The ability of disease modifying antirheumatic drugs to induce and maintain improvement in patients with rheumatoid arthritis. Epidemiology of DMARDs treatment in Japan

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Abstract

Objective

The effectiveness of the disease-modifying antirheumatic drugs (DMARDs) methotrexate (MTX), bucillamine (BUC), salazosulphapyridine (SASP) and gold sodium thiomalate (GST) over two courses of treatment with a follow-up period of at least 12 months was evaluated in 425 patients with rheumatoid arthritis.

Methods

Clinical efficacy was evaluated on the basis of the numbers of painful and swollen joints, morning stiffness, grip strength, erythrocyte sedimentation rate, C-reactive protein and rheumatoid factor levels before and after treatment. Results were evaluated on the basis of the survival rate (Kaplan-Meier method) and the incidence and types of adverse drug reactions (ADR) following single and combined therapies.

Results

In the first course of treatment, the survival rates for MTX, GST, BUC and SASP were 52.3%, 40.4%, 33.0% and 24.8%, respectively. The rates of development of ADR were 22.9%, 23.5%, 26.3% and 30.0% for BUC, SASP, GST and MTX, respectively. In the second course, the survival rates for MTX, BUC and SASP were 36.6%, 14.1% and 10%, respectively.

Conclusion

DMARDs used in the first course of treatment improved the clinical parameters until the 6th month after initiation of treatment. Combination treatments showed some effectiveness, but because of the high incidence of ADR the survival rate was low. DMARDs used in the second course of treatment were not efficacious and there was no improvement in the survival rate compared to the first course of treatment.

Key words

Rheumatoid arthritis, disease modifying antirheumatic drugs, survival rate, adverse drug reactions, escape phenomenon.

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Introduction

Rheumatoid arthritis (RA) is usually a progressive, long-term disease requiring drug therapy for many years, and therefore it is important to select the appropriate disease-modifying antirheumatic drugs (DMARDs), which are the second-line of medical treatment. How long the selected drugs can be used (i.e. the cumulative continuation or survival rate) depends on their type. Long-term studies of more than 5 years on the performance and survival rate of methotrexate (MTX) (1-4) and salazosulphapyridine (SASP) (5-7) have been reported, as have comparisons of the performance and survival rates of various DMARDs (8-13). However, because of adverse drug reactions (ADR), lack of or inadequate efficacy, current treatment guidelines recommend selecting a DMARD and then switching to or adding another DMARD for a combination regimen after stopping the drugs used in the first course of treatment (14).

We need to clarify fully the role of DMARDs because biological agents, such as tumor necrosis factor (TNF) and TNF receptor blocking agents (15, 16), which effectively suppress disease activity and may retard or restrict radiological progression, have been developed and introduced as treatments. The present study used various clinical parameters to compare not only the survival rates of various DMARDs used singly in the first course of treatment, but also the efficacy, the type of ADR and when they developed of those DMARDs used in combination treatments. In addition, we compared the survival rates with newly selected drugs used in the second course of single-drug treatment and combination treatments with the survival rates for drugs used in the first course of treatment.

We have identified the most effective single drug treatment on the basis of survival rates and ADR in the patients to whom DMARDs were administered, and the best combination of them. In addition, we have determined DMARDs which should be selected for first treatment of RA by statistically analyzing incidence rates, types, and intervals between commencement of administration of various DMARDs and occurrence of ADR. To clarify features and ADR of DMARDs and to assess the survival rate of the patients to whom DMARDs were given are extremely important for pursuing rational pharmacological treatment.

Methods

Selection of patients

The study group comprised 425 outpatients suffering from RA who visited the department between May 1997 and April 2002, and who satisfied the ACR criteria (17). Some of patients have been newly prescribed DMARDs and some of patients have been prescribed other DMARDs after a DMARD has been washed out for two to four week by one of three rheumatologists: bucillamine (BUC) was given to 192 patients, MTX to 78 patients, SASPto 68 patients and gold sodium thiomalate (GST) to 19 patients. The combination treatments were as follows: BUC + MTX was given to 26 patients, BUC + SASPto 11 patients, and SASP + MTX to 9 patients. The remaining 22 patients were given other DMARDs: auranofin to 7 patients, D-penicillamine to 5 patients, actarit to 4 patients and other combinations to 6 patients (SASP + GST and BUC + GST to 2 patients, respectively, MTX + GST to 1 patient and BUC + MTX + SASPto 1 patient). The patients were not always randomized. Because three rheumatologists have prescribed several DMARDs according to the clinical activity.

Table I and Table II show profiles of patients who were given DMARDs as the first and second courses of treatment, and the previous DMARDs history before commencement of the drug treatment. The second course of treatment means switching or new added DMARDs therapies because of inefficacy or ADR in the first course of treatment. There were 70 males and 355 females (n = 425). The average age was 56.6 years (15-85 years) and the average disease duration was 7.8 years (0.1-59 years). Prednisolone was prescribed for 254 patients at an average dose of 5.2 mg (1-25 mg); the remaining 171 patients were not given it. In the second

Table I. Comparison of clinical profiles before administration of the various DMARDs used in the first course and second course of treatment.

	First course	Second course
Total	425	114
Male	70	11
Female	355	103
Age (years)*	56.6 ± 12.6 (15-85)	58.8 ±10.7 (19-78)
Disease duration (years)*	7.8 ± 9.1 (0.1-59)	8.4 ± 9.8 (0.1-59)
Follow-up periods (months)	21.4 ± 17.0 (1-60)	11.5 ±10.4 (1-42)
Prednisolone (mg)*	5.2 ± 2.5 (1-25)	5.5 ± 2.2 (2-25)
BUC	4.7 ± 2.0	5.8 ± 1.1
MTX	5.3 ± 2.9	5.8 ± 2.9
SASP	5.3 ± 2.3	4.4 ± 2.1
GST	4.3 ± 2.1	7.0 ± 2.8
BUC+MTX	5.7 ± 2.5	5.5 ± 2.0
SASP+MTX	6.4 ± 3.8	4.6 ± 0.9
BUC+SASP	5.9 ± 2.3	6.3 ± 2.1

*: mean±SD

Table II. The previous DMARDs history before commencement of the drug treatment for these patients.

Previous DMARDS	BUC	MTX	SASP	GST	BUC+MTX	SASP+MTX	BUC+SASP
None	97	31	41	9	10	2	3
BUC	44	9	5	1	5	0	2
MTX	3	20	5	0	5	2	0
SASP	2	2	11	0	1	2	0
GST	7	2	1	9	0	0	1
Others*	39	14	5	0	5	3	5
Total	192	78	68	19	26	9	11

* Others include D-penicillamine and auranofin etc.

Table III. Clinical parameters before the administration of the various DMARDs.

Clinical parameter	BUC	MTX	SASP	GST	Others
Number of painful joints	3.8 ± 4.7	4.1 ± 4.5	3.5 ± 4.5	1.8 ± 2.9	2.4 ± 3.3
Number of swollen joints	6.9 ± 6.1	8.3 ± 5.8	5.3 ± 5.1	2.2 ± 2.6	5.5 ± 5.9
ESR (mm/hr)	45.8 ± 28.9	57.8 ± 32.8	46.0 ± 29.4	31.8 ± 23.7	32.3 ± 16.0
MS (min)	46.2 ±112.2	41.7 ±107.7	28.2 ± 86.8	23.7 ± 49.3	22.0 ± 46.4
GS (mmHg)	151.3 ± 67.3	127.7 ± 62.1	155.5 ± 68.5	188.8 ± 62.3	169.7 ± 63.5
CRP(mg/dl)	2.3 ± 3.1	3.7 ± 3.4	2.3 ± 2.5	1.2 ± 1.2	1.3 ± 1.6
RF (IU/ml)	152.0 ±218.8	153.1 ±171.7	185.3 ±204.4	143.5 ±266.5	207.0 ±250.1

course of treatment, there were 11 males and 103 females (n = 114), the average age was 58.8 years (19-78 years) and the average disease duration was 8.4 years (0.1-59 years). Of these 72 patients were given prednisolone at an average dose of 5.5 mg (2-25 mg).

The standard dosages of DMARDs were as follows: 100-200 mg/day for BUC (maximum dose in Japan: 300 mg), 1000-1500 mg/day for low-dose SASP (maximum dose in Japan: 1000 mg), 6-8 mg/week for low-dose MTX (18) (maximum dose in Japan: 8 mg) and 25 mg/ two weeks for GST. However, in the case of nausea caused by administration of MTX, folate supplementation can be initiated at a low dose of 5 mg/week. Most of patients were given nonsteroidal anti-inflammatory drugs.

Procedure

Clinical symptoms and clinical parameters were evaluated every 6 months for a maximum period of 5 years; the items evaluated were the number of painful joints (NPJ), the number of swollen joints (NSJ), the concentration of C-reactive protein (CRP, mg/dl), erythrocyte sedimentation rate (ESR, mm/hr) and rheumatoid factor (RF, IU/ I). We used the Kaplan-Meier method to calculate the survival rates of the DMARDs used in single or combination treatment with inefficacy, inadequate efficacy and ADR as the endpoints. The types of ADR, their incidence and time of development were investigated. We calculated and compared their associated survival rates using the same endpoints as in the first and second courses of treatment.

Statistical analysis

All data were expressed as the mean ± SD in the tables and the mean ± SE in the figures. During the course of the evaluation, statistical analysis was suspended when the number of patients receiving a particular DMARD fell below six. Differences for each data were analyzed by the 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 was used to estimate the probability of discontinuation for each DMARD.

Results

Improvement of clinical parameters by DMARDs in the first course of treatment

Tables II and III shows clinical parameters before the administration of the various DMARDs. These data were compared for each drug and the following results were obtained. No differences were found among the BUC, MTX and SASP recipients; however, compared with the patients who were given those three DMARDs, it appears that GSTwas administered more frequently to patients with mild symptoms. Figures 1-3 show changes in NPJ, NSJ and CRPlevels with time.

The effect of BUC, MTX and SASP on

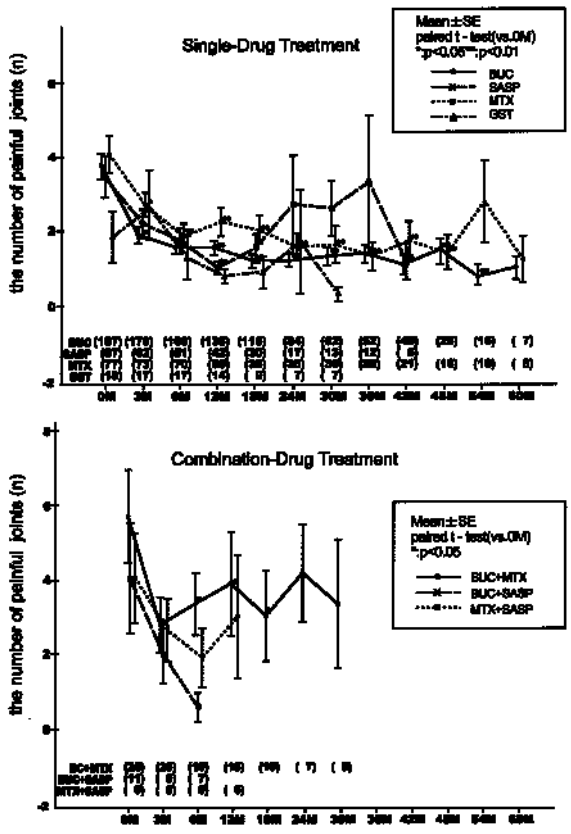

Fig. 1. Changes in efficacy of the various DMARDs in terms of the number of painful joints. The effects of BUC, MTX and SASPin terms of the number of painful joints (NPJ) were observed within the first 3 months after the initiation of treatment. Although the efficacy of GST was delayed compared with the three drugs, a reduction in NPJ was observed within 6 months of administration. In particular, NPJ statistically significantly decreased during BUC and MTX administration until 54 and 48 months.

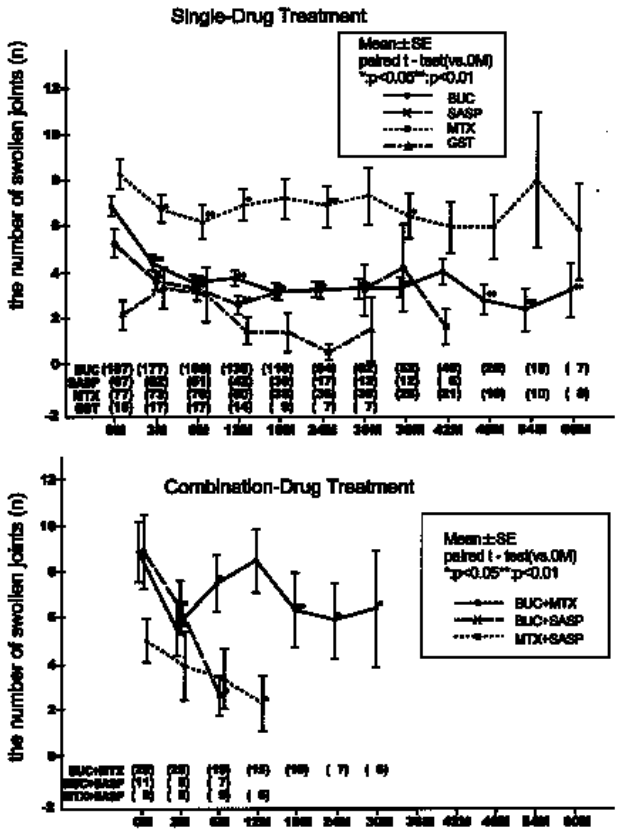

Fig. 2. Changes in efficacy of the various DMARDs in terms of the number of swollen joints. The number of swollen joints (NSJ) statistically significantly decreased during BUC, MTX and SASPadministration until 60, 36 and 12th months. BUC+MTX shows the significance decrease in NSJ until 30 months.

the NPJ and NSJ was observed within the first 1-3 months after the initiation of single treatment (Figs.1 and 2). Although the efficacy of GST was delayed compared with the other three drugs, a reduction in NPJ was observed within 6 months of therapy. In particular, the NPJ significantly decreased during BUC and MTX administration until 54 and 48 months, respectively. The BUC + MTX combination showed a significant decrease in the NPJ from 3 to 18 months after the initiation of treatment. Similar to the trends for NPJ, the NSJ significantly decreased during BUC, MTX and SASP administration until 60, 36 and 12 months, respectively, and the BUC+MTX combination showed a significant decrease in NSJ until 30 months without at 12 months.

The CRP and ESR levels significantly improved during the first 1-3 months after the initiation of BUC, MTX and SASP treatment (Fig. 3). There was a statistically significant improvement at 6 months after the initial administration of GST, which was later than for the other three drugs. BUC and MTX, in particular, significantly improved CRP levels for almost 60 months, which was similar to the improvement in the NPJ and NSJ. However, as with the trends for the NPJ and NSJ during treatment with SASP, the CRP levels increased slightly after the 24th month. The RF levels did not change significantly (data not shown).

Using the same endpoint as in the first course of treatment, we found no significant differences in NPJ, NSJ, ESR and CRPlevels among the patients who were given as second-course treatment either single-drug treatment with BUC, MTX and SASPor SASP+ MTX, BUC + MTX and BUC + SASP. For all drug combinations, there was no significant improvements in the clinical parameters, as observed in the first course, after beginning second-course treatment (data not shown).

Survival rate and development of ADR of the DMARDs in the first course of treatment

Figure 4 shows the survival rates of the various DMARDs. For single-drug treatments, at the 5-year point MTX had the highest survival rate (52.3%), followed by GST (40.4%), BUC (33.0%) and SASP (24.8%). For the combination treatments, the order of the survival rates was BUC + SASP (32.7%) at the 24-month point, BUC + MTX (24.7%) at the 5-years point, and SASP + MTX (20.8%) at the 30-month point.

The incidence of ADR was 22.9%, 21.8%, 14.7%, and 21.1% for BUC, MTX, SASPand GST, respectively and

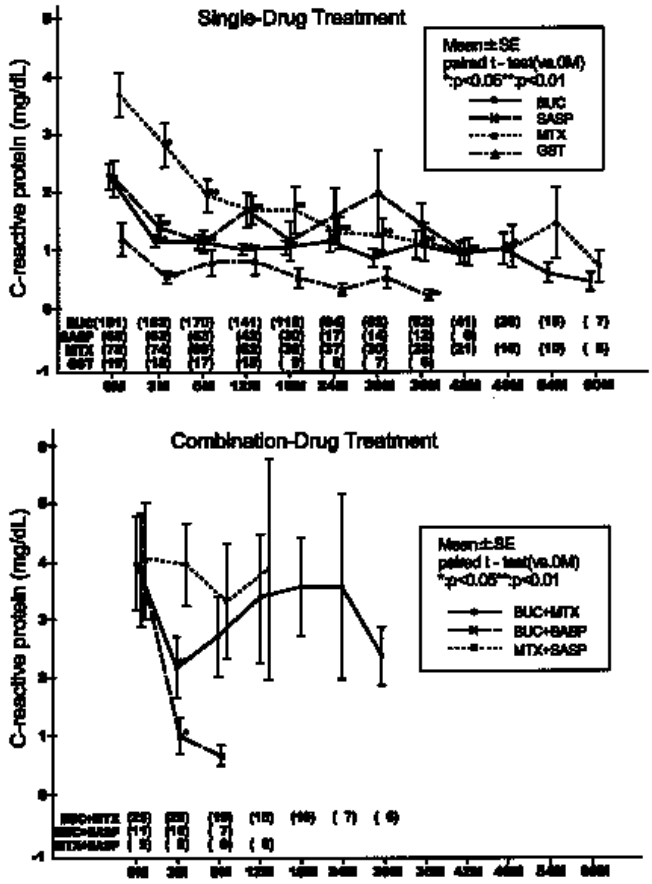

Fig. 3. Changes in efficacy of the various DMARDs in terms of the concentration of C-reactive protein. CRPconcentration significantly improved during the first 1-3 months after the initiation of BUC, MTX and SASP administration. BUC and MTX, in particular, significantly improved CRP level for almost 48 months similar to the improvement in NPJ and NSJ. However, in the case of treatment with SASP, CRPlevel tended to increase slightly after the 24th months.

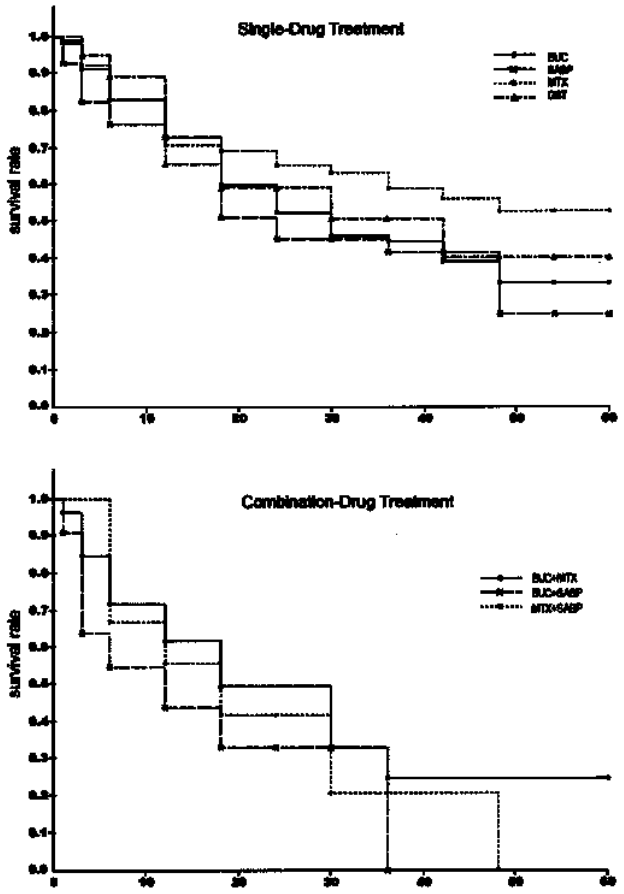

Fig. 4. Survival rates of the various DMARDs used in the first course of treatment.The survival rates for MTX, GST, BUC and SASP were 52.3%, 40.4%, 33.0% and 24.8%, respectively. In the case of combination-drug treatment, the order of survival rates was 32.7%, 24.7% and 20.8% for BUC + SASP, BUC + MTX and SASP+ MTX.

for the combination treatments it was 30.8% for BUC + MTX, 27.3% for BUC + SASP, and 66.7% for SASP + MTX; these rates were fairly high (Table IV).

As shown in Table IV and Figure 4, the combination treatment is not necessarily more effective than the single-drug treatment when the efficacy of the different drugs is evaluated in terms of survival rate and the development of ADR. Rather, in the case of SASP+ MTX, the survival rate was low because of the high incidence of ADR rather than because of a high incidence of inefficacy of that combination. The incidence of ADR in patients receiving combination treatments was higher than in patients treated with single drugs, which we speculate is reflected in the low survival rate of the combination therapies.

With regard to the time of onset of ADR, the average for BUC, MTX, SASP and GST was 12.8 months, 19.3 months, 13.1 months and 10.5 months, respectively, and for BUC + MTX, BUC + SASP and SASP+ MTX it was 10.4 months, 15.0 months and 16.0 months, respectively. As shown in Table IV, cutaneous symptoms and renal dysfunction were the main ADR with BUC and SASP treatment, occurring about 1 year after the initiation of single-drug treatment; in the case of MTX treatment, ADR usually occurred after 1.5 year and were organ disorders such as pulmonary and renal dysfunction without liver dysfunction. With GST treatment, cutaneous symptoms developed at an early stage and proteinuria developed 2-3 years after the initiation of treatment (data not shown). For the BUC + MTX, BUC + SASPand SASP + MTX treatments, as with single-drug treatment with BUC or SASP, mainly cutaneous symptoms developed early in treatment.

Survival rate and development of ADR of the DMARDs in the second course of treatment

As shown in Figure 5, the cumulative survival rates for MTX, BUC and SASP was 36.6% at the 36-month point, 14.1% at the 36-month point and 10.0% at the 36-month point, respectively, and for the combination treatments, it was 13.9% at the 42-month point, 16.4% at the 36-month point and 25.0% at the 18-month, and for BUC+ MTX, SASP+ MTX and BUC + SASP, respectively.

The incidence of ADR was 35.7%,

Table IV. Types of adverse drug reactions, incidence and time of development for the drugs used in the first course of treatment.

Symptoms	BUC	MTX	SASP	GST	BUC+MTX	SASP+MTX	BUC+SASP	Others
Cutaneous	15	4	3	1	3	2	2	2
Liver	3	2	2	0	0	0	1	0
Renal	16	6	1	2	4	1	2	2
Pulmonary	0	3	1	0	0	0	0	0
Gastrointestinal	7	1	3	0	2	3	0	0
Hematologic	3	1	0	0	0	0	0	0
Others	2	4	0	1	1	1	0	1
Total (%)	44/192	17/78	10/68	4/19	8/26	6/9	3/11	4/22
	22.9%	21.8%	14.7%	21.1%	30.8%	66.7%	27.3%	18.20%
Average period of incidence (months)	12.8±11.9	19.3±15.8	13.1±14.7	10.5±5.7	10.4±9.4	16.0±16.4	15.0±18.2	13.5±5.7

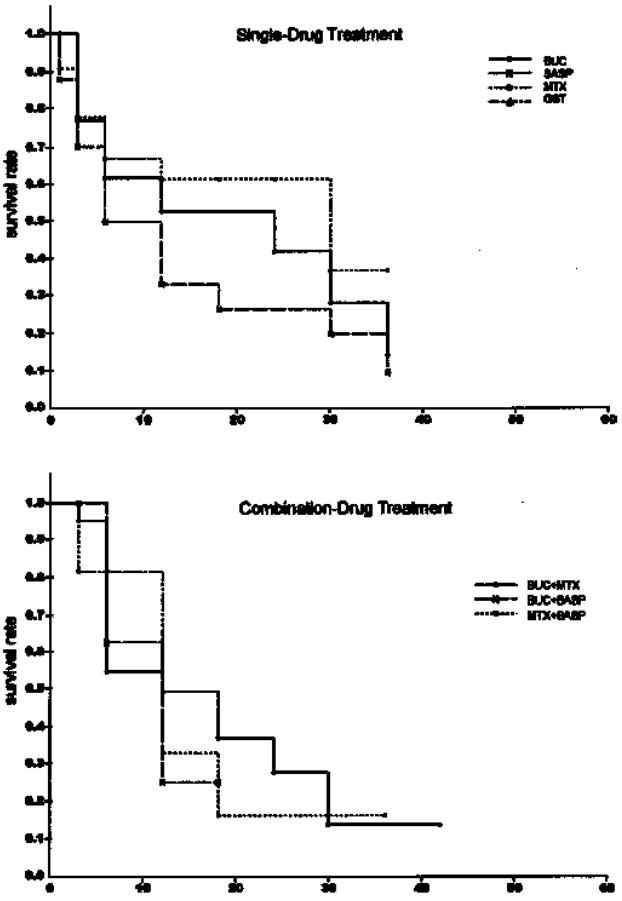

Fig. 5. Survival rates with the various DMARDs used in the second course of treatment. The survival rates for MTX, BUC and SASPwere 36.6%, 14.1% and 10.0%, and for the combinations of drugs, those of BUC + SASP, SASP + MTX and BUC + MTX were 25.0%, 16.4% and 13.9%, respectively.

18.8% and 25.0% for BUC, MTX and SASP, respectively and for the combination treatments, it was 23.8% for BUC + MTX, 22.2% for BUC + SASP, and 18.2% for SASP+ MTX; these rates were fairly high (Table V). With regard to the time of onset of ADR, the average time for BUC, MTX and SASP was 9.0 months, 8.7 months and 8.5 months, respectively, and for BUC + MTX, BUC + SASP and SASP + MTX, it was 13.8 months, 3.5 months and 12.0 months, respectively.

Discussion

The final goal of pharmacological treatment for RA is to achieve remission. To achieve remission, it is important to administer DMARDs continuously and serially in early stages. Fries defined the sawtooth strategy as follows (19). The goals of the sawtooth strategy are to improve the disease outcome to more satisfactory levels and at the same time to keep overall drug toxicity, early DMARD use, continual serial DMARD use, regular quantitative monitoring of disability, setting a disability ceiling for individual patients, sequential change in DMARD treatment when the ceiling is reached. Sokka *et al*. (20) also reported that a prospective study of early RA patients treated for up to 15 years according to the sawtooth strategy indicated that the use of serial and continual DMARDs or combination treatment was safe even in the long run.

DMARDs improved the clinical parameters of NPJ and NSJ in the first 6 months of treatment, and also improved CRPlevels. However, the continued efficacy varied greatly among the DMARDs. With respect to the inflammation parameters and the NPJ and NSJ, MTX and BUC improved these significantly up to the 60th month, whereas SASP improved them significantly until approximately the 18-24th month, after which the values either increased or decreased only slightly.

Regarding the long-term use of MTX, Kremer (1) and Weinblatt *et al*. (3) reported that the NPJ and NSJ improved significantly at the 6-month point, after which the values plateaued. Wolfe *et al*. (8) reported a survival rate at the 4-year point of 50%, which is comparable with the 52.3% obtained in the present study. However, Alarcon *et al.* (21) and Pincus *et al*. (14) reported survival rates of 50% and 55%, respectively, at the 5-year point.

As for suspending treatment with DMARDs in the first course, main reasons are ADR, inefficacy, and decline of efficacy. For SASP, the 5-year survival rate was approximately 20%, and the incidence of ADR was relatively low compared with other drugs, so the

Table V. Types of adverse drug reactions, incidence and time of development for the drugs used in the second course of treatment.

Symptoms	BUC	MTX	SASP	GST	BUC+MTX	S ASP+MTX	BUC+SASP
Cutaneous	2	2	5	0	0	1	0
Liver	0	2	1	0	0	0	0
Renal	4	3	0	0	3	0	0
Pulmonary	0	0	0	0	1	0	1
Gastrointestinal	1	0	1	0	1	0	0
Hematologic	0	0	0	0	0	0	0
Others	1	2	0	0	0	0	1
Total cases (%)	5/14 35.7%	6/32 18.8%	6/24 25.0%	0/2 0%	5/21 23.8%	2/11 18.2%	2/9 22.2%
Average period of incidence (months)	9.0±6.0	8.7±10.0	8.5±11.4	0	13.8±7.2	12.5±8.5	3.5±3.5

main reason for suspension of treatment was the recurrence of symptoms (6, 22-24). In the present study, there was gradual decrease in the improvements of the NPJ and CRP levels and ESR from approximately the 24th month of treatment, which suggests a reduction in the efficacy of SASP, possibly because of the development of the 'escape phenomenon'However, Galindo-Rodriguez (10) and Aletaha (12) 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 34% (10) or 40% (12), followed by GST and SASP, both of which had survival rate of approximately 20%, and D-pencillamine with a survival rate of 20% or lower.

BUC and GST, with survival rates greater than 30%, follow MTX, but the incidence of the organ dysfunction such as pulmonary and renal dysfunction caused mainly by accumulation of the drug that are frequently observed with MTX treatment is low and the ADR are mainly limited to cutaneous disorders and renal dysfunction. According to the report of Ichikawa *et al*. (7), the incidence of suspending MTX treatment because of ADR was higher than for SASP treatment. The ADR of MTX can be serious, such as interstitial pneumonia, but although the ADR of SASP are mild, such as eczema. Jones *et al.* (6) reported that these mild symptoms developed within the first 3 months of treatment. BUC, N-(2-mercapto-2-methylpropionyl)-L-cysteine is similar to D-penicillamine and has two SH residues in its structure and -S-S- bond in metabolic pass way (25). Nishimura *et al*. (26) reported that the survival rate at the 5-year point was 20.6%, the incidence of ADR was 23.5%, and the incidence of suspension of treatment because of inefficacy was 17.6% in RApatients in Japan.

Munro *et al.* studied the ESR, CRPlevels, NPJ and the Ritchie articular index for GST for each disease duration and found improvements in the clinical parameters up to 1 year from the initiation of treatment; however, they did not observe significant improvements thereafter for up to 5 years (27). The survival rate was 42% within 2 years, and 34% for longer than 5 years, which are comparable results to the 40.4% for the 5-year survival rate of GST in the present study. Bendix *et al.* reported that a factor influencing the survival rate of GST, was ADR developing within the first 3 years of treatment, and this was the major reason for suspending treatment (28). Others have reported that because of ADR within the first year of treatment the survival rate of MTX was 62%, and that of GST was 43% (29) and the survival rate of MTX within the first 3 years was 64% and that of GST was 41% (30).

With the MTX + SASP and MTX + BUC combinations in the present study, the ADR observed during single-drug treatments with SASP and BUC occurred in the early stage and caused the combination-drug treatment to be suspended, which explains the low incidence of organ disorders for MTX alone. Paulus reported that combination of drugs with different toxicities or the use of lower doses of toxic drugs in combination may decrease the risks associated with combination DMARDs therapy while maintaining or increasing their efficacy (31). McCarty *et al.* reported remission in 43% of patients receiving the combination of MTX, azathioprine and hydroxychloroquine (32). Morand *et al*. (33) and Axtens *et al*. (34) both reported that the survival rate of MTX + SASP was comparable with that of MTX alone and was higher than that attained using SASP. Landewe *et al*. also reported that the combination of prednisolone, MTX and SASP was superior to the administration of SASP alone because the combination treatment suppressed the activity and radiological progression of early RA(35).

The number of reports of basic evidence of the efficacy of the combination drug treatments is limited. In the present study, the order of the survival rates of the combination treatments was BUC+ SASP, MTX+ BUC, and MTX + SASP, which is similar to results were obtained from a study of the efficacy of combinations of DMARDs in terms of the suppression of VEGF and b-FGF production *in vitro* (36).

In our study of the drugs used in the second course of treatment, the subjects were patients in whom the drugs used in the first course of treatment were ineffective; that is, patients in whom either the effectiveness of the drugs had disappeared (i.e. 'escaped patients'). When SASP was used after switching, there was a similar phenomenon to that observed in the first course of treatment; that is, the 'escape phenomenon'

18-24 months after the initiation of the second course of treatment. Only in the case of administration of MTX alone was some efficacy observed, and the combination of MTX + BUC was relatively efficient. The incidence and onset of ADR of the second course are similar to that of the first course for MTX+BUC and MTX +SASP, but earlier than that of the first course for BUC+SASP.

In these days, Pincus *et al*. (37) and Aletaha *et al*. (38) reported that MTX is the routine or standard drug and probably should be the first DMARD used in the majority of patients with RA. Only a few newly diagnosed RA patients received MTX as their initial therapy in 1990, whereas since 2000 more than 50% of patients have been treated initially with MTX. The median time to first use of MTX in RApatients in the year 2000 was 7 months, whereas 1991-1993 it was 18 months (38). These investigators suggest that a combination of MTX with TNF-α blockers in preference to single agent therapy will become available later.

In this study, we have assessed the efficacy of individual DMARDs mainly from the point of view of improving clinical symptoms and clinical parameters and also decreased occurrence of ADR. The clinical course of patients with RA and long-term efficacy of DMARDs should be evaluated from the point of view of arthritic destruction characteristic of RA (39, 40). Jantti *et al*. followed progression of arthritic destruction over 20 years in terms of radiographic remission on the Larsen damage scoring system, and reported that 26% of patients attained remission (39). Reilly followed one hundred patients with RA starting at one year after onset. One-third of the 63 patients who died during 25 years, had more functional impairment than the rest at one year after onset. However, 11 of the 37 patients were well with no functional impairment (40).

These results indicate that early diagnosis of RA and the commencement of therapy with the most effective DMARDs in the first course or at early stages is very important.

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