Multicenter, observational clinical study of abatacept in Japanese patients with rheumatoid arthritis

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ABSTRACT

The aim of this study was to assess abatacept in rheumatoid arthritis (RA) patient. Patients (20 men, 89 women, aged 61.9 ± 10.4 y) who responded inadequately to conventional synthetic disease-modifying anti-rheumatic drug were treated with abatacept for 24-months. Disease activity score in 28 joints (DAS28-CRP) was evaluated. Of 109 patients, 82 (75.2%) were on methotrexate (MTX; mean dosage 9.0 ± 2.7 mg/week); 48 (44.0%) were naive to biologics and 61 (56.0%) had failed biologics. The 1- and 2-year retention rates were 77% and 53%, respectively. At 24-months, the DAS28-CRP remission rates were 62.8% in the biologic-naive patients, and 33.3% in the biologic-failure patients (p < .01), while the structural remission rates were 83.9% and 73.1%, respectively (p = .461). Abatacept was equally effective in RA patients who were and were not on concomitant MTX. Biologic-naive was associated with better clinical outcome. Abatacept was effective in patients who showed decreasing anti-CCP antibody titers or serum MMP-3 levels during treatment. Infection was the most frequent adverse effect of abatacept therapy. In conclusion, abatacept is more effective in biologic-naive than in biologic-failure RA patients with or without concomitant use of MTX. Abatacept is more effective in RA patients with than without decreasing serum MMP-3 or anti-CCP antibody titers during treatment.

1. Introduction

Various biological disease-modifying anti-rheumatic drugs (bDMARDs) are currently used to treat patients with rheumatoid arthritis (RA). Among these bDMARDs, abatacept has a unique mechanism of action, in that it inhibits interactions between T cells and antigen-presenting cells by blocking CTLA4. Abatacept was first reported to be effective in RA patients refractory to tumor necrosis factor (TNF) inhibitors [1] and methotrexate [2] (MTX). Although the efficacy of abatacept in RA patients with an inadequate response to MTX was similar to that of infliximab, abatacept was safer and better tolerated than infliximab [3]. In MTX-naive early RA patients with poor prognostic factors, the combination of abatacept and MTX showed significantly better clinical and radiographic efficacy than MTX alone, with a comparable safety profile [4]. Moreover, abatacept plus MTX was shown to achieve drug-free remission in patients with early RA [5]. Compared with TNF inhibitors, abatacept was found to have similar clinical and radiographic efficacy, with greater safety, in patients at all stages of RA, with the 2016 European League Against Rheumatism (EULAR) guidelines classifying abatacept as a phase 2 bDMARD, similar to TNF, IL-6 and Jak inhibitors, in the treatment of RA [6]. Abatacept showed similar efficacy and safety when administered subcutaneously or intravenously, as well as low immunogenicity, in MTX-resistant Japanese RA patients [7,8]. Moreover, abatacept was shown to suppress joint destruction for 104 weeks in 92 Japanese RA patients [9], and a postmarketing surveillance (PMS) study showed that abatacept was safe and effective in Japanese RA patients [10].
addition, some Japanese patients with established RA who attained clinical remission following abatacept treatment subsequently achieved biologic-free remission [11]. These findings suggested that abatacept was safe and could induce clinical remission in Japanese RA patients. To individualize treatment, however, it is necessary to identify clinical factors related to the efficacy and safety of abatacept in Japanese RA patients.

The multicenter observational clinical study for RA using abatacept in Japanese RA patients with inadequate response to DMARDs, called the Mt. Fuji Study, assessed the efficacy and safety of abatacept in a real world clinical setting. Factors influencing the efficacy and safety of abatacept, including concentrations of cytokines and anti-citrullinated peptide antibodies (ACPA), were analyzed in Japanese RA patients who showed an inadequate response to at least one conventional synthetic (cs) DMARD.

2. Patients and methods

2.1. Patient population

This study included 109 adult Japanese RA patients, 89 women and 20 men, of mean age 61.9 ± 10.4 years (range 32–84 years), who fulfilled the 2010 American College of Rheumatology (ACR)/EULAR criteria for RA and had an inadequate response to at least one csDMARD. Eligible patients were from the 12 institutes belonging to the Shizuoka Rheumatism Network (http://www.hamamed.ac.jp/docs/rheumatism/), an RA clinical and research consortium, established in 2007. The inclusion period was from November 2011 to October 2012.

All patients provided written informed consent. This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. All experimental protocols were approved by the Institutional Review Board of Hamamatsu University School of Medicine.

2.2. Study protocol

Abatacept was administered as an iv infusion, and was administered during weeks 0, 2 and 4, and every 4 weeks, thereafter. The abatacept dose was based on patients’ body weight, with patients weighing < 60 kg, 60–100 kg and >100 kg administered doses of 500 mg, 750 mg and 1000 mg, respectively, in accordance with prescribing information and the guidelines of the Japanese College of Rheumatology (JCR).

Data collected included age, sex, body weight, disease duration, past medical history, comorbidities, prior use of biologics, concomitant use of MTX and other DMARDs and glucocorticoids or other medications.

Patients were monitored for adverse events throughout the study period. Adverse drug reactions (ADRs) were defined as any noxious or unintended response for which a causal relationship with the use of the drug could not be ruled out. Serious ADRs were defined as any ADR that caused death, was life-threatening, or caused hospitalization or prolongation of hospitalization, disability, or permanent injury.

2.3. Efficacy assessments

RA disease activity was assessed by measuring 28-joint disease activity score with CRP (DAS28-CRP) at 0, 3, 6, 9, 12, 15, 18, 21 and 24 months. DAS28-CRP scores of < 2.3, ≥ 2.3 to < 2.7, ≥ 2.7 to ≤ 4.1 and > 4.1 were classified as remission (< 2.3) and low, moderate and high disease activity, respectively [12]. The proportion of patients in each disease activity class at each specified time and the proportion of patients in DAS28-CRP remission at 12 and 24 months were calculated.

Functional ability was analyzed by determining patients’ Health Assessment Questionnaire-Disability Index (HAQ-DI) at 0, 3, 6, 9, 12, 15, 18, 21 and 24 months. An HAQ-DI < 0.5 was considered functional remission.

Radiographic progression of joint destruction was assessed by determining total Sharp scores (mTSS) at 0, 12 and 24 months or at the time of withdrawal from the study. Changes in mTSS from baseline were determined at 12 and 24 months (ΔmTSS), with patients classified as having no (ΔmTSS ≤ 0), slight (ΔmTSS ≤ 0.5) and or clinically relevant (ΔmTSS ≥ 3) radiographic progression (CRRP).

2.4. Determination of serum concentrations of cytokines and anti-citrullinated peptide antibody (ACPA)

Serum concentrations of TNFα and IL-6 at 0 and 12 months were measured by enzyme-linked immunosorbent assays (ELISA; SRL, Tokyo, Japan), according to the manufacturer’s instructions. Antibodies to cyclic citrullinated peptide (anti-CCP Ab) at 0 and 12 months were also measured by ELISA (EUROIMMUN, Luebeck, Germany) according to the manufacturer’s instructions.

2.5. Statistical analysis

All statistical analysis was performed using SAS9.4 software (SAS Institute Inc., Cary, NC) by
3. Results

3.1. Patient disposition and baseline characteristics

Table 1 shows the baseline demographic and clinical characteristics of all patients, and of those classified as naïve to biologics and failing biologics. The dosage of MTX or prednisolone was calculated and expressed as mean ± sd among those taking these medications. Most of these characteristics were similar in the biologic-naïve and biologic-failure groups, except the biologic-naïve group contained a greater proportion of patients of older age, shorter disease duration, higher MTX dosages, lower HAQ-DI scores and lower serum TNFα concentrations than the biologic-failure group. Of the 109 patients included in this study, 51 (47%) discontinued prematurely, 15 due to inadequate responses, nine due to adverse events, three due to achievement of remission and 24 due to withdrawal of consent and other reasons (Figure 1). The 1- and 2-year retention rates were 77% and 53%, respectively.

Eleven patients (10.1%) experienced ADRs associated with abatacept therapy (Table 2). Four of these 11 events were serious ADRs, including bacterial pneumonia in two patients, pneumocystis jirovecii pneumonia in one and nontuberculous mycobacteriosis in one. All patients who experienced ADRs recovered completely without any sequela. Infection was the most frequent adverse event in this study. One patient died during this study due to RA with severe vasculitis, however, this event was considered unrelated to abatacept.

3.2. Clinical efficacy

Clinical disease activity evaluated by the DAS28-CRP improved significantly following abatacept treatment (Figure 2(A)), with the DAS28-CRP remission rates at 12 and 24 months being 42.5% and 43.4%, respectively. The functional status of these patients, as evaluated by the HAQ-DI, also improved significantly (Figure 2(B)), with the HAQ-DI remission rates being 41.7% at both 12 and 24 months. Radiographic progression, as assessed by cumulative probability plot analysis (Figure 2(C)),
showed that the CRRP rate was 10.5% (6/57) and the remission rate was 87.2%.

Classification of these patients into biologic-naïve and biologic-failure groups showed that improvements in clinical disease activity, as assessed by the DAS28-CRP, were significantly greater in the biologic-naïve than the biologic-failure group throughout the study (Figure 3(A)). The swollen joint counts of the biologic-naïve group were 8.0 ± 5.7 at baseline, 1.8 ± 2.6 at 12 months, 1.8 ± 2.8 at 24 months, those of the biologic-failure group were 8.7 ± 5.7, 3.2 ± 3.8 and 3.1 ± 4.1, respectively. The swollen joint counts were improved in the biologic-naïve group compared with the biologic-failure group at 12 months (p < .05), and at 24 months (p < .01). The HAQ-DI also showed significantly greater improvement in the biologic-naïve than in the biologic-failure group (Figure 3(B)), with HAQ-DI remission rates of 43.8% and 21.3%, respectively (p < .01). These findings suggest that abatacept is more effective in the biologic-naïve than in the biologic-failure group, as determined by clinical disease activity and functional ability.

Interestingly, structural remission rates did not differ significantly in these two groups at 12 (83.9% vs. 80.8%, p = .759) and 24 (83.9% vs. 73.1%, p = .461) months (Figure 3(C,D)). By analyzing serum cytokine or autoantibodies, we attempted to find the reason why abatacept had a similar effect on the structural change between the biologic-naïve group and the biologic-failure group. The serum TNFα level of the biologic-failure group was dramatically suppressed from 18.1 ± 38.2 pg/ml at baseline to 3.40 ± 4.30 pg/ml at 12 months, whereas that of the biologic-naïve group was slightly suppressed from 2.09 ± 1.65 pg/ml at baseline to 1.52 ± 0.63 pg/ml at 12 months. Conversely, the serum IL-6 level at baseline was comparable between the two groups (biologic-naïve: 45.3 ± 68.5 pg/ml, biologic-failure: 39.1 ± 49.6 pg/ml), and the serum IL-6 level at 12 months was significantly elevated in the biologic-failure group compared with the biologic-naïve group (biologic-naïve: 5.50 ± 6.55 pg/ml, biologic-failure: 24.1 ± 39.7 pg/ml, p < .05).

Rheumatoid factor showed a significant decrease in the biologic-naïve group compared with the biologic-failure group (biologic-naïve: biologic-failure, 101.2 ± 150.4 U/ml: 153.6 ± 159.3 U/ml at baseline, 77.5 ± 90.8 U/ml: 145.5 ± 168.3 U/ml at 12 months, p < .05, 157.6 ± 213.0 U/ml: 168.9 ± 187.6 U/ml at 24 months, p < .05). There was no significant difference in anti-CCP antibody titer between the biologic-naïve and biologic-failure groups at baseline or at 12 months (biologic-naïve: biologic-failure, 161.5 ± 156.7 U/ml: 321.9 ± 687.7 U/ml at baseline, 157.6 ± 213.0 U/ml: 454.8 ± 722.0 U/ml at 12 months).

Collectively, the most significant and differential findings of abatacept on the suppression of radiographic progression in the biologic-failure group could be related to the greater suppression of TNFα levels in this group. However, it is well-known that anti-TNF therapy raises the serum TNFα levels in patients who show an inadequate response to the therapy. The decrease of serum TNFα levels in biologic-failure group after abatacept therapy may be due to the gradual disappearance of previously administered anti-TNF inhibitors. Abatacept contribution to the
suppression of radiographic progression through TNF suppression cannot be denied but not clear. This needs to be further addressed in the future.

To assess the effects of MTX on abatacept therapy, patients were divided into those who were and were not being treated with MTX. Because the biologic-naïve group of 48 patients included only four who were being treated with MTX, we analyzed the biologic-failure group of 61 patients, which consisted of 38 (62.3%) patients being treated with MTX and 23 (38.7%) who were not. Except for age, there were no significant between-group differences in baseline demographic and clinical factors (Table 3). DAS28-CRP (Figure 4(A)) and HAQ-DI (Figure 4(B)) did not differ significantly between subgroups who were and were not being treated with MTX. These findings suggest that abatacept is effective in RA patients with or without concomitant use of MTX.

### 3.3. Factors influencing efficacy and safety outcomes

Univariate analysis showed that baseline factors associated with a better DAS28-CRP outcome included being biologic-naïve, TNFα < 2.2 pg/ml, and IL-6 < 25.8 pg/ml (Table 4). However, multivariate analysis showed that being biologic-naïve was the only factor associated with a better DAS28-CRP outcome at 24 months. Neither univariate nor multivariate analysis identified factors significantly associated with safety (data not shown).

This study also analyzed the associations between treatment efficacy and changes in MMP-3 and ACPA levels. Study subjects were divided into two groups based on the difference between baseline and 24 months in case of MMP-3, baseline and 12 months in case of anti-CCP antibody levels. Subjects that showed any increase in 12 or 24 months compared to baseline were categorized...
into 'elevated group', and that showed any decrease in 12 or 24 months compared to baseline were categorized into 'reduced group'. 21 patients of elevated MMP-3 group showed an increase in MMP-3 level from baseline (132.5 ± 87.9 ng/ml) to 24 months (207.9 ± 190.3 ng/ml), and 77 patients of reduced MMP-3 group showed a decrease in MMP-3 level from baseline (224.8 ± 205.6 ng/ml) to 24 months (74.8 ± 53.8 ng/ml). There were no significant differences in the baseline characteristic of these two groups (data not shown). DAS28-CRP outcomes were significantly better in patients with reduced than elevated MMP-3 levels, with 24-month DAS28-CRP remission rates of 54.5% and 15.0%, respectively \( (p < .01; \text{Figure 5(A)}) \).

Similarly, eight patients of reduced anti-CCP antibody group showed a decrease in anti-CCP antibody titer from baseline (198.9 ± 180.7 U/ml) to 12 months

Figure 3. Clinical efficacy of abatacept in biologic-naïve and biologic-failure groups, as shown by the proportion of patients in each disease activity class of DAS28-CRP (A), the transition of mean HAQ-DI (biologic-naïve: solid line, biologic-failure: dotted line) and remission rates (filled column) (B), and the probability of radiographic progression at 12 (C), and 24 (D) months. LDA: low disease activity; MDA: moderate disease activity, HDA: high disease activity. ** \( p < .01 \) vs. biologic-failure.
Table 3. Baseline characteristics of patients in the biologic-failure group who were and were not receiving concomitant MTX.

|                      | MTX (−) (n = 23) | MTX (+) (n = 38) | p value |
|----------------------|------------------|-----------------|---------|
| Age, years           | 64.1 ± 7.9       | 57.1 ± 11.0     | .018    |
| Male/Female          | 5 (21.7%)/18 (78.3%) | 6 (15.8%)/32 (84.2%) | .558    |
| Body weight, kg      | 54.1 ± 10.3      | 51.8 ± 9.4      | .443    |
| Disease duration, years | 11.9 ± 8.3       | 10.6 ± 9.7      | .390    |
| MTX dose, mg/week    | 8.6 ± 2.9        | –               | .703    |
| Prednisolone use, n (%) | 14 (60.9%)       | 17 (44.7%)      | .222    |
| Prednisolone, mg/day | 4.3 ± 2.2        | 3.6 ± 2.0       | .477    |
| TJC, n               | 8.1 ± 4.5        | 7.1 ± 6.3       | .162    |
| SJC, n               | 9.0 ± 6.1        | 8.5 ± 5.6       | .777    |
| CRP, mg/dl           | 1.9 ± 2.1        | 2.0 ± 2.5       | .760    |
| ESR, mm/h            | 41.1 ± 27.7      | 50.0 ± 37.3     | .485    |
| RF, U/ml             | 190.0 ± 156.3    | 137.0 ± 160.7   | .234    |
| MMP-3, ng/ml         | 199 ± 113        | 203 ± 221       | .219    |
| DAS28-CRP            | 4.98 ± 1.00      | 4.79 ± 1.32     | .409    |
| DAS28-ESR            | 5.43 ± 1.13      | 5.20 ± 1.53     | .558    |
| CDAI                 | 29.1 ± 12.0      | 26.4 ± 12.8     | .351    |
| SDAI                 | 31.0 ± 12.7      | 28.4 ± 13.6     | .399    |
| HAQ-DI               | 1.30 ± 0.73      | 1.21 ± 0.82     | .587    |
| Anti-CCP positive, (%) | 85.7%            | 88.9%           | .765    |
| Anti-CCP, U/ml       | 180 ± 269        | 151 ± 202       | .862    |
| TNFα, pg/ml          | 7.9 ± 8.3        | 23.9 ± 46.8     | .874    |
| IL-6, pg/ml          | 47.5 ± 43.6      | 36.3 ± 57.2     | .086    |
| Bio, n               | 2.0 ± 0.9        | 1.6 ± 0.7       | .066    |

Figure 4. Clinical efficacy of abatacept in biologic-failure patients who were and were not receiving concomitant MTX, as shown by the proportion of patients in each disease activity class of DAS28-CRP (A) and the transition of mean HAQ-DI (B).
(125.4 ± 145.1 U/ml) and 19 of elevated anti-CCP antibody group showed an elevation in anti-CCP antibody titer from baseline (149.9 ± 168.2 U/ml) to 12 months (404.9 ± 636.4 U/ml). These groups did not differ significantly in baseline characteristics (data not shown). DAS28CRP outcomes at 3, 12, 18 and 21 months were significantly better in patients with reduced than elevated anti-CCP antibody group (Figure 5(B)).

### 4. Discussion

To identify the factors affecting the efficacy and safety of iv abatacept in a real world clinical setting, this observational, multicenter clinical study, the Mt. Fuji study, analyzed its clinical efficacy and safety in Japanese RA patients. In agreement with a previous study [13], this study found that abatacept was more effective in biologic-naïve than in biologic-failure patients, as determined by clinical disease activity and functional ability [13]. Abatacept also suppressed structural progression in both groups of patients, as well as being equally effective in patients who were and were not receiving concomitant MTX, perhaps because abatacept has low immunogenicity in the presence or absence of MTX [14].

A 24-week PMS in Japan [10] included a patient population consisting of 82.3% women, of mean age 61.4 ± 12.6 years and median disease duration 8.2 years. Of these patients, 69.6% had been exposed previously to biologics other than abatacept, and 66.3% were being treated concomitantly with MTX. The patients in the this study were of similar gender distribution, ages and disease duration. However,
the percentages of biologic-failure patients (56%) were lower and those receiving concomitant MTX (75.2%) were higher in our study.

Of our patients, 6.4% reported serious ADRs and 23.9% reported all-grade ADRs, with a high percentage of ADRs categorized as infections and infestations (10.1%). In the PMS [10], age ≥ 65 years, comorbidity of hepatobiliary disorders, comorbidity or history of respiratory disease, history of allergy, prior use of biologics and concomitant use of glucocorticoid (>5 mg/day of prednisolone) were associated with a significantly higher risk for infections. Although we could not identify the factors related to the safety of abatacept use in this study, patients, especially elderly patients, those with comorbidities and patients receiving concomitant glucocorticoids, should be carefully monitored for infections [15,16].

We observed 1- and 2-year abatacept retention rates of 77% and 53%, respectively, slightly lower than in similar studies. For example, the 1- and 2-year abatacept retention rates in a 104-week study were reported to be 83.7% and 73.9%, respectively [9]. The lower retention rate in our study may have been due to our inclusion of a higher percentage of biologic-failure patients (56% vs. 38%). A higher drug retention rate has been reported in RA patients with fewer anti-TNF failures [17]. Another possible explanation for the lower retention rate was the high percentage of patients who withdrew consent (22%), resulting from the withdrawal of one institution from this multicenter clinical study.

We also found that abatacept was more effective in RA patients who showed reductions in serum MMP-3 concentration and anti-CCP antibody titer during abatacept treatment. Abatacept has been reported to be more effective in anti-CCP positive patients [18,19] and in RA patients with a higher titer of rheumatoid factor [20]. In addition, lower baseline HAQ-DI or CRP may predict maintenance of remission or low disease activity after discontinuation of abatacept [11]. Among bDMARDs, rituximab and abatacept were shown to significantly reduce anti-CCP antibody levels [21]. These findings may support the use of abatacept in RA patients who show decreasing serum MMP-3 levels and/or anti-CCP antibody titers during treatment. Low dose abatacept could be used as a treatment option for maintenance therapy in patients with low disease activity [22]. Abatacept dose reduction may also be achievable in RA patients who show decreasing serum levels of MMP-3 and/or anti-CCP antibody.

In conclusion, abatacept is more effective in biologic-naïve than in biologic-failure patients with or without concomitant use of MTX. Infection is the most frequent adverse effect of abatacept therapy. Positive for anti-CCP antibody at baseline and decreasing serum MMP-3 levels and/or anti-CCP antibody titer during therapy could be a useful efficacy marker for abatacept treatment.

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