Fukushima J. Med. Sci.,
Vol. 69, No. 1, 2023

[Original article]

Feasibility of methotrexate discontinuation following tocilizumab and methotrexate combination therapy in patients with long-standing and advanced rheumatoid arthritis : a 3-year observational cohort study

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(Received January 27, 2022, accepted January 30, 2023)

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Abstract

Objectives : Methotrexate (MTX) is associated with extensive side effects, including myelosuppression, interstitial pneumonia, and infection. It is, therefore, critical to establish whether its administration is required after achieving remission with tocilizumab (TCZ) and MTX combination therapy in patients with rheumatoid arthritis (RA). Therefore, the aim of this multicenter, observational, cohort study was to evaluate the feasibility of MTX discontinuation for the safety of these patients.

Methods : Patients with RA were administered TCZ, with or without MTX, for 3 years ; those who received TCZ+MTX combination therapy were selected. After remission was achieved, MTX was discontinued without flare development in one group (discontinued [DISC] group, $n = 33$) and continued without flare development in another group (maintain [MAIN] group, $n = 37$). The clinical efficacy of TCZ+MTX therapy, patient background characteristics, and adverse events were compared between groups.

Results : The disease activity score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) at 3, 6, and 9 months was significantly lower in the DISC group ($P < .05$, $P < .01$, and $P < .01$, respectively). Further, the DAS28-ESR remission rate at 6 and 9 months and Boolean remission rate at 6 months were significantly higher in the DISC group ($P < .01$ for all). Disease duration was significantly longer in the DISC group ($P < .05$). Furthermore, the number of patients with stage 4 RA was significantly higher in the DISC group ($P < .01$).

Conclusions : Once remission was achieved, MTX was discontinued in patients who responded favorably to TCZ+MTX therapy, despite the prolonged disease duration and stage progression.

Key words : methotrexate, tocilizumab, discontinuation, rheumatoid arthritis, long-standing

Abbreviations : ACR, American College of Rheumatology ; b-DMARD, biological disease-modifying anti-rheumatic drug ; CRP, C-reactive protein ; cs-DMARD, conventional synthetic disease-modifying anti-rheumatic drug ; DAS28-ESR, disease activity score in 28 joints-erythrocyte sedimentation rate ; DISC, discontinued ; EULAR, European League Against Rheumatism ; IR, inadequate response ; MAIN, maintain ; MTX, methotrexate ; PGA-VAS, patient global assessment-visual analog scale ; RA, rheumatoid arthritis ; SJC, swollen joint count ; TCZ, tocilizumab ; TJC, tender joint count.

Introduction

The European League Against Rheumatism (EULAR) recommends that in patients with rheumatoid arthritis (RA), methotrexate (MTX) should be prescribed first if there are no contraindications because the drug is effective alone and may be more effective when used in combination with other conventional synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs) or biological DMARDs (b-DMARDs).[1,2] Combination therapies comprising b-DMARDs - especially tumor necrosis factor inhibitors - and MTX have been shown to be more efficacious than b-DMARD monotherapies.[3,4] Indeed, the more b-DMARDs are extensively used, the more MTX is recognized as a useful therapy. However, MTX has several serious side effects such as myelosuppression, interstitial pneumonia, and infection ; hence, caution must be exercised when using it, particularly with highly efficacious b-DMARDs.

Monotherapy with the b-DMARD tocilizumab (TCZ), a humanized monoclonal antibody against the interleukin (IL)-6 receptor that functions by inhibiting interaction between IL-6 and the IL-6 receptor, reportedly affords more evident repair of existing bone erosions than combination therapy with MTX and the most commonly used b-DMARD, adalimumab.[5] Furthermore, the effectiveness of TCZ monotherapy was reported as comparable to that of TCZ and DMARD combination therapy, although the observation period was as short as 24 weeks.[6] Meanwhile, consensus is lacking on whether TCZ used in combination with MTX is useful, although the utility of TCZ used in combination with MTX, and as a monotherapy, has been documented.[7]

Recently, two milestone studies compared the efficacy of TCZ+MTX combination therapy and TCZ monotherapy. The first study was the ACT-RAY study, which compared TCZ+MTX combination

therapy and TCZ monotherapy in patients with RA with an inadequate response (IR) to MTX. Clinical and radiographic findings suggested that both treatments are effective and comparable, indicating that combination therapy does not afford a significant improvement.[8] In the second study, termed the SURPRISE study, TCZ+MTX combination therapy was compared with TCZ monotherapy switched from MTX in patients with RA with an IR to MTX. The combination therapy suppressed inflammation more rapidly than TCZ monotherapy, indicating the superior efficacy of the combination therapy based on both clinical and radiographic findings.[9]

However, there are some notable fundamental differences between these studies. For example, the disease duration in the SURPRISE study was 3.6 to 3.8 years, which was shorter than that in the ACT-RAY study (8.2 to 8.3 years). Moreover, conventional DMARDs were administered to patients with a disease activity score in 28 joints (DAS28) of > 3.2 at week 24 in the ACT-RAY study, which complicated the comparison between TCZ monotherapy and TCZ+MTX combination therapy.

Nevertheless, both studies reported that a combination including MTX increases the incidence of adverse events, such as gastrointestinal, respiratory, thoracic, and mediastinal disorders as well as laboratory test abnormalities. In both studies, the goal was to determine the necessity of using MTX in combination with TCZ to achieve remission in patients with RA. Although achieving clinical remission is the target of RA treatment,[10] prolonged treatment with MTX necessitates close monitoring for possible complications, such as infectious diseases, lung disorders, bone marrow suppression, renal disorders, liver disorders,[11] and lymphoproliferative diseases. Hence, the aim of the present study was to evaluate the feasibility of MTX discontinuation after achieving RA remission for the safety of patients treated with TCZ+MTX combination therapy.

Methods

Study protocol and patients

For this multicenter, observational, cohort study, data were collected by the Michinoku Tocilizumab Study Group (MTSG ; Michinoku is the ancient name of today's Tohoku region in Northeastern Japan). Forty-five physicians from 37 facilities participated in this study. The group was originally formed to investigate effects of long-term administration of TCZ with or without MTX on clinical and structural remission rates in patients with RA.[12] In this study, patients with RA diagnosed according to the American College of Rheumatology (ACR) 1987 revised RA classification criteria and newly treated with TCZ between April 1, 2008, and December 31, 2010, were enrolled. Patients were selected according to the guidelines of the Japan College of Rheumatology. In brief, patients with RA not controlled with traditional DMARDs therapy for 3 months, patients with progressive bone erosion, or patients with moderate activity were selected.[13]

Each patient's comorbidities were treated or controlled in advance to avoid adverse events following TCZ treatment. For example, if interferon-gamma release assays were positive, an antituberculosis drug was prophylactically administered. If a patient had otitis media or periodontitis, treatment from an otolaryngologist or dentist was provided. The patients were then intravenously administered TCZ (8 mg/kg) every 4 weeks for 3 years (36 months). Assuming that there are 700,000 patients with RA in Japan, the number of patients needed for statistical analysis was calculated based on a confidence interval of 95%, accuracy of 5%, and population ratio of 0.5, which resulted in a sample size of 389 patients. We followed up a total of 693 patients who started TCZ therapy to evaluate the effect of TCZ on clinical and structural remission rates ; of these, 544 patients completed the 3-year observation period.[12] The percentage of patients who completed the 3-year follow-up was 78.50%, which is almost the same as that in a post-marketing surveillance study (81.23%) conducted in Japan by Yamamoto *et al.*[14] Of the 544 patients, 307 who achieved remission (a disease activity score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) <2.6) were evaluated. Patient disposition and the study flowchart are shown in Fig. 1. Based on the attending physician's discretion, patients were started on TCZ alone or TCZ+MTX combination therapy. One hundred and eighty-seven patients were treated with TCZ+MTX, and 120 received TCZ alone. Using the original data gathered by the MTSG, we examined whether MTX is necessary for maintaining remission in the TCZ+MTX group. Patient disposition and the study flowchart are shown in Fig. 1. Thirty-seven patients were excluded from the TCZ+MTX group because data on their MTX doses were unclear. Thus, 150 patients were ultimately included in the TCZ+MTX group. For patients treated with TCZ+MTX, MTX was discontinued, decreased, maintained, or increased at the attending physician's discretion.

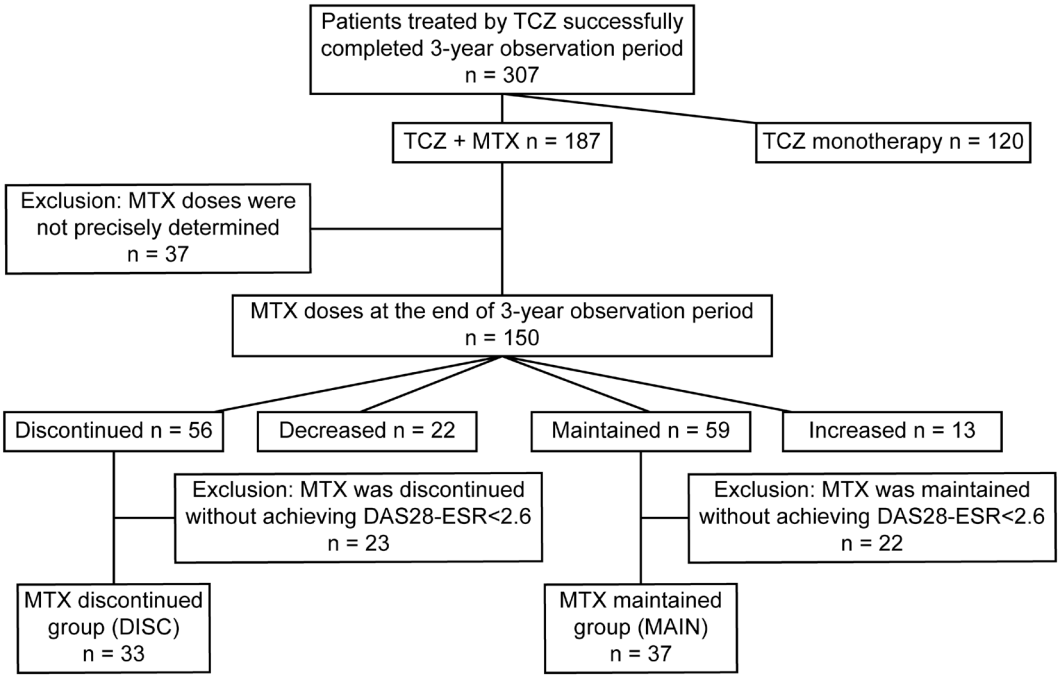

Fig. 1. Patient selection and study flow chart
TCZ, tocilizumab ; MTX, methotrexate ; DAS28-ESR, DAS28 score calculated using ESR

MTX doses and disease activity were monitored every 3 months for a 3-year observation period.

Of 56 patients in whom MTX was discontinued, 23 were excluded because MTX was discontinued before DAS28-ESR < 2.6 was achieved.[15,16] The remaining 33 patients in the MTX-discontinued (DISC) group were evaluated. Of the 59 patients in whom MTX was maintained, 22 were excluded for similar reasons as stated above. The remaining 37 patients in the MTX-maintained (MAIN) group were evaluated. These DISC and MAIN groups were compared.

The study protocol was reviewed and approved by the ethics committee of Tohoku University and each participating medical institution. The study was conducted according to the principles of the Declaration of Helsinki and was prospectively registered with the University Hospital Information Network Clinical Trials Registry (#UMIN000011584). Informed consent for study participation was documented in writing for all patients.

Assessment of patient baseline characteristics, disease activity data, and adverse events

For each patient, the following data were collected : patient global assessment-visual analog scale (PGA-VAS) score, tender joint count (TJC), swollen joint count (SJC), ESR, C-reactive protein (CRP) level, and remission rates based on the DAS28-ESR remission criteria (DAS28-ESR < 2.6)[15,16] as well as the 2011 ACR/EULAR Boolean-based remission criteria (i.e., TJC ≤ 1, SJC ≤ 1, PGA-VAS ≤ 1 cm, and CRP ≤ 1 mg/dL).[17,18] Patient background characteristics and adverse events from the MTSG data sheets were analyzed.

Annotation

To estimate the efficacy of drugs for the treatment of RA, this study applied DAS28-ESR and Boolean-based remission criteria to the overall disease activity data, but did not evaluate quality of life. This is a very important perspective to be considered as a key issue in the future.

Statistical analysis

We analyzed differences in baseline characteristics between the groups using the *t*-test, Mann-Whitney U-test, and Fisher's exact test, as appropriate (Table 1). Differences in DAS28-ESR scores between the DISC and MAIN groups were analyzed using Welch's *t*-test (Fig. 2). Differences in remission rates based on the DAS28 score[15,16] and the Boolean definition[17,18] between the DISC and MAIN groups were analyzed using Fisher's exact test (Figs. 3 and 4). Differences in adverse events between the groups were analyzed using the Chi-squared test (Table 2). All statistical analyses were performed using IBM SPSS Statistics ver. 27 (Samuraiz Corporation, Tokyo, Japan). Significance was set at $P < .05$.

Table 1. Baseline characteristics

	DISC group	MAIN group	*p*-value
Number of patients	33	37	
Age, mean ± SD	61.4 ± 9.3	56.5 ± 12.6	>.05*
Women, n (%)	26 (78.8)	(86.5)	>.05**
Weight (kg), mean ± SD	51.6 ± 9.5	54.3 ± 11.1	>.05*
Duration of RA (years), mean ± SD	11.8 ± 10.8	6.4 ± 5.5	<.05***
Categories for RA duration years, n (%)			
< 2	5 (15)	7 (19)	
≤ 2 to < 10	14 (42)	20 (54)	
≥ 10	14 (42)	10 (27)	
Stage 1/2/3/4, n (%)	2 (6)/8(24)/5(15)/18(55)	6(16)/10(27)/14(38)/7(19)	<.01**
Class I/II/III/IV, n (%)	6(18)/26(79)/1(3)/0(0)	9(24)/24(65)/3(8)/1(3)	>.05**
CRP (mg/dL), mean ± SD	2.41 ± 3.1	2.26 ± 2.6	>.05*
TJC, mean ± SD	6.1 ± 7.3	4.3 ± 4.1	>.05*
SJC, mean ± SD	5.4 ± 5.4	4.3 ± 4.4	>.05*
VAS (mm), mean ± SD	51.1 ± 21.9	55.7 ± 27.6	>.05*
DAS-ESR, mean ± SD	5 ± 1.4	4.7 ± 1.4	>.05*
Patients treated with b-DMARDs, n (%)	10 (30.3)	20 (54.1)	.056**
Number of b-DMARDs ≥ 2, n (%)	2 (6.1)	8 (21.6)	.09**
Initial MTX dose (mg/w), mean ± SD	6.4 ± 1.4	7.2 ± 1.8	<.05***
Oral steroid use, n (%)	21 (63.6)	19 (51.5)	>.05**

DISC : MTX discontinued group, MAIN : MTX maintained group, TJC : tender joint count, SJC : swollen joint count, VAS : visual analog scale, DAS28-ESR : disease activity score based on 28 joints-erythrocyte sedimentation rate, b-DMARDs : biological disease modifying anti-rheumatic drugs
* : t-test
** : Fisher's exact test Stage 4 was compared with Stages 1-3, Class I-II was compared with Class III-IV
*** : Mann-Whitney U test

Results

In the DISC group, the time point at which MTX was discontinued varied among the patients. In 58% and 79% of the patients, MTX was discontinued by 3 and 12 months, respectively, after treatment initiation. All patients in the DISC group discontinued MTX within 2 years (data not shown). Table 1 summarizes results of the comparison of characteristics between the DISC and MAIN groups. RA durations in the DISC were significantly longer than those in the MAIN group ($P < .05$). The proportion of patients in stage 4 was significantly higher in the DISC group than in the MAIN group ($P < .01$). The initial MTX dose was less in the DISC group than in the MAIN group ($P < .05$).

At month 0, DAS28-ESR scores in the DISC and MAIN groups were 5.0 ± 1.4 and 4.7 ± 1.4, respectively (Fig. 2). The DAS28-ESR scores decreased gradually over 12 months in both the DISC and MAIN groups. However, DAS28-ESR scores were significantly lower in the DISC group at 3 ($P < .05$), 6 ($P < .01$), and 9 months ($P < .01$) compared to the MAIN group.

Fig. 3 shows the DAS28-ESR remission rates in both groups. The remission rates gradually increased in DISC group. Remission rates were significantly higher in the DISC group at 6 ($P < .01$) and 9 months ($P < .01$). Moreover, remission rates were significantly higher in the DISC group than in the MAIN group at 18, 21, 24, and 30 months ($P < .05$).

As shown in Fig. 4, the Boolean remission rates were significantly higher in the DISC group at 6 ($P < .01$) and 33 months ($P < .05$) compared to the MAIN group.

Table 2 shows adverse events in the two groups classified according to the classification system of the Medical Dictionary for Regular Activities (version 17.1). The main adverse events in the groups were as follows. There were 20 infection and infestation events in 10 of the 33 patients (30.3%) in the DISC group and nine such events in three of the 37 patients (8.1%) in the MAIN group (for the number of patients, $P < .002$; for the number of events,

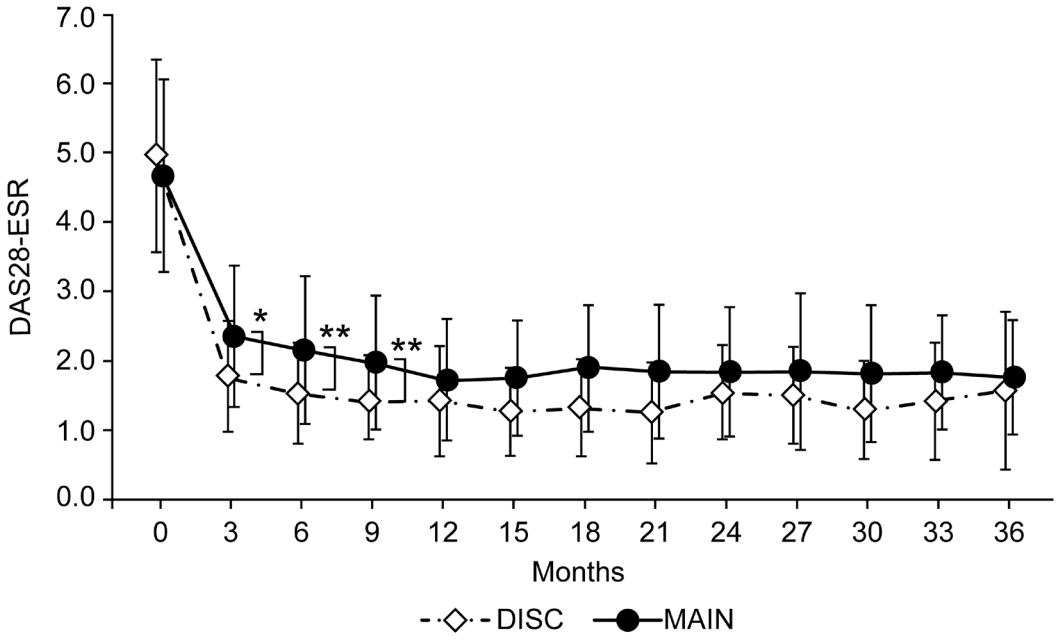

Fig. 2. Changes in DAS28–ESR in the DISC and MAIN groups
Mean values are shown.
Bars indicate SD.
Changes in the DAS28–ESR scores in the DISC and MAIN groups were assessed every 3 months up to 36 months. DAS28–ESR scores were significantly lower in the DISC group at 3 ($P < .05$), 6 ($P < .01$), and 9 months ($P < .01$) and consistently lower than the scores in the MAIN group.
** $P < .01$; * $P < .05$

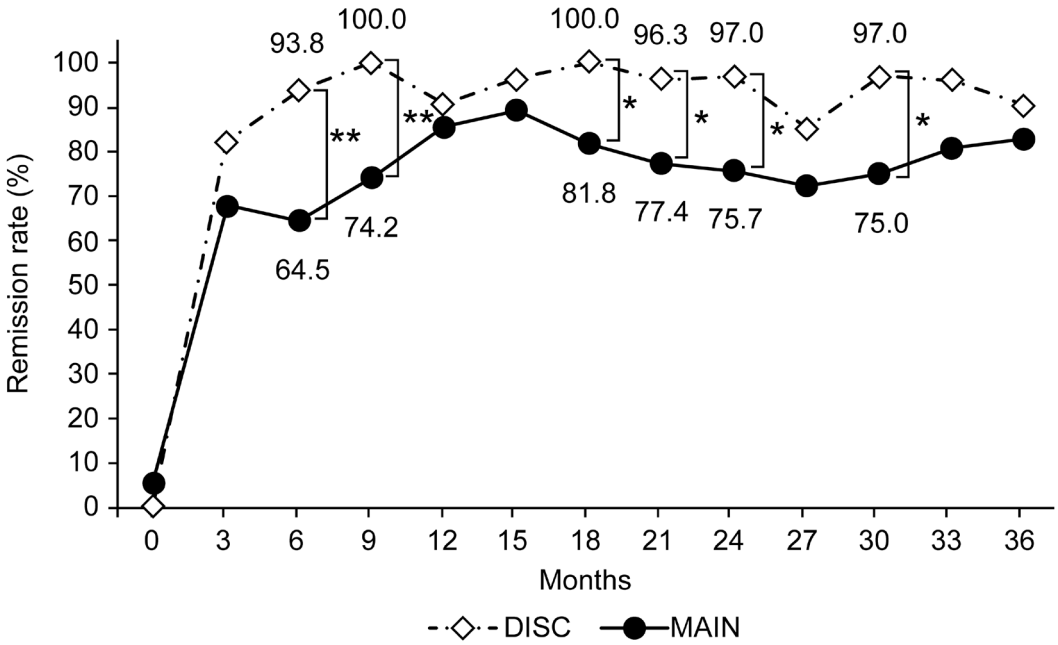

Fig. 3. Changes in DAS28–ESR remission rates in the DISC and MAIN groups
Changes in DAS28–ESR remission rates in the DISC and MAIN groups were assessed every 3 months up to 36 months. DAS28–ESR remission rates were significantly higher in the DISC group at 6 ($P < .01$) and 9 months ($P < .01$). DAS28–ESR remission rates were significantly higher in the DISC group than in the MAIN group at 18, 21, 24, and 30 months ($P < .05$).
** $P < .01$; * $P < .05$

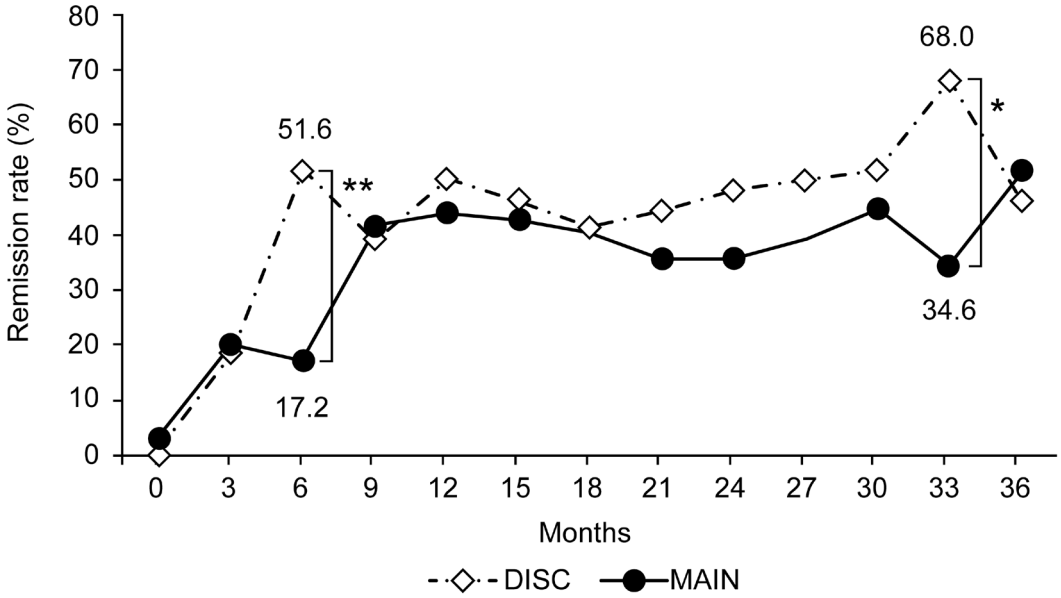

Fig. 4. Changes in Boolean remission rates in the DISC and MAIN groups
Changes in Boolean remission rates in the DISC and MAIN groups were assessed every 3 months to 36 months. The Boolean remission rates were significantly higher in the DISC group at 6 ($P < .01$) and 33 months ($P < .05$).
$^{**}P < .01$; $^{*}P < .05$

Table 2. Adverse events according to SOC

MedDRA17.1 System Organ Class (SOC)	DISC group (n = 33)			MAIN group (n = 37)		
	Number of patients	Events rate (%)	Events number	Number of patients	Events rate (%)	Events number
Gastrointestinal disorders	2	6.1	2	0	0	0
General disorders and administration site conditions	1	3	1	1	5.4	6
Infections and infestations	10 $P < .002$	30.3	20 $P < .001$	3	8.1	9
Hepatobiliary disorders	2	6.1	3	2	5.4	2
Musculoskeletal and connective tissue disorders	2	6.1	2	1	2.7	1
Blood and lymphatic system disorders	1	3	2	0	0	0
Ear and labyrinth disorders	1	3	1	0	0	0
Injury, poisoning, and procedural complications	2	6.1	2	0	0	0
Nervous system disorders	1	3	1	0	0	0
Renal and urinary disorders	0	0	0	1	2.7	1
Metabolism and nutrition disorders	1	3	1	0	0	0
Endocrine disorders	1	3	1	0	0	0
Skin and subcutaneous disorders	0	0	0	2	5.4	2
Immune system disorders	1	3	1	0	0	0
Neoplasm benign, malignant and unspecified (including cysts and polyps)	1	3	1	0	0	0
Investigations	3	9.1	3	4 n.s.	54.1	20 $P < .01$

Chi-square test was used to compare the DISC and MAIN groups.

$P < .01$). There were three instances of laboratory test abnormalities (Investigation) in three of the 33 patients (9.1%) in the DISC group and 20 events in four of the 37 patients (10.8%) in the MAIN group (for the number of patients, no significance ; for the number of events, $P < .01$).

Discussion

In this study, we investigated whether MTX could be safely and effectively discontinued after achieving RA remission for the safety of patients treated with TCZ+MTX. MTX could be successfully discontinued in the DISC group ; conversely, MTX was continuously administered in the MAIN group. The comparison of the clinical findings and background characteristics of the patients in the DISC and MAIN groups revealed factors related to MTX discontinuation. The DISC group responded promptly to TCZ+MTX. In the DISC group, MTX was discontinued in 58% and 79% of the patients by 3 and 12 months, respectively ; this was consistent with a decrease in disease activity (data not shown). The good therapeutic response in this group could be attributed to most attending physicians discontinuing MTX therapy for these patients. Further, fewer b-DMARDs and lower MTX doses were used in the DISC group than in the MAIN group. Biologic-naive patients have been reported to show superior responses to b-DMARDs.[19] Moreover, the use of significantly lower MTX doses may have favored MTX discontinuation in the DISC group. As stated in the Results, the disease duration was longer and more patients had stage 4 disease in the DISC group than in the MAIN group.

We hypothesized that longer disease duration and advanced disease stage in the DISC group favored MTX discontinuation. That is, shorter disease duration and an early disease stage might have made MTX discontinuation difficult. Despite its subcutaneous administration, MTX has been reported to be significantly more effective in younger patients with RA, presenting a shorter disease duration.[20] Given that the efficacy of MTX varies with the duration of RA, it can be presumed that the importance of MTX used in combination with TCZ also varies with disease duration. This may be related to the difference in the conclusions of the ACT-RAY study[8] and the SURPRISE study,[9] although this is somewhat speculative. The two studies described the differences in the therapeutic effects of MTX discontinuation and switching to TCZ monotherapy and starting TCZ and combining it with MTX in the induction of remission. The major difference between the studies in terms of patient background was the disease duration, which was 8.2-8.3 and 3.6-3.8 years in the ACT-RAY and SURPRISE studies, respectively. In the ACT-RAY study, TCZ+MTX had an effect comparable to stopping MTX and switching to TCZ monotherapy. On the contrary, in the SURPRISE study, TCZ+MTX had a superior effect compared to stopping MTX and switching to TCZ monotherapy. The difference in disease duration may be related to the difference in MTX efficacy results between the studies.

It remains challenging to avoid MTX side effects and elicit its efficacy in elderly patients with RA, because those with long-standing RA and advanced disease show more comorbidities, with possibly more complications during therapy. In this study, attending physicians discontinued MTX in patients with a favorable response to the combination therapy. Additionally, they might have been concerned about patient conditions and comorbidities, such as pulmonary fibrosis, chronic renal failure, and chronic liver damage,[11] especially in those with a long disease duration and advanced disease.

TCZ and MTX combination therapy was effective in patients with long-standing RA as well as advanced disease, and MTX could be discontinued in cases in which the treatment was highly effective. The mean age of the patients in the DISC group was 61.4 years ; however, the patients had long-standing and advanced disease. Therefore, there were many common points between this group and elderly patients with RA. This finding will provide some avenues for treating elderly RA patients, especially as the prevalence of elderly RA has increased in recent years.

There are some limitations of the present study. First, the sample size was small. Furthermore, this was an observational, non-intentional, not randomized, prospective study. Originally, this study was planned as a multicenter cohort study to verify the efficacy of TCZ treatment for 3 years. In the actual clinical setting, the physicians in charge judged their patients' conditions and selected TCZ+MTX combination therapy to achieve low disease activity or remission. During treatment, MTX was discontinued or continued considering not only the disease activity but also factors such as patient comorbidities ; age ; disease duration, stage, and class ; and treatment history. For this study, we extracted only patients in remission. As a result, the number of patients in both the DISC and MAIN groups decreased. Second, decisions to discontinue or continue MTX were made by attending physicians. In the absence of specific decision criteria, there may be concerns that this may be a hindrance when analyzing the results. However, the physicians in this study were all aware of the following : TCZ is sufficiently effective as monothera-

py ; in addition, MTX is particularly prone to side effects in older, long-standing patients with advanced RA. Based on these common recognitions, they are presumed to discontinue MTX if possible after achieving remission.

To increase clinical applicability in the future, it is necessary to confirm the effectiveness of TCZ+MTX combination therapy in elderly patients with RA, randomly assign patients who have achieved remission to MTX continuation or discontinuation groups, and perform follow-up to evaluate the clinical course to compare efficacy and complications between groups.

Further studies are needed to confirm the findings of this study in elderly patients with RA. Hence, the following treatment strategy is proposed. Elderly patients with RA should be treated with TCZ+MTX combination therapy. After remission has been achieved in cases with high treatment effectiveness, MTX can be discontinued without flares or exacerbation of comorbidities and with minimal MTX side effects.

Funding :

Research and training expenses came from the Fukushima Red Cross Hospital

Conflicts of interest :

The authors of this work have nothing to disclose.

Ethics approval :

The study protocol was reviewed and approved by the ethics committees of Tohoku University and each participating medical institution.

Consent to participate :

Informed consent was documented in writing for all patients who participated in the study.

Availability of data and material :

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

The authors would like to thank other members of the Michinoku Tocilizumab Study Group who supported this project : Dr. Naohiko Gunji, Dr. Hideo Harigae, Dr. Satoshi Hoshi, Dr. Ryo Ichinohasama, Dr. Yoh Ishiguro, Dr. Eiji Itoi, Dr. Nobuki Maki, Dr. Takatomo Moro, Dr. Hiromasa Ohira, Dr. Naohisa Ouchi, Dr. Yuta Oyama, Dr. Akira Rikimaru, Dr. Souichi Saito, Dr. Akiko Sasaki, Dr. Takeshi Sasaki, Dr. Akira Sekiguchi, Dr. Tadashi Shimamura, Dr. Mikio Suzuki, Dr. Yuji Wakai, and Dr. Seiji Yamaya. The authors would also like to thank the Clinical Research Innovation and Education Center at Tohoku University Hospital for data analysis. Furthermore, the authors would like to express our gratitude to Ms. Miwa Saito, Mr. Yuhei Nikaido, and Mr. Kenji Nozaki for their help in preparing this manuscript. The authors are grateful to the Ichinohasama READ Memorial Blood Academy, Spellman Hospital, and Fukushima Red Cross Hospital for their cooperation in this project. Data collection was partially supported by the Chugai Pharmaceutical Company. Finally, the authors would like to thank Editage (www.editage.com) for English language editing.

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