Concise report

Use of a 12-week observational period for predicting low disease activity at 52 weeks in RA patients treated with abatacept: a retrospective observational study based on data from a Japanese multicentre registry study

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Abstract

Objective. Only a few studies have assessed predictive factors for the long-term efficacy of abatacept. This study aimed to provide clinical evidence of an adequate observational period for predicting low disease activity (LDA) achievement at 52 weeks in RA patients treated with abatacept.

Methods. Participants were all patients registered in a Japanese multicentre registry who were treated with abatacept and had at least 52 weeks of follow-up (n = 254).

Results. Areas under the receiver operating characteristic curves for the 28-joint count with CRP (DAS28-CRP) at each time point for LDA achievement at 52 weeks were: 0.686 (cut-off score: 4.6) at baseline, 0.780 (3.8) at 4 weeks, 0.875 (3.3) at 12 weeks, and 0.900 (3.0) at 24 weeks. Although patients with a DAS28-CRP score <3.0 at 24 weeks had the highest proportion of LDA achievement at 52 weeks (79.3%), the proportion for those with a score <3.3 at 12 weeks was comparable (77.2%, P = 0.697). Proportions were significantly lower in patients with a score >3.8 at 4 weeks or >4.6 at baseline. Multivariate logistic regression demonstrated that a DAS28 score of <3.3 at 12 weeks was an independent strong predictor for LDA at 52 weeks (adjusted odds ratio: 15.2, P < 0.001).

Conclusion. Twelve weeks is an adequate observational period to judge the long-term clinical efficacy of abatacept, and is about as early as the period for assessing TNF blockade therapy.

Key words: predictors, adequate observational period, long-term efficacy, abatacept, RA, Japanese, multicentre registry system.
Introduction

Abatacept is the first member of a new class of biologic DMARDs for RA that inhibits T-cell activation by binding to CD80/86, modulating its interaction with CD28. The efficacy and safety of abatacept have been reported in several clinical trials [1-3] and in clinical practice [4, 5]. There is a high level of interest in defining predictive factors for the long-term clinical response to abatacept, with the aim of minimizing patient exposure to ineffective therapy; however, only a few studies have assessed this aspect. Our previous study demonstrated that high disease activity at baseline was an independent predictor of clinical response at 24 weeks [6]. Although baseline predictors are of interest, therapy should not be abandoned based on the baseline characteristics of patients in need. There is therefore a great need in medical practice for clinical indices after therapy initiation that can judge and predict the long-term efficacy of abatacept.

Several studies have reported adequate observational periods that predict long-term efficacy of TNF blockade therapies. Van der Cruyssen et al. [7] reported that disease activity measured by DAS28 at 14 or 22 weeks of infliximab therapy was the best predictor of long-term attrition. Van der Heijde et al. [8] found that failure to achieve improvement in DAS28 within the first 12 weeks of certolizumab pegol therapy independently predicted a low probability of achieving low disease activity (LDA) at 1 year. No similar data currently exist for abatacept.

This study aimed to provide clinical evidence for an adequate observational period that predicts long-term clinical efficacy of abatacept. We determined the prognostic significance of disease activity measured by DAS28-CRP at baseline and after 4, 12 and 24 weeks of abatacept treatment, as well as baseline characteristics, to predict LDA at 52 weeks.

Methods

Participants

All eligible patients were registered in and followed by the Tsurumai Biologics Communication Registry (TBCR) [9]. TBCR was initiated in October 2008 to study the long-term efficacy and safety of biologics used to treat RA. Data were collected retrospectively from 2003 to 2008 and prospectively after 2008. Patient characteristics and disease activity data are available for all RA patients treated with commercially available biologics at TBCR institutes in Japan. Registered data are updated once per year and include drug continuation, reasons for switching drugs and adverse events that may have occurred during treatment.

The present study included all patients who started i.v. abatacept treatment and were prospectively observed for longer than 52 weeks at TBCR-affiliated institutes (n = 254). All patients met the 1987 ACR classification criteria for RA. Patients received i.v. abatacept three times at 2-week intervals, and thereafter at 4-week intervals. Patient anonymity was maintained during data collection, and security of personal information was strictly controlled. This study was approved by the Nagoya University Graduate School of Medicine Ethics Committee. Written informed consent was obtained from all participants in this study.

Data collection

Demographic data recorded at initiation of treatment (baseline, week 0) included age, gender, disease duration, RF positivity (≥ 20 IU/ml), history of previous treatment with biological DMARDs, pulmonary comorbidity and concomitant treatment [MTX or prednisolone (PSL)]. Bilateral hand radiographs were used to classify severity of peripheral joint destruction into the four Steinbrocker classification stages I-IV [10]. The following disease parameters were recorded at baseline and after 4, 12, 24 and 52 weeks of treatment: tender joint count and swollen joint count on 28 joints, patient and physician global assessment of disease activity, modified HAQ (mHAQ) score, serum CRP levels and matrix metalloproteinase-3 levels. Disease activity was evaluated at each time point by DAS28-CRP.

The DAS28-CRP is known to underestimate disease activity significantly and overestimate improvement in disease activity significantly compared with the DAS28-ESR [11]. We used different criteria from those for DAS28-ESR. Disease activity was categorized as follows: DAS28-CRP remission (DAS28-CRP < 2.3), LDA (2.3 ≤ DAS28-CRP < 2.7), moderate disease activity (2.7 ≤ DAS28-CRP < 4.1) and high disease activity (DAS28-CRP > 4.1). These criteria were defined using a large Japanese cohort study [12].

Statistical analysis

Demographic and disease characteristics are reported using descriptive statistics. All results are expressed as mean (s.d.) or as a percentage. Student’s t-test was used for two-group comparisons and the Chi-squared test for categorical variables. The last observation carried forward method was used in each analysis.

Receiver operating characteristic (ROC) curves were constructed to determine the best cut-off point for DAS28-CRP at each time point, and the area under the ROC curve (AUC) was calculated as a measure of the overall discriminative ability of the DAS28-CRP score. The cut-off point was identified as the one closest to the (0, 1) point and taken to be the cut-off point that best differentiated between patients with and without LDA achievement at 52 weeks [13].

Multivariate analysis (logistic regression) was performed to determine predictive factors of LDA achievement at 52 weeks. Variables significantly associated with the endpoint in univariate analysis (P < 0.05) and the stepwise selection process were used to select the final model. Adjusted odds ratios with 95% CIs were calculated.

All statistical tests were two-sided, and significance was defined as P < 0.05. All analyses were performed with SPSS version 20.0.0 software (IBM Corp., Armonk, NY, USA).
Results

Demographic data

A total of 254 patients were enrolled in this study, with four excluded due to incomplete data, giving a final total of 250 patients through October 2013. Mean age was 64.5 (12.3) years, and mean disease duration was 11.3 (12.6) years. Of this cohort, 80.8% were female, 56.4% showed RF positivity, 47.2% had previous biologic DMARD history [mean: 1.6 (0.8)], 48.8% had concomitant MTX treatment [mean dose: 7.4 mg/week (s.d. 2.6)] and 51.2% reported oral steroid usage [mean dose: 4.5 mg/day (s.d. 2.6)]. Of the 250 patients, 176 (70.4%) were categorized into advanced Steinbrocker Stages (III and IV), indicating established RA and joint damage. Mean mHAQ score was 0.70 ± 0.73. Disease activity was high, as shown by a mean DAS28-CRP of 4.50 (1.28) and a mean CRP level of 2.2 mg/dl (s.d. 2.8).

ROC curves

ROC curves for DAS28-CRP at 0, 4, 12 and 24 weeks for achievement of LDA at 52 weeks are shown in Fig. 1A. The AUC and cut-off DAS28-CRP score at each timepoint are also shown. The sensitivity and specificity of each cut-off score was 62.4% and 70.9%, respectively, at baseline, 67.75 and 81.8% at 4 weeks, 79.75 and 81.8% at 12 weeks and 80.55% and 87.3% at 24 weeks. We then compared the DAS28-CRP categorical distribution of disease activity status at 52 weeks between patient groups that achieved the cut-off score at each timepoint. Patients with a DAS28-CRP < 3.0 at 24 weeks also had the highest proportion of LDA achievement at 52 weeks (79.3%) (Fig. 1B). There was no significant difference in the proportion of LDA at 52 weeks for patients with a score of < 3.3 at 12 weeks (77.2%, P = 0.697), while proportions were significantly lower for patients with a score of < 3.8 at 4 weeks (67.7%, P = 0.039) and those with a score of < 4.6 at baseline (54.6%, P < 0.001).

Factors predicting achievement of LDA at 52 weeks

Univariate analysis and multivariate logistic regression were performed to identify predictors of LDA achievement at 52 weeks. Univariate logistic regression showed that the following variables were associated with achievement of LDA at 52 weeks after abatacept initiation: no previous biologic DMARD history, concomitant PSL usage, mHAQ score less than the median value (0.50) and DAS28-CRP score less than the cut-off score (3.3) at 12 weeks (Fig. 2A).

Multivariate logistic regression showed that no previous biologic DMARD history, concomitant PSL and low DAS28-CRP score at 12 weeks were independently associated with achievement of LDA at 52 weeks (Fig. 2B).

Discussion

Our analysis demonstrates that the predictability of achieving LDA at 52 weeks after starting abatacept therapy is almost equivalent between cut-off DAS28-CRP

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(A) Receiver operating characteristic (ROC) curves of the 28-joint count DAS28-CRP at each time point to predict the achievement of low disease activity (LDA) at 52 weeks after starting abatacept treatment. The table displays the area under the ROC curve (AUC), standard error (S.E.), 95% CI and cut-off DAS28-CRP score for each time point.

(B) Categorical distribution of disease activity status at 52 weeks in patients with less than each cut-off DAS28-CRP score. The proportions of patients that achieved LDA at 52 weeks were statistically compared between groups with less than each cut-off score at each time point using the chi-squared test. HDA: high disease activity; MDA: moderate disease activity; LDA: low disease activity; REM: remission, *P < 0.05, **P < 0.01.
scores at 12 and 24 weeks. The AUC was also almost equivalent at 12 and 24 weeks, and there was no significant difference in the proportion of patients who achieved LDA at 52 weeks. Predictability at baseline and 4 weeks was lower than at those two timepoints. Although a longer observational period allows for a more accurate prediction of long-term response, a longer period of persistent active arthritis leads to irreversible joint destruction and disability. Therefore, a major challenge in the management of RA is to predict long-term response in as short a period as possible to minimize patient exposure to ineffective therapies. It appears that 12 weeks after starting abatacept treatment is an adequate time point for predicting clinical response at 52 weeks. The cut-off DAS28 score of 3.3 at 12 weeks should not be a strict value, but it may help physicians decide whether to continue abatacept therapy in patients who have not achieved LDA at this time.

As baseline factors, multivariate logistic regression analysis demonstrated that previous biologic DMARD history and concomitant PSL therapy were independent negative predictors of LDA achievement at 52 weeks. We previously reported that previous biologic DMARD history was negatively associated with LDA at 24 weeks [5]. Abatacept appears to demonstrate its maximal clinical performance when used as a first biologic DMARD, similar to anti-TNF agents [15].

The present study suggests that the long-term response to abatacept may be impaired by concomitant PSL. No data are available on the effect of concomitant steroids on the long-term efficacy of abatacept. The effects of concomitant steroid use on the clinical efficacy of biologic DMARDs differ between agents, and the conclusions are inconsistent [16–18]. Further clinical data would be necessary to resolve these discrepancies.

One important finding in this study was that concomitant MTX was not an independent predictor of clinical response, in contrast to what was found for TNF inhibitors. Previous studies have emphasized that TNF inhibitors required sufficient concomitant MTX therapy to maximize their clinical efficacy against RA [19]. A smaller combined effect with MTX is a unique characteristic of abatacept relative to TNF inhibitors.

This study has several limitations. First, given the retrospective observational setting, a future prospective study would be necessary, especially to verify the external validity of our findings or our DAS28 cut-off score. In addition, the Steinbrocker’s stage classification could
have been underestimated, as these classifications were based on each attending physician’s report and no data are available on when the radiographs used for evaluation were taken relative to participant entry into this study. In addition, sequential radiographic data were not available. Given the importance of joint protective effects in demonstrating clinical efficacy, evaluating radiographic changes in patients treated with abatacept will be necessary in the future. Finally, the present study findings were all based on the use of i.v. abatacept. However, the use of a new s.c. formulation is now widespread, and further study is needed to identify whether our above results apply to s.c. abatacept as well.

Conclusion

It appears that 12 weeks after starting abatacept treatment is an adequate time point at which clinical response at 52 weeks can be predicted. This strategy complies with the 2013 European League Against Rheumatism recommendation update that a therapy should be adjusted if there is no improvement by at most 3 months after the start of treatment or if the target has not been reached by 6 months [20].

Rheumatology key messages

- DAS28-CRP at 12 weeks independently and strongly predicts low RA disease activity achievement at 52 weeks.
- Twelve weeks is an adequate observational period for predicting abatacept efficacy at 52 weeks in patients with RA.
- Twelve weeks is sufficient to decide on abatacept continuation in patients with RA and fits the EULAR recommendation.

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References

8. van der Heijde D, Keystone EC, Curtis JR et al. Timing and magnitude of initial change in disease activity score 28


