

Clinical efficacy of abatacept compared to adalimumab and tocilizumab in rheumatoid arthritis patients with high disease activity

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Abstract Favourable clinical results in rheumatoid arthritis (RA) patients with high disease activity (HDA) are difficult to achieve. This study evaluated the clinical efficacy of abatacept according to baseline disease activity compared to adalimumab and tocilizumab. This study included all patients registered in a Japanese multicenter registry treated with abatacept ($n=214$),

adalimumab ($n=175$), or tocilizumab ($n=143$) for 24 weeks. Clinical efficacy of abatacept in patients with HDA (DAS28-CRP >4.1) and low and moderate disease activity was compared. Clinical efficacy of abatacept, adalimumab, and tocilizumab was compared in patients with HDA at baseline. In patients treated with abatacept, multivariate logistic regression

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identified HDA at baseline as an independent predictor for achieving low disease activity (LDA; DAS28-CRP < 2.7) [OR 0.26, 95 % CI 0.14–0.50] or remission (DAS28-CRP < 2.3) [OR 0.26, 95 % CI 0.12–0.56] at 24 weeks. In patients with HDA at baseline, logistic regression did not identify treatment with adalimumab or tocilizumab as independent predictors of LDA or remission compared to abatacept. Retention rates based on insufficient efficacy were significantly higher in patients treated with abatacept compared to adalimumab and lower than tocilizumab. Retention rates based on adverse events in patients treated with abatacept were significantly lower compared to tocilizumab. Clinical efficacy of abatacept was affected by baseline disease activity. There were no significant differences between the three different classes of biologics regarding clinical efficacy for treating RA patients with HDA, although definitive conclusions regarding long-term efficacy will require further research.

Keywords Abatacept · Adalimumab · High disease activity · Japanese multicenter registry system · Rheumatoid arthritis · Tocilizumab

Introduction

Biological disease-modifying antirheumatic drugs (DMARDs) are standard treatment for rheumatoid arthritis (RA). Several clinical trials have demonstrated that biological agents significantly reduce disease activity and that suppression of synovitis significantly reduces subsequent joint destruction. However, favourable clinical results are often difficult to achieve in patients with high disease activity (HDA), even in this ‘bio-era’ of drug discovery. Previous reports have demonstrated that lower disease activity at baseline is a predictor of clinical efficacy when using anti-tumour necrosis factor (TNF) agents and tocilizumab, which is a humanized monoclonal antibody against the interleukin-6 receptor. Hydrich et al. reported that a lower Disease Activity Score 28 (DAS28) score at baseline was a significant predictor of clinical remission at 6 months in patients treated with infliximab and etanercept [1]. The TEMPO etanercept study indicated that patients with lower disease activity at baseline were more likely to achieve remission [2]. Similar results were reported in Japanese RA patients treated with infliximab, etanercept [3, 4], and tocilizumab. A higher proportion of patients with moderate disease activity achieved LDA and clinical remission at week 24 [5].

Abatacept is the first member of a new class of biologic agents for RA treatment that inhibits T-cell activation by binding to CD80/86, modulating its interaction with CD28. This strategy is expected to achieve clinical efficacy in patients who are naïve or inadequately respond to other classes of biologics. The efficacy and safety of abatacept has been reported in several clinical trials [6–10]. The effectiveness of

abatacept has also been reported in clinical practice in Denmark and Japan [11, 12]. However, there are no available reports describing the effects of baseline disease activity on the clinical efficacy of abatacept. In this study, we evaluated clinical data of patients treated with abatacept and compared the clinical efficacy of adalimumab, tocilizumab, and abatacept in patients with HDA at baseline.

Materials and methods

Participants

All eligible patients were registered in and followed by the Tsurumi Biologics Communication Registry (TBCR), a RA research consortium that includes Nagoya University Hospital and 12 affiliated institutes [13]. TBCR was initiated in October 2008 to study the long-term efficacy and safety of biologics used to treat RA. Data were retrospectively collected 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 (e.g. surgery, pregnancy) that may have occurred during treatment. The present study included all patients who were treated with abatacept (ABT, $n=214$), adalimumab (ADA, $n=175$), or tocilizumab (TCZ, $n=143$) for 24 weeks at TBCR-affiliated institutes. All patients met the 1987 American College of Rheumatology classification criteria for RA. Patients received abatacept infusions three times every 2 weeks followed by every 4 weeks, adalimumab infusions every 2 weeks, or tocilizumab infusions every 4 weeks according to drug labels and Japan College of Rheumatology guidelines for treatment. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled. This study was approved by the Nagoya University Graduate School of Medicine ethics committee.

Data collection

Data were retrospectively collected from clinical records. The following demographic data were recorded at the initiation of treatment (baseline, week 0): disease duration, concomitant treatment (methotrexate (MTX) or prednisolone (PSL)), joint damage (Steinbrocker stage), and daily dysfunction (Steinbrocker class). The following disease parameters were recorded at baseline and after 4, 12, and 24 weeks of treatment: tender joint count (TJC) and swollen joint count (SJC) on 28 joints, general health on a visual analogue scale (GH-VAS), and serum c-reactive protein (CRP) levels. Disease activity was evaluated at each time point using DAS28 with CRP (DAS28-CRP).

Disease activity and EULAR response

Disease activity was categorised as follows: DAS28 remission (DAS28-CRP < 2.3), low disease activity (LDA; $2.3 \leq \text{DAS28-CRP} < 2.7$), moderate disease activity (MDA; $2.7 \leq \text{DAS28-CRP} \leq 4.1$), and high disease activity (HAD; DAS28-CRP > 4.1) [14]. Disease activity was evaluated at baseline and 24 weeks after treatment. The European League Against Rheumatism (EULAR) response was evaluated at 24 weeks [15].

Statistical analysis

Demographic and disease characteristics are reported using descriptive statistics. All results are expressed as mean \pm standard deviation or percentage. Student's *t* test was used for two-group comparisons, and the chi-square test was used for categorical variables. The last observation carried forward (LOCF) method was used in each analysis. To determine predictors of LDA, clinical remission, and a moderate EULAR response at 24 weeks, multivariate logistic regression analysis was performed. 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

We compared the clinical parameters of patients with low and moderate disease activity (\leq MDA, DAS28-CRP ≤ 4.1) and HDA at baseline. Characteristics of patients treated with abatacept in the \leq MDA and HDA groups are shown in Table 1. There were no significant differences in age, RA disease duration, gender, stage, and class. There were no differences in the proportion of patients treated concomitantly with MTX and PSL and mean MTX and PSL doses. Mean DAS28-CRP and related components (SJC, TJC, CRP, and GH) were higher in the HDA group, while mean matrix metalloproteinase-3 (MMP-3) values did not differ between groups.

Clinical efficacy and retention in patients treated with abatacept in the \leq MDA and HDA groups

As shown in Fig. 1a, the mean DAS28-CRP score significantly decreased from baseline to 4 weeks at 3.23 ± 0.64 to 2.95 ± 0.81 in the \leq MDA group ($p < 0.01$) and 5.35 ± 0.86 to 4.44 ± 1.14 in the HDA group ($p < 0.01$). Significant differences in DAS28-CRP scores were observed between 4 and 12 weeks (4.16 ± 1.24 , $p < 0.01$) and 12 and 24 weeks (3.87 ± 1.33 , $p < 0.01$) in the HDA group, while only 4 and 24 weeks (2.74 ± 0.85 , $p < 0.028$) in the \leq MDA group. The

difference between the \leq MDA and HDA groups remained significant at 24 weeks.

Disease activities as assessed by DAS28-CRP score at baseline and after 24 weeks of abatacept therapy in the \leq MDA and HDA groups are shown in Fig. 1b. The proportion of patients who achieved LDA gradually increased over time after initiation of abatacept treatment in the \leq MDA and HDA groups. The proportion of patients who achieved LDA was significantly higher in the \leq MDA group (48.8 %) compared to the HDA group (20.3 %, $p < 0.001$). The proportion of patients who achieved a moderate or good EULAR response was significantly higher in the HDA group (64.1 %) compared to the \leq MDA group (40.7 %, $p < 0.001$; Fig. 1c).

Given that multiple confounding factors may contribute to the clinical efficacy of abatacept, multivariate logistic regression was performed to confirm the influence of disease activity at baseline on disease activity at 24 weeks (Table 2). Odds ratios (ORs) were adjusted for the following parameters: age, gender, disease duration, class, DAS28-CRP at baseline, prior use of biologics, and concomitant MTX and PSL use. Multivariate analysis confirmed that HDA (DAS28-CRP > 4.1) at baseline, class 3 or 4, and prior use of biologics were independent negative factors for achieving LDA or a moderate EULAR response at 24 weeks.

The retention rate of patients treated with abatacept was compared between the \leq MDA and HDA groups and analysed based on reasons for discontinuation. Kaplan–Meier curves for time to discontinuation due to insufficient efficacy (insufficiency) and adverse events (AEs) were generated. Over 24 weeks, 3 of the 86 patients in the \leq MDA group and 16 of the 126 patients in the HDA group withdrew from abatacept treatment due to insufficiency. The retention rate based on insufficiency was significantly higher in the \leq MDA group compared to the HDA group (96.4 vs. 88.4 %, $p = 0.023$). There were no significant differences in retention rates due to AEs (95.2 vs. 97.5 %, $p = 0.226$).

Clinical efficacy of abatacept, adalimumab, and tocilizumab in patients with HDA at baseline

Clinical efficacy of abatacept in patients with HDA was insufficient compared to efficacy in patients with lower activity. Therefore, we compared the clinical efficacy of abatacept with agents in different biologic classes in patients with active RA. RA patients with HDA at baseline were treated with the TNF inhibitor adalimumab ($n = 120$) and the IL-6R inhibitor tocilizumab ($n = 97$).

Table 1 shows baseline characteristics of patients with HDA treated with abatacept, adalimumab, and tocilizumab. Post hoc analysis demonstrated that patients treated with abatacept were significantly older ($p < 0.001$, vs. ADA and TCZ). Fewer patients treated with adalimumab had a history of being treated with biologics ($p = 0.002$, vs. ABT; $p < 0.001$, vs. TCZ) and a

Table 1 Baseline characteristics of rheumatoid arthritis patients who received abatacept and of the patients with high disease activity who received adalimumab or tocilizumab

	Abatacept			Adalimumab	Tocilizumab	<i>p</i> value ^b
	Disease activity at baseline			(in patients with HDA)		
	≤MDA (<i>n</i> =86)	HDA (<i>n</i> =128)	<i>p</i> value	(<i>n</i> =120)	(<i>n</i> =97)	
Age (years)	64.1±11.4	64.9±10.9	0.64	57.3±14.4	55.8±13.8	<0.001
Gender (% female)	82.6	80.5	0.725	82.5	78.4	0.761
Disease duration (years)	10.9±10.1	13.0±10.8	0.177	13.8±10.6	10.7±8.9	0.074
Stage (I/II/III/IV %)	11.6/26.7/34.9/26.7	10.2/12.5/41.4/35.9	0.052	12.5/15.0/30.0/42.5	13.4/23.7/24.7/38.1	0.097
Class (I/II/III/IV %)	11.6/45.3/41.9/1.2	3.2/45.3/48.4/3.1	0.071	8.3/50.8/37.5/3.3	12.4/44.3/43.3/0.0	0.069
Prior use of biologics (%)	51.2	52.3	0.89	32.5	62.9	<0.001
MTX use (%)	51.2	48.4	0.781	76.7	36.1	<0.001
MTX dose (mg/week) ^a	7.3±2.5	7.2±2.3	0.79	7.0±1.9	7.9±1.6	0.106
Oral steroid use (%)	52.3	54.7	0.779	60.8	71.9	0.041
Oral steroid dose (mg/day) ^a	4.2±2.0	4.4±2.3	0.643	5.2±2.7	4.8±2.1	0.181
MMP-3 (ng/mL)	226.9±746.5	276.7±271.6	0.568	335.1±365.1	378.1±307.8	0.066
SJC, 0–28	2.7±3.0	7.2±5.9	<0.001	7.9±5.5	8.2±5.9	0.357
TJC, 0–28	2.7±2.4	10.4±7.2	<0.001	9.2±6.3	10.5±7.6	0.345
CRP (mg/dL)	0.9±1.3	3.1±3.2	<0.001	3.7±3.3	3.7±2.9	0.257
GH, VAS 0–100 mm	32.8±20.8	70.4±20.1	<0.001	64.6±20.6	61.5±23.6	0.007
DAS28-CRP	3.2±0.6	5.4±0.9	<0.001	5.3±0.9	5.5±1.0	0.656

Data are presented as mean±standard deviation except when otherwise indicated

Stage Steinbrocker’s stages, Class Steinbrocker’s classes, MTX methotrexate, MMP-3 matrix metalloproteinase-3, SJC swollen joint count, TJC tender joint count, CRP c-reactive protein, GH general health, VAS visual analog scale, DAS28 Disease Activity Score in 28 joints

^a Mean among patients receiving the drug

^b Obtained from analysis of variance (ANOVA) between Abatacept (HDA), Adalimumab, and Tocilizumab groups

higher proportion concomitantly used MTX ($p < 0.001$, vs. ABT and TCZ). A lower proportion of patients treated with abatacept concomitantly used oral steroids ($p = 0.013$, vs. TCZ). Disease activity parameters (DAS28, TJC, SJC, CRP, and MMP-3) did not show significant differences,

except for increased GH-VAS in patients treated with abatacept ($p = 0.007$, vs. TCZ).

As shown in Fig. 2, changes in disease activity parameters were similar between patients treated with abatacept and adalimumab throughout the study period. Because clinical

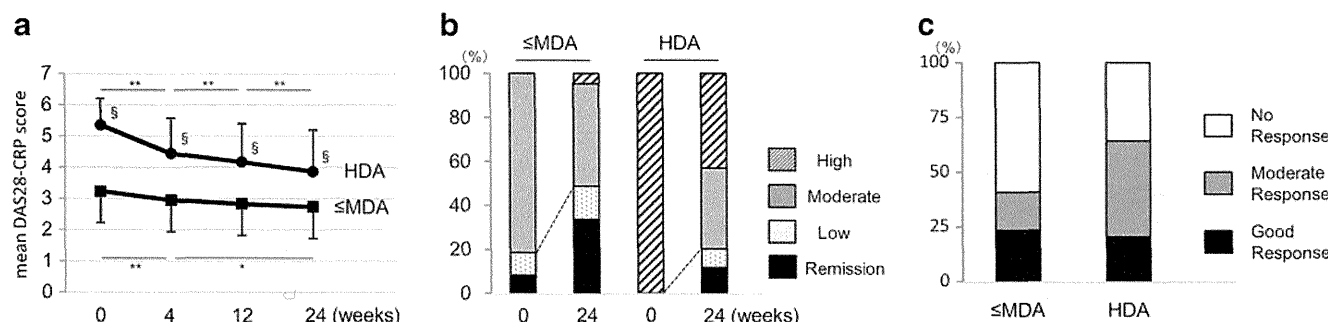


Fig. 1 a Clinical efficacy of abatacept in rheumatoid arthritis patients. Mean and standard deviation for the Disease Activity Score based on 28 joints (DAS28-CRP). § $p < 0.01$ between the HDA and ≤MDA groups. b Changes in DAS28-CRP defined disease activity over 24 weeks of abatacept treatment. High DAS28-CRP > 4.1, Moderate 4.1 ≥ DAS28-

CRP ≥ 2.7, Low 2.7 > DAS28-CRP ≥ 2.3, Remission DAS28-CRP < 2.3. c Comparison of European League Against Rheumatism (EULAR) responses at 24 weeks between patients with high disease activity at baseline (HDA) and patients with lower disease activity (≤MDA) at baseline. * $p < 0.05$; ** $p < 0.01$

Table 2 Multivariate logistic regression analysis for the achievement of low disease activity (LDA), clinical remission, and moderate or good EULAR response at 24 weeks in the overall patients using abatacept (upper column) or in the patients with high disease activity at baseline using abatacept, adalimumab, or tocilizumab (lower column)

	LDA at 24 weeks		Remission at 24 weeks		Moderate or good EULAR response at 24 weeks	
	Adjusted OR (95 % CI)	<i>p</i> value	Adjusted OR (95% CI)	<i>p</i> value	Adjusted OR (95% CI)	<i>p</i> value
Overall patients taking abatacept						
DAS28-CRP>4.1	0.261 (0.135–0.503)	<0.001	0.264 (0.124–0.564)	0.001	3.010 (1.626–5.574)	<0.001
Steinbrocker class 1–2 (years 3–4)	2.427 (1.145–5.147)	0.021	2.003 (0.853–4.707)	0.111	1.670 (0.841–3.318)	0.143
No previous use of biologics	2.346 (1.185–4.642)	0.014	2.056 (0.938–4.508)	0.072	2.824 (1.520–5.250)	0.001
Concomitant MTX use	0.698 (0.353–1.381)	0.302	0.652 (0.299–1.425)	0.284	0.798 (0.433–1.472)	0.47
Patients with HDA at baseline						
Adalimumab use (vs abatacept)	1.361 (0.683–2.711)	0.381	1.611 (0.712–3.648)	0.252	0.740 (0.402–1.363)	0.334
Tocilizumab use (vs abatacept)	1.479 (0.733–2.983)	0.275	1.057 (0.430–2.598)	0.904	2.594 (1.316–5.114)	0.006
DAS28-CRP score at baseline	0.768 (0.551–1.070)	0.119	0.600 (0.386–0.933)	0.023	0.929 (0.700–1.232)	0.608
Steinbrocker class 1–2 (years 3–4)	2.809 (1.570–5.029)	0.001	3.254 (1.509–7.019)	0.003	1.830 (1.119–2.994)	0.016
No previous use of biologics	2.030 (1.187–3.473)	0.01	3.070 (1.558–6.049)	0.001	2.152 (1.299–3.567)	0.003
Concomitant MTX use	0.934 (0.522–1.672)	0.818	1.102 (0.543–2.237)	0.788	1.157 (0.676–1.982)	0.594

OR odds ratio, CI confidence interval, EULAR European League Against Rheumatism, DAS28 Disease Activity Score in 28 joints, MTX methotrexate

data at 4 and 12 weeks were unavailable for patients treated with tocilizumab, we only show data at baseline and 24 weeks. ANOVA demonstrated significant differences in TJC (*p* = 0.029), CRP (*p* = 0.004), and MMP-3 (*p* = 0.036) at 24 weeks between the three treatments. Post hoc analysis (Bonferroni method) showed a significant difference in TJC between abatacept and adalimumab (6.5±7.0 vs. 4.4±5.1, *p* = 0.029)

and CRP and MMP-3 between adalimumab and tocilizumab (1.8±2.5 vs. 0.76±2.1, *p* = 0.003; 219.1±373.3 vs. 130.8±102.8, *p* = 0.048, respectively).

The proportion of patients who achieved LDA, clinical remission, a moderate or good EULAR response, and a good EULAR response at 24 weeks was compared following treatment with abatacept, adalimumab, and tocilizumab (Fig. 3).

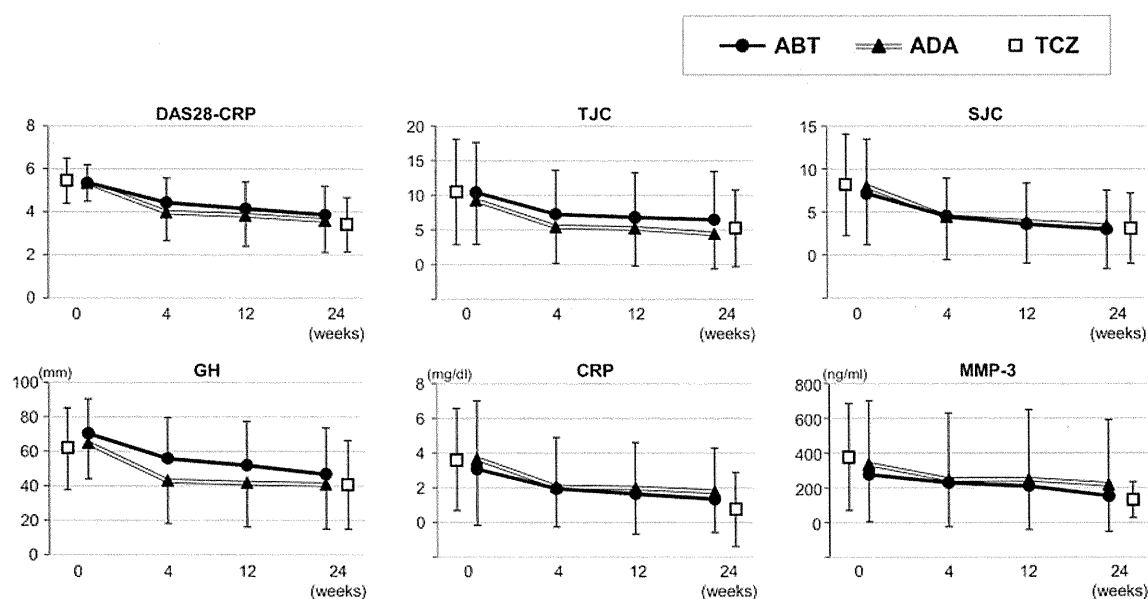
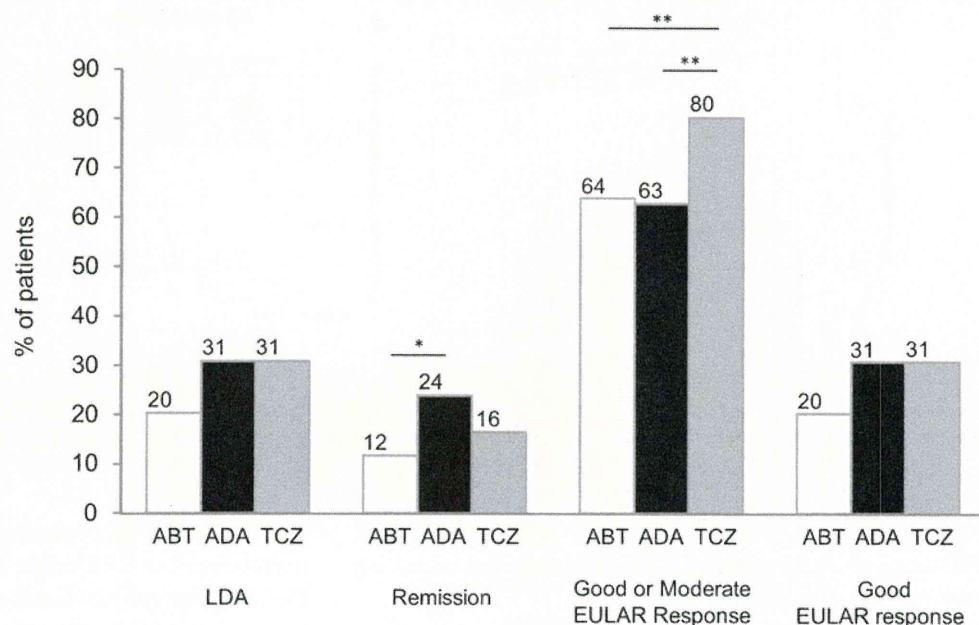


Fig. 2 Overall clinical efficacy of abatacept (ABT), adalimumab (ADA), and tocilizumab (TCZ) in rheumatoid arthritis patients with high disease activity at baseline. Mean and standard deviations for the Disease Activity Score based on 28 joints (DAS28-

CRP) and tender joint count (TJC), swollen joint count (SJC), general health on a visual analogue scale (GH-VAS), c-reactive protein (CRP), and matrix metalloproteinase-3 (MMP-3) are shown

Fig. 3 Proportion of patients who achieved DAS28-CRP defined as low disease activity (LDA), clinical remission, good or moderate EULAR response, and good EULAR response. * $p < 0.05$; ** $p < 0.01$. *ABT* abatacept, *ADA* adalimumab, *TCZ* tocilizumab, *EULAR* European League Against Rheumatism



There was no significant difference in the proportion of patients who achieved LDA at 24 weeks. Although a lower proportion of patients treated with abatacept achieved clinical remission compared to adalimumab, the difference was not significant compared to tocilizumab. A higher proportion of patients treated with tocilizumab achieved a moderate or good EULAR response compared to patients treated with abatacept and adalimumab. There was no significant difference in the proportion of patients who achieved a good EULAR response between the three groups.

Multivariate analysis confirmed that none of the three biologics had significant advantages in achieving LDA or clinical remission at 24 weeks (Table 2). Adalimumab was not an independent factor for achieving LDA, remission, or a moderate EULAR response at 24 weeks. Tocilizumab was an independent factor for achieving a moderate EULAR response at 24 weeks compared to abatacept. Class 1 or 2 and no prior history of biologic use were independent factors for LDA, remission, and a moderate EULAR response. ORs were adjusted for the following parameters: age, gender, disease duration, class, DAS-CRP at baseline, prior biologic use, and concomitant MTX and PSL treatment.

Retention rates in patients with HDA at baseline treated with abatacept, adalimumab, and tocilizumab

Retention rates were evaluated based on reasons for discontinuation. Kaplan–Meier curves for time to discontinuation for each agent due to insufficient efficacy and AEs are shown in Fig. 4a, b, respectively. Retention rates due to insufficient efficacy in patients treated with abatacept were significantly higher than in patients treated with adalimumab and lower

than in patients treated with tocilizumab. Retention rates due to AEs in patients treated with abatacept were significantly lower than in patients treated with tocilizumab.

Discussion

Baseline disease activity had a significant influence on the clinical efficacy of abatacept. In patients with HDA, the clinical efficacy of abatacept appeared to be insufficient compared with efficacy in patients with a lower disease activity. The clinical efficacy of abatacept in HDA patients was similar to the efficacy of adalimumab and tocilizumab. Some physicians perceive abatacept as being difficult to use in RA patients with HDA due to insufficient efficacy. However, adequate clinical responses were not obtained in any of the patients evaluated, regardless of the class of biologic used. Based on the present data, abatacept can be selected to treat RA patients with low, moderate, and high disease activity.

A recent head-to-head clinical trial (AMPLE trial) demonstrated that subcutaneous abatacept was not inferior to adalimumab [16]. The ADACTA head-to-head trial reported that tocilizumab monotherapy was superior to adalimumab monotherapy in reducing RA activity in patients for whom MTX was ineffective or inappropriate [17]. Although the data suggest equivalent clinical efficacies between different classes of biologics, patients in these trials were generally uniform and are different from real-world patients with diverse characteristics seen in clinical practice. The Danish DANBIO registry reported similar abatacept and tocilizumab efficacies in RA patients in clinical practice [11]. Multicenter registries can provide real-world long-term data relevant to safety,

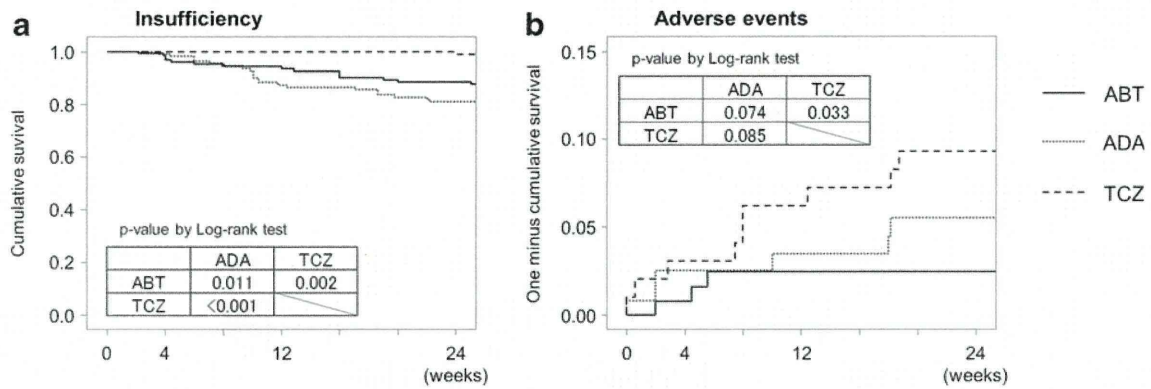


Fig. 4 Kaplan–Meier curves for time to discontinuation for each biologic. Withdrawal was due to **a** insufficient clinical efficacy (insufficiency) and **b** adverse events. Retention rates were compared using the log-rank test among groups. *ABT* abatacept, *ADA* adalimumab, *TCZ* tocilizumab

efficacy, or future outcomes in patients with comorbidities. The value of such registries in accumulating and evaluating relevant data cannot be underestimated.

In this study, differences in the DAS28-CRP score between patients treated with abatacept in the \leq MDA and HDA groups were consistent throughout the study period and remained significant at 24 weeks. The proportion of patients who achieved LDA or remission at 24 weeks was significantly lower in the HDA group. Multivariate regression analysis demonstrated that HDA at baseline was an independent negative predictor for achieving LDA and remission. Abatacept treatment in patients with HDA appeared to yield poor clinical results. However, similar results have been reported in previous studies related to TNF inhibitors and tocilizumab [1–5, 18]. Thus, inferior clinical efficacy in HDA patients is not abatacept specific, but is likely due to common features of DMARDs. The proportion of patients who achieved a moderate or good EULAR response was higher in the HDA group at 24 weeks. There was a sharp downward trend in the HDA group between 12 and 24 weeks, whereas the trend was gradual in the \leq MDA group after 4 weeks. A longer period is necessary to evaluate whether disease activity in the HDA group can eventually correspond to activity in the \leq MDA group.

Clinical efficacy in patients with HDA was similar between abatacept, adalimumab, and tocilizumab. This is the first study to demonstrate the clinical efficacy of three different classes of biologics in RA patients with HDA in clinical practice from the TBCR. Given that neither adalimumab nor tocilizumab were independent factors for achieving LDA or remission compared with abatacept, we suggest that there are no significant differences between the three biologics regarding clinical efficacy for HDA RA. However, several differences were observed. Tocilizumab treatment resulted in a higher proportion of patients who achieved a moderate EULAR response at 24 weeks and was an independent factor for a moderate EULAR response at 24 weeks compared to abatacept. Cytokine-blocking biologics, specifically tocilizumab, led to normal acute phase reactants (e.g. CRP or ESR) in almost all

patients. While this constitutes a positive treatment effect, improvement in CRP might lead to an overestimation of the EULAR response rate based on DAS28-CRP [19]. Abatacept had an average discontinuation rate due to insufficient clinical efficacy. Adalimumab had the highest discontinuation rate due to insufficiency despite a higher proportion of biologic-naïve patients and concomitant MTX use compared to abatacept and tocilizumab, which could be due to relatively low MTX doses in Japan compared to doses used in European countries and the USA. It will be necessary to study patients treated with higher doses of MTX in the future. Tocilizumab had the lowest discontinuation rate due to insufficiency despite having the lowest proportion of biologic-naïve patients and concomitant MTX use. This could be partially explained by a higher rate of achieving a EULAR response, which generally encourages physicians to continue treatment even if clinical efficacy appears to be inadequate. It will be necessary to study whether low discontinuation rates can be maintained for longer periods of time. In contrast, tocilizumab demonstrated the highest discontinuation rate due to adverse events compared to abatacept. Abatacept satisfactorily balances clinical efficacy and safety in RA patients with HDA.

‘Biologic-naïve’ was an independent factor for achieving LDA or EULAR responses at 24 weeks in patients treated with abatacept. Similar to other classes of biologics, abatacept likely demonstrates optimal efficacy in biologic-naïve patients. Several reports have indicated that adalimumab or tocilizumab demonstrate higher efficacy in biologic-naïve patients compared to patients with a history of prior biologic use [5, 20–26]. Advanced functional impairment has also been reported as a negative factor regarding clinical efficacy of adalimumab and tocilizumab [1, 18, 27, 28]. ‘Better physical function’ in all patients treated with abatacept was an independent factor for achieving LDA. In patients with HDA at baseline using abatacept, adalimumab, or tocilizumab, ‘biologic-naïve’ or ‘better physical function’ were independent factors for achieving LDA or remission rather than the specific agent used. Thus, baseline characteristics are more critical

than treatment agents for predicting favourable clinical efficacy in RA patients with HDA.

This study has several limitations. It was observational and not randomised, and treatments were likely influenced by patient characteristics and other factors such as preference of administration routes. Although concomitant MTX use was not an independent factor for achieving LDA, remission, or a moderate EULAR response in all patients treated with abatacept and patients with HDA treated with abatacept, adalimumab, or tocilizumab, the mean MTX dose was relatively low in this study. Future studies with higher MTX doses are necessary to conclude whether MTX has a synergistic effect. In addition, radiographic data were not available. Due to the importance of joint protective effects in demonstrating clinical efficacy, evaluating radiographic changes in patients treated with abatacept will be necessary in the future.

In conclusion, this study demonstrated the clinical efficacy of abatacept, adalimumab, and tocilizumab in clinical practice. The clinical efficacy in RA patients with HDA was similar between the three classes of biologics. We suggest that abatacept can be used to treat patients with low, moderate, and high disease activity in clinical practice.

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Pathogenic conversion of Foxp3⁺ T cells into T_H17 cells in autoimmune arthritis

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Autoimmune diseases often result from an imbalance between regulatory T (T_{reg}) cells and interleukin-17 (IL-17)-producing T helper (T_H17) cells; the origin of the latter cells remains largely unknown. Foxp3 is indispensable for the suppressive function of T_{reg} cells, but the stability of Foxp3 has been under debate. Here we show that T_H17 cells originating from Foxp3⁺ T cells have a key role in the pathogenesis of autoimmune arthritis. Under arthritic conditions, CD25^{lo}Foxp3⁺CD4⁺ T cells lose Foxp3 expression (herein called exFoxp3 cells) and undergo transdifferentiation into T_H17 cells. Fate mapping analysis showed that IL-17-expressing exFoxp3 T (exFoxp3 T_H17) cells accumulated in inflamed joints. The conversion of Foxp3⁺CD4⁺ T cells to T_H17 cells was mediated by synovial fibroblast-derived IL-6. These exFoxp3 T_H17 cells were more potent osteoclastogenic T cells than were naive CD4⁺ T cell-derived T_H17 cells. Notably, exFoxp3 T_H17 cells were characterized by the expression of Sox4, chemokine (C-C motif) receptor 6 (CCR6), chemokine (C-C motif) ligand 20 (CCL20), IL-23 receptor (IL-23R) and receptor activator of NF-κB ligand (RANKL, also called TNFSF11). Adoptive transfer of autoreactive, antigen-experienced CD25^{lo}Foxp3⁺CD4⁺ T cells into mice followed by secondary immunization with collagen accelerated the onset and increased the severity of arthritis and was associated with the loss of Foxp3 expression in the majority of transferred T cells. We observed IL-17⁺Foxp3⁺ T cells in the synovium of subjects with active rheumatoid arthritis (RA), which suggests that plastic Foxp3⁺ T cells contribute to the pathogenesis of RA. These findings establish the pathological importance of Foxp3 instability in the generation of pathogenic T_H17 cells in autoimmunity.

Foxp3-expressing T_{reg} cells have an essential role in suppressing immune responses¹⁻⁵. Mice deficient in Foxp3 develop fatal autoimmune disease^{3,4}, and continuous expression of Foxp3 throughout life prevents autoimmunity⁶. Thus, the stability of Foxp3 expression influences the balance between tolerance and autoimmunity, as well as the efficacy of T_{reg} cell-based therapies. The instability of Foxp3 may underlie the pathogenesis of autoimmune diabetes and lethal protozoa infection⁷⁻⁹, but this concept has been challenged by a report showing that Foxp3 expression is stable in *in vivo* disease models, including autoimmune arthritis¹⁰. A debate has arisen as to whether the plasticity of Foxp3-expressing T_{reg} cells is pathologically relevant. T_{reg} cell development and function are regulated by IL-2, which binds to the receptor complex containing IL-2Rα (also called CD25). It was recently shown that Foxp3⁺ cells are comprised of Foxp3-stable CD25^{hi} and Foxp3-unstable CD25^{lo} populations^{11,12}, the former of which is composed of *bona fide* T_{reg} cells with sustained Foxp3 expression¹¹. However, the pathological importance of the latter Foxp3-unstable CD25^{lo} population remains unclear.

RESULTS

T_H17 cells arise from CD25^{lo}Foxp3⁺ T cells in arthritis

To evaluate the *in vivo* stability of Foxp3 in Foxp3⁺CD4⁺ T cells and its impact on collagen-induced arthritis (CIA), we adoptively transferred CD25^{hi}Foxp3⁺CD4⁺ or CD25^{lo}Foxp3⁺CD4⁺ T cells into mice that we immunized with type II collagen 3 weeks before. One day after transfer, we subjected the mice to secondary immunization with collagen. We efficiently obtained Foxp3⁺ cells by sorting hCD2⁺ cells from Foxp3^{hCD2} knock-in mice¹¹. hCD2-mediated enrichment of Foxp3⁺ cells enabled us to isolate CD25^{lo}Foxp3⁺ cells with high purity (**Supplementary Fig. 1**). We found that the transfer of CD25^{hi}Foxp3⁺CD4⁺, but not CD25^{lo}Foxp3⁺CD4⁺, T cells reduced joint swelling (**Fig. 1a**) and bone destruction (**Fig. 1b**) without affecting the production of collagen-specific antibodies (**Supplementary Fig. 2**). To examine the stability of Foxp3, we labeled donor CD25^{hi}Foxp3⁺CD4⁺ or CD25^{lo}Foxp3⁺CD4⁺ T cells with carboxyfluorescein succinimidyl ester (CFSE) and monitored Foxp3 expression in donor-derived (CFSE⁺) CD4⁺ T cells 1 week after secondary immunization. The majority of CD25^{hi}Foxp3⁺CD4⁺ T cells

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