.5) | 2.0 (0.0, 83.0) | 4.0 (0.0, 68.0) | 4.5 (0.0, 111.5) |

*Note: Values are expressed as median (IQR).*
| Erosion score | 2.0 (0.0, 35.0) | 3.8 (0.0, 58.0) | 3.5 (0.0, 149.5) | 5.8 (0.0, 75.0) | 10.3 (0.0, 121.5) | 5.5 (0.0, 58.0) | 5.5 (0.0, 149.5) | 4.8 (0.0, 73.5) | 4.0 (0.0, 88.0) | 5.0 (0.0, 58.0) |
|---------------|----------------|----------------|-----------------|----------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| Estimated annual TSS progression | 3.6 (0.0, 365.0) | 4.6 (0.0, 93.8) | 5.0 (0.0, 51.7) | 6.6 (0.0, 228.8) | 8.9 (0.0, 567.5) | 6.0 (0.0, 275.0) | 7.0 (0.0, 130.0) | 6.0 (0.0, 176.7) | 4.5 (0.0, 420.0) | 5.0 (0.0, 57.5) |

Data are expressed as median (min, max), unless otherwise stated.
ABA, abatacept; ADA, adalimumab; CCP2, cyclic citrullinated peptide-2; CRP, C-reactive protein; DAS28, Disease Activity Score 28; Q, quartile; TSS, total Sharp score; VAS, visual analogue scale.