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ORIGINAL ARTICLE

The efficacy and safety of bucillamine as a second-line DMARD in the treatment of rheumatoid arthritis: a retrospective cohort study

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Abstract We investigated the efficacy and safety of bucillamine administered as a second-line DMARD compared to administration as a first-line DMARD in the treatment of rheumatoid arthritis (RA). We conducted a retrospective cohort study and reviewed medical records of 86 patients with active RA who began to receive bucillamine at Yokohama Minami Kyosai Hospital between January 1998 and July 2004. The efficacy of treatments was compared based on rates of achievement of 20, 50, and 70% improvement in ACR core set 6 months after initiation of the therapy. In the group administered bucillamine as a first-line DMARD (18 patients), 44.4, 22.2, and 11.1% of patients achieved ACR 20, 50, 70, respectively, while 56.5, 34.1, and 19.5% achieved ACR 20, 50, 70, respectively, in the group administered bucillamine following switching from MTX (46 patients), and 53.3, 33.3, and 13.3% achieved ACR 20, 50, and 70, respectively, in the group administered bucillamine following switching from Sulfasalazine (SSZ) (15 patients). The rates of achievements of ACR 20, 50, 70 did not differ statistically between the three groups and there was no increase in risk of serious adverse effects related to previous DMARDs. The usefulness of bucillamine as a second-line DMARD was demonstrated.

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Introduction

Bucillamine is a DMARD that was developed in Japan in 1987 [1, 2], and is one of the DMARDs most often administered in Japan for the treatment of RA [3, 4]. The "Therapeutic guidelines based on EBM" published by the Ministry of Health, Labour, and Welfare's Research Group in 2004 has given bucillamine the highest level of recommendation (recommendation level A) as a "DMARD to be administered for RA patients in relatively early stages of RA with moderate or severe symptoms and inflammatory reaction" [5]. As such, bucillamine tends to be administered for the treatment of RA as the first-line DMARD to patients with highly active RA early after onset, or to RA patients who have had an insufficient response to treatment with gold or SSZ while their disease is not serious [3, 4]. Bucillamine is thus considered an option before treatment with MTX, and the general impression of clinicians is that strong efficacy with it cannot be expected for patients in whom a sufficient effect has not been achieved with MTX.

However, in many cases in our hospital, treatment with MTX is selected rather than bucillamine for RA patients relatively early after onset who have moderate or severe disease activity, and sufficient therapeutic efficacy is obtained although bucillamine tends to be administered as the second-line DMARD to patients who cannot be treated or have been insufficiently treated with MTX or SSZ. Although no study has proven the clinical usefulness of bucillamine in patients who are insufficiently treated with MTX, a clinical study by Ichikawa et al. [6] recently

reported potentiation of therapeutic effects with the combination of MTX and bucillamine compared with monotherapy with either alone. The potentiation of therapeutic effects with the combination of two drugs suggests differences in the site or mechanism of action at or by which these two DMARDs exhibit anti-rheumatoid effects. According to a recent report, bucillamine suppresses IgM production by B cells [7], VEGF production by synoviocytes [8], and differentiation of monocytes into osteoclasts [9] based on a mechanism of action completely different from that of MTX or SSZ. In fact, it has been reported in two large clinical trials in European countries that combined treatment with MTX and SSZ, which have the similar mechanism of action [10, 11], dose not provide a clear benefit, when compared with monotherapy using either agent [12, 13]. These findings suggest that switching to bucillamine is useful for patients who have been insufficiently treated with MTX or SSZ. We therefore compared the therapeutic efficacy and safety of bucillamine in a group administered bucillamine as a first-line DMARD, a group administered bucillamine following switching from MTX, and a group administered bucillamine following switching from SSZ in a retrospective study of patients who began to receive monotherapy with bucillamine between January 1998 and July 2004 in our hospital.

Patients and methods

We conducted a retrospective cohort study and reviewed all medical records of 86 patients with active RA who began to receive monotherapy with bucillamine at Yokohama Minami Kyousai Hospital between January 1998 and July 2004. The diagnosis of RA was made following the diagnostic criteria of the American College of Rheumatology (ACR) modified in 1987 [14]. In addition, RA patients with $\geq$3 tender joints and $\geq$3 swollen joints (investigated total 68 joints for tender joint counts and 66 joints for swollen joints counts), as well as CRP $\geq$1.0 mg/dL or erythrocyte sedimentation rate (ESR) $\geq$30 mm/h, were considered to have active RA.

The baseline demographic characters of the 86 patients are shown in Table 1. The patient's assessment of global status and overall pain score were scored using a visual analog scale, with 0 being normal and 100 representing severe problems. Thirteen were male and 73 were female, mean age was 57.0 ± 12.8 years, and mean duration of disease was 7.5 ± 8.1 years. The numbers of patients classified in Stages I, II, III, and IV based on Steinbrocker radiographic stage were 19, 23, 17, and 27 patients, respectively. In addition, the numbers of cases classified in functional classes 1, 2, 3, and 4 were 9, 64, 11, and 2 patients, respectively. In all, 28 patients received prednisolone (32.6%), with a mean dosage of 5.0 ± 2.5 mg. The mean count of swollen joints was 4.9 ± 6.6, mean count of tender joints 4.6 ± 5.7, mean pain score 55.8 ± 23.1, mean patient's global score 54.4 ± 22.9, mean modified health assessment questionnaire (modified HAQ) 0.81 ± 0.45, mean ESR 72.0 ± 34.8 mm/h, and mean CRP 3.12 ± 3.0 mg/dL. Administration of bucillamine was initiated at 100 mg once daily, and increased to 100 mg twice daily after 2–4 weeks. Patients switching from MTX were initially prescribed MTX 4 mg/week, and the MTX was escalated each 2 weeks in 2 mg increments until good disease control was obtained. The final dosages of MTX were 8 mg/week in 44 of 46 cases and 6 mg/week in the other two cases. Patients switching from SSZ were initially prescribed SSZ 500 mg twice a day. The efficacy of bucillamine therapy was determined based on the rate of patients who achieved 20% improvement in the ACR core set 6 months after the initiation of therapy (ACR 20), the rate of patients who achieved 50% improvement (ACR 50), and the rate of patients who achieved 70% improvement (ACR 70). Cumulative continuation rate for the 86 patients on bucillamine monotherapy was determined by the Kaplan-Meier method. A 3-year follow-up period was set after the initiation of therapy, and the occurrence of adverse effects was observed until bucillamine therapy was discontinued.

Comparison of parameters before therapy among the group initially administered bucillamine, the group administered bucillamine following switching from MTX, and the group administered bucillamine following switching from SSZ was performed by *t*-test. Comparison of ACR 20, 50, and 70 rates among these three groups was performed by the χ-square test.

Table 1 Baseline demographic characteristics of patients ($n = 86$)

Age (years)	57.0 ± 12.8
Male/Female (*n*)	13/73
Duration of disease (years)	7.5 ± 8.1
Steinbrocker stage, mean (I/II/III/IV)	2.6 ± 1.1(19/23/17/27)
Steinbrocker class, mean (1/2/3/4)	1.9 ± 0.5(9/64/11/2)
Patients using corticosteroid (%)	32.6
Dose (PSL eq) (mg/day)	5.0 ± 2.5
Swollen joint counts	4.9 ± 6.6
Tender joint counts	4.6 ± 5.7
Paint's pain VAS (1–100 mm)	55.8 ± 23.1
Patient's global VAS (1–100 mm)	54.4 ± 22.9
Modified HAQ	0.8 ± 0.5
ESR (mm/h)	72.0 ± 34.8
CRP (mg/dL)	3.1 ± 3.0

Results

Efficacy and safety of bucillamine

Forty-four of the 86 patients (51.2%) achieved ACR 20, 25 (29.0%) achieved ACR 50, and 13 (15.1%) achieved ACR 70 6 months after the initiation of bucillamine therapy (Fig. 1). The cumulative continuation rates of the 86 patients who received bucillamine are shown in Fig. 2. As indicated, the cumulative continuation rate 1 year after initiation of therapy was 64.2%, that at 3 years was 46.4%, and that at 5 years was 33.5%.

Reasons for discontinuation in 53 cases during the 3-year follow-up included inefficacy in 18 cases (20.9%), adverse effects in 17 cases (19.7%), and loss of efficacy in ten cases; four patients completed therapy after remission, three patients could not be followed due to change of address or transfer to other hospitals, and one patient discontinued therapy due to the wish to have a child. Seventeen adverse effects resulted in discontinuation of administration of bucillamine. They included nine cases of skin rash, five cases of proteinuria, two cases of gastrointestinal symptoms, and one case of interstitial pneumonia. Improvement of symptoms was observed in all 17 cases after discontinuation of administration of bucillamine.

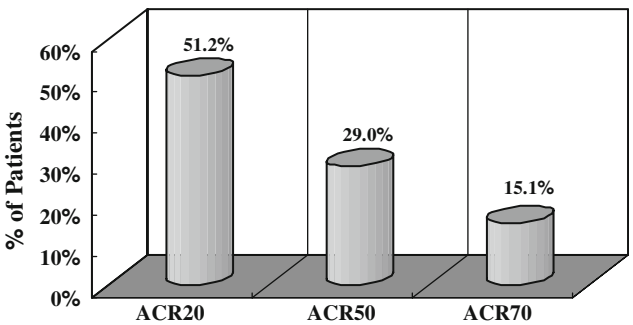

Fig. 1 Percentages of patients treated with bucilamine who achieved the ACR 20, 50, and 70% improvement criteria at 6 months

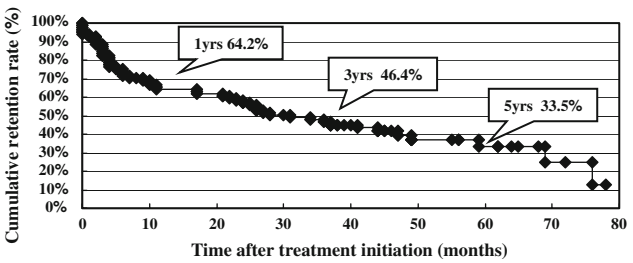

Fig. 2 Kaplan-Meier cumulative survival curve of the patients who received treatment with bucillamine. The cumulative survival rates of the patients at 1, 3, and 5 years after initiation of treatment with bucillamine were 64.2, 46.4, and 33.5%, respectively

The time to discontinuation due to adverse effects from initiation of therapy was between 2 months and 11 months for proteinuria and between 3 days and 11 months for skin rash. The mean duration of administration for patients who discontinued therapy due to loss of efficacy was 36.9 ± 16.1 months.

Efficacy and safety of bucillamine as second-line DMARD

Bucillamine alone is not often administered as a first-line DMARD in our hospital (18 of 86 cases in this study), and is mainly administered following switching from treatment with DMARDs other than bucillamine for reasons such as adverse effects, insufficient efficacy, and inefficacy. Of such cases, those switched from MTX or SSZ are common, and numbered 46 and 15 of 86 cases, respectively, in this study. Three groups were therefore established to examine the usefulness of bucillamine as a second-line DMARD, and the efficacy and safety of bucillamine therapy in each group were compared, with 18 patients administered bucillamine as the first-line DMARD, 46 administered bucillamine following switching from MTX, and 15 administered bucillamine following switching from SSZ.

Patient background factors for the three groups are shown in Table 2. Compared to the group administered bucillamine as the first-line DMARD, no significant differences in any such factors except mean ESR level were observed in the group administered bucillamine by switching from MTX or the group administered bucillamine by switching from SSZ. The group administered bucillamine following switching from MTX exhibited significantly higher mean ESR level than the group administered bucillamine as a first-line DMARD. Mean CRP level was 3.9 ± 3.3 mg/dL compared to 2.0 ± 2.0 mg/dL, indicating apparent higher trend although it was not statistically significant. These data mean that inflammatory activity in patients administered bucillamine by switching from MTX would be higher than that of the group administered bucillamine as a first-line DMARD.

Therapeutic effects 6 months after initiation of treatment with bucillamine in the three groups are shown in Fig. 3. While ACR 20 rate was 44.4%, ACR 50 rate was 22.2% and ACR 70 rate 11.1% in the group administered bucillamine as the first-line DMARD, while ACR 20 rate was 56.5%, ACR 50 rate 34.1%, and ACR 70 rate 19.5% in the group administered bucillamine following switching from MTX, and ACR 20 rate was 53.3%, ACR 50 rate 33.3%, and ACR 70 rate 13.3% in the group administered bucillamine following switching from SSZ. Although there were no statistically significant differences in therapeutic efficacy among the three groups, clinical efficacy was higher in the group administered bucillamine following switching from MTX than in the other two groups for each

Table 2 Baseline demographic characteristics of patients, according to study groups

	No DMARDs	MTX	SSZ
Age (years)	58.6 ± 15.1	57.5 ± 11.8	54.4 ± 13.8
Male/female (n)	4/14	7/39	1/14
Duration of disease (years)	7.7 ± 8.9	7.6 ± 8.1	7.3 ± 8.7
Steinbrocker stage	2.4 ± 1.2	2.8 ± 1.1	2.7 ± 1.1
Steinbrocker class	1.9 ± 0.5	2.1 ± 0.5	2.3 ± 0.7
Patients using corticosteroid (%)	44.4	26	46.6
Dose (PLS eq) (mg/day)	5.2 ± 2.1	5.3 ± 2.6	4.6 ± 2.8
Swollen joint counts	7.1 ± 11.6	4.9 ± 5.6	3.3 ± 2.9
Tender joint counts	5.1 ± 9.6	4.6 ± 4.0	4.8 ± 6.5
Patient's pain VAS (1–100 mm)	49.4 ± 21.9	58.0 ± 24.1	54.4 ± 23.7
Patient's global VAS (1–100 mm)	46.4 ± 19.8	56.9 ± 24.4	53.7 ± 21.9
Modified HAQ	0.65 ± 0.5	0.85 ± 0.46	0.64 ± 0.55
ESR (mm/h)	54.1 ± 36.0	81.0 ± 32.8*	68.0 ± 33.7
CRP (mg/dL)	2.0 ± 2.0	3.9 ± 3.3	1.9 ± 1.6

PSL eq prednisolone equivalent, *Modified HAQ* Modified Health-Assessment Questionnaire, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein. All values represent mean and standard deviation range. * $P < 0.05$ No DMARDs versus MTX

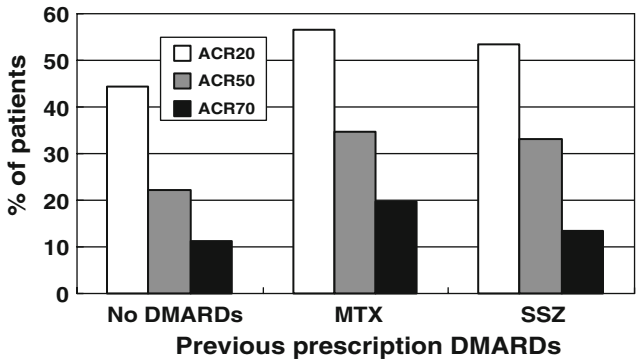

Fig. 3 Percentages of patients who achieved the ACR 20, 50, and 70% improvement criteria at 6 months in three treatment group

Table 3 Summary of adverse events

No DMARDs	4	Rash
		Proteinuria
		Swollen lips
		Vesicle
		Eruption
MTX	5	Nausea
		Proteinuria
		Eruption ×2
		Rash
SSZ	5	Stomatitis
		Proteinuria ×3
		Eruption

of the criteria. In particular, ACR 70 rate reached 19.5% in the group administered bucillamine following switching from MTX, indicating high therapeutic efficacy with the possibility of remission in 1 of 5 patients.

Adverse effects, which resulted in discontinuation of administration during the three-year follow-up period, are summarized for each group in Table 3. Adverse effects were observed in four cases in the group administered bucillamine as the first-line DMARD, five in the group administered bucillamine following switching from MTX, and five in the group administered bucillamine following switching from SSZ. Based on these results, it was concluded that there was no notable increase in risk of the occurrence of adverse effects or increase in risk of serious adverse effects related to the DMARDs administered before bucillamine.

Discussion

Our findings indicate that compared with use as a first-line DMARD, bucillamine has similar efficacy following switching from MTX or SSZ due to reasons such as adverse effects and insufficient efficacy. These findings suggest that bucillamine is useful as a second-line DMARD for patients who cannot be treated with other DMARDs such as MTX, and as a first-line DMARD for RA patients with relatively high activity in the early stage of disease. Furthermore, the rates of patients who achieved relatively good improvement of symptoms such as ACR 50 and ACR 70 were higher in patients administered bucillamine following switching from MTX. The finding that the rate of patients who achieved ACR 70 reached 19.5% after 6 months of treatment means that one of five patients obtained a strong therapeutic effect

with the possibility of remission [15]. In fact, two patients (out of 46) in the group administered bucillamine following switching from MTX could discontinue DMARD treatment due to remission during the 3-year follow-up period. Yokota et al. [16] reported that bucillamine leads to a high rate of remission when it is continued long term (six of 18 cases when continued for 10 years), consistent with our finding that bucillamine has therapeutic effects leading to remission of RA. Recently, selection of biological agents has been recommended for patients with an insufficient response to MTX, considering long-term therapeutic outcome such as suppression of bone destruction and improvement of quality of life [17]. However, administration of bucillamine to patients with insufficient response to MTX is likely to be an option, considering the high cost of biological agents and the risk of serious adverse effects such as infections [18, 19].

The findings for therapeutic efficacy and rate of continuation of treatment of all patients administered bucillamine in this study were similar to those previously reported by other institutions [3, 20], confirming that the groups subjected to analysis in this study were not selected from a particular population with a high degree of therapeutic responsiveness to bucillamine. Incidence of side effects in this study (19.7%) did not exceed the incidence of side effects in the previous studies conducted by Sekiguchi et al. [20] (20.4%) and by Ichikawa et al. [6] (25.0%).

The difference between the mechanisms of action of bucillamine and MTX is considered one of the reasons for similar therapeutic effect in the patients switched from MTX to those administered bucillamine as a first-line DMARD. In a recent study by Tsuji et al. [8] regarding the mechanism of action of bucillamine, it was reported that bucillamine selectively suppresses the signal via phosphorylation of Akt induced by the stimulation of IL-1 receptor. This suggests that bucillamine exhibits anti-rheumatoid effects by a mechanism of action completely different from those of MTX and SSZ, which exhibit principally inhibition of nucleic acid synthesis and induction of adenosine accumulation [10, 11]. On the other hand, the difference in inflammatory activity between the patients administered bucillamine as the first-line DMARD and patients administered by switching from MTX was observed, suggesting the presence of some difference in pathological background between two groups. This difference in pathological background between the two groups may have resulted in the difference in responsiveness to bucillamine therapy.

This study has some limitations for analysis. First of all, this is a retrospective study from only one facility (Yokohama Minami Kyosai Hospital), facility-related bias may need to be taken into account in interpreting the results of this study. However, patient selection bias appeared to be minimal in this study, because almost all patients who began to receive monotherapy with bucillamine at this hospital were enrolled in this study. This cohort can therefore be considered appropriate for the present type of study, which involved stratification of patients within a cohort. Second, the maximum approved weekly dosage of MTX is 8 mg. Thus, in Japan, MTX is administrated to patients with RA at a lower dose than that used in the US and European countries. The results of the present analysis may not necessarily apply to these countries.

In conclusion, bucillamine was therapeutically effective even for patients who were insufficiently treated with other DMARDs. In particular, therapeutic efficacy with the possibility of remission was obtained for patients administered bucillamine following switching from MTX, suggesting that treatment with bucillamine be considered an option before treatment with biological agents for patients with an insufficient response to MTX.

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