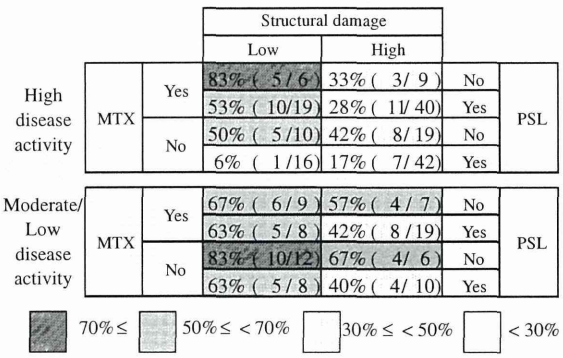
TABLE 3 Independent impacts of baseline variables on remission by level of baseline disease activity

Variables	High disease activity subgroup (DAS28 > 5.1, *n* = 161), OR (95% CI)	Low to moderate disease activity subgroup (DAS28 ≤ 5.1, *n* = 79), OR (95% CI)
Age/1 year	1.01 (0.98, 1.05)	0.99 (0.95, 1.03)
Male	2.45 (0.92, 6.48)	2.49 (0.51, 12.2)
Disease duration ≤3 years	2.01 (0.68, 5.91)	2.68 (0.52, 13.9)
Steinbrocker stage I + II	1.49 (0.55, 4.03)	2.29 (0.71, 7.39)
Steinbrocker class I + II	1.28 (0.54, 3.03)	0.32 (0.08, 1.32)
Previous biologics	0.73 (0.31, 1.71)	0.57 (0.20, 1.60)
Concomitant PSL	0.28 (0.12, 0.67)*	0.57 (0.19, 1.71)
Concomitant MTX	2.55 (1.11, 5.87)*	1.07 (0.38, 3.00)
DAS28/1 point	0.41 (0.24, 0.72)*	1.00 (0.51, 1.94)

Multiadjusted OR calculated by the model included age, sex, disease duration, Steinbrocker class, use of previous biologics, concomitant PSL use, MTX use and DAS28 at baseline. *$P < 0.05$. DAS28: 28-item DAS; OR: odds ratio; PSL; prednisolone.

FIG. 3 Remission rates for patients with TCZ treatment categorized by disease activity, Steinbrocker stage, concomitant PSL use and concomitant MTX use



The DAS28-ESR category was used as a cut-off for disease activity (high disease activity: DAS28-ESR > 5.1). The non-responder imputation method was used for patients who withdrew before 52 weeks. TCZ: tocilizumab; PSL: prednisolone; DAS28: 28-item DAS.

<20%, regardless of the stage of structural damage. Concomitant MTX users showed relatively high remission rates if they had high baseline disease activity with low structural damage (Steinbrocker stage I or II).

Discussion

The present study identified predictive factors for achievement of remission at 52 weeks based on the DAS28 in RA patients with TCZ treatment in clinical practice. Shorter disease duration, less structural damage and no concomitant PSL use were significant predictive factors for remission regardless of the level of baseline disease activity. In particular, concomitant MTX use was beneficial only for the patients with high disease activity at baseline; there was no association between concomitant MTX use and remission among those with low to moderate baseline disease activity. Previous use of biologics was inversely associated with remission, but its association was not statistically significant after controlling for age and baseline disease activity.

Using data from 123 patients who received TCZ for 52 weeks [20], we previously reported the importance of shorter disease duration [<4.8 years; OR 2.5 (95% CI 1.4, 4.7)] and lower disease activity [DAS28 < 5.23; OR 5.23 (95% CI 1.2, 5.1)] to achieve remission as defined by the ACR/EULAR in 2011. The present study results are consistent with our previous findings and add some information regarding concomitant use of MTX and PSL with TCZ.

The optimal use of MTX and PSL with and without biologics is an important issue for the management of RA [2]. Recent clinical trials have provided some interesting results regarding the use of concomitant MTX. The adalimumab and TCZ (ADACTA) study showed that clinical outcomes from TCZ monotherapy were superior to adalimumab monotherapy in patients with MTX intolerance [21]. Furthermore, the ACT-RAY study of TCZ and MTX [22] reported that a switch from MTX to TCZ monotherapy was comparable to an add-on strategy of TCZ to MTX in patients with inadequate MTX response and no previous use of biologics for achieving remission at 24 weeks. According to these results, TCZ monotherapy could be a superior alternative to TNF-α inhibitors for patients with contraindications or intolerance to MTX.

One question that follows these findings is whether or not we need concomitant MTX use in order to have better clinical outcomes during TCZ treatment. We found that concomitant MTX use was an independent predictive factor in achieving remission when the patient had high disease activity at baseline. It is not surprising that the

benefit of concomitant MTX use was not apparent among those who had low to moderate baseline disease activity, as MTX would contribute to remission achievement with its anti-inflammatory effect.

The beneficial effects of glucocorticoids on symptom suppression and inhibiting radiographic progression in RA are well established [23]. Nevertheless, we observed a strong negative impact of concomitant PSL use on remission achievement in the present study. Glucocorticoids are often prescribed to patients with severe disease and those with co-morbidities [2]. In the present study, in order to evaluate the effectiveness of treatment in real clinical settings we did not exclude from the analysis patients who had co-morbidities. Therefore concomitant PSL use in the present study may simply reflect the vulnerability of those patients. The cross-tabulation shown in Fig. 3 indicates that the remission rates are comparable to those with concomitant PSL use, if the patients had low baseline disease activity and concomitant MTX use. Optimal use of glucocorticoids with TCZ and/or MTX should be clarified in future prospective studies with a larger sample size and more diverse sample population.

In the present analysis, male sex was a marginally significant beneficial predictor for remission after controlling for possible confounding factors. Most of the background characteristics were comparable across sexes, except for disease duration and MTX dose; men had significantly shorter disease duration (those with a disease duration $\leq$3 years were 39.1% of men but 20.4% of women, $P = 0.001$) and lower doses of MTX [mean 8.40 mg/day (S.D. 2.23) *vs* 7.04 (2.30), $P = 0.008$). Although RA is more prevalent in women than in men worldwide, the gender difference in treatment response has not yet been established. Recent studies have shown consistent results indicating better outcomes in men compared with women [24–30]; however, the reasons for the gender differences have not been fully elucidated. Generally, socioeconomic factors can strongly influence disease perception, adherence to treatment and long-term prognosis of RA [31–34]. Unfortunately, information on factors such as education and income was not available for the present study participants, which may explain some of the gender-dependent variability. Further studies should examine whether a substantial gender difference exists in the response to RA treatment as well as what clinicians need to consider in terms of gender differences for RA management.

There are some limitations to consider when interpreting the results of this study. First, this is an observational cohort study of RA patients with TCZ therapy. We are able to evaluate the effectiveness of treatment in real clinical settings, but it contains many potential biases. In particular, the study begins with the initiation of TCZ therapy, and no clear criteria define the patients to whom TCZ should be applied, as the treating doctors made the judgement call. Moreover, the decisions to use and stop previous biologics and/or use concomitant PSL and MTX were made by the doctors. We observed relatively low remission rates in patients with high baseline disease activity and concomitant PSL use without MTX. It is possible that some clinical difficulties existed, discouraging patients from taking MTX and leading to poor outcomes. We should assess the backgrounds of the patients in more detail, which may affect doctors' decisions and patients' responses to the treatment. Second, this study is based on a multicentre registry consisting of a university hospital and 12 affiliated institutes. The doctors who participated in this study were expert rheumatologists and most of their patients were referred from local clinics. Therefore many of the patients included in the present study had relatively long and severe disease histories and high compliance. Finally, the sample size is too small to have robust results, and the significance of some of the findings may change with a larger dataset.

Despite these limitations, the present data collected from complex daily practice settings provide some information for rheumatologists. Randomized controlled trials (RCTs) are essential to estimate the efficacy of treatment, but they also greatly restrict the characteristics of study participants. It is necessary to collect prospective evidence from daily practice to evaluate the effectiveness of the treatment. Finally, a well-designed RCT is still required to determine the optimal dose of MTX with TCZ.

In conclusion, DAS28 remission rates at 52 weeks of TCZ treatment could be predicted by baseline factors obtained in daily practice. Concomitant MTX use may effectively yield better clinical outcomes in patients with high disease activity.

Rheumatology key message

- Concomitant MTX therapy with tocilizumab is effective in achieving remission in RA patients with high disease activity.

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ORIGINAL ARTICLE

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 Tsurumai 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≤DAS28-CRP<2.7), moderate disease activity (MDA; 2.7≤DAS28-CRP≤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±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 (≤MDA, DAS28-CRP≤4.1) and HDA at baseline. Characteristics of patients treated with abatacept in the ≤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 ≤ 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 ≤ 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 ≤MDA group. The difference between the ≤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 ≤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 ≤MDA and HDA groups. The proportion of patients who achieved LDA was significantly higher in the ≤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 ≤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 ≤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 ≤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 ≤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	
	Disease activity at baseline			(in patients with HDA)		
	≤MDA (n=86)	HDA (n=128)	p value	(n=120)	(n=97)	p value[b]
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

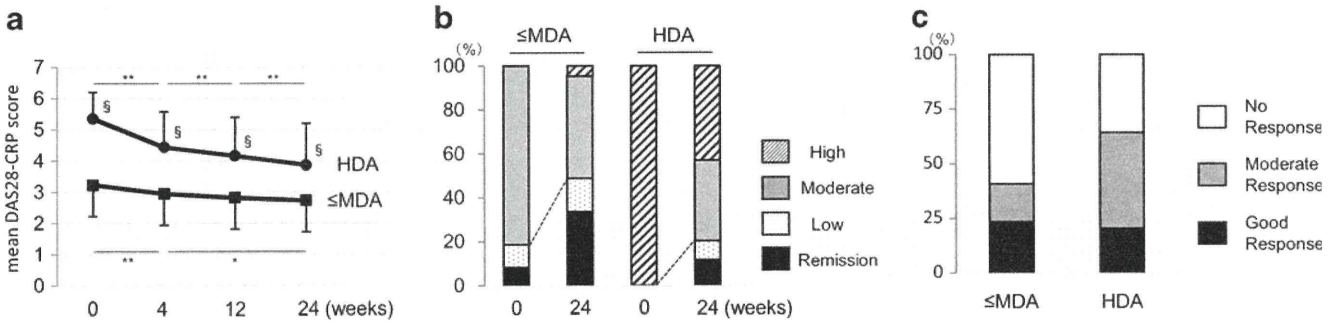

Fig. 1 **a** Clinical efficacy of abatacept in rheumatoid arthritis patients. Mean and standard deviation for the Disease Activity Score based on 28 joints (DAS28-CRP). §p<0.01 between the HDA and ≤MDA groups. **b** Changes in DAS28-CRP defined disease activity over 24 weeks of abatacept treatment. *High* 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)	*p* value	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* 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 (vears 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 (vears 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).

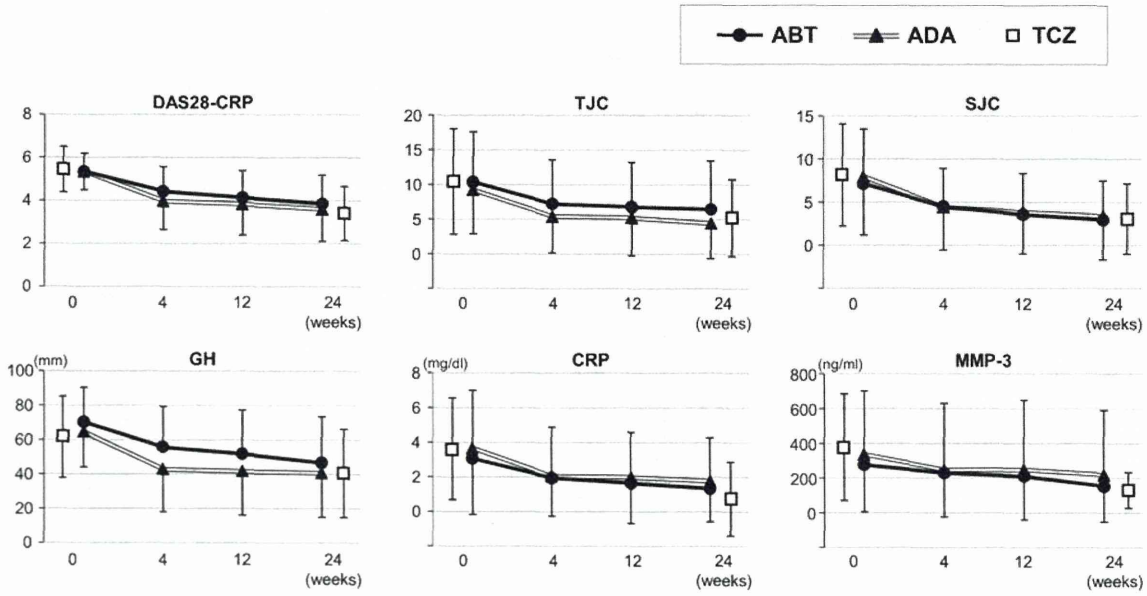

Fig. 2 Overall clinical efficacy of abatacept (ABT), adalimumab (ADA), and tocilizumab (TCZ) in rheumatoid arthritis patients with high disease activity at baseline. Mean and standard deviations for the Disease Activity Score based on 28 joints (DAS28-CRP) and tender joint count (TJC), swollen joint count (SJC), general health on a visual analogue scale (GH-VAS), c-reactive protein (CRP), and matrix metalloproteinase-3 (MMP-3) are shown

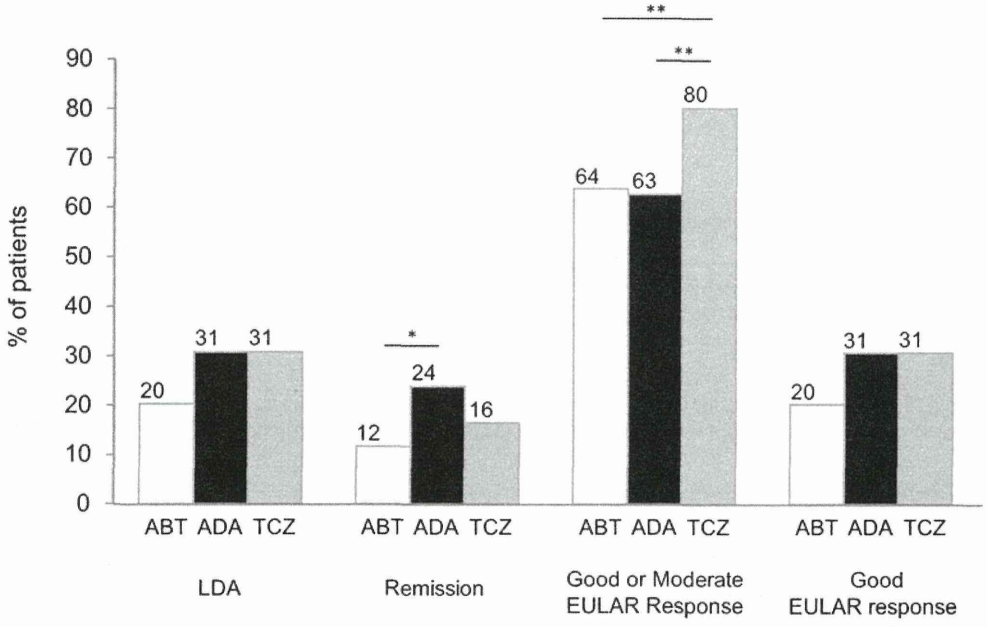

Fig. 3 Proportion of patients who achieved DAS28-CRP defined as low disease activity (LDA), clinical remission, good or moderate EULAR response, and good EULAR response. *$p<0.05$; **$p<0.01$. *ABT* abatacept, *ADA* adalimumab, *TCZ* tocilizumab, *EULAR* European League Against Rheumatism

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,