Impact of anti-citrullinated protein antibody on tumor necrosis factor inhibitor or abatacept response in patients with rheumatoid arthritis

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Abstract

Objective: To assess the impact of anti-citrullinated protein antibody (ACPA) serostatus on response to treatment with either tumor necrosis factor inhibitors (TNFi) or abatacept in patients with rheumatoid arthritis (RA).

Methods: Data was obtained from the Optimizing Patient outcomes in Australian Rheumatology (OPAL) dataset. Patient data were included in the analysis if they commenced treatment with abatacept or TNFi between 01 August 2006 and 30 June 2017 and had at least 12 months’ follow-up. The primary outcome was the mean change in the clinical disease activity index (CDAI) score from baseline to 12 months.

Results: A total of 2,052 patients were included of which 1,415 were in the TNFi cohort (n=1,053 ACPA positive) and 637 in the abatacept cohort (n=445 ACPA positive). Patients were predominantly female (75% TNFi; 80% abatacept) with no significant difference in age between cohorts. Patients with ACPA positivity had longer disease duration before commencing treatment in both the TNFi and abatacept cohorts compared to ACPA negative patients. No difference in disease severity was observed in those with ACPA negativity compared to those with ACPA positivity. Patients treated with TNFi and abatacept had significantly improved mean change in CDAI after 12 months; ACPA positivity was associated with greater response to treatment with abatacept compared to that in patients with ACPA negativity (p=0.011). No difference in response was observed based on ACPA serostatus in patients treated with TNFi (p=0.73).

Conclusion: Baseline ACPA positivity was associated with improved clinical response using CDAI outcome measure at 12 months for abatacept but not for TNFi therapies.

Keywords: Arthritis, rheumatoid, abatacept, tumor necrosis factor inhibitors, anti-citrullinated protein antibody

Introduction

The natural history of rheumatoid arthritis (RA) is well known (1). Disease modification involves treatment to control symptoms and signs of inflammation, prevent progressive structural damage, preserve and normalize function and social participation, and target remission or at least low disease activity (2, 3). Treatment strategies for RA usually involve conventional and targeted synthetic or biological disease modifying antirheumatic drugs (DMARDs) (2, 3); however, between 20% and 40% of patients fail to respond clinically to biological DMARDs (bDMARDs) (4).

Therefore, there is a clinical need to identify biomarkers which are associated with treatment response in RA, which would allow more personalized treatments and improved patients outcomes (5).

Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) markers are included in the European League against Rheumatism (EULAR) diagnostic algorithm (6). Both markers appear to play a role in predicting the response to bDMARDs (5). Previous randomized controlled studies have suggested that abatacept has a greater efficacy in patients who are ACPA positive compared to that in those who are ACPA negative (7). These results have been supported by the results of observational studies both in the United States and Europe (7-10). Similar studies have shown a relationship between RF status and treatment outcomes with patients who were RF positive/ACPA positive having improved outcomes compared to those who were RF negative/ACPA negative (10, 11).
The aim of this study was to assess whether ACPA status impacts the treatment response to abatacept and tumor necrosis factor inhibitors (TNFi) therapies in patients with RA in real-world clinical practice from Australia.

Methods

Data were extracted from the OPAL dataset for the period from 1 August 2006 until 30 June 2018. The OPAL Quality Use of Medicines Initiative is a point-of-care observational dataset which is a collection of clinical information captured by an individual clinician’s routine clinical consultations using purpose-built worksheets in Audit4 software (Software-4Specialists). Pathology and imaging reports are electronically transferred from the provider into Audit4, and this software serves as the patient’s medical record (12, 13). The activities of OPAL Rheumatology Ltd have received overarching ethics approval from the University of New South Wales Human Research Ethics Committee, based on a patient opt-out consent arrangement. The research protocol for this study was approved by the University of New South Wales Human Research Ethics Committee (Approval Date: August 3, 2018; Approval Number: HC16891).

Patients

Patients over 18 years of age diagnosed with RA (International Classification of Diseases (ICD-10) M05.* or M06.*) who commenced treatment with either abatacept or a TNFi (adalimumab, certolizumab, etanercept, or golimumab) between 01 August 2006 and 30 June 2017, who had a baseline ACPA recorded, and who had at least 12 months’ (+3 months) follow-up were eligible for inclusion in the analysis. Patients who died during the analysis period, who had concomitant inflammatory diseases, (ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, or ulcerative colitis), and those with no visit data recorded were excluded from the analysis.

Data extraction

Data on patient demographics (age and sex), clinical characteristics at index and follow-up: clinical disease activity index (CDAI), disease activity score-28 creative protein (DAS28-CRP), DAS28-CRP-3, DAS28-ESR, simplified disease activity index (SDAI), tender joint count, swollen joint count, patient and physician global assessment, health assessment questionnaire disability index (HAQ-DI), RF, ACPA status, concomitant medications (corticosteroids, cDMARDs, NSAIDs), comorbidities, and bDMARD or abatacept treatments (treatment index date, line of treatment, treatment persistence, and treatment discontinuation date) were extracted from the dataset. The Australian cut-off level for ACPA positivity (≥5 Ru/mL) was used.

CDAI and DAS28-CRP-3 are both established clinical tools used to assess the impact and severity of RA on a patient’s wellbeing and health-related outcomes. The patients are assigned a score based on their symptoms. CDAI scores can range between 0 and 76; a score between 0 and 2.8 is indicative of remission (14). The DAS28-CRP-3 is a shortened version of the DAS and allows for the inclusion of the patients’ C-reactive protein. Results of the composite score range between 0.96 and 9.6; a score of less than 2.6 indicates disease remission (15).

Statistical analysis

Sample size calculations were based on the Consortium of Rheumatology Researchers of North America (CORRONA) study and assumed a mean change in the CDAI score of -3.8±11.2 for those with poor prognostic factors and -8.6±10.9 in those with good prognostic factors (10). Using a two-sided alpha set at 0.05 and 80% power, 85 patients per arm were required to show a difference between the 2 arms. However, we planned to use all available data, and it was estimated that 2000 patients would be enrolled in the study.

Propensity score matching was planned to account for the observational nature of the data. The propensity score was calculated as the conditional probability of receiving treatment (abatacept vs. TNFi) given the patient’s age group at index, sex, baseline CDAI score, and line of treatment. It was planned that patients prescribed abatacept would be matched to those prescribed TNFi through propensity score matching in a ratio of one abatacept user to one TNFi user (1:1). The use of an initial caliper width of 0.20 was the starting point, and this was varied as needed. However, propensity score matching was unsuccessful owing to a high proportion of missing data. Instead, a post hoc analysis was conducted using a ‘typical patient analysis,’ similar to that performed by Harrold et al. (10). This typical patient analysis was built using multiple linear regression with change in CDAI score as the dependent outcome and sex, age, line of therapy, baseline CDAI and treatment by ACPA group as independent variables. The typical patient was considered to be female, aged 57, with a baseline CDAI of 20 and one prior biological line.

The primary objective was to compare the change in CDAI from baseline (+1 month) to 12 months (+3 months) in patients treated with either abatacept or TNFi in any line of therapy who had poor prognostic factors (ACPA positivity). Secondary objectives included comparing DAS28-CRP-3 score from baseline to 12 months to determine the proportion of patients achieving disease remission or low disease activity at 12 months (+3 months) by CDAI or by DAS28-CRP-3 by treatment group, line of therapy, and ACPA status. Differences in the change in CDAI or DAS-28CRP-3 from baseline to 12 months were assessed using linear regression with disease duration, baseline score (either CDAI or DAS28-CRP-3), treatment, and ACPA status included as independent variables. Disease remission, for both CDAI and DAS-28CRP-3, was calculated using logistic regression using baseline categories, treatment, and ACPA status as independent covariates.

The final secondary objective was to determine treatment persistence in patients prescribed abatacept or TNFi by treatment, line of therapy, and ACPA status. Treatment persistence was defined as the time, in consecutive days, from the date of first prescription of the drug until the time that drug was ceased, censored at 30 June 2018. Cox’s proportional hazards were used to assess treatment persistence using age at index, sex, baseline CDAI score, and line of treatment as covariates. Kaplan-Meier analysis was used to determine the median time on treatment.

This study was not designed to capture safety events.

All analyses were conducted using Stata MP v15 for Mac (StataCorp; Texas Station, USA), with p values of <0.05 considered statistically significant.
Results

Patients
Data from the OPAL dataset from 2,052 patients were included in this analysis of which 1,415 patients were in the TNFi cohort and 637 patients in the abatacept cohort. There were 1,053 (74.1%) and 445 (69.8%) ACPA positive patients in the TNFi and abatacept populations, respectively. There were no statistically significant differences in the demographic and baseline characteristics between ACPA positive and ACPA negative cohorts treated with either abatacept or TNFi including age and sex (Table 1). Patients with ACPA positivity had longer disease duration before receiving therapy in both the abatacept and TNFi cohorts compared to that in patients with ACPA negativity. TNFi’s were predominantly described as first line therapy, whereas abatacept was mostly prescribed in later lines of therapy. The majority of patients had baseline CDAI scores in the moderate (≥10 but <22.0) and high (≥22.0) range. No significant CDAI differences were observed within the 4 groups at baseline despite numerically high baseline CDAI seen in the TNF initiator groups receiving first line therapy.

Approximately, one-third of ACPA negative and two-thirds of ACPA positive patients were positive for RF; 14% of the TNFi population were ACPA and RF negative compared to 17% in the abatacept cohort (data not shown).

![Figure 1. a, b. Change in CDAI from baseline to 12 months (±3 months) by treatment and ACPA status (all patients) abatacept (a) TNFi (b). CDAI: clinical disease activity index; ACPA: anti-citrullinated protein antibody.]

![Figure 2. a, b. Change in CDAI by line of therapy from baseline to 12 months (±3 months) by treatment and ACPA status (all patients) abatacept (a) TNFi (b). CDAI: clinical disease activity index; ACPA: anti-citrullinated protein antibody.]

Table 1. Baseline patient characteristics by ACPA status and abatacept or TNFi treatment.

| Outcome                      | Abatacept initiators (n=637) | TNFi initiators (n=1415) |
|------------------------------|-------------------------------|--------------------------|
|                              | ACPA + (n=445)    | ACPA - (n=192) | p   | ACPA + (n=1053) | ACPA - (n=362) | p   |
| Patient age, mean (SD)       | 60.8 (12.5)       | 61.6 (12.6)   | n/s | 58.8 (14.2)     | 57.5 (14.1)   | n/s |
| Female, %                    | 78.4             | 84.4          | n/s | 77.7            | 74.3           | n/s |
| Disease duration, months (SD)| 141.1 (124.8)     | 105.6 (98.4)  | 0.008 | 123.6 (115.0) | 90.2 (102.4)  | <0.001 |
| Line of therapy              | n/s              | n/s           |     | n/s             | n/s            | n/s |
| 1                            | 41.9%            | 45.2%         |     | 94.3%           | 91.9%          | n/s |
| 2                            | 29.3%            | 33.0%         |     | 5.4%            | 6.7%           |     |
| 3+                           | 28.8%            | 21.8%         |     | 0.3%            | 1.4%           |     |
| Baseline CDAI                | n/s              | n/s           |     | n/s             | n/s            | n/s |
| Remission                    | 8.6%             | 3.0%          |     | 4.9%            | 2.9%           |     |
| Low                          | 15.2%            | 11.9%         |     | 7.9%            | 8.6%           |     |
| Moderate                     | 25.4%            | 37.3%         |     | 14.4%           | 13.3%          |     |
| High                         | 50.8%            | 47.8%         |     | 72.8%           | 75.2%          |     |

n/s: not significant; SD: standard deviation; ACPA: anti-citrullinated protein antibody; CDAI: clinical disease activity index; TNFi: tumor necrosis factor inhibitor.
CDAI change by treatment and ACPA status: Primary objective

At 12 months (±3 months), there was a mean improvement in CDAI score in both ACPA positive (n=67) and ACPA negative (n=52) patients in all treatment groups (Figure 1). In the abatacept population, ACPA positive patients had a greater improvement in their CDAI score compared to those who were ACPA negative (-19.01 and -10.8, respectively; p=0.011).

Secondary objectives included response to treatment as measured by a change in CDAI by line of therapy (Figure 2). This was better in patients receiving an early line of treatment, with either abatacept or TNFi, compared to those receiving later lines of treatment, with either abatacept or TNFi. Patients receiving treatment in the first line setting had a greater mean change in their CDAI score compared to those receiving treatment in later lines, irrespective of treatment or ACPA serostatus.

ACPA positive (n=67) and ACPA negative (n=52) patients treated with TNFi as the first line therapy had a change in CDAI from baseline to 12 months (±3 months), a change of approximately -28 points. This was similar to that observed in ACPA positive patients treated with first line abatacept (-29 points), but not in those who were ACPA negative (-15.9 points) (Figure 2). The mean change in CDAI status was smaller for the ACPA negative patients treated with abatacept compared to those in the TNFi cohort.

DAS28-CRP-3 remission by treatment and ACPA status

ACPA positivity in both treatment groups had a better response for the DAS-28-CRP-3 remission measure at 12 months. A significantly greater proportion of patients who ACPA positivity treated with TNFi achieved disease remission than those who were ACPA negative (37.7% vs. 29.0%; p=0.003) (Figure 3). This was not observed in the CDAI scores of remission (15% vs. 12%, p=0.20). While there was a numerical difference in rates of remission as measured by DAS28-CRP-3 in patients treated with abatacept by serostatus, it was also not statistically significant (33.3% ACPA positive, 25.8% ACPA negative; p=0.053) (Figure 3).

Treatment persistence

The overall median persistence on treatment was 4.6 years (95% confidence interval, 2.0 years to 5.3 years). Treatment persistence was longer in ACPA positive patients compared to patients who were ACPA negative, irrespective of treatment with abatacept or a TNF inhibitor (Figure 4).
Patients receiving earlier lines of treatment had better treatment responses compared to those in later lines of therapy. This finding is similar to other studies which indicate that early treatment in patients with RA, with any therapy, is more effective than in those with more established disease (20, 21). Further, early intervention in patients with RA has been shown to lead to less radiologic joint damage at 2 years compared to those who receive delayed treatment (22). The use of DMARDs earlier in a patient’s presentation is recommended in an effort to modify the course of the disease (21, 23). Another potential reason for improved outcomes in earlier lines of therapy may be the development of resistance to treatment with DMARDs or TNFi inhibitor therapies.

Irrespective of treatment, the median persistence on treatment was longer in patients who were ACPA positive compared those who were ACPA negative. Therefore, ACPA status may potentially be a surrogate for treatment efficacy. These results suggest that further studies are required to determine the impact of ACPA status on long-term treatment outcomes.

Over 90% of patients enrolled in this study received TNFi as a first line treatment; abatacept was more commonly prescribed to patients receiving later lines of treatment. This observation, which makes any comparison of demographics between the 2 groups impossible, may be reflective of the study methodology which used the first bDMARD found in the dataset as the index DMARD.

This study uses data from a retrospective, observational dataset and is therefore limited by the available data which is only collected in the outpatient setting. Due to a high proportion of missing data, propensity score matching was not possible. We attempted to control for potential bias by using multiple linear regression similar to that reported in the CORRONA studies (10), but excluded patient body mass index (due to a high proportion of missing data). Given that abatacept entered the market later than other treatments, we may have observed changes in treatment practice and treatment patterns because of the changing treatment landscape.

Baseline ACPA positivity was associated with improved clinical response using CDAI outcome measure at 12 months for abatacept but not for TNFi therapies. Response to therapy for both abatacept and TNFi was better with earlier lines of therapy. Median persistence on treatment was longer in ACPA positive patients irrespective of TNFi or abatacept therapy. Further studies beyond 12 months are needed to determine impact of ACPA on long-term treatment outcomes.

**Discussion**

Results of this real-world evidence study suggest that ACPA positivity is associated with a better CDAI response in patients with RA treated with abatacept, similar to what has been observed in other studies (7, 9, 10, 16, 17). Others have reported the titre of ACPA may be important in predicting response to abatacept, but not to TNFi, with higher titres associated with better clinical responses (7). Our study found similar results to those from international studies in Europe (8) and the United States (10, 11) where ACPA status has been noted as being an important factor in determining patients outcomes. For example, one report from the United States indicated that patients with RF positivity or ACPA positivity had improved clinical outcomes compared to those who were RF and ACPA negative (11).

Of particular relevance to this study is the CORRONA study (10), on which this Australian study was based. It must be noted that the cut-off values for ACPA positivity were different in that study (positivity where ACPA ≥20 U/mL), which reflects differences between the US and Australian laboratory practice. In that study, the adjusted change in CDAI score at 6 months in ACPA positive patients treated with abatacept was -8.53 (95% CI 9.73 to -7.33), and -4.03 (95% CI -5.62 to -2.44) in negative patients. For TNFi, the values were -7.43 (95% CI -8.08 to -6.78) and -6.43 (95% CI -7.31 to -5.55), respectively. The lower scores reported in this study might reflect the time course of response given that our study assessed response at 12 and not 6 months. However, the same direction of responses was observed.

This suggests that ACPA positivity could potentially be used as a marker of response in patients treated with abatacept, but not in patients treated with TNFi. This possibly reflects the fact that abatacept modulates T-cell co-stimulation, affecting ACPA maturation and seroconversion of IgM (9, 18). Using the DAS28-CRP-3 scale, ACPA positivity was also associated with an improved response in patients treated with either abatacept or TNFi therapies. The discrepancy between the CDAI and the DAS23-CRP-3 scores may be due to differences in underlying constructs for each measure, resulting in the classification of different disease states for RA activity (19). CDAI and SDAI are considered more stringent indices of remission.

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Supplemental Figure 1. Mean change in CDAI from baseline to 12 months by treatment and ACPA status, typical patient analysis.

CDAI: clinical disease activity index; ACPA: anti-citrullinated protein antibody.