



Effectiveness and safety of subcutaneous abatacept in biologic-naïve RA patients at Week 52: A Japanese multicentre investigational study (ORIGAMI study)

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ABSTRACT

Objectives: To evaluate the effectiveness and safety of abatacept over 52 weeks in biologic-naïve rheumatoid arthritis (RA) patients with moderate disease activity in the prospective, 5-year, observational study (ORIGAMI study) in Japan.

Methods: Abatacept (125 mg) was administered subcutaneously once a week. Clinical outcomes included Simplified Disease Activity Index (SDAI) remission at Week 52 (primary endpoint), Japanese Health Assessment Questionnaire (J-HAQ), EuroQol 5-Dimension Questionnaire (EQ-5D), treatment retention, and safety. The results were compared with those of conventional synthetic disease-modifying antirheumatic drug (csDMARD) controls from the ongoing Institute of Rheumatology, Rheumatoid Arthritis (IORRA) registry.

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Results: Overall, 325 patients were enrolled, with a mean age of 66.9 ± 12.7 years. The proportion of patients achieving SDAI remission (≤ 3.3) at Week 52 was 18.9% (95% CI: 14.3–23.6) and low disease activity (≤ 11) was 53.3% (95% CI: 47.4–59.1). A significant improvement was observed in J-HAQ and EQ-5D over 52 weeks in both the abatacept and csDMARD groups. The probability of abatacept treatment retention at Week 52 was 69.9% (95% CI: 64.7–75.5). Adverse events and serious adverse events were reported in 50.0% and 12.1% of patients, respectively.

Conclusions: Abatacept significantly improved disease activity, physical disability, and quality of life for up to 52 weeks in RA patients in a real-world setting.

KEYWORDS: Abatacept; Japan; moderate disease activity; real-world; rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease presenting with synovitis, leading to progressive joint damage and resulting in impaired physical function and reduced quality of life [1]. The estimated prevalence of RA in Japan is 0.65%, with the highest age-stratified prevalence reported in adults aged 70–79 years [2].

The American College of Rheumatology (ACR) [3] and the European Alliance of Associations for Rheumatology (EULAR) [4] recommend early intervention for RA. The treatment goal for RA should be to achieve low disease activity (LDA) or remission within 6 months (or $\geq 50\%$ clinical improvement within 3 months) for the prevention of joint damage or deformity and preservation of functional status and quality of life, using a treat-to-target approach.

In Japan, the wide range of available treatment options has increased the number of patients achieving remission or LDA. However, despite availability of therapeutic options, including biologics, remission or LDA is not achieved in all patients [5]. Furthermore, differences in patient characteristics between randomized controlled trials (RCTs) and the real world have been demonstrated [6]. In clinical settings, patients with moderate disease activity are likely to be treated with biologics, although supporting evidence for this patient population is not available.

The Japanese guidelines [7] recommend abatacept in patients not responding to initial treatment with disease-modifying antirheumatic drugs (DMARDs) over 3 months. Abatacept [cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin (CTLA4-Ig)], a fusion protein composed of the extracellular domain of human CTLA4 and the modified Fc region (hinge, CH2, and CH3) of human immunoglobulin G1, is the only biologic that regulates T-cell function [8]. Abatacept has been evaluated in several clinical studies [9–12], and its efficacy and safety have been confirmed in RA patients refractory to methotrexate (MTX) and anti-tumour necrosis factor therapy [13–15].

Long-term (5-year) efficacy of subcutaneous (SC) abatacept has been demonstrated in biologic-naïve patients in an international Phase IIIb study Abatacept Comparison of Sub[QU]cutaneous Versus Intravenous in Inadequate Responders to Methotrexate (ACQUIRE) [16, 17]. In addition, pooled data from eight clinical trials assessing intravenous (IV) abatacept have demonstrated long-term safety (up to 8 years), which is consistent with that observed during short-term exposure [18].

In Japan, a short-term (6-month) postmarketing surveillance (PMS) study of IV abatacept was conducted in 3882 RA patients with favourable outcomes [19]; however, the long-term evidence for the effectiveness and safety of SC abatacept, especially in patients with moderate disease activity, is not enough. Consequently, the ongoing ORIGAMI (Orencia Registry in Geographically Assembled Multicenter

Investigation) study (UMIN000021263) was initiated as a 5-year, multicentre, prospective, observational study in Japan, focusing on the long-term effectiveness and safety of SC abatacept, including patient-reported outcomes (PROs), in biologic-naïve RA patients with moderate disease activity in clinical settings.

This analysis of the ORIGAMI study reports the effectiveness and safety of abatacept over 52 weeks in biologic-naïve RA patients with moderate disease activity in Japan, with the proportion of patients with Simplified Disease Activity Index (SDAI) remission at Week 52 as the primary endpoint.

Materials and Methods

Study design

The ongoing ORIGAMI study is a 5-year, open-label, multicentre, prospective, observational study in biologic-naïve RA patients with moderate disease activity who were newly initiated on SC abatacept at 64 facilities across Japan. The enrolment period was from June 2016 to October 2018. Eligible patients are being followed up at Weeks 0, 4, 24, and 52 and every 6 months thereafter for up to 5 years.

This study was approved by the ethics committees, independent review committees, regulatory authorities, and/or other local governance bodies at each study site. This study was conducted in accordance with the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects [20]. Written informed consent was obtained from all patients before enrolment.

Data collection

The ORIGAMI study records data on biologic-naïve RA patients with moderate disease activity who have been treated with abatacept in routine clinical practice at 64 facilities across Japan, using electronic data capture (eDC). Data on characteristics, investigations, treatment, PROs, and clinical outcomes have been included in the database. For the ORIGAMI study, data for 325 patients were collected using eDC. PROs such as the Japanese Health Assessment Questionnaire (J-HAQ) and EuroQol 5-Dimension Questionnaire (EQ-5D) were collected via eDC using a site PRO tool, such as an iPad, with or without hospital staff support at each 6-month visit.

For historical controls [e.g. patients treated with conventional synthetic DMARDs (csDMARDs)], data were extracted from the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) registry. The Institute of Rheumatology at Tokyo Women's Medical University Hospital has been developing this large observational cohort since October 2000 and has published more than 100 papers so far (IORRA registry). During each survey period, approximately 6000 questionnaires are collated [5, 21].

Patient data, including age, sex, disease duration, comorbidities, investigations, disease activity scales, concomitant medications, and PROs, were prospectively extracted for both groups. The results were compared with those of weighted controls from the ongoing IORRA registry that included patients with moderate disease activity who were newly initiated on or had added another csDMARD including MTX, within 3 months before enrolment, during the enrolment period of the ORIGAMI study, without using concomitant biologics. We used the medication history within 6 months, collected as a PRO from IORRA, for comparison of the proportion of concomitant drug (MTX, prednisolone, etc.) use and concomitant drug dose in the ORIGAMI study.

Patients

Inclusion criteria

Patients who met all of the following six criteria were included in this study: (1) RA patients who met the 2010 ACR/EULAR RA classification criteria; (2) RA patients who had moderate disease activity (SDAI: >11 to ≤ 26); (3) biologic-naïve patients who had an inadequate response to ≥ 1 csDMARD during the previous treatment; (4) patients who met the blood test criteria (peripheral white blood cell count: $\geq 4000/\text{mm}^3$; peripheral blood lymphocyte count: $\geq 1000/\text{mm}^3$; and blood β -D-glucan negative); (5) patients aged ≥ 20 years at the time of obtaining consent for participation in this study (both male and female); and (6) patients who understood the explanation given by the principal investigator or coinvestigator about the study procedures and gave written consent to participate in the study.

Exclusion criteria

Patients were excluded from the study if they had a history of hypersensitivity to any component of the abatacept formulation, had malignant tumours, had an active infectious disease, had hepatitis B or were hepatitis B surface antigen positive (carriers), were or may be pregnant or breastfeeding, and were judged as being ineligible at the investigator's discretion.

Treatment

Treatment with abatacept was determined at the physician's discretion before enrolment in the study. Abatacept (125 mg)

was administered SC once a week (irrespective of the presence/absence of a loading dose at the start of administration). Abatacept discontinuation criteria included withdrawal of consent, significant protocol deviation, treatment missed three times in a row, adverse events (AEs) requiring discontinuation, failure to meet inclusion criteria after enrolment, and physician's discretion.

Outcomes and assessments

The primary endpoint was the proportion of patients with SDAI remission (≤ 3.3) at Week 52. Secondary endpoints included the proportion of patients with SDAI-LDA (≤ 11) at Week 52, including changes in the proportions of disease activity categories over 52 weeks; changes in SDAI scores and Disease Activity Score-28 for RA with C-reactive protein (DAS28-CRP) over 52 weeks as observed and using the last observation carried forward (LOCF) method; changes in PROs (J-HAQ score and EQ-5D) over 52 weeks as observed and using the LOCF method (PRO questionnaires were completed using an iPad and stored in the eDC database); changes in other parameters, including Clinical Disease Activity Index (CDAI) scores, visual analogue scale (VAS) for pain (pain VAS), and global VAS at Week 52; and probability of treatment retention over 52 weeks and reasons for discontinuation. All the above-mentioned assessments were performed at Weeks 0, 4, 24, and 52. Observations will continue every 6 months for the next 5 years.

Disease activity was categorized as remission [scores: SDAI ≤ 3.3 , CDAI ≤ 2.8 , DAS-28 for RA with erythrocyte sedimentation rate (DAS28-ESR) < 2.6 , and DAS28-CRP < 2.3], LDA (scores: $3.3 < \text{SDAI} \leq 11$, $2.8 < \text{CDAI} \leq 10$, $2.6 \leq \text{DAS28-ESR} < 3.2$, and $2.3 \leq \text{DAS28-CRP} < 2.7$), moderate disease activity (scores: $11 < \text{SDAI} \leq 26$, $10 < \text{CDAI} \leq 22$, $3.2 \leq \text{DAS28-ESR} \leq 5.1$, and $2.7 \leq \text{DAS28-CRP} \leq 4.1$), and high disease activity (scores: SDAI > 26 , CDAI > 22 , DAS28-ESR > 5.1 , and DAS28-CRP > 4.1), based on the original definition [22, 23].

Safety was assessed by collecting all AEs from the initiation of abatacept treatment to the end of the observation period or until treatment discontinuation, regardless of the presence/absence of their causal relationship with abatacept. Nonserious and serious AEs (SAEs), pregnancy, maternal exposure-related AEs, and outcomes of pregnancy identified

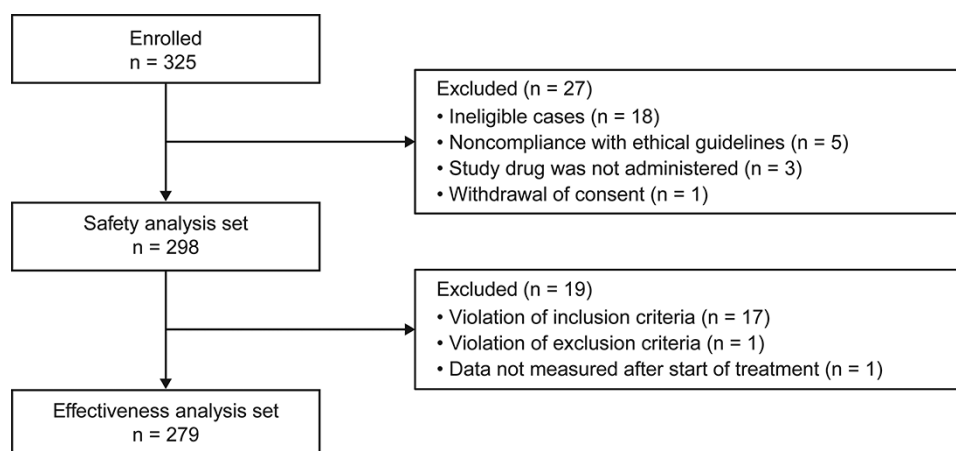


Figure 1. Patient disposition.

during the study were collected, regardless of their causal relationship with abatacept.

Statistical analysis

The effectiveness analysis set comprised patients who gave consent for this study, completed baseline examination, were treated with abatacept, and had ≥ 1 observation during the treatment period. The safety analysis set comprised all subjects treated with abatacept. For the analysis of the primary endpoint, the proportion of patients achieving SDAI remission at Week 52 and its 95% confidence interval (CI) were calculated. The remission status of patients who discontinued the study before 52 weeks was determined by prespecified criteria in the statistical analysis plan. The remission status of discontinued patients who could not be judged by the prespecified criteria was assessed by the multiple imputation by the chained equations method, and Rubin's rule was used to combine the results of multiply-imputed datasets. Other continuous and dichotomous outcomes were analysed by the *t*-test and chi-square test, respectively. The probability of treatment retention over 52 weeks was evaluated using the Kaplan–Meier (KM) method. Ad hoc analysis was performed to evaluate changes in SDAI scores, DAS28-CRP, and PROs (J-HAQ score and EQ-5D) over 52 weeks using the LOCF method.

For comparison with the external cohort, a propensity score was calculated using logistic regression, with sex, age, baseline SDAI, J-HAQ, MTX use, glucocorticoid use, RA duration, and comorbidities (lung diseases, heart diseases, and diabetes) as variables. The validity of the propensity score was confirmed using concordance statistics (c-statistics). Covariate imbalances between groups were assessed by standardized differences. Between-group differences in outcomes were analysed by the propensity score-weighting method, where weights based on standardized mortality rates were applied to make the ORIGAMI dataset the reference group. The 95% CIs of the between-group differences in outcomes were calculated using the robust standard error method. The significance level was set at 0.05.

Results

Patient background

A total of 325 patients were enrolled. In accordance with a predetermined case-handling procedure, 279 and 298 patients comprised the effectiveness and safety analysis sets, respectively (Figure 1). The mean \pm standard deviation (SD) age of patients in the effectiveness analysis set in the ORIGAMI study (abatacept group) was 66.9 ± 12.7 years (≥ 65 years, 64.9%), and a majority of the patients were women (81.0%) and had comorbidities (80.3%). The proportions of patients with a disease duration <1 year and ≥ 10 years were 24.4% and 29.0%, respectively. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) positivity were reported in 73.0% and 83.7% of patients, respectively (Table 1).

A majority of the patients had a history of treatment with MTX (64.6%), non-MTX csDMARDs (including MTX combinations, 63.1%), and prednisolone (52.8%; Table 1 and Supplementary Table S1). The proportion of patients using concomitant MTX at the start of abatacept treatment

Table 1. Baseline demographics and clinical characteristics of patients treated with abatacept (effectiveness analysis set).

	Week 0	
	<i>n</i> ^a	Mean ± SD or <i>n</i> (%)
Variables (eDC)		
Age, years	279	66.9 ± 12.7
≤64/≥65 to ≤74/≥75		98 (35.2)/96 (34.4)/85 (30.4)
Sex, female	279	226 (81.0)
Disease duration, years	279	
<1/≥1 to <2		68 (24.4)/41 (14.7)
≥2 to <3/≥3 to <5		18 (6.5)/28 (10.0)
≥5 to <10/≥10		43 (15.4)/81 (29.0)
Comorbidities	279	224 (80.3)
CRP, mg/dl	277	1.66 ± 2.25
ESR, mm/h	215	43.57 ± 28.01
SDAI	273	19.74 ± 5.65
CDAI	274	18.08 ± 5.10
DAS28-CRP	273	4.07 ± 0.75
DAS28-ESR	212	4.74 ± 0.85
PhGA (0–100 mm)	279	40.39 ± 14.85
ACPA positive (≥4.5 U/ml)	270	226 (83.7)
ACPA, U/ml	270	234.76 ± 359.80
RF positive (>15 U/ml)	270	197 (73.0)
RF, U/ml	270	149.74 ± 283.63
Abatacept IV loading	279	57 (20.4)
MTX use ^c	279	148 (53.0)
MTX use (by age)		
≤64/≥65 to ≤74/≥75		70 (71.4 ^b)/45 (46.9 ^b)/33 (38.8 ^b)
MTX dose, mg/week ^c	148	8.95 ± 3.19
csDMARD use (except for MTX) ^c	279	146 (52.3)
Prednisolone use ^c	279	127 (45.5)
Prednisolone, mg/day ^c	84	4.79 ± 3.25
Variables (PROs)		
J-HAQ (0–3)	279	1.16 ± 0.74
EQ-5D (0–1)	272	0.66 ± 0.15
Pain VAS (0–100 mm)	275	47.39 ± 24.08
Global VAS (0–100 mm)	275	45.08 ± 23.36
MTX use ^c	271	175 (64.6)
MTX dose, mg/week ^{c,d}	175	8.93 ± 7.52
csDMARD use (except for MTX) ^c	263	166 (63.1)
Prednisolone use ^c	269	142 (52.8)
Prednisolone, mg/day ^c	142	3.58 ± 2.70

^aTotal number of evaluable patients.

^bProportion by age category.

^cIn addition to the concomitant medication information entered by the doctor in the eDC, there is drug use information within the past 6 months that the patient directly entered into the iPad as a PRO; therefore, the results are different in terms of proportion and dosage.

^dPRO data obtained from patients as number of tablets or capsules were converted considering one tablet or capsule is equivalent to 2 mg of MTX. Mean \pm SD is shown for continuous variables, and *n* (%) is shown for categorical variables.

decreased with increasing age (Table 1), and only 7.1% of patients aged ≥ 75 years successfully used the >8 mg/week concomitant dose (data not shown).

Effectiveness

Observed SDAI remission and LDA at Week 52 was 46 (16.5%) and 93 (33.3%), respectively. Imputing the remission status by prespecified criteria and performing the multiple

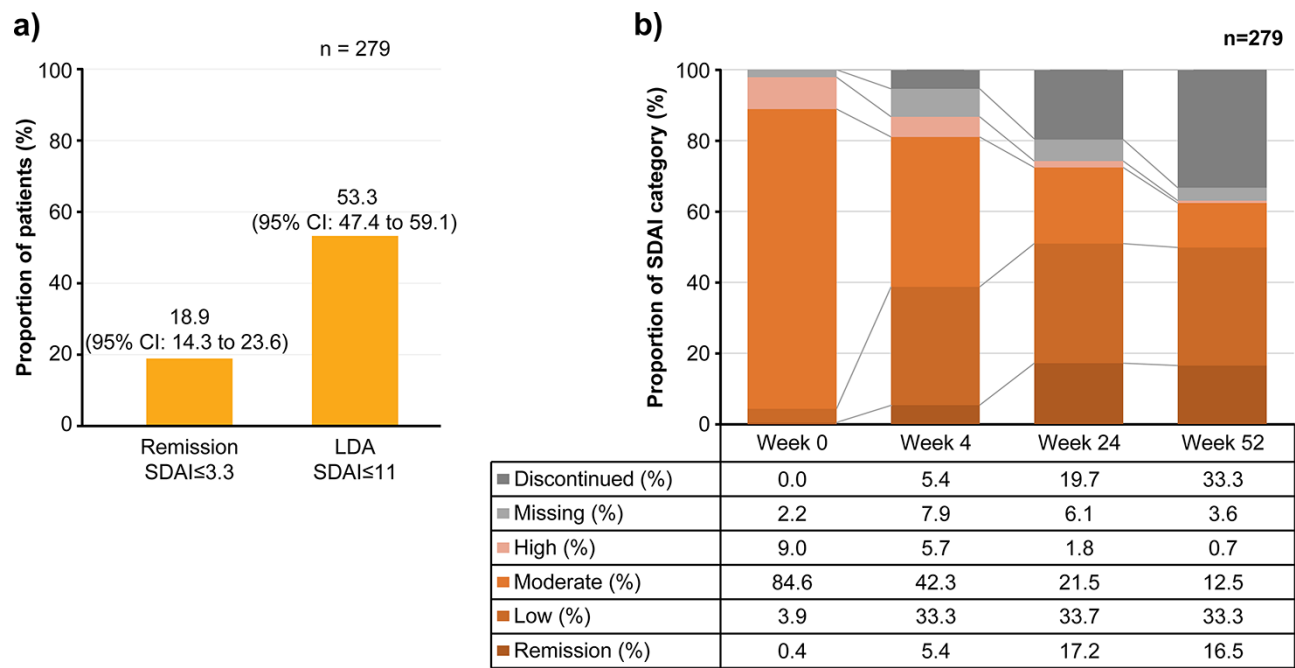


Figure 2. Changes in disease activity categories: (a) proportion of patients with SDAI remission (primary endpoint) and LDA achievement at Week 52 were calculated using multiple imputation for missing data and (b) proportion of patients with changes in SDAI categories (secondary endpoint) over 52 weeks were calculated without using multiple imputation for missing data. In Figure 2(a), multiple imputation was performed. In Figure 2(b), withdrawn/missing is shown in grey, without missing data imputation.

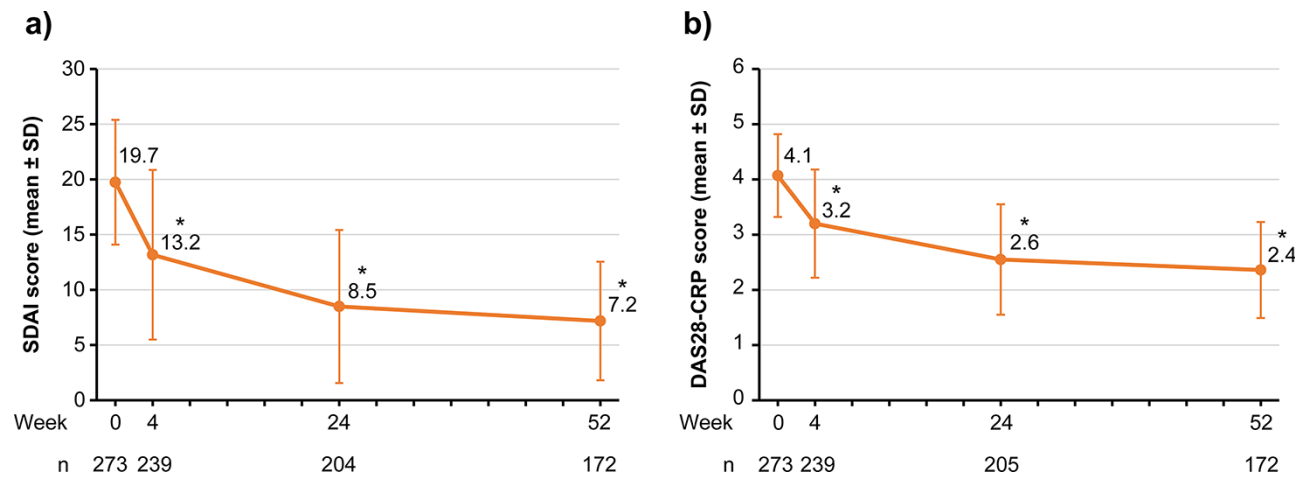


Figure 3. Changes in the disease activity scores: (a) SDAI mean score and (b) DAS28-CRP mean score in the abatacept group over 52 weeks are shown. * $p < .001$ (vs Week 0; Student's t -test).

imputation method on the remission status of the remaining eight patients, SDAI remission at Week 52 was 18.9% (95% CI: 14.3–23.6) and SDAI-LDA at Week 52 was 53.3% [95% CI: 47.4–59.1; Figure 2(a)]. The proportion of patients with improvement in SDAI disease activity over 52 weeks is presented in Figure 2(b); the proportion of patients with high and moderate disease activity decreased from 9.0% and 84.6% at Week 0 to 0.7% and 12.5% at Week 52, respectively. An improvement in the SDAI and DAS28-CRP scores was observed as early as Week 4, which continued to improve over 52 weeks (Figure 3). Ad hoc analysis using the LOCF method also showed similar improvements in the SDAI and DAS28-CRP scores over 52 weeks (Supplementary Figure S1).

These results also reflected in the improvement in the J-HAQ score and EQ-5D. An increase in the proportion of patients achieving J-HAQ remission was observed as early as Week 4 (27.9%) compared with the baseline (19.4%), which continued to improve over 52 weeks (36.2%); the EQ-5D scores followed a similar pattern (Figure 4). Ad hoc analysis using the LOCF method also showed similar improvements in the J-HAQ score and EQ-5D over 52 weeks (Supplementary Figure S2). An improvement was observed in inflammatory markers (CRP levels and ESR), tender joint count (TJC) and swollen joint count (SJC), Physician's Global Assessment of Disease Activity (PhGA) scores, other DASs (CDAI and DAS28-ESR), pain VAS, global VAS, and quality of life (EQ-5D) at Week 52 compared with the baseline. Moreover,

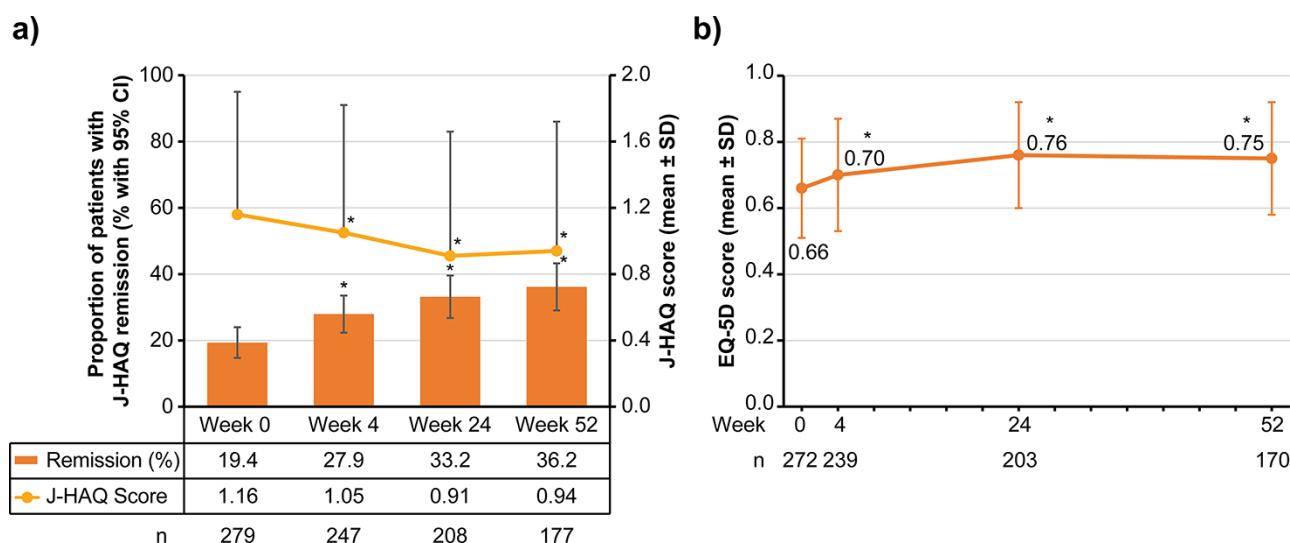


Figure 4. Changes in quality of life: (a) proportion of patients with J-HAQ remission and J-HAQ mean score and (b) EQ-5D mean score in the abatacept group over 52 weeks are shown. * $p < .001$ (vs Week 0). J-HAQ remission: binominal test; J-HAQ and EQ-5D scores: Student's t -test.

Table 2. Changes in assessed parameters over 52 weeks in the abatacept group (effectiveness analysis set).

	Week 0		Week 52		<i>p</i> value ^b
	<i>n</i> ^a	Mean ± SD or <i>n</i> (%)	<i>n</i> ^a	Mean ± SD or <i>n</i> (%)	
Variables (eDC)					
CRP, mg/dl	277	1.66 ± 2.25	183	0.65 ± 1.41	<.01
ESR, mm/h	215	43.57 ± 28.01	140	29.58 ± 25.33	<.01
TJC (28)	278	4.38 ± 3.12	182	1.08 ± 1.93	<.01
SJC (28)	278	5.15 ± 3.09	182	1.28 ± 1.96	<.01
PhGA (0–100 mm)	279	40.39 ± 14.85	183	14.90 ± 14.16	<.01
SDAI	273	19.74 ± 5.65	172	7.18 ± 5.37	<.01
CDAI	274	18.08 ± 5.10	173	6.71 ± 5.21	<.01
DAS28-ESR	212	4.74 ± 0.85	132	3.03 ± 0.98	<.01
DAS28-CRP	273	4.07 ± 0.75	172	2.36 ± 0.87	<.01
ACPA positive (≥4.5 U/ml)	270	226 (83.7)	166	139 (83.7)	.13
ACPA, U/ml	270	234.76 ± 359.80	170	238.98 ± 385.00	.15
RF positive (>15 U/ml)	270	197 (73.0)	166	119 (71.7)	.45
RF, U/ml	270	149.74 ± 283.63	170	192.01 ± 528.55	.22
Variables (PRO)					
J-HAQ (0–3)	279	1.16 ± 0.74	177	0.94 ± 0.78	<.01
EQ-5D (0–1)	272	0.66 ± 0.15	170	0.75 ± 0.17	<.01
Pain VAS (0–100 mm)	275	47.39 ± 24.08	174	24.66 ± 22.58	<.01
Global VAS (0–100 mm)	275	45.08 ± 23.36	174	30.15 ± 23.50	<.01
MTX use	271	175 (64.6)	162	89 (54.9)	<.01
MTX dose, mg/week ^c	175	8.93 ± 7.52	89	8.16 ± 2.87	.75
csDMARD use (except for MTX)	263	166 (63.1)	153	66 (43.1)	<.01
Prednisolone use	269	142 (52.8)	166	52 (31.3)	<.01
Prednisolone, mg/day	142	3.58 ± 2.70	52	3.18 ± 2.30	.01

^aTotal number of evaluable patients.

^bThe Wilcoxon signed-rank test was used for continuous variables, and the binominal test, for categorical variables.

^cPRO data obtained from patients as number of tablets or capsules were converted considering one tablet or capsule is equivalent to 2 mg of MTX. Mean \pm SD is shown for continuous variables, and n (%) is shown for categorical variables.

the use of concomitant medications (MTX, csDMARDs, and prednisolone) significantly decreased from the baseline to Week 52 (Table 2).

Treatment retention

By KM analysis, the probability of abatacept treatment retention at Week 52 was 69.9% (95% CI: 64.7–75.5) (Figure 5).

A total of 111 patients discontinued abatacept treatment over 52 weeks because of physician's discretion ($n = 57$), AEs ($n = 32$), violation of inclusion criteria ($n = 13$), and consent withdrawal ($n = 9$). Physicians chose to discontinue abatacept due to the achievement of insufficient effectiveness in 30 (10.1%) patients and sufficient effectiveness in 6 (2.0%) patients (Table 3).

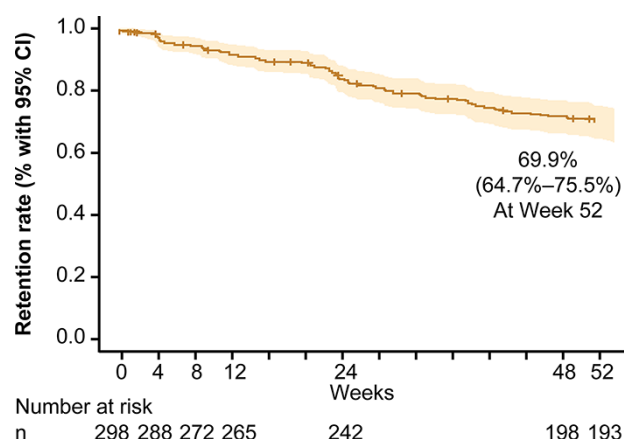


Figure 5. Drug retention rate of abatacept: probability of abatacept treatment retention over 52 weeks was analysed by the Kaplan–Meier method.

Table 3. Reasons for treatment discontinuation in the abatacept group (safety analysis set).

Reasons for discontinuation (total: <i>n</i> = 105)	<i>n</i> = 298 <i>n</i> ^a (%)
Consent withdrawal	9 (3.0)
AE	32 (10.7)
Violation of inclusion criteria after enrolment	13 (4.4)
Physician's discretion	57 (19.1)
Sufficient effectiveness	6 (2.0)
Insufficient effectiveness	30 (10.1)
Financial reasons	4 (1.3)
Patient's will	5 (1.7)
Unable to visit hospital	1 (0.3)
Hospital transfer	2 (0.7)
Treatment strategy change	3 (1.0)
Dosing interval prolonged	2 (0.7)
Unable to self-inject	1 (0.3)
Others	9 (3.0)

^aData included duplication of reasons for discontinuation.

Safety

AEs were observed in 149 (50.0%) patients, and AEs with a causal relationship with abatacept were identified in 67 (22.5%) patients. A total of 39 SAEs were observed in 36 (12.1%) patients, of which 16 SAEs with a causal relationship to abatacept were identified in 14 (4.7%) patients. Serious infections were observed in seven (2.3%) patients. A total of nine (3.0%) patients had malignant tumours, of which three were regarded as serious adverse drug reactions (ADRs; 1.0%; gastrointestinal lymphoma, prostate cancer, and malignant peritoneum neoplasm in one patient each). Two deaths were reported. One patient died from suspected gastrointestinal lymphoma, which was reported to be causally associated with abatacept. The other patient died of cervical adenocarcinoma without a causal relationship with abatacept (Table 4 and Supplementary Table S2).

Comparison between the abatacept and csDMARD groups

In the csDMARD group, the proportions of patients achieving SDAI remission and LDA at Week 52 were 9.9% (95% CI: 0.0–22.3) and 41.3% (95% CI: 20.7–61.9), respectively, and

Table 4. Safety in the abatacept group (safety analysis set).

<i>n</i> = 298 <i>n</i> (%)		
All AEs		
149 (50.0)		
AEs with a causal relationship		
67 (22.5)		
Deaths		
2 (0.7)		
SAEs		
36 (12.1)		
SAEs with a causal relationship		
14 (4.7)		
Serious ADRs (SAEs with a causal relationship)		
Number of events (%)	SAEs	
Infection	7 (2.3)	7 (2.3)
Malignancy	9 (3.0)	3 (1.0)
Fracture	5 (1.7)	0 (0.0)
Cardiovascular disorder	6 (2.0)	2 (0.7)
Interstitial pneumonia	0 (0.0)	0 (0.0)
Others	12 (4.0)	4 (1.3)

the ratios of proportions in the csDMARD group to the abatacept group were 0.522 (95% CI: 0.228–1.193; *p* = .123) and 0.775 (95% CI: 0.537–1.118; *p* = .173), respectively (Supplementary Table S3). Other clinical outcome assessments, including SDAI, CDAI, DAS28-ESR, DAS28-CRP, J-HAQ, and EQ-5D, showed improvements in the abatacept group compared with the csDMARD group (Supplementary Table S3 and Figure 6). The minimum clinically important difference (MCID) in J-HAQ at Week 52 in the abatacept and csDMARD groups was 52.5% and 24.4%, respectively. A total of five patients started biologics between Weeks 24 and 52 in the csDMARD group.

Discussion

The results of this multicentre, prospective, observational study (ORIGAMI study) demonstrate the effectiveness and safety of abatacept over 52 weeks in biologic-naïve RA patients with moderate disease activity in clinical practice. Abatacept significantly improved disease activity, physical disability, and quality of life for up to 52 weeks in RA patients in a real-world setting. The primary endpoint, SDAI remission rate at 52 weeks (18.9%), was similar to that reported in the ACQUIRE [17] and AMPLE [24] studies, which were Phase IIIb studies in biologic-naïve RA patients who showed an inadequate response to MTX.

The 52-week probability of treatment retention was 69.9% (95% CI: 64.7–75.5), and the reasons for discontinuation included both insufficient and sufficient effectiveness. This treatment retention rate was similar to the 12-month retention rate (69.4%; 95% CI: 65.6–72.8) reported in the biologic-naïve group treated with abatacept in an international observational cohort study AbataCepT In rOutiNe clinical practice (ACTION) [25]. In Japan, patients other than biologic-naïve patients were included, but a 6-month retention rate of 78.9% was reported in a PMS study [19] in patients with RA. However, it is important to evaluate long-term retention rates and reasons for discontinuation in routine clinical settings, which are being evaluated over 5 years in this study.

The average age of this patient population treated with abatacept was higher (mean: 66.9 years), with a majority of the patients being in the elderly age group (≥ 65 years, 64.9%),

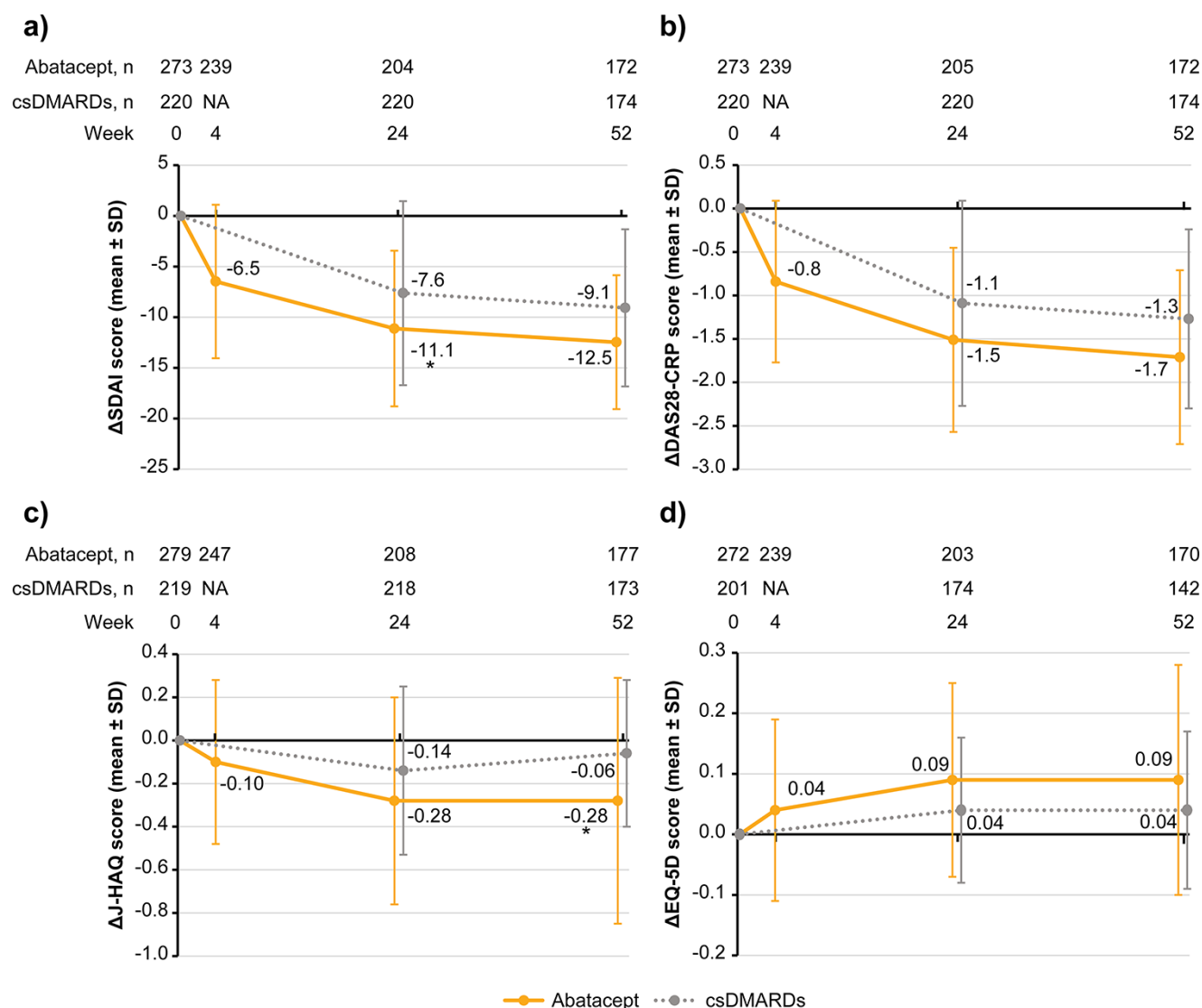


Figure 6. Comparison between abatacept and csDMARD groups. Changes from the baseline (Week 0) in the (a) SDAI scores, (b) DAS28-CRP scores, (c) J-HAQ scores, and (d) EQ-5D scores were compared between the abatacept and csDMARD groups. * $p < .05$ (vs the csDMARD group; weighted Z-test). Δ , change from the baseline; NA, not available.

compared with that of the population of the effectiveness analysis set of the PMS study (mean: 61.1 years; ≥ 65 years, 43.4%) [19] and the multicentre, retrospective The Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort study (abatacept group: age, 63.9 years; 2009–2017) [26] conducted in Japan. The proportion of patients using concomitant MTX at the start of abatacept administration was lower (53.0%) than that reported in the previous PMS study (66.7%) [19]. The proportion of patients with comorbidities in the abatacept group was higher than that in the csDMARD group and in the previous PMS study (69.5%; 2010–2011) [19]. These results suggest the possibility of abatacept having been selected as a treatment option for elderly patients and patients with comorbidities who were not eligible for MTX treatment.

Furthermore, RA is commonly associated with comorbidities such as osteoporosis and respiratory diseases, the incidence of which increases with age [27]. Comorbidities in this study were reported in 80.3% of patients, and 8.6% of

patients had interstitial pneumonia (IP) and 16.8% had respiratory diseases other than IP. The consideration of comorbidities is important because the treatment of RA-associated interstitial lung disease (RA-ILD) remains challenging, given the lack of RCTs and the possible role of DMARDs in lung toxicity and acute exacerbation of ILD [28–33]. The safety and stability of pulmonary function with abatacept in RA-ILD have been reported [34–36]. Although it is possible that RA-ILD patients who had difficulty selecting other treatments were also registered in this study, we do not report any SAE of IP over 52 weeks.

Overall, no new safety concern was detected over 52 weeks. Although a direct comparison cannot be made, the incidence of ADRs (22.5%) and serious ADRs (4.7%) was not notably different from that reported at 6 months (15.66% and 2.52%, respectively) in the previous PMS study [19], despite differences in the observation period and a greater proportion of elderly patients enrolled in this study.

Similarly, considering the possible increase in the risk of infection with biologic treatment in patients with RA, the incidence of serious infection in this study (2.3%), in the previous 6-month PMS study (1.03%) [19], and in other studies reporting the safety concern of abatacept was low [24, 37, 38]. Since abatacept's mechanism of action involves the regulation of T-cell activation [39–41], it can be assumed that the effect of abatacept on innate immunity is limited.

We report malignancies in nine patients (3.0%), of which three were regarded as serious ADRs. All nine patients were relatively elderly (mean: 76.4 years; min–max, 50–88 years). The somewhat skewed age distribution of the enrolled patients, as mentioned above, may have increased the incidence of malignancies compared with the previous cohorts in Japan. One of the three patients with serious ADRs was reported to have died of suspected gastrointestinal lymphoma. This patient, aged 77 years, was suspected of having diffuse large B-cell lymphoma and liver metastasis; 1-week later, haematemesis occurred, and the patient died. Data from the global database (VigiBase, 2007–2017) showed that in RA patients without a history of cancer, no significant difference in the risk for developing any cancer in patients treated with abatacept was observed compared with other biologic DMARDs, except for an increased risk of melanoma reported in the abatacept-treated group [42]. While the literature does support the possibility of an increased carcinogenic risk for specific cancer types or any cancer with biologics [43–45], observations regarding the carcinogenic risk with abatacept use are very diverse [16, 18, 46, 47]. Long-term observation is required to evaluate the malignancies reported in this study.

We used the propensity score-weighting method to enable the comparison of this single-arm study with the csDMARD group as a historical control. Although both groups had similar RA disease activity, many items such as disease duration and proportion of patients with comorbidities were not statistically balanced and had a standardized difference of > 0.1 after weighting, making it difficult to completely align the characteristics of both groups (Supplementary Table S1). The greater improvement in DAs, reduction in the J-HAQ score, and improvement in EQ-5D with abatacept compared with csDMARDs in this study were consistent with those reported in previous RCTs of abatacept [48, 49], but these results should be carefully interpreted after considering the differences in patients' background.

The J-HAQ improvement and proportion of patients achieving MCID (0.22) in the abatacept group were significantly higher compared with those in the csDMARD group. Notably, the proportion of patients achieving MCID (frequently used in RA studies) was significantly higher in the abatacept group than in the csDMARD group. The results were similar to those reported in the AMPLE study [24] in biologic-naïve RA patients with a short disease duration.

Limitations

The study limitations include the fact that this was a single-arm, open-label study; patient selection at each facility (facility selection bias) or by an individual physician (patient selection bias) could vary and limit generalizability of the results, despite the provision of clear instructions and recommendations on methodological requirements for patient selection and training for rheumatologists; loss to follow-up and case reduction bias, as well as missing data and case

reduction bias, may exist as some data may not be measured, obtained, or available systematically.

Conclusions

Abatacept, as a first-line biologic, significantly improved disease activity, physical disability, and quality of life as early as 4 weeks of treatment, for up to 52 weeks in RA patients in a real-world clinical setting, which is in line with previous reports from RCTs [16, 24, 49]. No new AE was identified over 52 weeks as we continue the long-term observation. The improvement trend in disease activity, J-HAQ, and EQ-5D was greater in the abatacept group than that adjusted by propensity score weighting in the csDMARD group.

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Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

Conflict of interest

N.T. received consulting fee or honorarium from Eli Lilly Japan K.K., AbbVie GK, Chugai Pharmaceutical Co., Ltd, GlaxoSmithKline K.K., Novartis Pharma K.K., Eisai Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Bristol-Myers Squibb K.K., and Janssen Pharmaceutical K.K. for the submitted work. K.M. received consulting fee or honorarium from Ono Pharmaceutical Co., Ltd, for the submitted work. K.M. also received consulting fee or honorarium from Eisai Co., Ltd, AbbVie GK, and Eli Lilly Japan K.K., for outside the submitted work. E.S. received speaker fees or research support from AbbVie GK, Asahi Kasei Pharma Corporation, AYUMI Pharmaceutical Corporation, Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd, Eisai Co., Ltd, Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Pfizer Japan Inc, and Mitsubishi Tanabe Pharma Corporation for the submitted work. D.K. received honoraria for lectures or presentations from Bristol-Myers Squibb K.K. for the submitted work. D.K. also received honoraria for lectures or presentations from Mitsubishi Tanabe Pharma Corporation, Kyowa Kirin Co., Ltd, and Eisai Co., Ltd, for outside the submitted work. Y.M. received funding from Asahi Kasei Pharma Corporation, Chugai Pharmaceutical Co., Ltd, Daiichi-Sankyo Co., Ltd, Teijin Pharma Ltd, Eisai Co., Ltd, Nippon Kayaku Co., Ltd, Mitsubishi Tanabe Pharma Corporation, and AbbVie GK for the submitted work. T.N. received honorarium and funding from Bristol-Myers Squibb K.K. and Ono Pharmaceutical Co., Ltd, for the submitted

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