

Is Methotrexate (MTX) Necessary in Combination Therapy with Tocilizumab and MTX for Rheumatoid Arthritis in Remission? Cohort Study Carried by the Michinoku Tocilizumab Study Group

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Abstract

Objectives: To determine the necessity of methotrexate (MTX) in patients with rheumatoid arthritis (RA) achieving clinical remission treated by tocilizumab (TCZ) and MTX (TCZ+MTX).

Methods: A 3 year, multicenter, observational cohort study was performed. RA patients were treated by TCZ with or without MTX depending on the attending doctor's decision. Of the patients treated with TCZ+MTX, the patients who discontinued MTX after achieving clinical remission (discontinued group: DISC) were compared with those who maintained the same dose of MTX after achieving clinical remission (maintained group: MAIN).

Results: The DISC and MAIN consisted of 33 patients and 37 patients, respectively. The mean DAS28-ESR was significantly lower in the DISC than in the MAIN at 3 months, 6 months and 9 months (3 months: 1.8 ± 0.8 and 2.4 ± 1.0 , $p=0.018$, 6 months: 1.5 ± 0.7 and 2.2 ± 1.0 , $p=0.009$ and 9 months: 1.4 ± 0.6 and 2.0 ± 1.0 , $p=0.008$, respectively).

The DAS28-ESR remission rate and Boolean remission rate were significantly higher in the DISC than in the MAIN (93.8% and 64.5%, respectively in the DAS28-ESR, $p=0.04$; 51.6% and 17.2%, respectively in the Boolean, $p=0.005$) at 6 months.

Conclusions: RA patients treated by the combination of TCZ and MTX who achieved deep remission (DAS28-ESR ≤ 1.98) at as early as 3 months could discontinue taking MTX.

Keywords: Rheumatoid arthritis; Methotrexate; Tocilizumab; Michinoku; Observational cohort study

Introduction

Methotrexate (MTX) is considered as an anchor drug because of its effectiveness and general versatility in the treatment of rheumatoid arthritis (RA) [1]. MTX is effective not only by itself, but also in combination with biological disease-modifying anti-rheumatic drugs (b-DMARDs). Combination therapy with b-DMARDs and MTX is more efficacious than a b-DMARD alone [2], especially in treatment with tumor necrosis factor (TNF) inhibitors [3-5]. The importance of MTX in the treatment of RA is emphasized along with the increasing use of b-DMARDs.

However, there are many debates on the clinical utility of MTX in tocilizumab (TCZ) treatment of RA. The efficacy of TCZ has been well validated, both in combination with MTX (TCZ+MTX) and TCZ monotherapy [6]. It has been suggested that the efficacy of TCZ monotherapy is comparable to that of combination therapy of TCZ at a dose of 4/8 mg/kg with DMARDs, however, the observational period was only 24 weeks [7].

Recently, there have been two milestone studies on the comparison between the efficacy of TCZ+MTX and TCZ monotherapy after a year. The first one was the ACT-RAY study, which reported a comparison between TCZ and TCZ+MTX. The data suggest that both TCZ add-on and switch strategies led to meaningful clinical and radiographic responses, despite a trend favoring the add-on strategy [8]. The second was the SURPRISE study. In RA patients with an inadequate response to MTX, TCZ added to MTX more rapidly suppressed inflammation than TCZ monotherapy switched from MTX, leading to superior clinical efficacy and prevention of joint destruction [9].

The results of the two studies differed, possibly because of the different disease duration in the SURPRISE study (3.6 years to 3.8 years), which was shorter than that in the ACT-RAY study (8.2 years to 8.3 years). Furthermore, in the ACT-RAY study, conventional DMARDs were added in patients with a DAS28 >3.2 at week 24, which complicated the comparison between TCZ and TCZ+MTX.

Both studies noted that the combination with MTX increased adverse events such as gastrointestinal disorders, respiratory, thoracic and mediastinal disorders, and laboratory test abnormalities.

The target of treatment of RA is clinical remission [10]. However, no clinical literature is available demonstrating whether patients can discontinue MTX in the clinical course of TCZ+MTX after achieving remission. The data of a cohort observational study performed by the Michinoku Tocilizumab Study Group (MTSG: Michinoku is the historical name for the Tohoku area in North Eastern Japan) examining the difference between an MTX continuation group and an MTX discontinuation group in patients started on TCZ+MTX therapy are described in this report.

Subjects and Methods

Study protocol and patients

This study was a multicenter, prospective, observational, non-interventional, cohort study performed by the MTSG [11]. Patients with RA diagnosed according to the 1987 revised RA classification criteria from the ACR, who had been newly treated with TCZ between 1st April 2008 and 31st Dec 2010, were registered. The patients were screened following the guideline of the Japan College of Rheumatology, and comorbidity was treated or controlled before administration of TCZ in order to prevent adverse events. Patients were then administered TCZ at 8 mg/kg intravenously every 4 weeks for 3 years (36 months). In total, 693 patients with RA who started TCZ therapy were followed and 307 patients successfully completed 36 month observational period.

The patients were treated by TCZ with or without MTX at the beginning of this study according to the decision of the attending physician in actual clinical practice. The numbers of the patients treated by TCZ+MTX (initial treatment was combination with MTX) and those treated by TCZ monotherapy were 187 patients and 120 patients, respectively. Thirty-seven patients, whose MTX doses were not precisely determined at the beginning or during the 36 month observational period, were excluded from 187 patients and 150 patients were analyzed in this study.

The dose of MTX depended on the discretion of the attending physician as well. The MTX doses and disease activities were precisely observed during 36 month observational period, and were classified into 4 groups by means of the MTX doses at the end of the observational period as follows: discontinued, decreased, maintained, or increased. The 33 patients who discontinued MTX after achieving DAS28-ESR remission (<2.6) were selected in this study. The 37 patients who maintained the same MTX dose after achieving DAS28-ESR remission (<2.6) at least for 6 months were selected in this study.

This study compared the discontinued patient group (DISC) and the maintained patient group (MAIN). The patient disposition and study flow chart is shown in Figure 1.

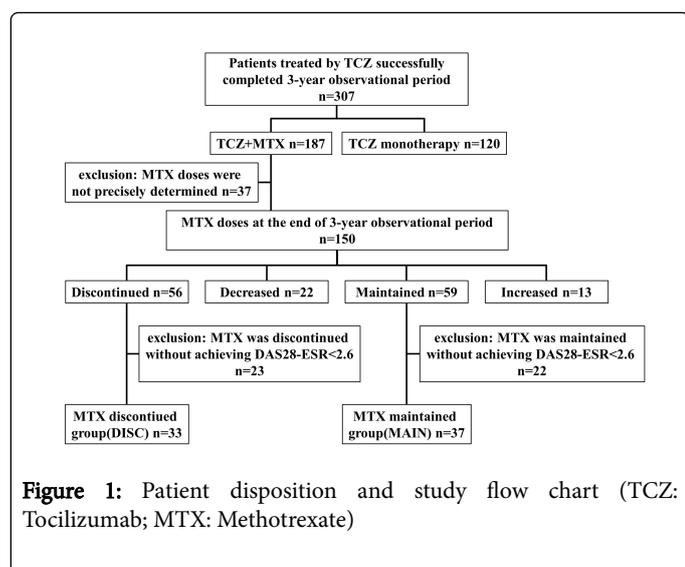


Figure 1: Patient disposition and study flow chart (TCZ: Tocilizumab; MTX: Methotrexate)

This study was approved by the Ethics Committee of Tohoku University and of each medical institution. This study was conducted in accordance with the Declaration of Helsinki and was registered with the University Hospital Information Network (UMIN) Clinical Trials Registry (#UMIN000011584). All participants gave their written informed consent.

Data collection and assessment

Each patient’s, adopted by TCZ+MTX treatment, tender joint count (TJC), swollen joint count (SJC), patient’s global assessment-Visual Analogue Scale (PGA-VAS) of disease status, erythrocyte sedimentation rate, and C-reactive protein (CRP) were assessed every 3 months. The DAS28 was calculated using the ESR.

The remission rate was assessed by the DAS28-ESR definition (DAS28-ESR<2.6) and by the 2011 ACR/EULAR Boolean-based remission criteria (TJC ≤ 1, SJC ≤ 1, PGA-VAS ≤ 1 cm, and CRP ≤ 1 mg/dl) [12,13].

Statistical analysis

The differences between the baseline characteristics of DISC and MAIN were analyzed by the t-test and Fisher’s exact test (Table 1). The differences between the DISC and MAIN in the DAS28-ESR were analyzed by Welch’s t-test. The differences between the DISC and MAIN in remission rates based on the DAS28 [14] and the Boolean definition [15] were analyzed by Fisher’s exact test.

period(months)	number of patients	(%)
3	19	58
6	22	67
9	24	73
12	26	79
15	27	82
21	29	88
24	30	91
27	31	94
33	33	100

Table 1: Period to discontinue MTX after remission.

Results

The period to discontinue MTX after remission was demonstrated in Table 1. The period for MTX discontinuation varies at the discretion of the attending physician in actual clinical practice, resulting in 58% of patients discontinued MTX until 3 months and 79% of patients discontinued until 12 months. In the clinical course of DISC, 2 patients’ DAS28-ESR temporarily exceeded 2.6 because of acute gingivitis or rhinopharyngitis, however, the disease activities became less than 2.6 after these complications were cured. The differences between the DISC and MAIN in background characteristics (Table 2), changes in the DAS28-ESR (Figure 2), DAS28-ESR remission rate (Figure 3) and Boolean remission rate (Figure 4) are shown.

	DISC		MAIN		p value
Number of patients	33		37		
Age (years), mean (SD)	61.4	-9.3	56.5	-12.6	0.0716*
Women, n (%)	26	-78.8	32	-86.5	0.5283*
Weight (kg), mean (SD)	51.6	-9.5	54.3	-11.1	0.2811*
Duration of RA (years), mean (SD)	11.8	-10.8	6.4	-5.5	0.0100*
Categorical duration of RA in years, n (%)					0.4282*
<2	5	-15	7	-19	
≥ 2 to <10	14	-42	20	-54	
≥ 10	14	-42	10	-27	
Stage I/II/III/IV, n (%)	2 (6)/8 (24)/5 (15)/18 (55)		6 (27)/14 (38)/7 (19)	16 (43)/10 (27)	0.0106*
Class I/II/III/IV, n (%)	6 (79)/1 (3)/0 (0)	18 (54)/26 (70)	9 (65)/3 (8)/1 (3)	24 (65)/24 (65)	0.5592*
CRP (mg/dl), mean (SD)	2.41	-3.1	2.26	-2.6	0.8232*
ESR (mm/hour), mean (SD)	49.1	-32.3	44.2	-33	0.5358*
TJC, mean (SD)	6.1	-7.3	4.3	-4.1	0.1932*

SJC, mean (SD)	5.4	-5.4	4.3	-4.4	0.3784*
VAS (mm), mean (SD)	51.1	-21.9	55.7	-27.6	0.4484*
DAS28-ESR, mean (SD)	5	-1.4	4.7	-1.4	0.4022*
Patients treated by b-DMARDs, n (%)	10	-30.3	20	-54.1	0.0557*
Oral steroid use, n (%)	21	-63.6	19	-51.5	0.4553*

DISC: MTX discontinued group, MAIN: MTX maintained group, TJC: tender joint count, SJC: swollen joint count, VAS: visual analogue 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

Table 2: Baseline characteristics

Background characteristics of the DISC and MAIN: As demonstrated in Table 2, the RA durations of the DISC and MAIN were 11.8 ± 10.8 years and 6.4 ± 5.5 years, respectively. The RA duration of the DISC was significantly longer than that of the MAIN ($p=0.01$). The ratio of RA stage 1/2/3/4 was 6/24/15/55% and 16/27/38/19% in the DISC and MAIN, respectively; the difference was significant ($p=0.0106$). The rate of patients with previous treatment by b-DMARDs was 30.3% in the DISC and 54.1% in the MAIN, respectively ($p=0.0557$).

Clinical efficacy: As shown in Figure 2, the DAS28-ESR values at 0 months were 5.0 ± 1.4 and 4.7 ± 1.4 in the DISC and MAIN, respectively. Those at 3 months were 1.8 ± 0.8 and 2.4 ± 1.0 in the DISC and MAIN, respectively. The DAS28-ESR was significantly lower in the DISC than in the MAIN ($p=0.018$). The DAS28-ESR was also significantly lower in the DISC than in the MAIN at 6 months ($p=0.009$) and at 9 months ($p=0.008$). The mean DAS28-ESR values were consistently lower, thereafter, in the DISC than in the MAIN (Figure 2).

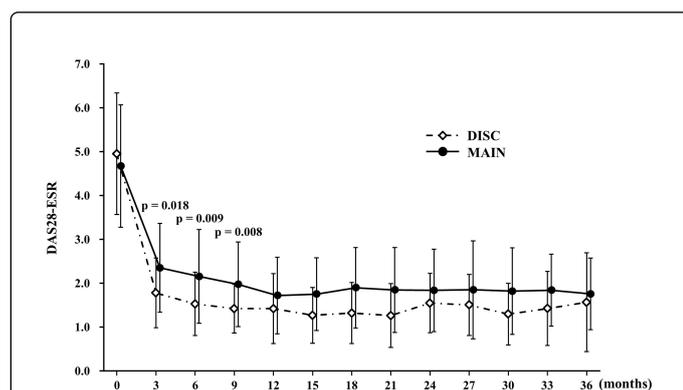


Figure 2: DAS28-ESR measured in the DISC and MAIN, Mean values are shown. Bars indicate SD. DAS28-ESR was measured in the DISC and MAIN every 3 months to 36 months. The DAS28-ESR is significantly lower in the DISC than in the MAIN at 3 months ($p=0.018$), 6 months ($p=0.009$), and 9 months ($p=0.008$). The DAS28-ESR is consistently lower in the DISC than in the MAIN.

The remission rates determined by the DAS28-ESR at 6 months were 93.8% and 64.5%, respectively in the DISC and MAIN. The remission rate was significantly higher in the DISC than in the MAIN ($p=0.004$). The remission rates were consistently higher, thereafter, in the DISC than in the MAIN as shown in (Figure 3).

The remission rates determined by the Boolean definition at 6 months were 51.6% and 17.2%, respectively in the DISC and MAIN. The remission rate was significantly higher in the DISC than in the MAIN ($p=0.005$) as shown in Figure 4. However, there were no differences between the DISC and MAIN thereafter until 36 months (Figure 4).

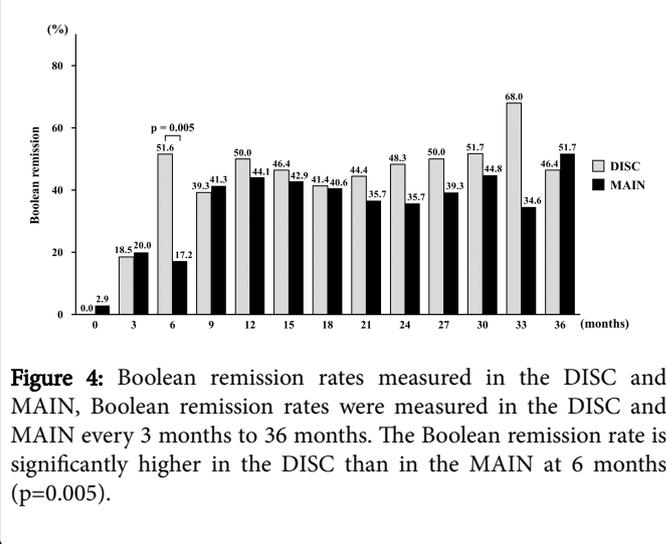
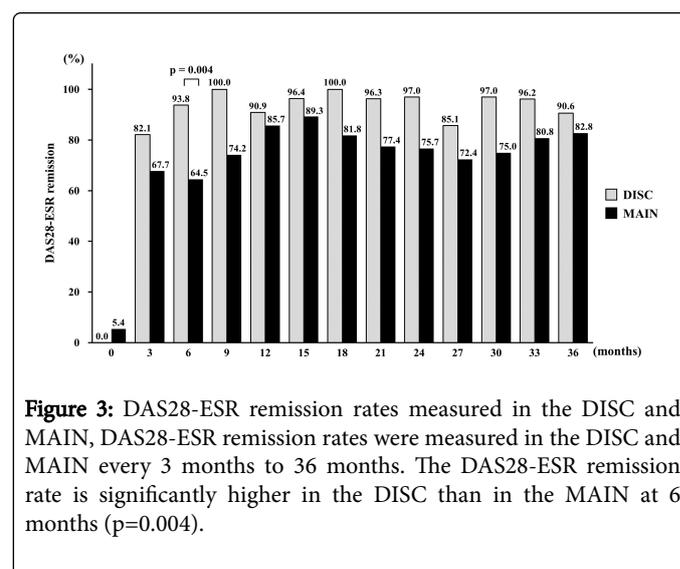


Figure 3: DAS28-ESR remission rates measured in the DISC and MAIN, DAS28-ESR remission rates were measured in the DISC and MAIN every 3 months to 36 months. The DAS28-ESR remission rate is significantly higher in the DISC than in the MAIN at 6 months ($p=0.004$).

Figure 4: Boolean remission rates measured in the DISC and MAIN, Boolean remission rates were measured in the DISC and MAIN every 3 months to 36 months. The Boolean remission rate is significantly higher in the DISC than in the MAIN at 6 months ($p=0.005$).

Adverse events were classified by system organ class of the Medical Dictionary for Regulatory Activities (version 17.1). The main adverse events observed in the DISC and MAIN are as follows; Infections and infestations affected 10 patients of 33 patients (20 events) in the DISC and 3 patients of 37 patients (9 events) in the MAIN. Laboratory test abnormalities were seen in 3 patients of 33 patients (3 events) in the DISC and 4 patients of 37 patients (20 events) in the MAIN. There were no significant differences in adverse events between them.

Discussion

The current goal of RA therapy is clinical remission. A treat to target (T2T) approach was introduced to achieve remission. In this regard, MTX and b-DMARDs play pivotal roles. TCZ monotherapy for controlling the progression of bone and joint destruction was effective in the SAMURAI study [16]. The high level of efficacy and continuity of long-term monotherapy was proved in the STREAM study [17]. In clinical practice, TCZ is used if the effect of MTX is insufficient to control disease activity or MTX is inadequate to achieve remission or the patients do not tolerate MTX. There are still debates about whether the efficacy of TCZ monotherapy is equivalent to that of TCZ+MTX [8,9]. Several papers have identified the effects of concomitant use with MTX to achieve remission. A 52-week observational study performed by Kojima et al. [17] suggested that concomitant use with MTX was superior to monotherapy to achieve remission in RA patients with high disease activity.

This 3-year observational study demonstrated that some patients treated by TCZ in combination with MTX could discontinue MTX. The background characteristics of DISC and MAIN were similar, but disease duration was significantly longer in the DISC. In general, RA patients with longer duration tend to have more comorbidities than those with shorter duration, and long-standing RA patients tend to fail to achieve remission by b-DMARDs treatment.

Four reasons why practicing doctors decided to discontinue MTX were turned out by interrogating the individual participating doctor.

The first, the TCZ+MTX administration sequence. The patients in the DISC responded more effectively and quickly to achieve deep remission (DAS28-ESR \leq 1.98) [18] at as early as 3 months. Moreover, the remission rates determined by both DAS28-ESR and Boolean criteria were significantly higher in the DISC than in the MAIN at 6 months, as shown in Figures 3 and 4, respectively. The second, advanced age, the comorbidities such as lung fibrosis, chronic renal disease or hepatitis of patients. The participating doctors take them into account to avoid serious complications. The third, the patients complicated infection. The participating doctors removed the MTX from the prescription according to the same reason described as above. The fourth, MTX caused side effect such as leukopenia and hepatitis. The main reasons were the first and second (data were not shown in the results).

As shown in Table 1, almost 60% and 80% in DISC were discontinued MTX administration until 3 months and 12 months, respectively, suggesting that most practicing doctors might have taken into consideration the effect of TCZ+MTX on the values of DAS28-ESR at 3 months, 6 months and 9 months, and figured to discontinue MTX.

Changes in the DAS28-ESR values of all patients (TCZ monotherapy groups as well as TCZ+MTX groups) were shown in our previous reports [11], and there at DAS28-ESR values were 2.8, 2.5, and 2.4, respectively at 3, 6, and 9 months. The DAS28-ESR remission rate and the Boolean remission rate were 54.2% and 21.7%, respectively, at 6 months. In the present study, DAS28-ESR values were much lower in the DISC, as shown in Figure 2. The DAS28-ESR remission rate and the Boolean remission rate were much higher in the DISC, as shown in Figures 3 and 4, respectively.

The present data demonstrated that the DISC responded quite well to TCZ+MTX combination therapy. The effect of b-DMARDs is more pronounced in bionative patients than in those who have had b-

DMARDs before [19,20]. The rate of bionative patients was comparatively higher, although not significantly, in the DISC than in the MAIN. This might have had an effect on the difference in the response to TCZ+MTX therapy between the DISC and MAIN.

Generally, there are many adverse events, such as gastrointestinal disorders, infections and infestations, and laboratory test abnormalities in MTX treatment. The present report demonstrated that certain patients at least, even if their disease duration is long, have a satisfactory chance of achieving remission and discontinuing MTX. Whether administration of MTX can be discontinued would be indicated by the response to TCZ+MTX therapy at 3 months to 9 months. The results of this study demonstrate the meaningful benefit for patients who are inadequate or unable to tolerate MTX over long term durations.

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