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ORIGINAL ARTICLE

**Hideto Kameda · Koichi Amano · Naoya Sekiguchi
Hirofumi Takei · Hiroe Ogawa · Hayato Nagasawa
Tsutomu Takeuchi**

Factors predicting the response to low-dose methotrexate therapy in patients with rheumatoid arthritis: a better response in male patients

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Abstract Methotrexate (MTX) is the most commonly used disease-modifying antirheumatic drug (DMARD) throughout the world. In Japan, MTX is recommended by the Japanese Ministry of Health, Labour, and Welfare to be given as the second or third DMARD and at a dosage of no more than 8 mg/week. We analyzed the efficacy of MTX in Japanese patients with RA in order to determine whether it is comparable to that in Western countries, where 15–20 mg/week of MTX is used, as well as to elucidate the factors associated with the favorable response to MTX. Around 8 mg/week of MTX was effective in half of the RA patients in the current study, and male sex was the only factor associated with a good response to MTX from a multivariate regression model analysis. Some of the patients who had a poor response to MTX showed an improvement with the addition of bucillamine or prednisolone. For the remaining patients, an increase in the MTX dosage to more than 8 mg/week or the use of biologics such as the anti-tumor necrosis factor (TNF)-α monoclonal antibody may be required.

Key words Bucillamine · Disease-modifying antirheumatic drug (DMARD) · Methotrexate (MTX) · Outcome · Remission

Introduction

Methotrexate (MTX) is a leading disease-modifying antirheumatic drug (DMARD) used world-wide in the treatment of rheumatoid arthritis (RA).[1] Indeed, MTX was regarded as a key drug in the management of RA in the 2002 update of treatment guidelines from the American College of Rheumatology (ACR) subcommittee.[2] The efficacy of MTX in the control of rheumatoid activity as well as in the retardation of the progression of joint destruction has been widely established.[3,4]

In Japan, however, MTX has been approved by the Japanese Ministry of Health, Labour, and Welfare only as a second-line agent for RA patients who have failed to respond to other DMARDs. Moreover, the approved maximum dosage of MTX is 8 mg/week, while 15–20 mg/week is the targeting dosage of MTX in the USA and many European countries, including the UK, France, and Germany. Therefore, the efficacy of MTX may be different in Japan compared with that in these other countries.

In order to elucidate the efficacy of MTX for RA patients in Japan and the factors determining the clinical response to MTX, we retrospectively analyzed the demographic features, clinical manifestations, and laboratory data obtained from the medical records of 217 RA patients who had been treated with MTX.

Patients and methods

Patients

The patients seen in our department were surveyed from December 2001 to February 2002, and 590 patients were found to have RA according to the 1987 revised ACR criteria.[5] A total of 318 (54%) patients were being treated (or had been treated) with MTX. Among these, 217 patients (37 males) had been started on MTX for the first time in our department, and their response to MTX had been observed for more than 6 months. Therefore, those 217 RA patients were included in this study.

Methods

All medical records of the 217 RA patients were reviewed.

Criteria of clinical response to DMARDs

The primary outcome of the patients was determined as described below.

H. Kameda (✉) · K. Amano · N. Sekiguchi · H. Takei · H. Ogawa · H. Nagasawa · T. Takeuchi
Second Department of Internal Medicine, Saitama Medical Center, 1981 Tsujido-cho, Kamoda, Kawagoe 350-8550, Japan
Tel./Fax +81-49-228-3574
e-mail: kamehide@saitama-med.ac.jp

Remission. Tender joint count (TJC) = 0, swollen joint count (SJC) = 0, and normal serum C-reactive protein (CRP) level (<0.5 mg/dl).

Improved. ≥50% decrease in (TJC + SJC) and ≥50% decrease in serum CRP level.

Insufficient. Not meeting the criteria of "remission" or "improved" while continuing to take the drug.

Ineffective. Not meeting the criteria of "remission" or "improved" and the drug was withdrawn without an adverse event (AE).

Withdrawn owing to an AE. The drug was withdrawn because of an AE.

Statistical analysis

A statistical analysis was performed using the Mann–Whitney *U*-test using StatView for nonparametric comparisons between subgroups, and using the Kaplan–Meier method for cumulative drug survival analysis. The difference was considered to be significant at $P < 0.05$.

Results

MTX was preferably given as the DMARD second to bucillamine

We examined the number of DMARDs given prior to MTX in the 217 RA patients. MTX was given as the first DMARD in 26 patients (12.0%), the second in 79 patients (36.4%), the third in 49 patients (22.6%), the fourth in 28 patients (12.9%), the fifth in 26 patients (12.0%), the sixth in 8 patients (3.7%), and the seventh in 1 patient (0.5%). We then investigated whether MTX was started in addition to, or as an alternative to, other DMARDs. MTX was added to the therapy without DMARDs in 66 cases, including 51 on prednisolone (PSL) monotherapy. MTX was started as an additional DMARD in 37 cases, including 18 cases on bucillamine treatment, and as a replacement for previous DMARDs in 48 cases on bucillamine therapy and 27 cases on salazosulfapyridine (SASP). Thus, a preference was noted for MTX to be given as the second DMARD after bucillamine.

MTX at 6–8 mg/week was effective in about half of the RA patients

We then determined the primary outcome of MTX treatment in the 217 RA patients. At first, 38 patients (17.5%) in whom MTX was finally discontinued during the observation period because of an AE were classed as "withdrawn owing to AE" even if they once satisfied the criteria for other categories such as remission. Other patients who once met the criteria for remission were then classified in the "remission" group ($n = 23$, 10.6%). Thirdly, those of the remaining patients who once met the criteria for ≥50% improvement in joint findings and serum CRP level ($n = 89$, 41.0%) were classified in the "improved" group. Finally, the last remaining patients were classified under either the "insufficient" ($n = 48$, 22.1%) or the "ineffective" ($n = 19$, 8.8%) group, which was on the basis of the continuation or discontinuation of MTX, respectively.

Demographic features, including age, disease duration, observation period after MTX, number of DMARDs used prior to MTX, Steinbrocker radiographic stage, maximum MTX dosage, and the rate of patients given a maximum MTX dosage over 8 mg/week, were not significantly different among the groups (Table 1). Moreover, TJC, SJC, serum CRP level, and the titer of rheumatoid factor (RF) were also similar in all the groups.

Male patients showed a better response to MTX than female patients

When we compared the proportions of male and female patients among the subgroups classified according to the primary outcome of MTX therapy, the proportion of male patients in the "remission" group was significantly higher than that in any other group (Fig. 1). Moreover, a compari-

Table 1. Comparison of demographic and clinical features at the start of MTX treatment among subgroups determined by the primary outcome of MTX therapy

	Remission $n = 23$ (10.6%)	Improved $n = 89$ (41.0%)	Insufficient $n = 48$ (22.1%)	Ineffective $n = 19$ (8.9%)	Withdrawn owing to an AE $n = 38$ (17.5%)
Age (years)	55	55	51	56	54
Disease duration (months)	70	107	88	64	133
Observation period after MTX (months)	31.2	31.5	25.8	35.6	41.2
Number of DMARDs used prior to MTX	1	2	1.5	2.6	2.3
Stage	2.1	3	2.7	2.8	2.9
Maximum MTX dosage (mg/week)	6.8	7	7.3	6.7	5.7
Maximum MTX dosage >8 mg/week (%)	4.3	10.1	12.5	10.5	2.6
TJC	6	7.5	5.7	5.8	6.7
SJC	6.3	7.9	8	5.5	6.8
CRP (mg/dl)	3.2	5.7	3.7	4.6	5
RF (IU/ml)	294	281	389	122	301

MTX, methotrexate; AE, adverse event; DMARD, disease-modifying antirheumatic drug; TJC, tender joint count; SJC, swollen joint count; CRP, C-reactive protein; RF, rheumatoid factor

Table 2. Male sex was identified as the only independent factor contributing to the response to MTX by a multiple regression model analysis

	Regression coefficient	*F*-value
Age	–	0.912
Disease duration	–	0.371
No. of DMARDs used prior to MTX	–	2.482
Stage	–	0.414
Maximum MTX dosage	–	0.852
TJC	–	3.762
SJC	–	0.286
CRP	–	0.220
RF	–	0.656
Male sex	0.588	11.857

Table 3. Comparison of clinical features between the cases whose primary or secondary outcomes of MTX therapy were "insufficient" and "ineffective"

	Addition $n = 50$ (22[a])			Replacement $n = 46$ (13)		
	Start	Addition	Δ	Start	Replacement	Δ
TJC	7.4	6.9	−0.5	6.4	9.6	3.1
SJC	8.0	8.7	0.7	6.6	8.4	1.8
CRP (mg/dl)	6.3	4.1	−2.2	4.3	4.4	0.1
DMARDs	Buc	20 (7)		SASP	12 (2)	
	Act	5 (1)		AZ	5 (1)	
	SASP	3 (0)		Act	5 (1)	
				Buc	4 (0)	
				Biologics	4 (3)	
Corticosteroid	PSL	14 (8)		PSL	12 (4)	

Buc, bucillamine; Act, Actarit; SASP, salazosulfapyridine; PSL, prednisolone; AZ, azathioprine
[a]The numbers in parentheses indicate the number of "remission" or "improved" cases after the treatment change.

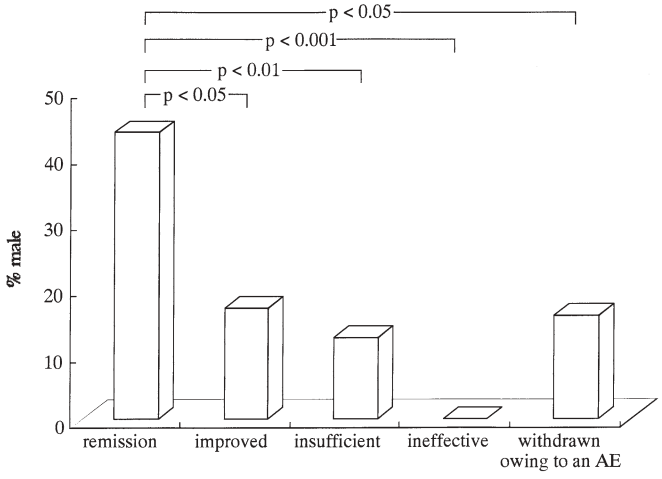

Fig. 1. Male patients show a better response to MTX than female patients. The proportions of male patients were compared among the subgroups classified according to their primary response to MTX. The proportion of male patients in the "remission" group was significantly higher than those in any other groups, and there was a decrease in the proportion of males in the group with the worse outcome. Note that the proportion of males in the "withdrawn owing to an AE" group was similar to overall proportion of males

son of the proportions of males and females between the "remission or improved" patients and the "insufficient or ineffective" patients also showed a significant difference ($P < 0.05$, data not shown).

Furthermore, we confirmed the influence of sex on the response to MTX by a multivariant regression model analysis (Table 2). For this purpose, the primary outcome was scored as 3 for "remission", 2 for "improved", 1 for "insufficient," and 0 for "ineffective." By a stepwise analysis, sex was found to be the only factor which independently contributed to the primary outcome of MTX therapy (*F*-value = 11.857, regression coefficient = 0.588) while all other factors shown in Table 1 did not (*F*-value <4).

Most of the patients who had not been successfully treated by MTX failed to be well controlled by the addition of, or replacement by, DMARDs other than MTX

We therefore investigated the clinical course of patients who had not been successfully controlled by MTX. These patients included those whose primary outcome was insufficient or ineffective, or those who had once responded very well to MTX and later shown insufficiency or ineffectiveness, i.e., the "escape phenomenon" (Table 3). In patients for whom another DMARD or PSL was added to MTX, the averages of TJC and SJC were unchanged (from 7.4 to 6.9 for TJC, and from 8.0 to 8.7 for SJC) with MTX treatment. However, their serum CRP level showed a small decrease from 6.3 to 4.1 on average. For these patients, bucillamine and prednisolone were preferably added to MTX and some showed an improvement, while other DMARDs resulted in a poor re-

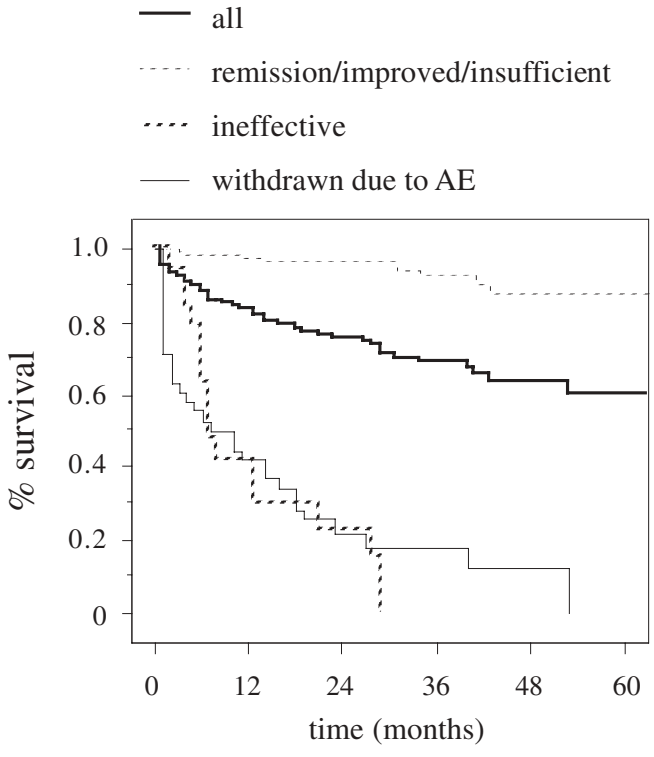

Fig. 2. Comparison of the cumulative MTX survival rates among subgroups classified by the primary outcome of MTX therapy. A *thick line* indicates all patients (n = 217), a *thin dotted line* indicates patients whose primary outcomes were either "remission," "improved," or "insufficient" (n = 160), while a *thick dotted line* and a *thin line* indicate patients in the "ineffective" (n = 19) and "withdrawn owing to an AE" groups (n = 38), respectively

sponse. In contrast, the averages of TJC and SJC were increased (from 6.4 to 9.6 and from 6.6 to 8.4, respectively) after MTX therapy in patients for whom MTX was finally replaced by another DMARD or PSL, and their serum CRP level did not fall (from 4.3 to 4.4). Thus, there was a tendency for MTX to be discontinued in patients whose serum CRP did not decrease with MTX therapy. Patients in whom MTX was replaced by another DMARD or PSL showed very poor responses**,** but biologics were considered to be exclusively effective for those patients.

The cumulative MTX survival rate was fair because of a low rate of escape (Fig. 2)

The overall 5-year survival rate of MTX therapy was 60%, which was the highest among the DMARDs available in Japan until 2002. Withdrawal owing to an AE was observed soon after starting MTX: 30% within 2 months, 45% within 6 months, and 59% within 1 year. Discontinuation owing to ineffectiveness peaked at 3–9 months after the start of MTX. In contrast, the patients whose primary outcome was either remission, improved, or insufficient showed a very high 5-year survival rate (89%).

Discussion

In this study, we have shown that low-dose weekly pulse (6–8 mg/week) MTX therapy is effective in about half of patients with active RA. Eighty-eight percent of patients were uncontrolled by at least one DMARD before MTX therapy (mostly owing to the lack of efficacy, but to an AE in some cases), and thus met the indication criteria for MTX therapy approved by the Japanese Ministry of Health, Labour, and Welfare. Therefore, the efficacy of MTX could be higher if MTX was given as the first DMARD in those patients. Because this study was retrospective, we could not directly compare our results with those previously published from the USA and other countries. However, a decrease of 50% or more in TJC or SJC was observed in 39%–54% of RA patients,[6,7] which was comparable to our results. Moreover, when we analyzed the efficacy of low-dose MTX (around 7 mg/week for Japanese patients) using DAS28–3(crp), which is equal to [0.56*sqrt(TJC28) + 0.28*sqrt(SJC) + 0.36*ln(10*CRP + 1)]*1.10 + 1.15 (http://www.das-score.nl/www.das-score.nl/index.html) in our series, a good response was observed in 3.1%, 3.0%, and 4.3% of patients after 3, 6, and 12 months of treatment, respectively; and a moderate response was observed in 51.5%, 57.1%, and 55.6% of patients after 3, 6, and 12 months, respectively. One paper reported that only 40% of MTX-treated RA patients showed a good or moderate response, while 83% of an anti-TNF group did so.[8] The rate of good or moderate responses increased to 63% when early (≤1 year duration) RA patients were investigated.[9]

One previous report identified a shorter disease duration as well as male sex, no prior DMARD use, a better functional class, and a worse patient global assessment as factors predicting a better response to MTX,[10] while another report claimed low disease activity at baseline, male sex, use of NSAIDs, and lower creatinine clearance as factors associated with a fair response to MTX.[11] In both studies, however, male sex was a common factor in predicting a better response to MTX. The multivariate regression model analysis in this study clearly confirmed a preferable response to MTX in male patients. The influence of sex on the response of rheumatoid activity to medication is not valid for all DMARDs because the response to bucillamine, a d-penicillamine analogue, was similar in both male and female patients with RA (data not shown). The fact that adverse events developed similarly in both sexes suggested that a better response to MTX in male patients could not simply be explained by RA-unrelated pharmacological factors, including absorption following oral administration, the enzymatic activity involved in the mechanisms of MTX action such as dihydrofolate reductase, or daily supplementation with folic acid. To clarify the mechanisms of the favorable response to MTX in male patients, further examinations should be performed, including the differences in the inhibitory effects of MTX on lymphocyte activation and proliferation in vivo and in vitro between male and female patients. Furthermore, it is important to determine whether the favorable response to MTX is also observed in patients with

other diseases, such as psoriasis and Wegener's granulomatosis. Other demographic or clinical features, including age, disease duration, radiographic stage, TJC, SJC, and the serum level of CRP or RF at the start of MTX therapy, as well as the maximum dosage of MTX or the usage of PSL, were not significantly different among the subgroups classified by the response to MTX. In this study, the proportion of patients with a short disease duration of ≤12 months was 16.1%, and that of patients with a disease duration ≤24 months was 24.9%. When we analyzed only those patients with a disease duration of ≤24 months, again about half of the patients showed a favorable response to MTX ("remission" or "improved"), although the remission rate tended to be higher in those patients (14.3% and 20.4% for ≤12 and ≤24 months, respectively).

The management of RA patients who do not respond well to MTX has been a major clinical challenge. Recently, some other treatment options have been proven to be effective in those patients, most of which entail the continuation of MTX therapy and the addition of another DMARD, including biologics such as anti-TNF-α antibodies. In Japan, the maximum dosage of SASP approved by the Japanese Ministry of Health, Labour, and Welfare is 1000 mg/day, and hydroxychloroquine is not available. Therefore, bucillamine was the only DMARD which had been successfully added to MTX therapy, although the addition of low-dose PSL was the alternative choice. Patients for whom bucillamine was added to MTX had been treated with GST ($n = 11$), SASP ($n = 10$), or bucillamine itself ($n = 7$) before MTX therapy, while those for whom PSL was added to MTX had been treated with SASP ($n = 7$) or bucillamine ($n = 7$). In cases of the discontinuation of MTX, the administration of biologic agents such as anti-TNF (etanercept or adalimumab) or monoclonal antibody against interleukin-6 receptor seemed to be the only effective alternative. In this study, only 8.7% of patients received a dose of MTX higher than 8 mg/week. Therefore, a gradual increase in MTX dosage to not more than 15 (or 20) mg/week until the appearance of a beneficial response should be the first step unless the development of an AE occurs.

The cumulative survival rate of MTX in this study was higher than one recently reported by Aletaha et al. (54.2% at 2.5 years).[12] We need to determine whether the cumulative MTX survival rate increases when we use a higher dosage of MTX for active RA patients. A high 5-year survival rate of MTX therapy suggested that pharmacological escape (secondary ineffectiveness) rarely developed, at least within 5 years, in RA patients. Indeed, it was reported that only 1 patient (4%) showed a lack of efficacy during 132 months of MTX therapy.[13] Suzuki et al.[14] reported that 12 of 71 RA patients showed a relapse following an initial improvement with MTX, and that the efficacy of MTX was restored in 11 patients by increasing the dose of MTX. It is also noteworthy that a rechallenge with MTX was prescribed in 34.8% of patients for whom MTX was once withdrawn owing to the lack of efficacy, and in 31.6% of patients in whom MTX was once discontinued because of an AE. This persistency in prescribing MTX further supported the fact that MTX is an indispensable drug in the treatment of patients with active RA, especially during the prebiological era in Japan.

In conclusion, MTX was shown to be effective in half of patients with RA, and its efficacy was higher in male patients than in females. When patients did not respond well to 8 mg/week of MTX, a gradual increase in dosage to not more than 15 (or 20) mg/week, and the addition of bucillamine, PSL, or an anti-TNF-α such as infliximab, are likely to be the treatments of choice.

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