of personal information was strictly controlled. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine.

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), joint damage (Steinbrocker stage), and daily dysfunction (Steinbrocker class). The following disease parameters were recorded at baseline and at 24 and 52 weeks of treatment: tender joint count (TJC) and swollen joint count (SJC) on 28 joints, general health on a visual analog scale (GH-VAS), and serum C-reactive protein (CRP) levels. Disease activity was evaluated at each time point using the 28-joint disease activity score with CRP (DAS28-CRP) and the clinical disease activity index (CDAI) which included data from the cited disease parameters.

Statistical analysis

Demographic and disease characteristics were reported using descriptive statistics. All results are expressed as mean±SD or percentage. Student's t-test was used for two-group comparisons and the chi-square test for categorical variables. The last observation carried forward (LOCF) method was used in each analysis. All statistical tests were two-sided, and significance was defined as $p<0.05$. Drug continuation rates were estimated by plotting Kaplan–Meier curves and were compared using log-rank test. Hazard ratios (HRs) for cause-specific drug discontinuation were calculated using the Cox proportional hazards model, adjusted for variables such as disease duration, age, sex, and concomitant use of MTX and CDAI. All analyses were performed with SPSS version 20.0.0 software (IBM Corp., Armonk, NY, USA).

Results

Patients

We examined 89 patients who switched to abatacept, tocilizumab, and etanercept as a second biologic agent from first-course anti-TNF monoclonal antibody therapy due to inadequate efficacy. Of these, 25 (28.1 %) had switched to abatacept, 38 (42.7 %) had switched to tocilizumab, and 26 (29.2 %) had switched to etanercept.

Baseline characteristics of all patients are shown in Table 1, categorized by the second biologic agent. Mean age was 58.7 ±12.1 years, mean disease duration was 9.8±8.3 years, and

mean DAS28-CRP and CDAI were 4.6±1.2 and 22.4±11.0, respectively. A significant difference was found in rheumatoid factor positivity among the three drugs. No significant differences were found in factors reported to affect the effects of biologics, including MTX use, MTX dose, and disease duration. In the present study, the rate of concomitant MTX use was 78.7 %, with a mean dose of 7.4 mg/week.

Drug continuation rates

Drug continuation rates were analyzed with Kaplan–Meier curves (Fig. 1). At 52 weeks, continuation rates for abatacept, tocilizumab, and etanercept were 72.0, 89.5, and 84.6 %, respectively (log-rank test, $p=0.121$), for discontinuation due to all unfavorable causes (Fig. 1a). When classified according to reasons for discontinuation, continuation rates at 52 weeks for abatacept, tocilizumab, and etanercept were 88.0, 97.1, and 90.5 % (log-rank test, $p=0.374$), respectively, for discontinuation due to adverse events (Fig. 1b), and 82.6, 91.9, and 95.7 % (log-rank test, $p=0.182$), respectively, for discontinuation due to inadequate efficacy (Fig. 1c). It should be noted that discontinuation of tocilizumab due to adverse events and discontinuation of etanercept due to inadequate efficacy were low, although there was no significant difference. All drugs exhibited good retention rates.

Clinical efficacy

Figure 2 shows changes in tender joint counts, swollen joint counts, GH-VAS, CRP, DAS28-CRP, and CDAI at 0, 24, and 52 weeks. The decline over time in TJC, SJC, GH-VAS, CRP, DAS28-CRP, and CDAI significantly improved at all time points. TJC and SJC showed similar improvements without significant differences among the three drugs. GH-VAS was clearly higher in abatacept-treated patients (44.2±27.3) compared to others (tocilizumab, 23.9±23.0, $p=0.004$; etanercept, 24.8±20.8, $p=0.007$) at 24 weeks, but there was no significant difference at 52 weeks. GH-VAS decreased more gradually in abatacept-treated patients. CRP levels were clearly lower with tocilizumab compared to abatacept at 24 weeks (tocilizumab, 0.16±0.85; abatacept, 0.87±1.16; $p=0.002$) and 52 weeks (tocilizumab, 0.21±0.87; abatacept, 0.91±0.98; $p=0.001$). DAS28-CRP showed no difference among the three drugs at 24 weeks but was lower with tocilizumab compared to abatacept at 52 weeks (tocilizumab, 2.51±1.12; abatacept, 3.22±1.11; $p=0.016$). As shown in Fig. 3, all three drugs demonstrated good efficacy at 52 weeks in the evaluation based on CDAI. Remission rates and percentages of subsequent low disease activity for abatacept, tocilizumab, and etanercept were 20.7, 28.6, and 20.6 %, respectively, and 49.8, 68.2, and 70.6 %, respectively.

Table 1 Baseline characteristics of patients with rheumatoid arthritis who switched from anti-TNF monoclonal antibodies

	Overall (n=89)	Abatacept (n=25)	Tocilizumab (n=38)	Etanercept (n=26)	p value
Age (year)	58.7±12.1	62.8±9.3	56.7±12.4	57.5±13.3	0.315
Sex (% female)	82	80	78.9	88.5	0.593
Disease duration (year)	9.8±8.3	11.4±9.5	7.9±6.1	11.0±9.6	0.207
Stage (I/II/III/IV, %)	19.1/21.3/24.7/32.6	20.0/20.0/24.0/36.0	19.4/22.2/33.3/25.0	19.2/23.1/15.4/42.3	0.627
Class (I/II/III/IV, %)	13.5/50.6/29.2/4.5	12.0/52.0/36.0/0	16.8/52.8/27.8/2.8	11.5/50.0/26.9/11.5	0.453
RF positive (%)	82.9	70.6	78.6	96	**0.002**
Previous biological DMARDs (%)					
Adalimumab	37.1	60	26.3	30.8	
Infliximab	62.9	40	73.7	69.2	
MTX use (%)	78.7	80	73.7	84.6	0.567
MTX dose (mg/week)[a]	7.4	7.5	7.3	7.8	0.716
Oral steroid use (%)	58.4	64	59.5	53.8	0.760
Oral steroid dose (mg/day)[a]	4.2	3.8	4	4.8	0.433
MMP-3 (ng/mL)	257.0±235.2	217.1±190.0	317.4±271.6	183.9±129.0	0.371
SJC, 0–28	5.4±4.8	5.9±5.6	5.7±4.9	4.7±3.7	0.546
TJC, 0–28	6.4±5.6	5.3±4.1	6.0±5.7	7.9±6.6	0.439
ESR (mm/h)	53.1±27.1	57.4±32.1	51.1±24.9	53.0±26.4	0.475
CRP (mg/dL)	2.6±2.6	1.7±1.9	2.9±2.8	3.0±2.9	0.374
GH-VAS 0–100 mm	54.1±22.9	53.7±25.2	53.9±22.4	54.6±22.3	0.514
DAS28-ESR	5.3±1.2	5.2±1.2	5.3±1.2	5.4±1.3	0.267
DAS28-CRP	4.6±1.2	4.4±1.1	4.7±1.2	4.8±1.1	0.266
CDAI	22.4±11.0	21.2±11.0	22.4±11.1	23.5±11.2	0.266
SDAI	24.8±11.6	23.1±11.3	24.7±11.5	26.4±12.3	0.335

Data are presented as mean±SD, unless otherwise indicated

Stage Steinbrocker stage, *Class* Steinbrocker class, *RF* rheumatoid factor, *MTX* methotrexate, *MMP-3* matrix metalloproteinase-3, *SJC* swollen joint count, *TJC* tender joint count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *GH-VAS* general health visual analog scale, *DAS28* disease activity score in 28 joints, *CDAI* clinical disease activity index, *SDAI* simplified disease activity index

[a] Mean among patients receiving the drug

Multivariate analysis

We calculated HRs for cause-specific drug discontinuation using multivariate Cox proportional HR analysis (Table 2) adjusted by disease duration, age, sex, concomitant MTX use, and CDAI. Discontinuation due to all unfavorable causes did not significantly differ among abatacept, tocilizumab, and etanercept, although discontinuation of tocilizumab due to adverse events and discontinuation of etanercept due to inadequate efficacy tended to be less common. There was no significant difference in inadequate efficacy and adverse events across the three drugs.

Discussion

The recent introduction of two new biologics, abatacept and tocilizumab, into the market represents interesting new therapeutic opportunities for patients with RA who are resistant to TNFi. In the present study, no apparent difference in terms of efficacy was observed among abatacept, tocilizumab, and etanercept after switching from anti-TNF monoclonal antibodies.

In general, when patients respond poorly to the first TNFi after 3 to 4 months, switching to a different biologic agent is considered [6]. If the secondary loss of efficacy is due to anti-drug antibodies, switching to a second TNFi might prove effective [16]. In many cases, the first treatment is discontinued due to immunogenicity-related problems associated with the concomitant use of low-dose MTX. In such cases, the biologics with low immunogenicity are useful. Etanercept does not require concomitant MTX necessarily and could thus demonstrate the expected efficacy [2]. In contrast, if the secondary loss of efficacy is due to TNF no longer being the primary cytokine, switching to other classes of biologics will be required. Whenever possible, the switching of biologics should be decided based on the cause of secondary loss of efficacy; however, there is currently no method to determine this. Moreover, there is no consensus regarding the strategy of switching biologics.
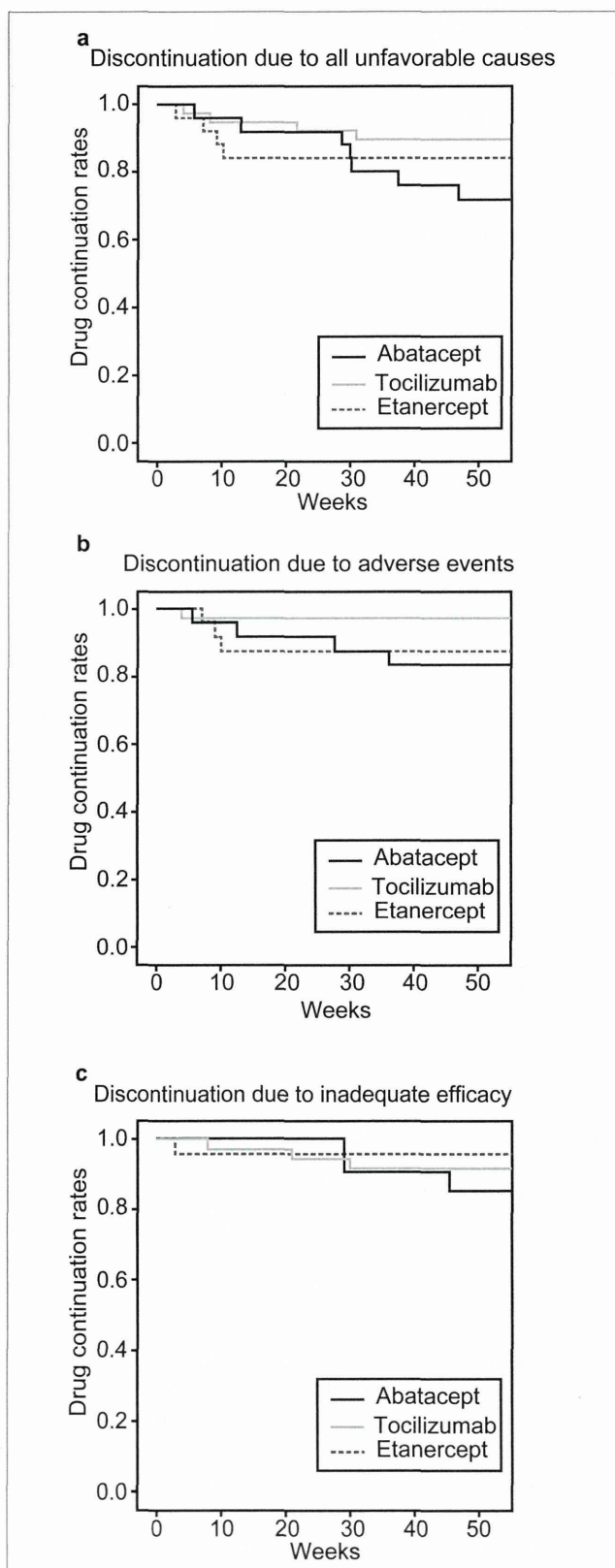
Fig. 1 Patient retention in abatacept, tocilizumab, and etanercept treatment. Kaplan–Meier curves of treatment continuation rates among patients with rheumatoid arthritis over 52 weeks of treatment. **a** Discontinuation due to all unfavorable causes. **b** Discontinuation due to adverse events. **c** Discontinuation due to inadequate efficacy

The present observational study was based on data from a multicenter registry regarding the clinical efficacy of abatacept, tocilizumab, and etanercept in patients with RA in whom anti-TNF monoclonal antibody therapy previously failed. Therefore, the present results reflect treatment outcomes of the "real world."

Several studies have reported on switching from TNFi to other biologics. One meta-analysis revealed no difference in ACR50 response to rituximab, tocilizumab, abatacept, and golimumab when switched from TNFi [15]. According to the Danish DANBIO study, 48-week retention rates of abatacept and tocilizumab after switching from TNFi were 54 and 64 %, respectively [7]. The retention rates in our study were better (68.0 % for abatacept and 89.5 % for tocilizumab). In the DANBIO study, the mean DAS28-CRP at 48 weeks was 3.3 for abatacept and 2.5 for tocilizumab, which were comparable to our results at 52 weeks (abatacept, 3.22 ± 1.11; tocilizumab, 2.51 ± 1.12). In addition, 48-week remission rate in the DANBIO study was 26 % for abatacept and 58 % for tocilizumab, which are better or almost the same as our results (17.4 and 55.6 %, respectively). The ATTAIN study, which examined patients who switched from TNFi to abatacept, reported the percentages of low disease activity and remission to be 24.2 and 13.9 %, respectively [25]. Compared to these, the percentages of low disease activity and remission in the present study were better (34.8 and 17.4 %, respectively). In the RADIATE study, DAS28 remission rate at 24 weeks (DAS28-CRP 2.6) was 30.1 % in patients who switched from TNFi to tocilizumab [20], compared to 50.0 % in the present study. This difference might be attributed to low DAS28CRP values at baseline and the short disease duration of 7.9 ± 6.1 years in our study. As for patients who switched to etanercept from TNFi, the RADIUS study [26] reported a 52-week retention rate of 74 % in comparison to 84.6 % in our study. Taken together, our results are in good agreement with previous reports.

It should be emphasized that, in the present study, response rates and survival could not be compared among abatacept, tocilizumab, and etanercept due to the non-randomized, retrospective design. However, slight differences in clinical responses and disease activity (as judged by DAS28 CRP) among the three drugs appeared to be primarily due to the large decrease of CRP and ESR in tocilizumab-treated patients. Given that tocilizumab is an IL-6 antagonist and since IL-6 enhances the formation of CRP and ESR, our findings raise the question as to whether DAS28 is a valid tool for assessing disease activity for drugs that affect CRP and ESR. When evaluating tocilizumab, we believe that CDAI would serve as a useful tool since it does not involve CRP and ESR. In the present study, significant differences were found in CRP and DAS28-CRP when abatacept and tocilizumab were compared; however, as shown in Fig. 2f, there was no significant difference among the three drugs in terms of CDAI. The
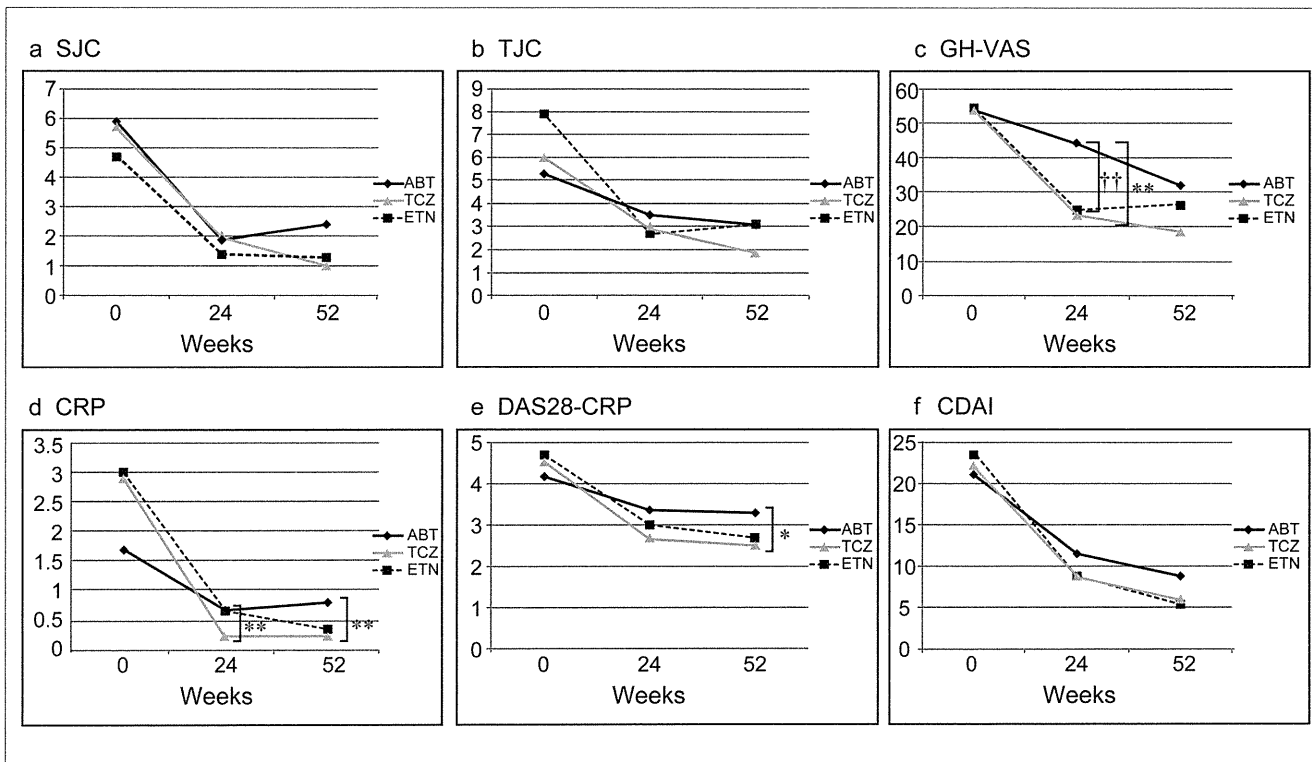
Fig. 2 Overall clinical efficacy of switching biologics in patients with rheumatoid arthritis. Mean values for **a** swollen joint count (*SJC*), **b** tender joint count (*TJC*), **c** general health on a visual analog scale (*GH-VAS*), **d** C-reactive protein (CRP), **e** 28-joint disease activity score with CRP (DAS28-CRP), and **f** clinical disease activity index (CDAI). *ABT* abatacept, *TCZ* tocilizumab, *ETN* etanercept. *$P<0.05$ tocilizumab vs. abatacept. **$P<0.01$ tocilizumab vs. abatacept. †$P<0.05$ etanercept vs. abatacept. ††$P<0.01$ etanercept vs. abatacept

efficacy of the three drugs was found to be similar in the evaluation without CRP. In addition, the efficacy of tocilizumab was unchanged when the effects of CRP negativity was excluded.

In the present study, the three drugs showed no difference in therapeutic effects in patients with inadequate responses to anti-TNF monoclonal antibodies. In other words, abatacept and tocilizumab, which were found to be effective when

Fig. 3 Clinical disease activity index (CDAI) with second-course biologics (0, 24, and 52 weeks). *ABT* abatacept, *TCZ* tocilizumab, *ETN* etanercept, *HDA* high disease activity (CDAI>22), *MDA* moderate disease activity (10<CDAI≤22), *LDA* low disease activity (CDAI≤10). Remission (CDAI≤2.8)

switched from an anti-TNF monoclonal antibody, would offer good therapeutic options, as would etanercept in these patients. These biologics should be selected based on consultation with the patient regarding the method of administration (intravenous/subcutaneous injection) and dosing interval.

Limitations of this study include the small number of patients treated with each biologic agent. In the present study, it was necessary to set the study period after September 2010 as this was the year when abatacept was released in Japan. In addition, the number of patients requiring switching of medications was low since the long-term efficacy and safety of anti-TNF agents had been established. Nonetheless, use of the
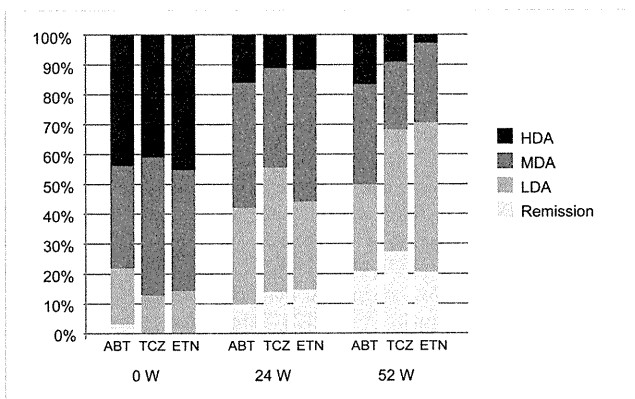
Table 2 Hazard ratios for discontinuation of the three drugs due to specific causes

	Etanercept (reference)	Tocilizumab HR (95 % CI)	Abatacept HR (95 % CI)
All unfavorable causes	1	0.58 (0.13–2.66)	1.21 (0.33–4.51)
Inadequate efficacy	1	1.37 (0.12–15.29)	2.14 (0.21–21.57)
Adverse events	1	0.28 (0.27–2.82)	0.77 (0.13–4.42)

Adjusted by sex, age, concomitant use of methotrexate, disease duration, and clinical disease activity index

HR hazard ratio, *CI* confidence interval

TBCR with over 2,000 cases enabled us to collect data for the present study. Given that the sample size might be insufficient to obtain strong statistical power, further studies will be necessary to reach the definite conclusion, yet our findings suggest no major differences among the three classes of biological DMARDs in terms of clinical efficacy after failure of first-course anti-TNF monoclonal antibody treatment. Additionally, given the retrospective design of the present study, drug selection was not randomized. Because of the bias of attending physicians, the number of cases that switched between anti-TNF monoclonal antibodies was quite low. As such, we were unable to evaluate in detail the switching between TNFi. Further evaluation is required for those who switch from anti-TNF monoclonal antibodies to another anti-TNF monoclonal antibody. Another limitation was the lack of data regarding the impact on structural damage (i.e., radiographic progression). These points should be addressed in the future.

In summary, we conclude that patients treated with either abatacept, tocilizumab, or etanercept can achieve a high response rate and that these biologics represent good therapeutic options in patients with RA who are refractory to first-course anti-TNF monoclonal antibody therapy. Moreover, the three biologics showed no significant difference in retention rate and efficacy. Further investigation to compare second-course anti-TNF monoclonal antibodies with the three drugs is needed to promote efficient drug selection when patients are switched from anti-TNF monoclonal antibodies.

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RHEUMATOLOGY

Original article

Importance of methotrexate therapy concomitant with tocilizumab treatment in achieving better clinical outcomes for rheumatoid arthritis patients with high disease activity: an observational cohort study

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Abstract

Objective. The purpose of this study was to identify the effects of concomitant use of MTX and baseline characteristics for remission in the treatment of RA with tocilizumab (TCZ) in daily clinical practice.

Methods. A total of 240 RA patients who received TCZ were selected from the multicentre Tsurumai Biologics Communication Registry. Predictive baseline factors for remission [28-item DAS (DAS28) < 2.6] at 52 weeks were determined by logistic regression analysis. To confirm whether the associations varied by the level of baseline disease activity, we also assessed the model including the interaction term (each baseline variable × DAS28).

Results. In total, 49.3% of the study participants used MTX with TCZ. Even after controlling for the baseline DAS28, shorter disease duration (≤3 year) [odds ratio (OR) 3.58 (95% CI 1.81, 7.07)], less structural damage [Steinbroker stage ≤II, OR 2.33 (95% CI 1.32, 4.12)] and concomitant prednisolone use [OR 0.38 (95% CI 0.21, 0.68)] showed significant predictive values for remission. Concomitant MTX use failed to show a significant association with remission, whereas a significant interaction was observed among concomitant MTX use × DAS28 ($P = 0.006$). In patients with high baseline disease activity (DAS28 > 5.1), concomitant MTX use was associated with increased odds for remission [adjusted OR for all baseline variables 2.54 (95% CI 1.11, 5.83)], while no association was indicated between them in patients with low to moderate baseline disease activity (DAS28 ≤ 5.1).

Conclusion. Concomitant MTX use is an important component of TCZ treatment for RA patients with high disease activity.

Key words: rheumatoid arthritis, tocilizumab, methotrexate, biologics.

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Introduction

The current treatment goal of RA is remission [1], and biologics are important tools for achieving good clinical outcomes. A variety of biologics including TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol), IL-6 inhibitors [tocilizumab (TCZ)], T cell activation modulators (abatacept) and anti-CD20 antibody (rituximab) are now available worldwide to treat RA.

MTX is an important anchor drug for RA therapy and the disease-modifying effects of glucocorticoids have been established [2]. The European League Against

Rheumatism (EULAR) recommendations [3] suggest that treatment with biologics should be considered when the response to MTX with or without glucocorticoids is insufficient and prognostically unfavourable factors are present.

A substantial amount of data suggests that the concomitant use of MTX increases the effectiveness of biologic therapy. However, according to the British Society for Rheumatology Biologics Register, approximately one-third of RA patients receive monotherapy without MTX due to MTX-induced gastrointestinal disorders, haematological issues and adverse hepatic events [4–7]. TCZ is a humanized monoclonal antibody against the IL-6 receptor, the effectiveness of which has been confirmed in several clinical trials [8–11] and in practice [12–14]. TCZ is currently the only biologic for which efficacy of monotherapy comparable to that of combination therapy with TCZ 4 mg/kg and MTX has been suggested [15].

The aim of this study was to identify predictive factors at baseline for achieving remission with TCZ treatment in daily clinical practice, focusing particularly on the impact of concomitant use of MTX. As the baseline disease activity was expected to have a strong influence both on the baseline characteristics and the achievement of remission, we estimated the impact of each baseline variable with and without adjustment of baseline disease activity. Furthermore, to confirm whether the associations varied by level of baseline disease activity, we also assessed the interaction between them.

Methods

Patients

All eligible patients were selected from the database of the Tsurumai Biologics Communication Registry (TBCR) Study Group. The TBCR is an RA research consortium that consists of Nagoya University Hospital and 12 affiliated institutes [16]. Briefly, TBCR was initiated in October 2008 to study the long-term efficacy and safety of treatments involving biologic agents in RA patients. Data from 2003 to 2008 were collected retrospectively until 2008 and prospectively after 2008. By the end of September 2011, 2176 RA patients treated with biologics were registered in the TBCR. The present study was approved by the ethics committee of the Nagoya University School of Medicine. We obtained written informed consent from all participants in this study. Patient anonymity was maintained during data collection and the security of personal information was strictly controlled. All selected patients met the 1987 ACR classification criteria for RA and received infusions of TCZ (8 mg/kg) every 4 weeks according to the drug label and Japan College of Rheumatology guidelines (http://www.ryuma-chi-jp.com/info/guideline_tcz_130524.html).

Information on demographic characteristics, disease duration, concomitant treatments [MTX and prednisolone (PSL)], previous use of any biologics, joint damage (Steinbrocker stage) and daily dysfunction (Steinbrocker class) at the start of the treatment were collected as baseline data. The following clinical data were also extracted from the database at baseline and at 52 weeks: tender joint count for 28 joints (TJC), swollen joint count for 28 joints (SJC), patient global assessment of disease activity (PGA), ESR and serum CRP levels. The 28-item DAS (DAS28) was calculated to quantify disease activity at baseline and 52 weeks using a formula that included PGA, TJC and SJC and ESR [17]. Remission was defined as a DAS28 <2.6 [18].

Statistical analysis

Data were analysed using SPSS for Windows version 20.0 (IBM, Armonk, NY, USA). All statistical tests were two-sided and P-values <0.05 were considered significant. Each variable was visually inspected to meet the assumption of normal distribution. Baseline data were compared by the use of concomitant MTX using unpaired t-test for continuous variables and χ^2 test for categorical variables. Mann–Whitney U test was used for variables that did not have a normal distribution.

Next, to elucidate the details of remission observed in this study, changes in variables that constitute the DAS28 were compared by achievement of remission at 52 weeks using the general linear model, adjusting for age and baseline DAS28.
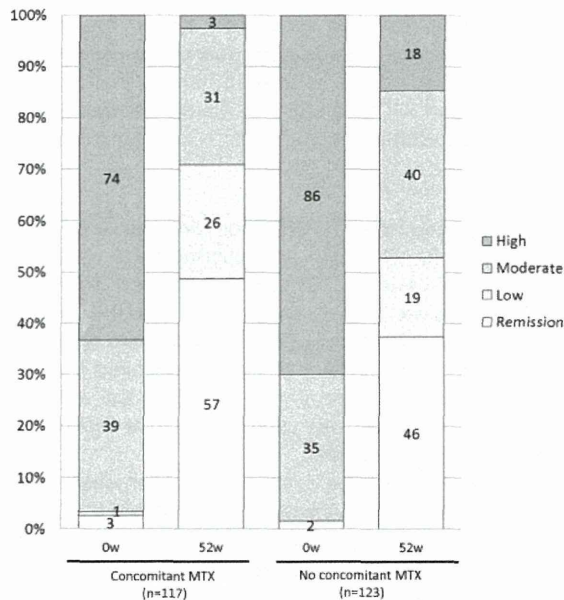
We performed logistic regression analysis in order to determine the predictive values of baseline characteristics for remission. We adopted non-responder imputation to avoid overestimating the results; cases in which TCZ therapy was discontinued before 52 weeks were not excluded, but rather were categorized as no remission. Variables that comprise the DAS28 were not included in the analysis so as to avoid overadjustment. We calculated the odds ratio (OR) and 95% CI with and without adjusting for age and baseline disease activity (DAS28). To confirm whether the impacts of possible predictors of remission vary by the level of baseline disease activity, we also assessed the model when interaction terms (each baseline variable × DAS28) were included. Finally, the multivariable model adjusted for all covariates was assessed according to the dichotomized level of baseline disease activity. In addition, a cross-tabulation was formulated to summarize the real proportion of remission by the predictive factors in patients and the level of baseline disease activity [19].

Results

Among 2176 RA patients who had registered with the TCBR, 268 patients received TCZ. Thirteen patients were excluded from the study because they relocated during therapy and final treatment status could not be determined; an additional 15 patients were excluded due to missing baseline data. Thus the data of 240 patients were analysed. TCZ treatment was discontinued in 34 cases due to adverse events (20 cases), inadequate response (11 cases), pregnancy (2 cases) and economic reasons (1 case); these were categorized as no remission in the analysis.

Of 240 patients, 48.8% ($n = 117$) used concomitant MTX with TCZ. The average dose of MTX was 7.59 mg/week

Fig. 1 Changes in DAS category for disease activity during TCZ treatment for 52 weeks by concomitant MTX ($n = 240$)
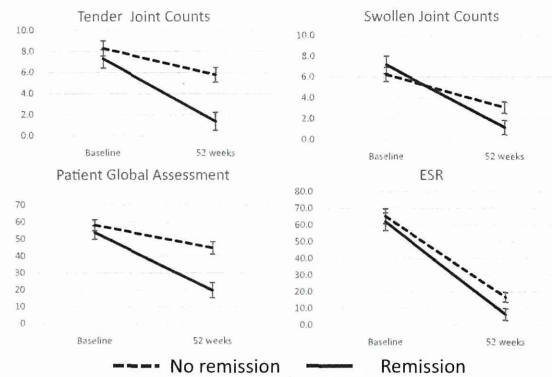

Fig. 2 Changes in DAS28 components during TCZ treatment for 52 weeks according to achievement of remission

The adjusted mean values of DAS28 components for age and baseline DAS28 were estimated with the general linear model. All values decreased significantly from baseline to 52 weeks. Significant interactions by remission status were observed in TJCs, SJCs and patient global assessment (P-value for interaction <0.001); remission subgroups showed larger decreases than non-remission subgroups. DAS28: 28-item DAS; TCZ: tocilizumab; TJC: tender joint count; SJC: swollen joint count.

Remission, DAS28-ESR < 2.6; low (low disease activity), $2.6 \leq$ DAS28-ESR ≤ 3.2; moderate (moderate disease activity), $3.2 <$ DAS28-ESR ≤ 5.1; high (high disease activity), DAS28-ESR > 5.1. The number of patients in each category is shown in the bar. The non-responder imputation method was used for patients who withdrew before 52 weeks. TCZ: tocilizumab; DAS28: 28-item DAS.

(s.d. 2.22, range 2.0–14.0). Overall, the mean DAS28 at baseline was 5.64 and decreased to 2.99 at 52 weeks. A total achievement rate for remission was 40.0% ($n = 96$). Clinical response to TCZ treatment at 52 weeks is shown by the use and non-use of concomitant MTX in Fig. 1. Remission rates at baseline were comparable between MTX users and non-users (2.6% vs 1.6%, $P = 0.68$). At 52 weeks the mean remission rate was marginally higher in the concomitant MTX users than in non-users (48.7% vs 37.4%, $P = 0.08$).

Changes in the DAS28 and variables that constitute the DAS28 (TJC, SJC, PGA and ESR) at baseline and 52 weeks are displayed in Fig. 2 by the achievement of remission at 52 weeks. All values are adjusted for mean age and baseline DAS28. Significant interactions with remission status were observed in TJC, SJC and PGA; the subgroup that achieved remission at 52 weeks showed a larger decrease than the group that showed no remission (P-value for interaction <0.001). ESR decreased significantly regardless of remission status ($P < 0.001$).

Table 1 displays baseline patient characteristics according to the use of concomitant MTX. TCZ was used as a first-line biologic in 32.1% of all the participants, 26.5% of patients with concomitant MTX use and 37.4%

of those without concomitant MTX use. Relative to those without concomitant MTX, patients who had concomitant MTX were more likely to maintain daily function (Steinbrocker class $\leq$II; 67.5% vs 52.0%, $P < 0.02$) and had a lower ESR [mean 57.5 mm/h (s.d. 28.0) vs 58.7 (36.2), $P = 0.003$], DAS28 [5.5 (1.2) vs 5.8 (1.3), $P = 0.03$] and PSL dose (in those prescribed PSL alone) {median 5.0 mg/day [interquartile range (IQR) 2.5–5.0] vs 5.0 (4.0–5.0), $P = 0.003$}.

Table 2 shows the impact of each baseline variable on achieving remission at 52 weeks. Univariate logistic regression analysis indicated that the increase in DAS28 was significantly associated with the decrease in OR for remission (43% decrease per point, $P < 0.001$). Those whose disease duration was $\leq$3 years (lower quartile) and who had minimum to moderate joint damage (Steinbroker stage $\leq$II) and daily dysfunction (Steinbroker class $\leq$II) at baseline were more likely to achieve remission, while previous use of biologics and concomitant PSL use showed an inverse association with remission. After adjusting for age and baseline disease activity, the association between daily dysfunction, previous use of biologics and remission was no longer statistically significant. Concomitant MTX use was not significantly associated with remission in the univariate analysis, but of the variables examined, a significant interaction was observed between concomitant MTX use and DAS28 ($P = 0.006$).

Next we performed a subanalysis dividing subjects by the level of baseline disease activity. Table 3 shows the independent impact of baseline variables while controlling

TABLE 1 Baseline characteristics of patients by concomitant and no concomitant use of MTX with tocilizumab

Variable	Total (*n* = 240)	Concomitant MTX (*n* = 117)	No concomitant MTX (*n* = 123)	*P*-value
Age, mean (s.d.), years	57.9 (13.2)	56.8 (12.4)	59.0 (13.8)	0.19[a]
Male, *n* (%)	46 (19.2)	18 (15.3)	28 (22.8)	0.15[c]
Disease duration, median (IQR), years	8.1 (3.7–14.4)	7.5 (3.5–14.8)	8.7 (3.8–14.2)	0.91[b]
≤3 years, *n* (%)	51 (21.3)	24 (20.5)	27 (22.0)	0.79[c]
Steinbrocker stage (I/II/III/IV), *n*	35/53/60/85	14/28/34/40	21/25/26/45	0.40[c]
Stage I + II, *n* (%)	88 (36.7)	42 (35.9)	46 (37.4)	0.81[c]
Steinbrocker class (I/II/III/IV), *n*	30/113/86/5	19/60/34/3	11/53/52/2	0.09[c]
Class I + II, *n* (%)	143 (59.6)	79 (67.5)	64 (52.0)	0.02[c]
Previous biologics, *n* (%)	163 (67.9)	86 (73.5)	77 (62.6)	0.07[c]
Concomitant PSL, *n* (%)	162 (67.5)	86 (73.5)	76 (61.8)	0.05[c]
PSL dose, median (IQR), mg/day	5.0 (3.0–5.0)	5.0 (2.5–5.0)	5.0 (4.0–5.0)	0.007[b]
DAS28, median (IQR)	5.6 (1.3)	5.5 (1.2)	5.8 (1.3)	0.03[a]
≤5.1, *n* (%)	79 (32.9)	42 (35.9)	37 (30.1)	0.54[c]
Tender joint count (per 28 joints), mean (s.d.)	7.9 (6.6)	7.1 (5.4)	8.7 (7.5)	0.07[a]
Swollen joint count (per 28 joints), mean (s.d.)	6.6 (5.1)	6.2 (4.4)	7.0 (5.6)	0.24[b]
Patient's global assessment VAS, mean (s.d.), mm	56.4 (24.4)	54.0 (23.2)	58.7 (25.3)	0.14[a]
ESR (per first hour), mean (s.d.)	63.9 (33.0)	57.5 (28.0)	70.0 (36.2)	0.003[a]
CRP, median (IQR), mg/dl	2.7 (1.1–4.7)	2.4 (1.0–4.5)	3.0 (1.1–5.1)	0.27[b]

IQR: interquartile range; PSL; prednisolone; DAS28: 28-item DAS; VAS; visual analogue scale. Continuous variables with a normal distribution are presented as mean (s.d.) and those that do not fit a normal distribution are presented as median (IQR). *P*-values were determined with the [a]unpaired *t*-test for variables with a normal distribution, [b]Mann–Whitney *U* test for variables without a normal distribution and [c]χ^2 test for categorical variables.

TABLE 2 Impacts of baseline variables on remission at 52 weeks and interaction with disease activity

Variable	Univariate analysis, OR (95% CI)	Adjusted for baseline disease activity, OR (95% CI)	*P*-value for the interaction with baseline disease activity
Age/1 year	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)	0.36
Male	1.66 (0.87, 3.17)	1.94 (0.96, 3.90)	0.28
Disease duration ≤3 years	2.96 (1.56, 5.59)*	3.58 (1.81, 7.07)*	0.17
Steinbrocker stage I + II	2.41 (1.40, 4.13)*	2.33 (1.32, 4.12)*	0.65
Steinbrocker class I + II	1.91 (1.11, 3.29)*	1.50 (0.85, 2.66)	0.05
Previous biologics	0.52 (0.30, 0.91)*	0.57 (0.32, 1.01)	0.59
Concomitant PSL	0.34 (0.19, 0.59)*	0.38 (0.21, 0.68)*	0.32
Concomitant MTX	1.44 (0.86, 2.41)	1.25 (0.72, 2.16)	0.006
DAS28/1 point	0.57 (0.45, 0.73)*	NA	

Adjusted OR was calculated by including continuous values of the DAS28 in the logistic regression model. The *P*-value for the interaction between each baseline variable and disease activity on remission was estimated by entering the interaction term (baseline variable × DAS28) in the logistic model. *$P < 0.05$. OR: odds ratio; PSL; prednisolone; DAS28: 28-item DAS.

for all other variables among patients with high baseline disease activity and those with low to moderate disease activity. Among subgroups with high baseline disease activity (DAS28 > 5.1), concomitant MTX use was associated with a significantly higher OR for remission, while concomitant use of PSL was inversely associated with remission even after controlling for all possible confounders. We found no significant predictor variables for the low to moderate disease activity group.

The cross-tabulation demonstrating the numbers and proportions of patients who achieved remission at 52 weeks according to dichotomized levels of baseline disease activity, Steinbrocker stage and concomitant use of MTX and PSL are shown in Fig. 3. Overall, the remission rates of those who took concomitant PSL were relatively low. This was particularly true for patients with high baseline disease activity (DAS28 > 5.1) and concomitant PSL use without MTX; for these patients, remission rates were