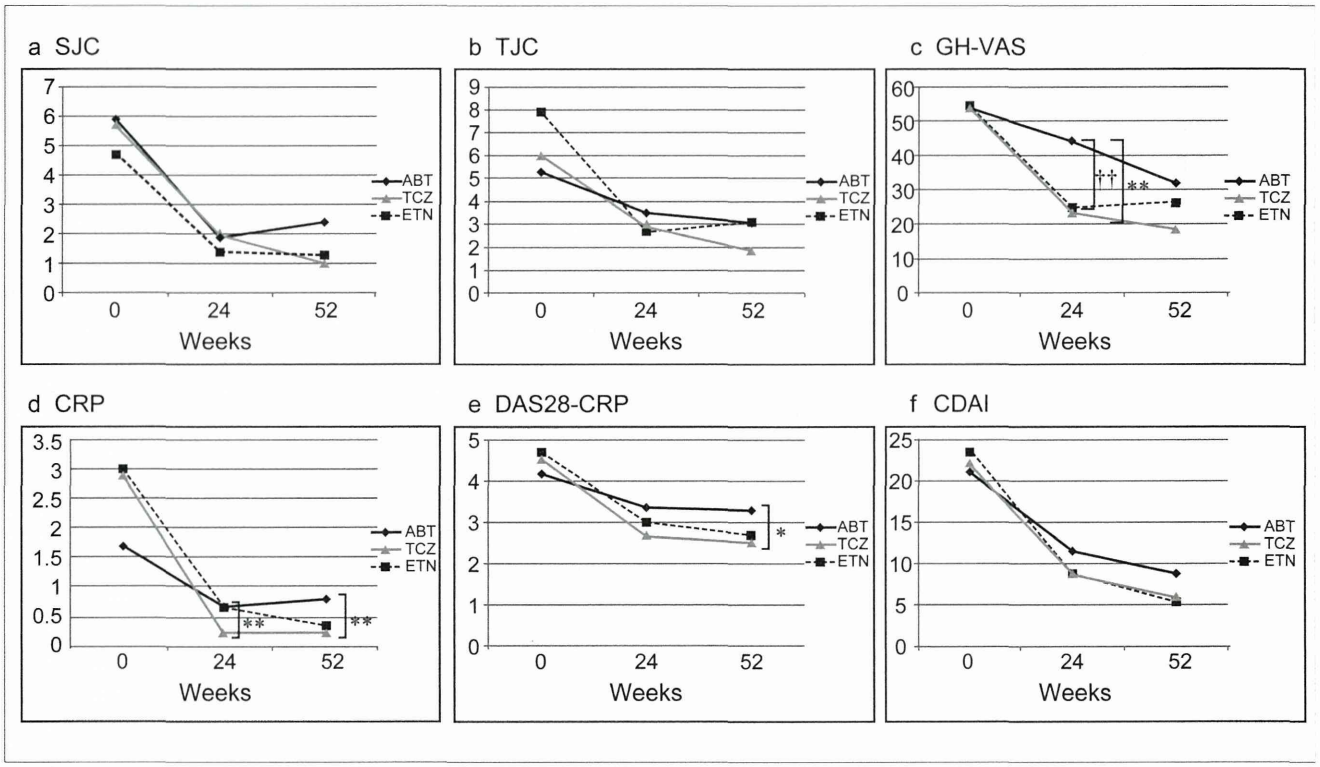

Fig. 2 Overall clinical efficacy of switching biologics in patients with rheumatoid arthritis. Mean values for **a** swollen joint count (*SJC*), **b** tender joint count (*TJC*), **c** general health on a visual analog scale (*GH-VAS*), **d** C-reactive protein (CRP), **e** 28-joint disease activity 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 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

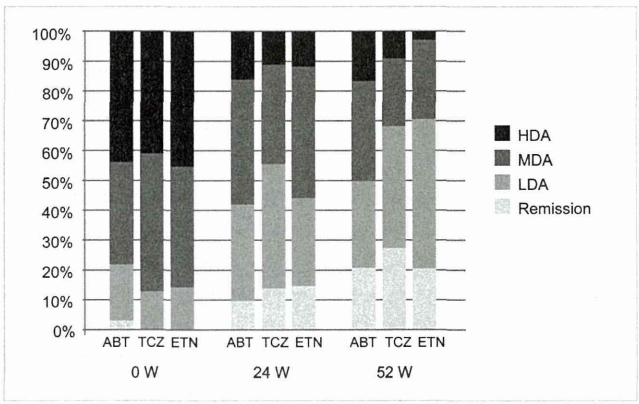

Fig. 3 Clinical disease activity index (CDAI) with second-course biologics (0, 24, and 52 weeks). *ABT* abatacept, *TCZ* tocilizumab, *ETN* etanercept, *HDA* high disease activity (CDAI>22), *MDA* moderate disease activity (10<CDAI≤22), *LDA* low disease activity (CDAI≤10). Remission (CDAI≤2.8)

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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Conflict of interest N. Ishiguro, Y. Yabe, T. Kojima, A. Kaneko, Y. Hirano and N. Takahashi have received speaking fees (<US$5,000) from AbbVie Inc., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Pfizer Co. Ltd., Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd. The other authors declare no conflicts of interest.

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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 $\times$ DAS28).

Results. In total, 49.3% of the study participants used MTX with TCZ. Even after controlling for the baseline DAS28, shorter disease duration ($\leq$3 year) [odds ratio (OR) 3.58 (95% CI 1.81, 7.07)], less structural damage [Steinbroker stage $\leq$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 $\times$ 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.ryumachi-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.

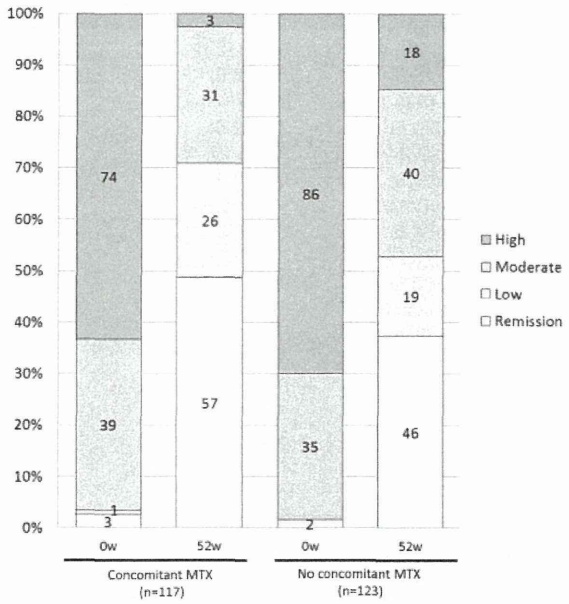
We performed logistic regression analysis in order to determine the predictive values of baseline characteristics for remission. We adopted non-responder imputation to avoid overestimating the results; cases in which TCZ therapy was discontinued before 52 weeks were not excluded, but rather were categorized 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.

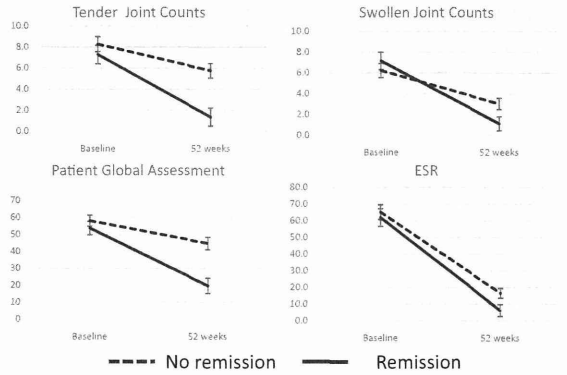
Of 240 patients, 48.8% ($n = 117$) used concomitant MTX with TCZ. The average dose of MTX was 7.59 mg/week

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



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.

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.

(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.

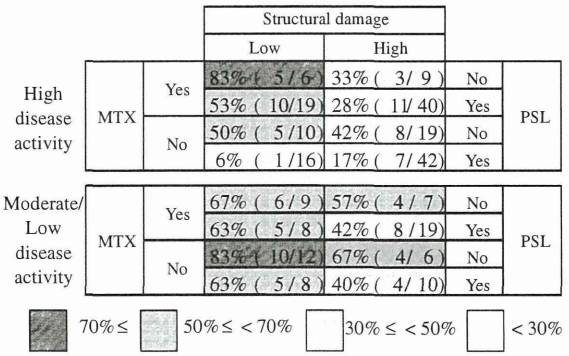
The cross-tabulation demonstrating the numbers and proportions of patients who achieved remission at 52 weeks according to dichotomized levels of baseline disease activity, Steinbrocker stage and concomitant use of MTX and PSL are shown in Fig. 3. Overall, the remission rates of those who took concomitant 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

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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