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ORIGINAL ARTICLE

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Influence of methotrexate dose on its efficacy and safety in rheumatoid arthritis patients: evidence based on the variety of prescribing approaches among practicing Japanese rheumatologists in a single institute-based large observational cohort (IORRA)

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Abstract The optimal methotrexate dose differs between rheumatoid arthritis (RA) patients, and dose-escalation strategies also differ among rheumatologists. By taking advantage of the heterogeneous methotrexate dosing that occurs among Japanese rheumatologists, we analyzed the efficacy and safety of different methotrexate doses. A large observational cohort of RA patients, IORRA, was established in 2000. A dataset from April 2003 that included 4578 RA patients was used for a cross-sectional analysis, while a dataset of 1649 patients who received methotrexate from October 2000 to October 2005 was used for a longitudinal analysis. The cross-sectional analysis included 12 rheumatologists who prescribed methotrexate to more than 60 patients. Mean methotrexate dose ranged widely (4.8–9.0 mg/week) among rheumatologists with a significant positive relationship between average methotrexate dose and the percentage of patients with Disease Activity in 28 Joints (DAS28) scores below 3.2. During the longitudinal analysis, both methotrexate prescription frequency and the average dose prescribed by 16 rheumatologists increased. Overall disease activity as assessed by DAS28-area under the curve (AUC) and disability progression as assessed by Japanese version of the Health Assessment Questionnaire (JHAQ)-slope inversely correlated with the extent of methotrexate use. This study demonstrated that extensive methotrexate use effectively suppressed RA disease activity and inhibits disability progression. In addition, we have found that it is critical to pay attention to patient-reported adverse reactions.

Key words Cohort study · Dose · Efficacy · Methotrexate · Rheumatoid arthritis

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Introduction

Following a long history of trial and error, a treatment paradigm for rheumatoid arthritis (RA) has been established. While the introduction of biologics in particular has provided new treatment options for RA,[1] most practicing rheumatologists still consider methotrexate to be the standard.[2,3] Up to the introduction of biologics, methotrexate has been considered to be the anchor drug[4] in the majority of RA treatment regimens, and it is widely used throughout the world. Methotrexate has potent antirheumatic effects that not only suppress joint destruction but also improve mortality.[5] One key issue regarding methotrexate use is that optimal dosing varies widely between patients. In many countries, the average methotrexate dose of 15–20 mg/week is based on the clinical experience of rheumatologists but not on well-established evidence. In fact, no well-designed clinical trials have been conducted to determine the optimal methotrexate dose for RA patients,[6] and it is often used in a dose-escalation manner.

In Japan, methotrexate had been previously introduced as an anticancer agent and was approved for RA in 1999. The approved dose is ≤8 mg/week based on the results of a clinical trial conducted in Japan published in 1996,[7] however, much higher doses are regularly used throughout the world. For example, the American College of Rheumatology (ACR) guideline for management of RA indicates that methotrexate should be used at 7.5–20 mg/week.[8] A French group recently published clinical practice guidelines recommending a methotrexate starting dose for RA patients of no less than 10 mg/week, to be increased following an inadequate response at intervals of 6 weeks, up to 20 mg/week, according to tolerance and other patient-related factors.[9] Finally, the average dose of methotrexate used in most RA clinical trials in recent years has ranged between 15 and 20 mg/week.[10,11]

In association with the current trend of attempting to strictly control disease activity, methotrexate doses prescribed for RA patients in Japan are increasing, and it is not

uncommon for it to be prescribed at doses exceeding the approved 8 mg/week. However, the methotrexate dosing approaches of Japanese rheumatologists are quite diverse: some prescribe methotrexate within the approved limit of 8 mg/week regardless of clinical effects, while others prescribe higher, off-label doses such as 15 mg/week. We took advantage of this diversity in methotrexate dosing among practicing Japanese rheumatologists to investigate the influence of methotrexate dose on efficacy and safety in RA patients in a prospective observational cohort.

Patients and methods

We established a prospective observational cohort of RA patients at the Institute of Rheumatology, Tokyo Women's Medical University in October 2000.[12–14] We designated this cohort the IORRA (Institute Of Rheumatology, Rheumatoid Arthritis) study. Patients with RA were registered, and their information was collected biannually (in April/May and in October/November) from October 2000 to October 2005 during consultations at the outpatient unit of our Institute of Rheumatology; thus, data were collected 11 times (Phase 1 through Phase 11). While the interval between patient visits varied, the majority (>80%) of patients visited the outpatient clinic every month. Informed consent was routinely received from each patient at each visit.

Clinical information consisted of three components. The first was the physician's evaluation, which included counting the number of tender joints and the number of swollen joints, as well as a visual analog scale (VAS) of disease activity rated by the physician. The second component consisted of information collected from patients, including VAS for pain, VAS for general health, disability level using the Japanese version of the Health Assessment Questionnaire (JHAQ),[12] height, body weight, comorbidities in the previous 6 months, and details about any medication(s) taken during the study period. Patients answered these questions by filling out a questionnaire sheet at home and mailing it back in a prestamped envelope within 2 weeks of their clinic visit. The third component involved collection of laboratory data from patients, including C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), blood count, transaminase levels, and urine analysis. All information collected during each phase was integrated into a single database that was used for analysis. DAS28 (Disease Activity Score for 28 joints) was calculated according to the original method.[15]

A total of 7512 patients were enrolled in this study. Throughout the study, over 99% of RA patients in our institute were enrolled and over 98% of patients answered and mailed back their questionnaires. Thus, patient selection bias is considered to be small, if not negligible. Data with missing value were excluded from the analysis. The ethical committee of the Tokyo Women's Medical University approved this study.

Cross-sectional analysis (April 2003)

The dataset from Phase 6 of the survey (April 2003; 4578 RA patients total) was used for a cross-sectional analysis. Among the 39 rheumatologists who participated in this study, 12 prescribed methotrexate to more than 60 patients, and the number of patients used in this analysis (n = 1155) is approximately 50% of all patients prescribed methotrexate. The dose range distribution, DAS28 distribution, frequency of abnormal laboratory data (particularly alanine aminotransferase [ALT] levels and white blood cell [WBC] count), frequency of adverse reactions judged by patients, and percentage of patients with folate supplementation[16] were determined for each rheumatologist. Adverse reactions of methotrexate by the judgment of patients were based on patient self-reported questionnaires in the previous 6 months.

Longitudinal analysis (2000 to 2005)

The entire dataset from Phase 1 (October 2000) through Phase 11 (October 2005) was included in this longitudinal analysis. Among a total of 3971 patients from whom data was collected more than seven times, 1649 patients who had consulted the same rheumatologist for these visits were selected, and among the 39 rheumatologists in this dataset, 16 who consulted more than 50 patients with RA were selected for further analysis. The frequency at which patients were prescribed methotrexate and the average dose prescribed was investigated for each rheumatologist, and the product (frequency × average dose) was calculated to produce an expected prescribed methotrexate dose per patient, which served as an index for extent of methotrexate use. Use of prednisolone by each rheumatologist was also evaluated in the same manner as a control. DAS28 and JHAQ trends were recorded longitudinally from Phase 1 (October 2000) through Phase 11 (October 2005), and the area under the curve (AUC) of DAS28 (DAS28-AUC) and the slope of the linear regression line for JHAQ (JHAQ-slope) were analyzed as an index for the progression of disability of patients. DAS-AUC was calculated based on the averages DAS28 of patients treated by each rheumatologist, using a standard trapezoid method.

Results

Cross-sectional analysis (Phase 6, April 2003)

Of 4578 RA patients who participated in Phase 6 (April 2003), 2308 patients (50.4%; mean age, 57.4 years; mean disease duration, 11.9 years) received methotrexate. The mean methotrexate dose was 6.36 mg/week, and 351 patients (15.2%) received >8 mg per week. Folic acid was supplemented in 704 patients (30.5%).

Among the 39 rheumatologists who participated in this phase, 12 prescribed methotrexate for >60 patients. The

Table 1. Cross-sectional analysis: Baseline characteristic of 1,155 patients treated by 12 rheumatologists

	N	Methotrexate dose (mg/week)	Female (%)	Bw (kg)	Ht (cm)	BMI	Age (years)
Dr. A	118	9.00	86.44	51.69	156.59	21.06	59.21
Dr. B	117	7.66	91.45	52.17	156.02	21.40	58.78
Dr. C	110	7.57	79.09	52.32	156.63	21.28	59.50
Dr. D	68	7.11	83.82	51.24	156.99	20.76	55.26
Dr. E	75	7.07	77.33	52.36	157.39	21.06	56.71
Dr. F	66	7.05	80.30	54.35	158.95	21.48	58.02
Dr. G	134	6.96	82.09	52.91	156.85	21.44	60.52
Dr. H	106	6.72	83.96	52.36	156.50	21.30	56.58
Dr. I	62	6.49	87.10	54.03	157.03	21.87	57.13
Dr. J	68	5.63	86.76	52.83	155.03	21.81	60.13
Dr. K	132	5.15	89.39	50.73	154.25	21.34	61.72
Dr. L	99	4.85	85.86	53.23	155.79	21.97	60.35

Bw, body weight; Ht, height; BMI, body mass index; DAS28, Disease Activity Score; JHAQ, Japanese version of Health Assessment Questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor

Table 1. *Continue*

Duration (years)	DAS28	JHAQ	CRP (mg/dl)	ESR (mm/1 h)	RF (IU/ml)	Folate use (%)	Steroid use (%)	Prednisolone dose (mg/day)
11.51	3.02	0.82	0.95	31.24	150.63	52.54	55.93	3.68
14.68	3.57	0.79	1.06	31.56	135.35	32.48	58.97	4.53
11.08	3.56	0.67	0.92	29.60	157.93	42.73	52.73	5.02
11.56	4.08	0.97	1.21	36.51	149.45	20.59	72.06	4.84
10.84	3.96	0.88	1.55	37.46	227.84	48.00	61.33	5.31
11.36	3.72	0.84	1.63	40.45	166.34	33.33	57.58	3.97
12.66	4.56	1.11	1.71	37.94	192.00	34.33	45.52	4.53
11.66	4.04	0.98	1.55	37.36	190.05	45.28	67.92	4.30
10.89	4.23	0.93	1.79	37.34	200.25	45.16	62.90	5.30
13.81	4.27	1.27	1.79	38.36	235.25	32.35	85.29	4.63
13.85	5.40	1.36	1.98	45.78	184.21	6.82	59.09	4.59
14.77	4.37	1.16	2.21	44.50	175.32	23.23	75.76	4.11

starting dose for all 12 rheumatologists was 4 or 6 mg/week, and while some rheumatologists maintained the dose at ≤8 mg/week as specified by the product labeling, others gradually escalated the dose up to 20 mg/week according to efficacy and safety in individual patients. The relationship between dose and the efficacy/safety profile was compared between these 12 rheumatologists. Baseline patient characteristics are shown in Table 1. Patient baseline data, including age and disease duration, did not differ widely between rheumatologists. In contrast, dosing distribution and median methotrexate dose widely differed (4.8–9.0 mg/week) between rheumatologists (Fig. 1).

Disease activity and safety profiles in patients treated by each rheumatologist were assessed and are listed in Table 2. In this cross-sectional analysis, 151 adverse reactions by the judgment of patients were self-reported. Frequent adverse reactions include stomatitis (17.7%), hair loss (9.8%), easy fatiguability (8.5%), and nausea (6.7%). In addition, 14.6% of patients had abnormal liver function tests. Overall, 29 patients (17.8%) discontinued methotrexate, indicating that the majority of these adverse reactions judged by patients were tolerable (Table 3).

There is a clear positive relationship between average methotrexate dose and the percentage of patients with DAS28 scores <3.2, and also between average methotrexate dose and the frequency of adverse reactions of methotrexate by the judgment of patients (Fig. 2). However, methotrexate dose did not correlate with either frequency of hepatotoxicity (ALT > 90 IU/l) or leukocytopenia (WBC <3000/mm^3) (Table 2).

Longitudinal analysis (Phase 1, October 2000 to Phase 11, October 2005)

Trends in the frequency and average dosing of methotrexate and prednisolone among the 16 rheumatologists who had consulted >50 RA patients are shown in Fig. 3. Ten out of 16 rheumatologists were identical to the physicians in the cross-sectional study. Both the frequency of methotrexate prescriptions and the dose prescribed increased from October 2000 to October 2005. In contrast, while the frequency of prednisolone prescriptions remained constant during this period, the average dose prescribed decreased over time. As an index for the extent of drug use, the expected dose of drug per patient was calculated as the product of prescription frequency × average dose prescribed of each drug. It is apparent that methotrexate use has increased over the past 5 years while prednisolone use has remained at the same level (Fig. 3).

Trends in DAS28 and JHAQ scores for patients treated by each rheumatologist are shown in Fig. 4. Overall, DAS28

Table 2. Cross-sectional analysis: disease control and safety profile of 1155 patients treated by 12 rheumatologists

	N	Methotrexate dose (mg/week)	Methotrexate dose >8 mg/week (%)	DAS28 <3.2 (%)	Adverse reactions by the judgment of patients (%)	WBC <3000/mm^3 (%)	ALT >90 I U/l (%)
Dr. A	118	9.00	51.28	58.93	21.19	0.00	1.79
Dr. B	117	7.66	29.20	35.96	17.09	0.86	0.00
Dr. C	110	7.57	36.54	39.25	17.27	0.93	0.95
Dr. D	68	7.11	25.00	24.62	14.71	0.00	0.00
Dr. E	75	7.07	20.55	27.03	10.67	0.00	0.00
Dr. F	66	7.05	24.59	35.00	15.15	1.61	1.61
Dr. G	134	6.96	18.60	14.06	15.67	0.00	0.78
Dr. H	106	6.72	24.27	24.27	16.04	0.00	0.00
Dr. I	62	6.49	6.90	22.03	14.52	0.00	0.00
Dr. J	68	5.63	3.08	14.29	13.24	0.00	0.00
Dr. K	132	5.15	3.97	6.61	9.09	0.00	0.00
Dr. L	99	4.85	7.14	13.48	8.08	0.00	1.10

WBC, white blood cells; ALT, alanine aminotransferase

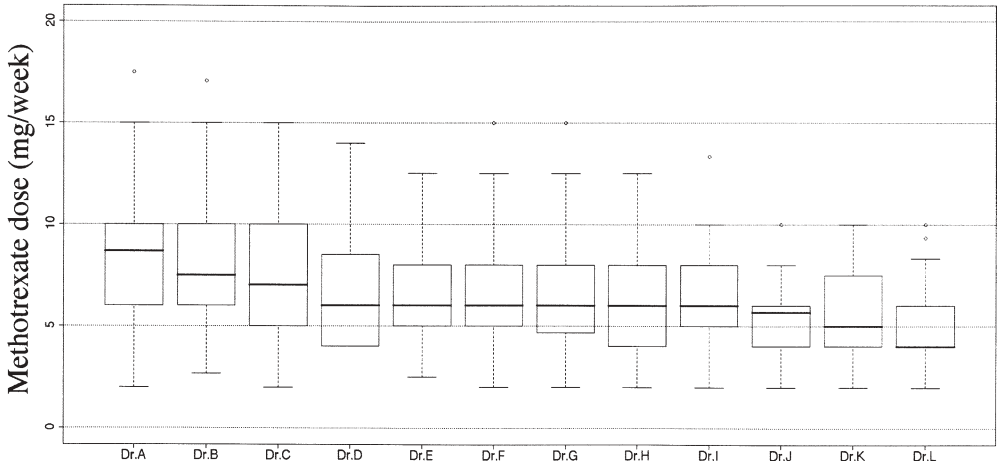

Fig. 1. Methotrexate dose prescribed by 12 rheumatologists in the cross-sectional analysis. Box plots of mean methotrexate dose prescribed by 12 rheumatologists in the IORRA cohort study are arranged from high to low. *Line in the box* represents the median and the *upper and lower end of the box* is 25th and 75th percentile of the population

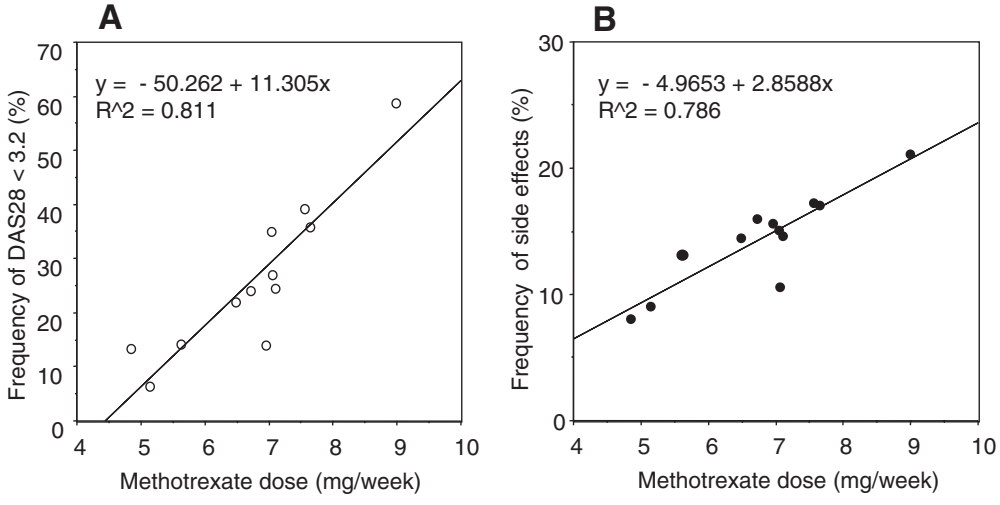

Fig. 2A,B. Efficacy and safety of methotrexate (*MTX*) use in the cross-sectional analysis. A significant relationship between average methotrexate dose (mg/week) and the frequency of patients with Disease Activity (*DAS28*) scores <3.2 (**A**) and with the frequency of adverse reactions judged by patients based on patient self-reports (**B**) were observed. Regression lines were analyzed by a descriptive method

scores constantly decreased while JHAQ scores gradually increased during this period. There was a tendency for the JHAQ score to be lower in patients with decreased DAS28 scores, while JHAQ scores increased in patients whose DAS28 scores remained high.

We next analyzed the relationship between the overall dose of methotrexate and overall disease activity (DAS28-AUC) or progression of disability (JHAQ-slope), as shown in Fig. 5. AUC of the expected prescribed dose of methotrexate per patient (= prescription frequency × average dose

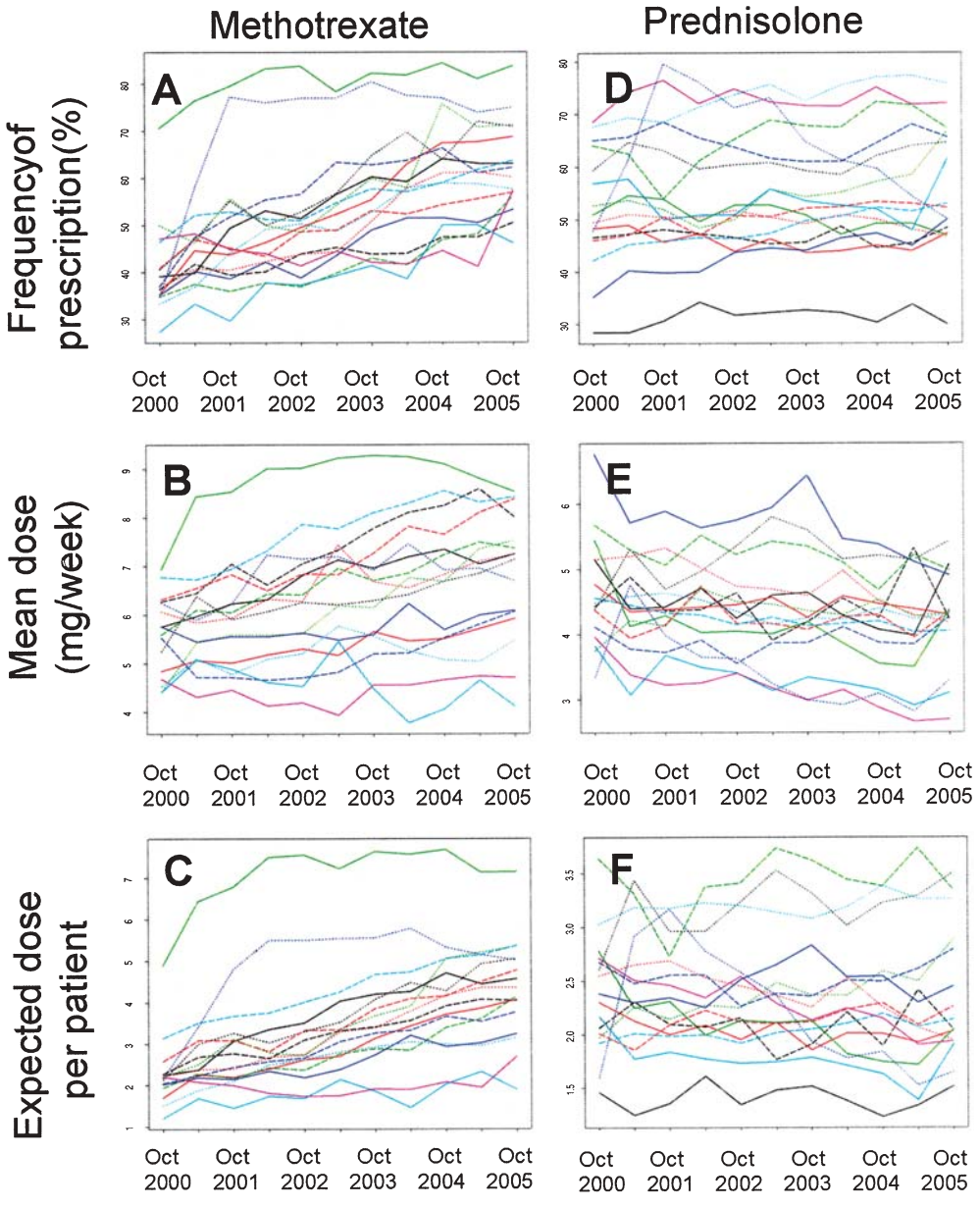

Fig. 3A–F. Trends of methotrexate and prednisolone use among 16 rheumatologists in the longitudinal analysis. Prescription frequency (**A, D**), mean dose prescribed (**B, E**), and their product (expected dose/patient; **C, F**) for methotrexate (**A, B, C**) and prednisolone (**D, E, F**) among 16 rheumatologists from October 2000 to October 2004 are shown. Note that methotrexate but not prednisolone has become extensively used in these 5 years and that approaches for using these drugs varies widely among rheumatologists

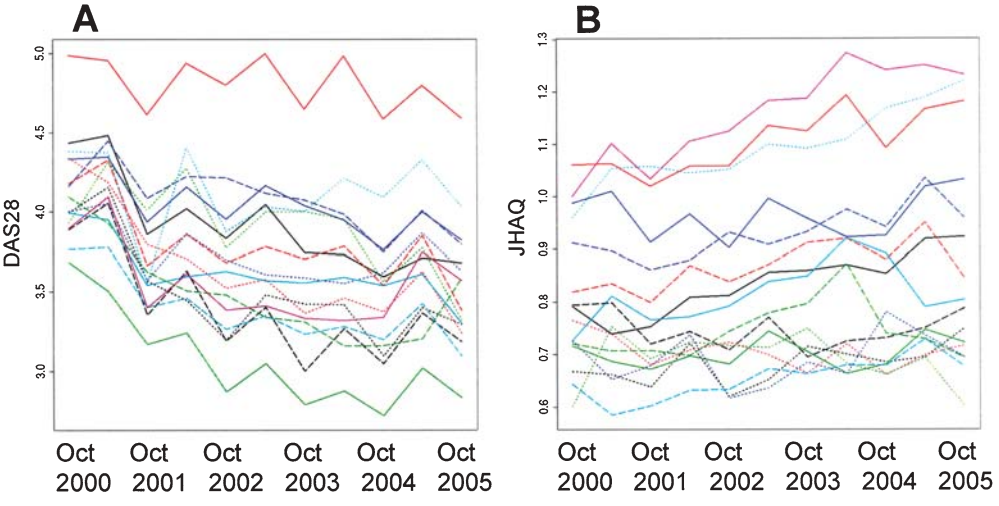

Fig. 4A,B. DAS28 and Japanese version of Health Assessment Questionnaire (JHAQ) trends in patients treated by 16 rheumatologists in the longitudinal analysis. Disease activity (*DAS28*, **A**) and disability index (*JHAQ*, **B**) of patients treated by 16 rheumatologists from October 2000 to October 2004 are shown. Note that patients with persistently high DAS28 scores had exacerbated JHAQ scores, while patients with decreasing DAS28 scores did not develop disability. Same color of line is used for the same rheumatologist in Figs. 3 and 4

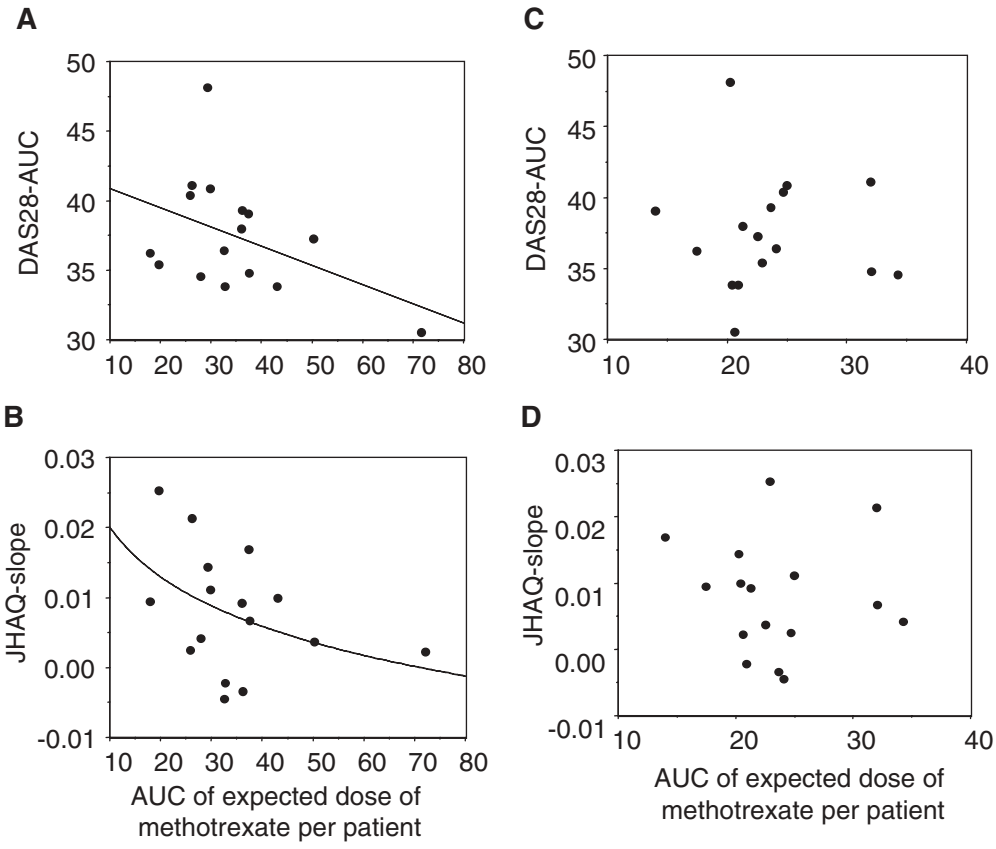

Fig. 5A–D. Influence of overall methotrexate or prednisolone use on overall disease activity and disability progression. Correlations between overall methotrexate use (area under the curve (*AUC*) of expected dose per patient) and DAS28-AUC (**A**) or JHAQ-slope (**B**) are shown along with those for prednisolone (**C, D**). A negative correlation was noted between expected dose of methotrexate per patient and DAS28-AUC ($y = 42.275 - 0.13851x$, $R^2 = 0.188$) or JHAQ-slope ($y = 4.3633e{-}2 + -2.3571e{-}2\,x\,\mathrm{LOG}(x)$, $R^2 = 0.162$) by a descriptive method, indicating that extensive use of methotrexate but not prednisolone decreased overall disease activity and inhibited disability progression

Table 3. Adverse reactions of methotrexate by the judgment of patients

	Number	%
Stomatitis	29	17.7
Liver dysfunction	24	14.6
Hair loss	16	9.8
Fatigue	14	8.5
Nausea	11	6.7
Heartburn	6	3.7
Stomachache	6	3.7
Appetite loss	6	3.7
Cough	5	3.0
Leukocytopenia	4	2.4
Skin itching	3	1.8
Eczema	3	1.8
Headache	3	1.8
Depression	3	1.8
Moon face	3	1.8
Others	15	9.9

prescribed) was used as the index for overall methotrexate dose. A similar analysis was done for prednisolone as a control. The expected prescribed dose of methotrexate, but not prednisolone, was inversely correlated with DAS28-AUC ($R = 0.433$) and JHAQ-slope ($R = 0.402$). Thus, it is likely that extensive use of methotrexate appears to effectively suppress disease activity and to inhibit progression of disability in RA patients.

Discussion

While it is well recognized that methotrexate is a standard drug for treatment of RA,[2,4] certain issues exist concerning methotrexate dosing in daily rheumatology practice. First, the optimal dose of methotrexate is quite diverse among patients;[17] second, no well-designed studies have been conducted to determine the optimal dose of methotrexate for RA patients;[6] and finally, in Japan, the approved methotrexate dose has been limited to a maximum of 8 mg/week. These issues have caused much uncertainty among rheumatologists, particularly in Japan, regarding optimal methotrexate dosing. In this study, we took advantage of the diversity in methotrexate dosing among Japanese rheumatologists to investigate the influence of different prescription protocols on the efficacy and safety of methotrexate in RA patients. We have clearly shown that higher methotrexate doses are associated with better efficacy as well as more, but largely tolerable, adverse reactions judged by the patients.

The IORRA cohort is a prospective observational cohort that reflects daily rheumatology practice.[14] While this study was not a controlled trial, because each rheumatologist treats RA patients based on his or her own protocol, the outcome measures may be analogous to those that would be used in an open-label controlled trial.

In this study, all rheumatologists initiated methotrexate dosing at 4 or 6 mg/week and then escalated the dose ac-

cording to the efficacy and safety profiles in each patient. There were differences between 16 rheumatologists in the final dose achieved at the end of dose escalation, with the average dose ranging from 4.85 to 9.0 mg/week. Considering that the baseline patient characteristics, including age and duration, for each rheumatologist did not largely differ, the different methotrexate dose escalation strategies likely influenced patient outcome.

Our cross-sectional and longitudinal analyses demonstrated that extensive methotrexate use is likely to be efficacious in suppressing disease activity as assessed by DAS28 scores, and our longitudinal analysis indicated that current methotrexate dosing strategies can help prevent progression of disability, as assessed by JHAQ scores. It is interesting that JHAQ scores increased gradually despite decreasing DAS28 scores over the 5-year period. We have previously shown that persistent high DAS28 scores result in progression of disability, and that a DAS28 score <3.2 is crucial for preventing disability.[18] Thus, even when DAS28 scores decrease, JHAQ scores are expected to increase for DAS28 scores ≥3.2.

We also notice from Table 1 and Fig. 3 that rheumatologists who frequently prescribed prednisolone had a tendency to prescribe methotrexate at lower doses, and that their patients progressed (as assessed by JHAQ scores) despite decreased DAS28 scores. This suggests that the degree of disease activity suppression is substantially different with methotrexate versus prednisolone. Thus, our data suggest that strict control of disease activity by sufficient use of methotrexate is crucial for better outcomes in RA patients.

Safety was monitored by the occurrence of adverse reactions judged by patients from patient self-reports as well as from laboratory data for abnormal liver function (defined as ALT >90 IU/l) or leukocytopenia (defined as WBC <3000/mm^3). Although neither hepatotoxicity nor leukocytopenia were correlated with methotrexate dose, the frequency of adverse reactions reported by patients increased with average methotrexate dose; the majority of these reactions were mild and well tolerated. These results indicate that caution must be heeded in patients who receive higher methotrexate doses, and they also highlight the importance of patient self-reporting in the clinical setting. It should be noted that the methotrexate doses in the IORRA database are primarily based on patient self-reports and not on their medical charts, and therefore reflect actual rather than prescribed doses. Patient compliance with taking prescribed medications at the correct doses is always a concern in clinical studies; however, our dataset is free from this kind of bias.

This study used a unique strategy to show the limitation of Japanese rheumatology clinics, but because of the nature of observational study, there are many limitations in the study itself. For example, methotrexate is often prescribed with prednisolone or other types of DMARDs, and the effect of these concomitant medications might be considered. However, the strategy for the comedication with prednisolone or other DMARDs differs among rheumatologists; thus, we did not analyze the effect of these concomitant medications.

In conclusion, the results of this study suggest that current methotrexate dose-escalation strategies are effective in RA management, and that methotrexate doses that maintain DAS28 at low levels are recommended when considering long-term patient outcome. Well-designed, controlled trials to assess the efficacy and safety of high-dose methotrexate should further support our findings, although it will be challenging to create a suitable study design because of the diverse responsiveness of RA patients to methotrexate,[16] as mentioned above. Finally, a critical component for any future clinical study will be for patients to self-report any adverse reactions experienced.

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