Treatment continuation rate in relation to efficacy and toxicity in long-term therapy with low-dose methotrexate, sulfasalazine, and bucillamine in 1358 Japanese patients with rheumatoid arthritis

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Abstract

Objective

To evaluate the effectiveness of disease-modifying antirheumatic drugs, namely, methotrexate (MTX), sulfasalazine (SSZ) and bucillamine (BUC) at low-doses (4, 6 or 8mg MTX, 500 or1000mg SSZ, and 100 or 200 mg BUC) in 1358 patients with a follow-up of at least 12 months and more than 120 months.

Methods

Clinical assessments were based on the number of painful joints (NPJ) and that of swollen joints (NSJ), CRP level, erythrocyte sedimentation rate, rheumatoid factor level and morning stiffness before and after treatment. Results were evaluated on the basis of the duration of treatment for each drug with inefficacy or inadequate efficacy as one endpoint for discontinuation and adverse drug reactions (ADRs) as the other in single agent and combination therapy. The incidence and nature of ADRs in single and combination treatment are described.

Results

The effects of MTX, SSZ and BUC on clinical parameters were monitored over the first three months, and in particular, NPJs and NSJs were found to decrease significantly during single agent MTX or BUC treatment over 108 months. CRP levels remained significantly improved for more than 120 months with MTX. In the single and combination long-term treatments, continuation rate with inefficacy or inadequate efficacy as the end point achieved for each of the treatments were 83.1% for MTX, 76.0% for BUC, 68.5% for SSZ, and in the case of the combination treatments, these rates were 83.3% for MTX + BUC and 71.0% for MTX+SSZ. Continuation rates using ADRs as the end point were 88% for SSZ, 79.6% for BUC and 79.4% for MTX. The incidences of ADRs for the various treatments were: MTX 22.2%, SSZ 11.0%, BUC 20.6%, MTX + BUC 30.0% and MTX + SSZ 31.2%.

Conclusion

MTX showed the highest efficacy even though it was administrated at a low dose (6-8 mg), as a single agent or in combination with other treatment. However, in combination treatments, the continuous duration of treatment ending in ADRs as the end point were lower than those in single treatments with MTX, SSZ and BUC.

Key words

Rheumatoid arthritis, Kaplan-Meier method, methotrexate, sulfasalazine, bucillamine, continuation rate, adverse drug reaction.

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Introduction

Rheumatoid arthritis (RA) is a progressive and chronic disease and requires drug treatment over many years. It is important to select the appropriate disease-modifying antirheumatic drugs (DMARDs), which are used in the second line treatment. The duration of treatment with a selected drug, that is cumulative continuation, hereafter referred to as continuation rate, depends on the type of DMARD. However, because of adverse drug reactions (ADRs), poor efficacy or inefficacy, alternate treatment strategies may be employed by either using a second drug in a saw tooth treatment regimen or including another DMARD in a combination regimen (1).

Thus far, long-term studies of more than 5 years duration on the performances and the survival rates of methotrexate (MTX) (2-4) and sulfasalazine (SSZ) (5-7), as well as comparisons of the performances and survival rates of various DMARDs have been reported (8-12). Wolfe *et al.* compared MTX to other DMARDs (gold sodium thiomalate, auranofin, hydroxychloroquine or penicillamine), and reported that the median time to discontinuation for these latter DMARDs was 2 years or less, but for MTX it was 4.25 years; moreover, ADRs were less common in patients taking MTX (8). However continuation/discontinuation rates of low-dose MTX, SSZ and bucillamine (BUC) after long-term use in Japanese patients with RA have not yet been reported.

The present study used various clinical parameters namely: the number of painful joints (NPJs); the number of swollen joints (NSJs); the serum level of C-reactive protein (CRP; mg/dl); erythrocyte sedimentation rate (ESR; mm/hr); the duration of continuous treatment with low-dose MTX, SSZ and BUC used in single and combination treatments of MTX + BUC, MTX + SSZ, and SSZ + BUC; improvement and the types of ADR to DMARDs in single and combination treatments.

Our findings may provide a basis for future measures and expectations of success for conventional DMARDs; that is, what types of drug should be selected in the first course, what types of another DMARDs or what types of combination drugs should be selected in the second course, which of the new or recently approved DMARDs such as should be used, and which of these TNF-α, IL-1 cytokine blockers will effectively suppress the disease activity as well as retard or restrict radiological progression (13-15).

Patients and methods

Patient selection

The study population comprised 1358 RA outpatients who visited our clinic between November 1978 and April 2002, and who satisfied the American College of Rheumatology criteria for RA (16). Some of the patients were prescribed DMARDs for the first time and some of the patients were switched to other DMARDs after a first DMARD had been washed out according to the saw tooth strategy (17): MTX was administered to 427 patients, SSZ to 200 patients, and BUC to 437 patients. The combination treatments were as follows: MTX + BUC were administered to 150 patients, MTX + SSZ to 93 patients, and SSZ + BUC to 51 patients. The remaining patients were administered other DMARDs: namely auranofin, D-penicillamine, gold sodium thiomalate and cyclophosphamide, among others.

Table I shows the profiles of the patients who received DMARDs as the first course of treatment and those who changed to a second DMARD because of inefficacy or ADRs in the first course of treatment. From a total of 1358 patients, 154 were men and 1204 were women. The mean age was 52.8 years (range, 15-85 years) and the mean disease duration was 101.0 months (range, 1-708 months). Prednisolone was prescribed to 969 out of the 1358 patients at a mean dose of 4.8 mg (range, 2-25 mg). Table II shows the patients and the mean duration of administration for several DMARDs in single and combination treatments. Single agent treatments were continued for more than 5 years in 109 of 427 patients (MTX), 14 of 200 patients (SSZ) and 64 of 437 patients (BUC). The numbers of patients who received

Table I. Comparison of clinical profiles before administration of methotrexate, sulfasalazine, and bucillamine.

	MTX	SSZ	BUC	MTX+BUC	MTX+SSZ	SSZ+BUC
Man	42	26	57	12	14	3
Woman	385	174	380	138	79	48
Ages (years)*	52.4 ± 11.1	52.5 ± 11.9	53.7 ± 12.0	53.5 ± 10.9	50.5 ± 10.1	51.3 ± 13.0
	(18-79)	(19-82)	(15-85)	(21-78)	(25-74)	(19-74)
Disease duration (months)*	113.8 ± 112.9	96.2 ± 103.9	95.1 ± 108.4	106.8 ± 111.8	80.2 ± 78.4	84.6 ± 73.6
	(1-708)	(1-504)	(1-708)	(1-708)	(1-376)	(1-300)
Prednisolone (mg)*	4.6 ± 2.0	5.1 ± 2.3	4.6 ± 2.1	5.0 ± 2.3	5.1 ± 2.1	5.4 ± 2.0
	(1-25)	(1-15)	(1-20)	(1.5-20)	(2.5 -15)	(2.5 -10)

Asterisks indicate each mean ± SD and ranges.

Table II. Mean duration of administration of methotrexate, sulfasalazine, and bucillamine, and the number of patients each year in the single and combination treatment.

DMARDs	Patients	Duration of administration (months)	1	1~2	2~3	3~5	5< years
MTX	427	42.8 ± 38.3 (1-120)	149	59	34	76	109
SSZ	200	21.7 ± 23.2 (1-120)	107	34	29	16	14
BUC	437	33.1 ± 28.4 (1-120)	143	92	55	83	64
MTX+BUC	150	34.1 ± 33.5 (1-120)	60	26	15	18	31
MTX+SSZ	93	28.2 ± 28.6 (1-120)	44	17	9	9	14
SSZ+BUC	51	19.3 ± 18.6 (1-108)	24	15	7	4	1

combination treatments for more than 5 years were 31 out of 150 patients for MTX+BUC, 14 out of 93 patients for MTX+SSZ, and 1 out of 51 patients for SSZ+BUC. The standard dosages of DMARDs were as follows: 4-8 mg/week (mean dose 4.6 ± 1.1mg) for MTX (maximum dose in Japan: 8 mg/week) (18), 500-1000mg/day (mean dose 862.0 ± 232.4 mg) for SSZ (maximum dose in Japan: 1000 mg), 100-200 mg/day (mean doses 120 ± 55.8 mg) for BUC (maximum dose in Japan:300 mg). Folate supplementation could be initiated at a low dose of 5 mg/week for nausea caused by administration of MTX or if the dose of MTX was 8 mg. Most of the patients were administered non-steroidal anti-inflammatory drugs.

Procedures
Clinical parameters were evaluated every 6 months for a maximum period of 23.0 years; the parameters evaluated were as follows: NPJs, NSJs, serum CRP (mg/dl), ESR (mm/hr), rheumatoid factor level (RF, IU/l) and morning stiffness (minutes). We used the Kaplan-Meier method to calculate the continuation rates of the DMARDs used in a single or combination treatment. The end points were; inefficacy or poor efficacy and ADRs. The types of ADR, their incidence and the time of their appearance were recorded.

Statistical analyses
All data were expressed as mean ± standard deviation (SD) in the tables and mean in the figures. Differences and the statistical significance for each parameters were analysed using the Student's paired t-test (within item) and by the two-way analysis of variance (between group: ANOVA). A *p* value less than 0.05 was considered statistically significant. The Kaplan-Meier method for continuation rates was used to estimate the probability of discontinuation of each DMARD.

Results
Improvement in clinical assessment in the single and combination treatments with DMARDs
Table III shows the clinical assessments before the administration of DMARDs. The parameters were compared for each drug and the following results were obtained. No differences in disease characteristics were found among the MTX, SSZ and BUC recipients. Figures 1-3 show the changes over time in NPJ, NSJ, and CRP. During the course of the evaluation, statistical analysis was stopped when the number of patients receiving a particular DMARD decreased to less than four.

The effects of MTX, SSZ and BUC on the NPJ and NSJ were observed for the first three months after the initiation of single treatments (Figs. 1 and 2). In particular, the NPJs and NSJs decreased significantly during MTX and BUC single treatments for 108 months. On the other hand, SSZ treatment could not significantly decrease the NPJs and the NSJs even after 48 months. As for the MTX + BUC, and MTX + SSZ combination treatments, NPJs and NSJs decreased significantly until about 60 months. CRP levels and ESR significantly improved during the first three months after the initiation of single treatments with MTX, SSZ and BUC (Fig. 3). In single treatments, CRP levels improved significantly for more than 120 months for MTX and 72 months for BUC; NPJs and NSJs also improved over the same time period. However, in the single treatment with

Table III. Clinical parameters before administration of methotrexate, sulfasalazine, and bucillamine.

Clinical parameters	MTX	SSZ	BUC	MTX+BUC	MTX+SSZ	SSZ+BUC
No. of painful joints	3.5 ± 4.0	3.1 ± 3.9	3.7 ± 4.6	3.7 ± 4.7	4.2 ± 4.4	3.8 ± 4.6
No. of swollen joints	8.2 ± 5.6	6.1 ± 5.8	7.0 ± 5.9	6.4 ± 5.9	8.7 ± 5.8	6.9 ± 5.8
CRP (mg/dl)	3.2 ± 2.9	2.6 ± 2.6	2.4 ± 2.9	2.9 ± 3.0	3.5 ± 3.3	2.4 ± 3.0
ESR (mm/hr)	59.8 ± 29.6	48.5 ± 29.0	48.1 ± 28.6	50.0 ± 30.3	61.4 ± 31.4	47.8 ± 29.5
MS (min)	22.9 ± 72.3	21.1 ± 74.7	35.6 ± 96.6	22.6 ± 71.9	32.9 ± 91.5	38.0 ±100.9
GS (mmHg)	124.0 ± 58.8	147.0 ± 64.6	149.2 ± 65.7	148.9 ± 66.9	122.4 ± 59.4	151.2 ± 67.1
RF (IU/ml)	200.7 ± 279.5	197.8 ± 351.9	175.5 ± 350.4	193.5 ± 246.5	214.0 ± 330.4	163.2 ±274.2
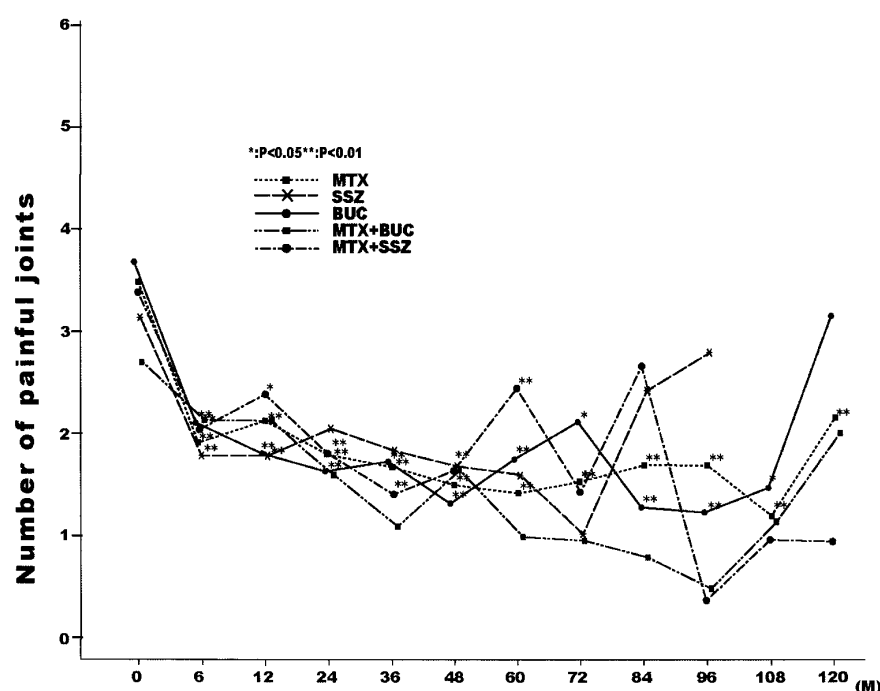
Fig. 1. Changes in the effect of low-dose MTX, SSZ and BUC on the NPJs in single and combination treatments.
The effects of low-dose MTX, SSZ and BUC on the NPJs were observed within the first three months after the initiation of single treatment. In particular, the NPJs decreased significantly during MTX and BUC single treatments for up to 108 months. However, SSZ could not significantly decrease NPJs after 48 months. The combination treatments, MTX + BUC, and MTX + SSZ, significantly decreased NPJs for up to 54 months.

ADRs were 22.2%, 11.0% and 20.6% for MTX, SSZ and BUC, respectively, and for the combination treatments they were 30.0% for MTX + BUC and 31.2% for MTX + SSZ; the incidences of ADRs for DMARD combination treatments were fairly high compared with the rates for single treatments (Table IV). Regarding the nature of the ADRs, for the single treatment with MTX, liver, renal and pulmonary dysfunctions were the main ADRs. On the other hand, for the single treatment with BUC, cutaneous disorders and renal dysfunctions were the main ADRs and for the single treatment with SSZ, cutaneous disorders and gastrointestinal dysfunctions were the main ADRs (Table IV).

Discussion

SSZ and BUC in Japan are the most commonly used DMARDs for first line treatment of early RA with similar usage as MTX, the main drug for the treatment of early RA (4, 19). The administration of MTX as the first DMARD for the treatment of newly diagnosed RA patients has increased considerably throughout the years (12). Currently, this regimen has also improved the condition of Japanese RA patients. Once MTX is employed, the probability of switching to another DMARD is low. This is in line with the high retention rate of MTX compared with other agents (8, 20). At the initiation of therapy, the CRP levels and ESR were higher for MTX than for SSZ and BUC (Table II). This suggests that patients with a more active disease were more likely to be treated with MTX than with other DMARDs, while SSZ and BUC were used more in patients with a low disease activity.
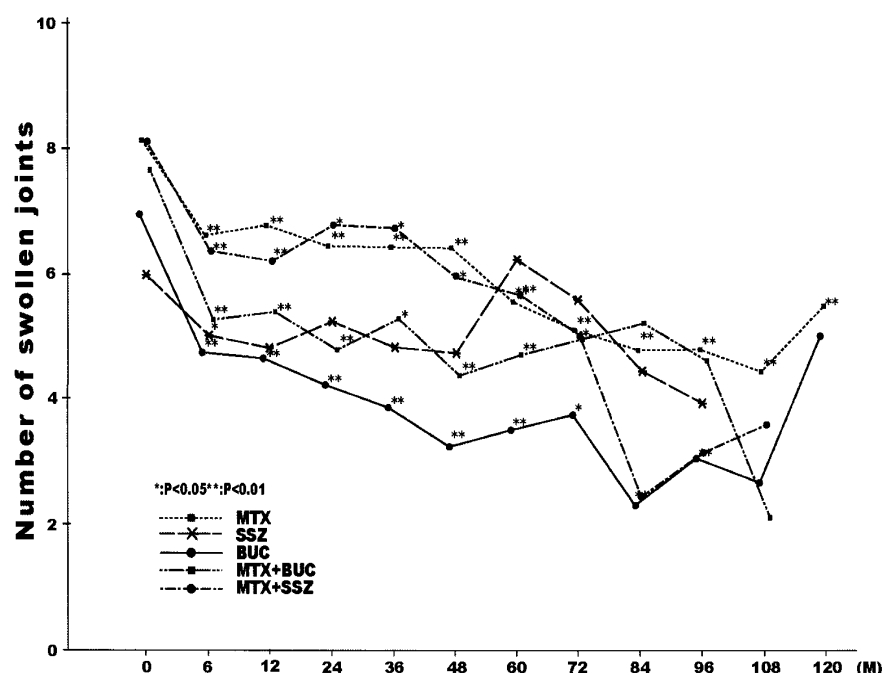Regarding the discontinuation of treat-

SSZ, CRP levels and ESR slightly improved for 48-60 months after the initiation of treatment as did the NPJs and NSJs. As for the combination treatment of MTX + BUC, CRP levels and ESR significantly improved for 108 months, whereas the MTX + SSZ, these levels significantly improved for 72 months.

Duration of continuous treatment with DMARDs in single and combination therapy
Figure 4 shows the continuation rates of MTX, SSZ and BUC with inefficacy and inadequate efficacy as the end point. For single drug treatments, at the 120 months point MTX had the highest continuation rates (83.1%), followed by BUC (76.0%) and SSZ (68.5%) and for the combination treatments, the continuation rates followed by MTX + BUC (83.3%) and MTX + SSZ (71.0%). Figure 5 shows the continuation rates of MTX, SSZ and BUC with ADRs as the end point. For single drug treatments, at the 120 months point SSZ had the highest continuation rate (88.0%), followed by BUC (79.6%) and MTX (79.4%). For the combination treatments, the continuation rates were MTX + BUC (73.3%) and MTX + SSZ (65.6%).

For single treatments, the incidences of

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Fig. 2. Changes in the effect of low-dose MTX, SSZ and BUC on the NSJs in single and combination treatments.
There was a statistically significant decrease in the NSJs during administration of single treatments with MTX and BUC for up to 108 months, however single treatment with SSZ did not decrease NSJs after 48 months and the combination treatments of MTX + BUC, and MTX + SSZ also did not significantly decrease NSJs after 54 months.
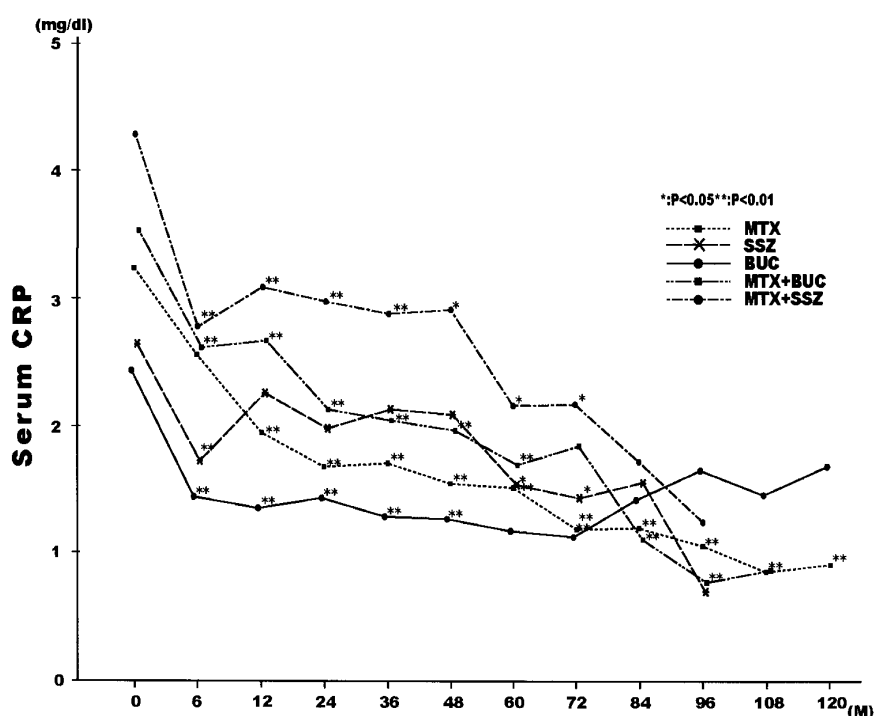

Fig. 3. Changes in the effect of low-dose MTX, SSZ and BUC on CRP levels in single and combination treatments.
CRP levels improved significantly during the first three months after the initiation of single treatments with MTX, SSZ and BUC. In particular, MTX and BUC showed lasting improvement in lowering CRP levels for up to 108 months, however SSZ significantly improved CRP levels for only 48-60 months. MTX+BUC combination treatment significantly decreased CRP levels for 108 months, MTX + SSZ decreased it for 72 months.

ment with DMARDs in the first course, the main reasons were ADRs, inefficacy, and decline of efficacy. For MTX, Alarcon *et al.*, Pincus *et al.* and Hoekstra *et al.* reported the survival rates of 50% (21), 55% (1) and 64% (22), respectively, at the 5-year point, in particular folate supplementation, and to a lesser extent prednisolone administration, were strongly associated with MTX survival (22). Weinblatt *et al.* (3) reported a survival rate of 49% at the 6-year point; the reason for discontinuing MTX treatment was primarily ADRs. In the present study, for MTX the discontinuations were mainly due to occurrence of ADRs. For SSZ, the 5-year survival rate was approximately 20%, and the incidence of ADRs was relatively low compared with the other drugs, therefore, the main reason for the discontinuation of treatment was the recurrence of symptoms (6, 23-25). In the present study, there was a significant decrease in the improvements of the NPJ, NSJ, CRP levels, and ESRs after 108 months of monotherapy with MTX or BUC. However, there was a gradual decrease in the improvement of these parameters from approximately the 30-36 month of treatment, which suggests a decrease in the efficacy of SSZ, possibly because of the development of the 'escape phenomenon'. In these cases we experienced that switching to MTX significantly improved the patient's conditions after SSZ became ineffective. On the other hand, Galindo-Rodriguez (10) and Aletaha (26) reported that the survival rates of the DMARDs used in the present study decreased similarly to those of other DMARDs after 6 years, even for MTX, which had the highest survival rate of 40%, followed by SSZ with a survival rate of approximately 20%, or lower than 20% for D-penicillamine. The survival rates of these drugs decreased sharply at the 6-year point compared with those at the 5-year point.

ADRs were the prime reason for discontinuing MTX, confirming that it is the main limiting factor in long-term MTX treatment (21). Compared with the other DMARDs, the incidence of ADRs to MTX, such as pulmonary and renal dysfunctions caused mainly by
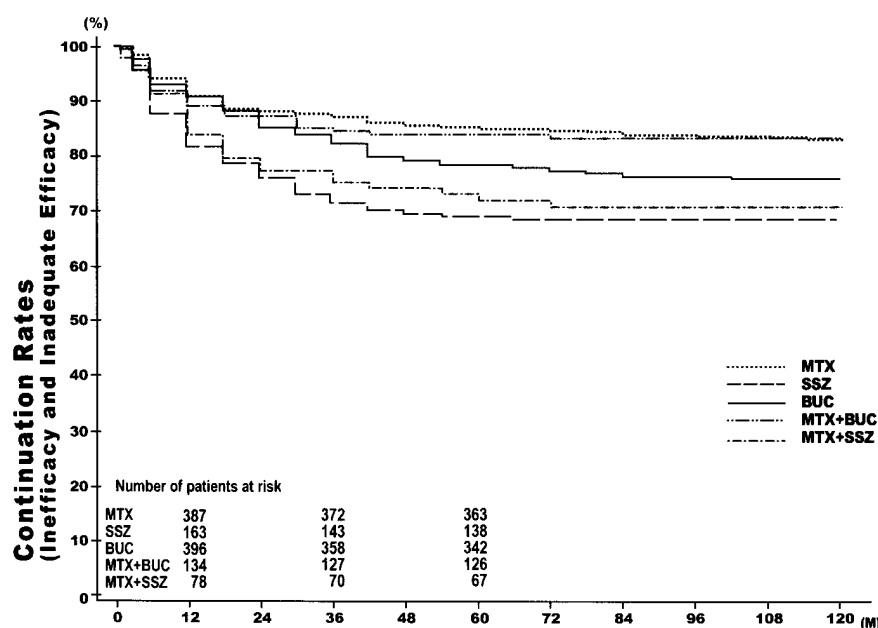
Fig. 4. Continuation rates of low-dose MTX, SSZ and BUC with inefficacy and inadequate efficacy as the end point in single and combination treatment.
The continuous rates of MTX, SSZ and BUC for single treatments were 83.1%, 68.5%, and 76.0%, respectively and those of MTX+BUC and MTX+SSZ for combination treatment were 83.3% and 71.0% respectively.
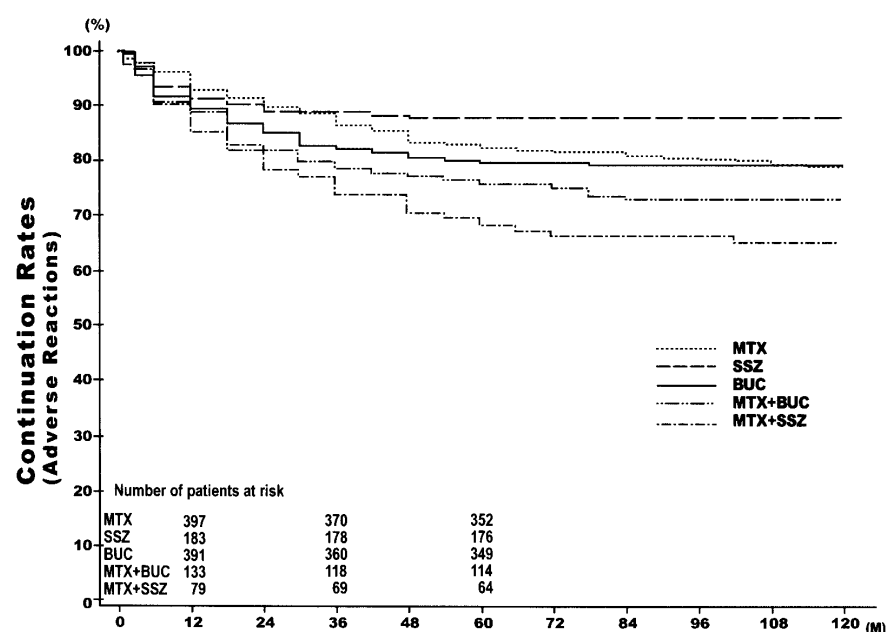

Fig. 5. Continuation rates of low-dose MTX, SSZ and BUC with ADRs as the end point in single and combination treatment.
The continuous rates of MTX, SSZ and BUC for single treatments were 79.4%, 88.0%, and 79.6%, respectively and those of MTX+BUC and MTX+SSZ for combination treatment were 73.3% and 65.6% respectively.

accumulation of the drug, is high. In particular, on the basis of a long-term (19 years) study, 44% of deaths were caused by cardiovascular diseases (27). In this study, the continuation rates of low-dose MTX with inefficacy or poor efficacy was also higher than that of BUC and SSZ both in single and combination treatment, even though the continuation rates of low-dose MTX with ADRs was lower than that of the other DMARDs. In this study, the inci-

dence of discontinuing treatment with single agent low-dose MTX as a result of serious liver dysfunction was only 22.2% (which we defined as persistent elevation of liver function enzymes to more than three times normal requiring discontinuation), or renal, or pulmonary dysfunctions. There is a difference in the toxicity of MTX between our study and that of De La Mata *et al.* (28) who stated that 37% of their discontinued treatments were due to ADRs, while the percentage in this study as well as that obtained in the study of Papadopoulos *et al.* with Greek RA patients were lower, although the dosage of MTX was very low (0.15 mg/kg) (29). The dose of MTX used in Japan is lower than reported in studies from other countries, when using survival rates in long-term follow-up or inefficacy, the continuation rate reported here is also lower than in other countries. However, we have established here that when ADRs are used as the end point, the continuation rate is higher than in other countries, because of the low-dose MTX regimen employed in Japan.

Our data may suggest that low-dose MTX, SSZ and BUC have efficacy at low dosages from the point of continuation rate. However, combination therapies result in less than the expected efficacy or continuation rate. Because Figure 5 indicates that combination therapy does not always show have a high continuation rate when ADRs are taken as the end point, Table IV also shows the high rates of ADRs on combination treatment (MTX+BUC and MTX+SSZ) compared with single agent treatment. In the present study, in the case of MTX+ SSZ and MTX + BUC combination treatments, the ADRs observed during single treatments with SSZ and BUC occurred in the early stage and caused the combination treatments to be discontinued; this explains the low incidence of organ disorders due to MTX alone (30). The combination of drugs with different toxicities or the use of low doses of toxic drugs in combination may decrease the risks associated with combination DMARD therapy while maintaining or increasing their efficacy

Table IV. Types of adverse drug reactions and incidence of development for methotrexate, sulfasalazine, and bucillamine in single and combination treatment.

Symptoms	MTX	SSZ	BUC	MTX+BUC	MTX+SSZ	SSZ+BUC
Cutaneous	28	9	35	17	10	2
Liver	20	3	3	3	2	1
Renal	17	2	37	14	5	3
Pulmonary	16	2	3	8	1	1
Gastrointestinal	8	5	3	4	11	3
Hematologic	6	1	6	0	2	0
Others	16	0	5	6	2	1
Total (%)	95/427 (22.2%)	22/200 (11.0%)	90/437 (20.6%)	45/150 (30.0%)	29/93 (31.2%)	11/51 (21.6%)

(31), and the survival rate of MTX + SSZ combination therapy was comparable to that of MTX monotherapy, and was higher than that of SSZ monotherapy (32). According to Landewe *et al.* (33), the combination of prednisolone with MTX+SSZ was superior to the administration of SSZ alone because the combination treatment suppressed the activity and radiological progression of early RA. Conversely, a prospective study of patients with early RA treated with MTX+SSZ during the first year did not show a bigger impact on the long-term inflammatory status, or disability, for the combination regimen compared to treatment with a single DMARD (34). In the present study, the order of the continuation rates with inefficacy and poor efficacy as the end point for the combination treatments were as follows: MTX + BUC >MTX + SSZ.

According to a short term follow-up study of 48 weeks, combination therapy with MTX and SSZ at the doses utilized here was not associated with greater toxicity than treatment with either agent alone, and neither was enhanced efficacy observed. There was a trend toward decreased radiologic progression in patients treated with MTX (35). However, Rau *et al.* (36) reported that combination therapy of MTX with other DMARDs is effective in reducing clinical disease activity; this study did not show a clear advantage for effectiveness for combination therapy versus monotherapy.

Despite clinical improvement on switching to a new DMARD or undertaking DMARDs combination therapy, articular erosion continues in RA and is associated with continuing synovial inflammation (37). In that study, radiological joint damage occurred early and progressed significantly during the 5-year follow-up. The rate of progression was most rapid during the first 2 years (38). Callahan *et al.* (39) reported that most measures of inflammatory activity were unchanged and sometimes even improved, while measures of damage indicated progressively worse status in the same patients over 5 years. Pincus *et al.* also reported that according to longitudinal observations over 5-20 years, Disease Activity Scores showing decreased inflammation do not prevent long-term joint damage (40) and they also suggested that the inclusion of patient questionnaire material would add quantitative data to document severity and monitor improvement in individual patients with RA (41). Even though several DMARDs therapies in RA suppress inflammation, but unfortunately not erosion, these findings suggest that the pathogenesis of articular erosion, namely bone and cartilage destruction may differ from that of synovial or systemic inflammation.

Among the several DMARDs studied here, MTX administered as a single agent or in combination with others had the highest efficacy and continuation rate compared with other DMARDs, SSZ and BUC. On the other hand, continuation rates of combination treatments with ADRs as the end point were lower than those of single treatments by MTX, SSZ and BUC, and the incidence of ADRs in combination treatments was higher than that in single treatments. We therefore recommend switching to a new DMARD in the case of inadequate efficacy of the first DMARD, rather than attempting combination therapy with that ineffective or toxic DMARD and another in addition.

References

1. PINCUS T, MARCUM SB, CALLAHAN LF: Long term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. *J Rheumatol* 1992; 19: 1885-94.
2. KREMER JM: Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: follow-up after a mean of 13.3 years. *Arthritis Rheum* 1997; 40: 984-5.
3. WEINBLATT ME, WEISSMAN BN, HOLDSWORTH DE *et al.*: Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1992; 35: 129-37.
4. BOLOGNA C, SANY JJ: Methotrexate as the initial second-line disease modifying agent in the treatment of rheumatoid arthritis patients. *Clin Exp Rheum* 1997; 15: 597-601.
5. CAPELL HA, MAIDEN N, MADHOK R, HAMPSON R, THOMSON EA: Intention-to-treat analysis of 200 patients with rheumatoid arthritis 12 years after random allocation to either sulfasalazine or penicillamine. *J Rheumatol* 1998; 25: 1880-6.
6. JONES E, JONES JV, WOODBURY JFL: Response to sulfasalazine in rheumatoid arthritis: Life table analysis of a 5-year follow up. *J Rheumatol* 1991; 18: 195-8.
7. ICHIKAWA Y, SHINOZAWA T, YOSHIDA T *et al.*: Methotrexate and salazosulphapyridine in the long term treatment of rheumatoid arthritis. *Ryumachi* 1995; 35: 663-70.
8. WOLFE F, HAWLEY DJ, CATHEY MA: Termination of slow acting anti-rheumatic therapy in rheumatoid arthritis: A 14-year prospective evaluation of 1017 consecutive starts. *J Rheumatol* 1990; 17: 994-1002.
9. SUAREZ-ALMAZOR ME, SOSKOLNE CL, SAUNDERS D, RUSSELL AS: Use of second line drugs for the treatment of rheumatoid arthritis in Edmonton, Alberta. Patterns of prescription and long term effectiveness. *J Rheumatol* 1995; 22: 836-43.
10. GALINDO-RODRIGUEZ G, AVINA-ZUBIETA JA, RUSSELL AS, SUAREZ-ALMAZOR ME: Disappointing long term results with disease modifying antirheumatic drugs. A practice based study. *J Rheumatol* 1999; 26: 2337-43.
11. MAETZEL A, WONG A, STRAND V, TUGWELL P, WELLS G, BOMBARDIER C: Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology* 2000; 39: 975-81.
12. ALETAHA D, SMOLEN JS: The rheumatoid arthritis patient in the clinic: comparing more than 1300 consecutive DMARD courses. *Rheumatology* 2002; 41: 1367-74.
13. MAINI R, ST CLAIR EW, BREEDVELD F *et al.*: Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving

concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999; 354: 1932-9.

14. SMOLEN JS, KALDEN JR, SCOTT DL *et al.*: Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomized, multicentre trial. European Leflunomide Study Group. *Lancet* 1999; 353: 259-66.

15. WEINBLATT ME, KREMER JM, BANKHURST AD *et al.*: A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-9.

16. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.

17. FRIES JF: Reevaluating the therapeutic approach to rheumatoid arthritis: the "sawtooth" strategy. *J Rheumatol* 1990; 17: 12-5.

18. KASHIWAZAKI S, ICHIKAWA Y, SUGAWARA S *et al.*: Determination of the clinical optimal dose of L-377 (methotrexate capsule) for the treatment of rheumatoid arthritis. *Jap J Inflammation* 1996; 16: 437-58.

19. PINCUS T, YAZICI Y, SOKKA T, ALETAHA D, SMOLEN JS: Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. *Clin Exp Rheum* 2003; 21 (Suppl. 31): S179-85.

20. KREMER JM, PHELPS CT: Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. Update after a mean of 90 months. *Arthritis Rheum* 1992; 35: 138-45.

21. ALARCON GS, TRACY IC, BLACKBURN WDJR: Methotrexate in rheumatoid arthritis: toxic effects as the major factor in limiting long term treatment. *Arthritis Rheum* 1989; 32: 671-6.

22. HOEKSTRA M, VAN DE LAAR MA, BERNELOT MOENS HJ, KRUIJSEN MW, HAAGSMA CJ: Long term observational study of methotrexate use in a Dutch cohort of 1022 patients with rheumatoid arthritis. *J Rheumatol* 2003; 30: 2325-9.

23. CARROLL GJ, WILL RK, BREIDAHL PD, TINSLEY LM: Sulphasalazine versus penicillamine in the treatment of rheumatoid arthritis. *Rheumatol Int* 1989; 8: 251-5.

24. SITUNAYAKE RD, GRINDULIS KA, MCCONKEY B: Long term treatment of rheumatoid arthritis with sulphasalazine, gold or penicillamine: a comparison using life-table methods. *Ann Rheum Dis* 1987; 46: 177-83.

25. MCENTEGART A, PORTER D, CAPELL HA, THOMSON EA: Sulphasalazine has a better efficacy/toxicity profile than auranofin- evidence from a 5 year prospective, randomized trial. *J Rheumatol* 1996; 23: 1887-90.

26. ALETAHA D, SMOLEN JS: Effectiveness profiles and dose dependent retention of traditional disease modifying anti rheumatic drugs for rheumatoid arthritis. an observational study. *J Rheumatol* 2002; 29: 1631-8.

27. CHOI HK, HERNAN MA, SEEGER JD, ROBINS JM, WOLFE F: Methotrexate and mortality in patients with rheumatoid arthritis: A prospective study. *Lancet* 2002; 359: 1173-7.

28. DE LA MATA J, BLANCO FJ, GOMEZ-REINO JJ: Survival analysis of disease modifying antirhumatic drugs in Spanish rheumatoid arthritis patients. *Ann Rheum Dis* 1995; 54: 881-5.

29. PAPADOPOULOS NG, ALAMANOS Y, PAPADOPOULOS IA, TSIFETAKI N, VOULGARI PV, DROSOS AA: Disease modifying antirheumatic drugs in early rheumatoid arthritis: A longterm observational study. *J Rheum* 2002; 29: 261-6.

30. NAGASHIMA M, SHU G, YAMAMOTO K, YAMAHATSU S, YOSHINO S: The ability of disease-modifying antirheumatic drugs to induce and maintain improvement in patients with rheumatoid arthritis -Epidemiology of DMARD treatment in Japan. *Clin Exp Rheum* 2005; 23: 27-35.

31. PAULUS HE: The use of combinations of disease modifying antirheumatic agents in rheumatoid arthritis. *Arthritis Rheum* 1990; 33: 113-20.

32. AXTENS RS, MORAND EF, LITTLEJOHN GO: Combination therapy with methotrexate and sulphasalazine in rheumatoid arthritis -tolerance of therapy. *Ann Rheum Dis* 1994; 53: 703.

33. LANDEWE RB, BOERS M, VERHOEVEN AC *et al.*: COBRA combination therapy in patients with early rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 347-56.

34. MAILLEFERT JF, COMBE B, GOUPILLE P, CANTAGREL A, DOUGADOS M: Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. *Ann Rheum Dis* 2003; 62: 764-6.

35. WILLKENS RF, SHARP JT, STABLEIN D, MARKS C, WORTMANN R: Comparison of azathioprine methotrexate, and the combination of the two in the treatment of rheumatoid arthritis. A forty-eight-week controlled clinical trial with radiologic outcome assessment. *Arthritis Rheum* 1995; 38: 1799-806.

36. RAU R, SCHLEUSSER B, HERBORN G, KARGER T: Long term combination therapy of refractory and destructive rheumatoid arthritis with methotrexate (MTX) and intramuscular gold or other disease modifying antirheumatic drugs compared to MTX monotherapy. *J Rheumatol* 1998; 25: 1485-92.

37. MULHERIN D, FITGERALD O, BRESNIHAN B: Clinical improvement and radiological deterioration in rheumatoid arthritis: Evidence that pathogenesis of synovial inflammation and articular erosion may differ. *Br J Rheumatol* 1996; 35: 1263-8.

38. FEX E, JONSSON K, JOHNSON U, EBERHARDT K: development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. *Br J Rheumatol* 1996; 35: 1106-15.

39. CALLAHAN LF, PINCUS T, HUSTON JW, III, BROOKS RH, NANCE EP JR, KAYE JJ: Measures of activity and damage in rheumatoid arthritis: Depiction of changes and prediction of mortality over five years. *Arthritis Care Res* 1997; 10: 381-94.

40. PINCUS T, SOKKA T: Partial control of Core Data Set measures and Disease Activity Score (DAS) measures of inflammation dose not prevent long-term damage: evidence from longitudinal observation over 5-20 years. *Clin Exp Rheumatol* 2002; 20 (Suppl. 27): S42-48.

41. PINCUS T, SOKKA T: Quantitative measures and indices to assess rheumatoid arthritis in clinical trials and clinical care. *Rheum Dis Clin North Am* 2004; 30: 725-51.