Mod Rheumatol (2006) 16:85–91
DOI 10.1007/s10165-005-0466-y

ORIGINAL ARTICLE

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Efficacy and safety of bucillamine, a D-penicillamine analogue, in patients with active rheumatoid arthritis

Received: December 2, 2005 / Accepted: February 21, 2006

Abstract Japanese rheumatologists consider bucillamine (Buc) to be a useful disease-modifying antirheumatic drug (DMARD) and often give Buc to patients with rheumatoid arthritis (RA) prior to administering methotrexate (MTX). However, no large studies on the efficacy and safety of Buc in RA patients have been published in English to date. We therefore investigated the clinical course of RA patients treated with Buc and compared the results with those for patients treated with MTX to evaluate and confirm the place of Buc in therapeutic strategies for RA in Japan. Our results suggested that Buc should be given to patients with moderately active RA either before or after the administration of MTX because its efficacy can be judged within 3 months and because serious adverse events are rare. Issues like the ability of Buc to prevent joint destruction and its efficacy and safety when combined with agents like etanercept require future study.

Key words Bucillamine (BUC) · Disease activity score (DAS) · Disease-modifying antirheumatic drug (DMARD) · Methotrexate (MTX) · Rheumatoid arthritis (RA)

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by symmetric erosive synovitis and, in some cases, extra-articular involvement.[1] Rheumatoid arthritis affects almost 1% of the adult population,[2] and is associated with rapid functional loss and reduced life expectancy. Ultimate goals in the treatment of RA are to prevent or control joint damage, prevent loss of function, and decrease pain. To achieve these goals, the American College of Rheumatology (ACR) recommends the administration of disease-modifying antirheumatic drugs (DMARDs) within 3 months of diagnosis.[3] In most patients with RA, methotrexate (MTX) is the DMARD of first choice because of its early onset of action and superior efficacy and tolerability, according to the ACR recommendation.

The treatment of RA patients in Japan, however, presents some special concerns.[4] First, the Japanese Ministry of Health, Labour and Welfare has approved MTX only as a second-line therapy for RA patients who have failed to respond to at least one other DMARD. Second, the maximum approved weekly dosage of MTX is 8 mg. Thus, in Japan, MTX is administered to patients with RA at a lower dose than that used in the United States and many European countries.

Ohno et al.[5] surveyed the preference for DMARDs in Japan by sending out a questionnaire to the participants of the 44th annual meeting of the Japanese College of Rheumatology (JCR) in 2000. A total of 464 rheumatologists responded, including 212 internists and 252 orthopedists. The results of this survey showed that 44.9% of the participants employed bucillamine (Buc), a D-penicillamine (D-pc) analogue (2-mercapto-2-methylpropanoyl-L-cysteine; see Fig. 1) that is only available in Japan and Korea, whereas 20.6% of the respondents employed MTX and 9.4% employed salazosulfapyridine (SASP). Moreover, in addition to SASP, MTX, and leflunomide, Buc has been approved by the subcommittee of the Japanese Ministry of Health, Labour and Welfare as a rank-A recommendation DMARD. Thus, Japanese rheumatologists consider Buc to be a useful DMARD and often prescribe Buc to patients with RA prior to the administration of MTX, as is the case in our clinic. However, no large studies on the efficacy and safety of Buc in RA patients have been published in English to date, although during the preparation of this paper, Ichikawa et al.[7] demonstrated that the combination of MTX and Buc was more effective than MTX or Buc monotherapy in small numbers of patients.

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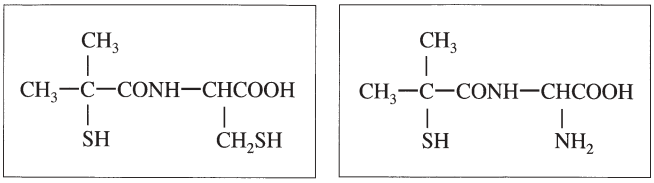

Bucillamine **D-Penicillamine**

Fig. 1. Structures of bucillamine and D-penicillamine[6]

We investigated the clinical course of 348 RA patients treated with Buc and compared our results with previously reported, in part, results for 217 RA patients treated with MTX[4] to evaluate and confirm the place of Buc in therapeutic strategies for RA in Japan.

Patients and methods

The medical records of RA patients who visited the Saitama Medical Center (SMC) before 2003 and who received Buc ($n = 348$, 50–300 mg per day) were intensively reviewed. All of these patients met the 1987 revised ACR classification criteria for RA. Disease activity was evaluated by the number of tender joints (tender joint count; TJC) and swollen joints (swollen joint count; SJC), and the serum level of C-reactive protein (CRP). The 20%, 50%, and 70% improvement rates for all of TJC, SJC, and CRP after treatment with Buc were retrospectively evaluated. The Disease Activity Score (DAS) 28-3(crp) (http://www.das-score.nl) was also calculated, and the clinical response to Buc was analyzed using the European League Against Rheumatism (EULAR) improvement criteria (http://www.das-score.nl). The 1-year and 3-year continuation rates for Buc treatment were calculated using a Kaplan–Meier survival analysis. The effects of Buc on TJC, SJC, and CRP, as well as DAS28-3(crp), and the Buc continuation rates were compared with previously reported results for MTX.[4] Bucillamine treatment was regarded as insufficient when prednisolone (PSL) or another DMARD was added or when the dosage of Buc was increased during the observation period. All adverse events that occurred while receiving Buc were also evaluated.

Statistical analysis

Tender joint count, SJC, and CRP were compared between the Buc and MTX groups using Student *t*-tests. We utilized a nonresponder imputation analysis (NRI) in evaluating the efficacy of the therapy. The Steinbrocker radiographic stage was compared between groups using a chi-square test. Multivariate studies and logistic analyses were used to predict good responses based on the EULAR improvement criteria. The Buc continuation rate was calculated using a Kaplan–Meier survival analysis.

Table 1. Comparison of demographic and clinical features of patients who received bucillamine or methotrexate

	Buc	MTX[4]
Male/female ratio	70:278	37:180
Age (years, mean ± SD, range)	53.8 ± 13.0; 16–84	54.0 ± 11.5; 21–85
Duration of disease (years, mean ± SD, range)	5.5 ± 6.8; 0–33	8.5 ± 8.7; 0.1–46.3
Stage (%)		
I	25.9	11.0
II	41.5	37.1
III	9.1	12.4
IV	23.5	39.5
TJC (mean ± SD, range)	5.1 ± 4.5; 0–29	6.7 ± 5.9; 0–30
SJC (mean ± SD, range)	6.3 ± 4.6; 0–23	7.4 ± 5.8; 0–40
CRP (mean ± SD, range)	2.9 ± 3.1; 0–16.7	4.9 ± 4.2; 0.1–23.6
Positive serum test for rheumatoid factor (%)	86.1	87.1

Buc, bucillamine; MTX, methotrexate; TJC, tender joint count; SJC, swollen joint count; CRP, C-reactive protein

Results

Efficacy of Buc and MTX treatments

Seventy-two (20.7%) of the Buc-treated patients received Buc and MTX, either separately or simultaneously, and therefore, were included in both this Buc study and the previously published MTX study.[4] Among them, 26 patients initially received Buc and subsequently were additionally given MTX because the Buc treatment was insufficient. One hundred eleven patients (31.8%) had been receiving PSL treatment (mean dose, 6.3 mg/day) when Buc administration was commenced. The clinical data obtained from patients at the beginning of the first Buc therapy were compared with the clinical data obtained from patients who had just started receiving MTX for the first time.[4] The demographic and clinical features of the patients who received Buc are shown in Table 1. When compared to the MTX study, significant differences were seen in disease duration (8.5 ± 8.7 years for MTX-treated patients; $P < 0.001$), stage (I: 11.0%, II: 37.1%, III: 12.4%, IV: 39.5% for MTX-treated patients; $P < 0.001$), TJC (6.7 ± 5.9 for MTX-treated patients; $P < 0.001$), SJC (7.4 ± 5.8 for MTX-treated patients; $P < 0.05$), and CRP (4.9 ± 4.2 for MTX-treated patients; $P < 0.001$) when evaluated using *t*-tests, suggesting that MTX tended to be given to those with longstanding and highly active RA, while Buc treatment was started earlier, as indicated by the fact that 25.9% of the patients were radiographically classified as Stage I. Changes from the baseline TJC, SJC, CRP, and DAS28-3(crp) values are shown for the Buc- and MTX- treated patients in Fig. 2. TJC, SJC, CRP and DAS28-3(crp) significantly decreased at 3 months after both Buc and MTX treatment, though the values tended to be higher in the MTX-treated patients than in the Buc-treated patients. Indeed, the mean DAS28-3(crp) value decreased from 3.5 at baseline to 2.5 at 12 months in the Buc-treated patients and from 3.9 to 2.9 in the MTX-treated patients.

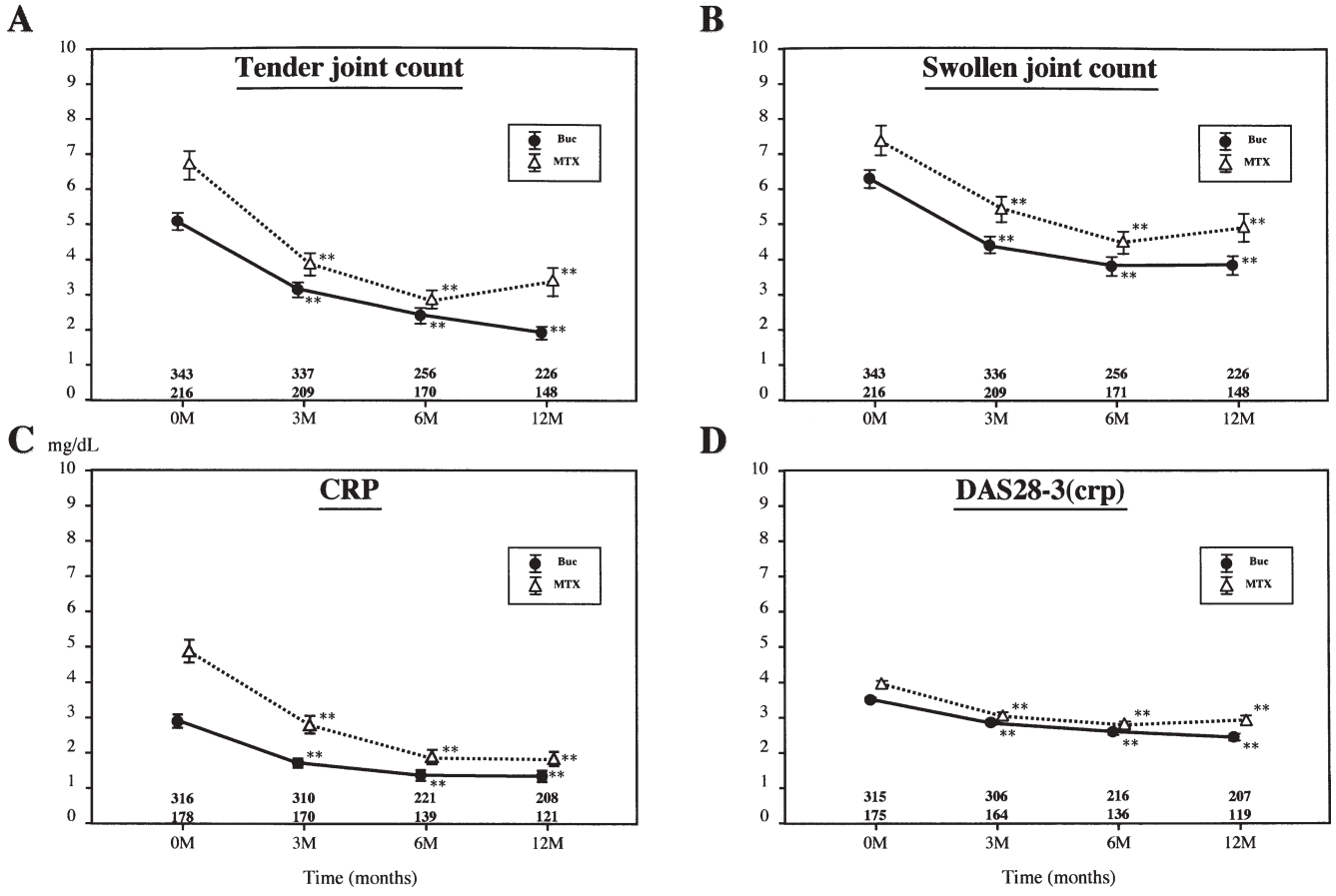

Fig. 2. Changes in tender joint count (TJC), swollen joint count (SJC), C-reactive protein (*CRP*), and DAS28-3(crp) from baseline values in patients who received bucillamine (*Buc*) or methotrexate (*MTX*). The *solid circles* show the Buc group, while the *open triangles* show the MTX group. The *numbers below the curves* show the number of patients in each group (*upper number*, Buc group; *lower number*, MTX group). Mean ± SE, paired *t*-test; $*P < 0.05$, $**P < 0.01$

Efficacy of Buc treatment and prior DMARD therapy

To elucidate the characteristic features of RA patients who show an optimal response to Buc and to establish the appropriate place for Buc in the management of RA, we investigated whether the response to Buc differed when it was prescribed as the first DMARD and when it was prescribed secondary to some other DMARD. The mean DAS28-3(crp) value of patients who received Buc as the first DMARD decreased significantly from 3.4 at baseline to 2.3 at 12 months ($P < 0.01$); this decrease was similar to that seen in patients who initially received a DMARD other than Buc (from 3.4 to 2.5; $P < 0.01$). Significant decreases in TJC, SJC, CRP, and DAS28-3(crp) were similarly observed in both groups as well (Fig. 3).

We then focused on the effect of previous MTX therapy prior to Buc on the response to Buc, since MTX is often used as a first-line drug outside of Japan. Patients who had received MTX prior to Buc treatment or who changed from MTX to Buc treatment (or received Buc in addition to MTX) because of a lack of efficacy or adverse events were compared with those who had never received MTX prior to Buc administration. The mean TJC of patients who had never received MTX decreased significantly from 5.1 at baseline to 1.9 at 12 months ($P < 0.01$), while that of patients who had previously received MTX decreased from 6.7 to 3.3 ($P < 0.01$); both of these values were significantly higher than those for MTX-naïve patients. Thus, these results are similar to the comparison of Buc treatment with MTX treatment shown in Fig. 2; the MTX-naïve group in Fig. 4 corresponds to the Buc group in Fig. 2 and, compared to them, patients who were previously treated with MTX showed a higher activity. Similar results were seen for SJC, CRP, and DAS28-3(crp). Nevertheless, our data suggested that the efficacy of Buc does not decline with previous DMARD therapy, including the use of MTX.

Rate and latency of the response to Buc therapy

Next, we examined the efficacy of Buc using evaluations of integrated activity. As a retrospective analysis, the 20%, 50%, and 70% improvement rates for TJC, SJC, and CRP after treatment with Buc were analyzed (Fig. 5A). A 20% improvement after Buc treatment was achieved by 39.3% and 49.7% of patients after 3 and 12 months of treatment, respectively. Furthermore, a moderate response according to the EULAR criteria was observed in 44.9% and 58.4% of

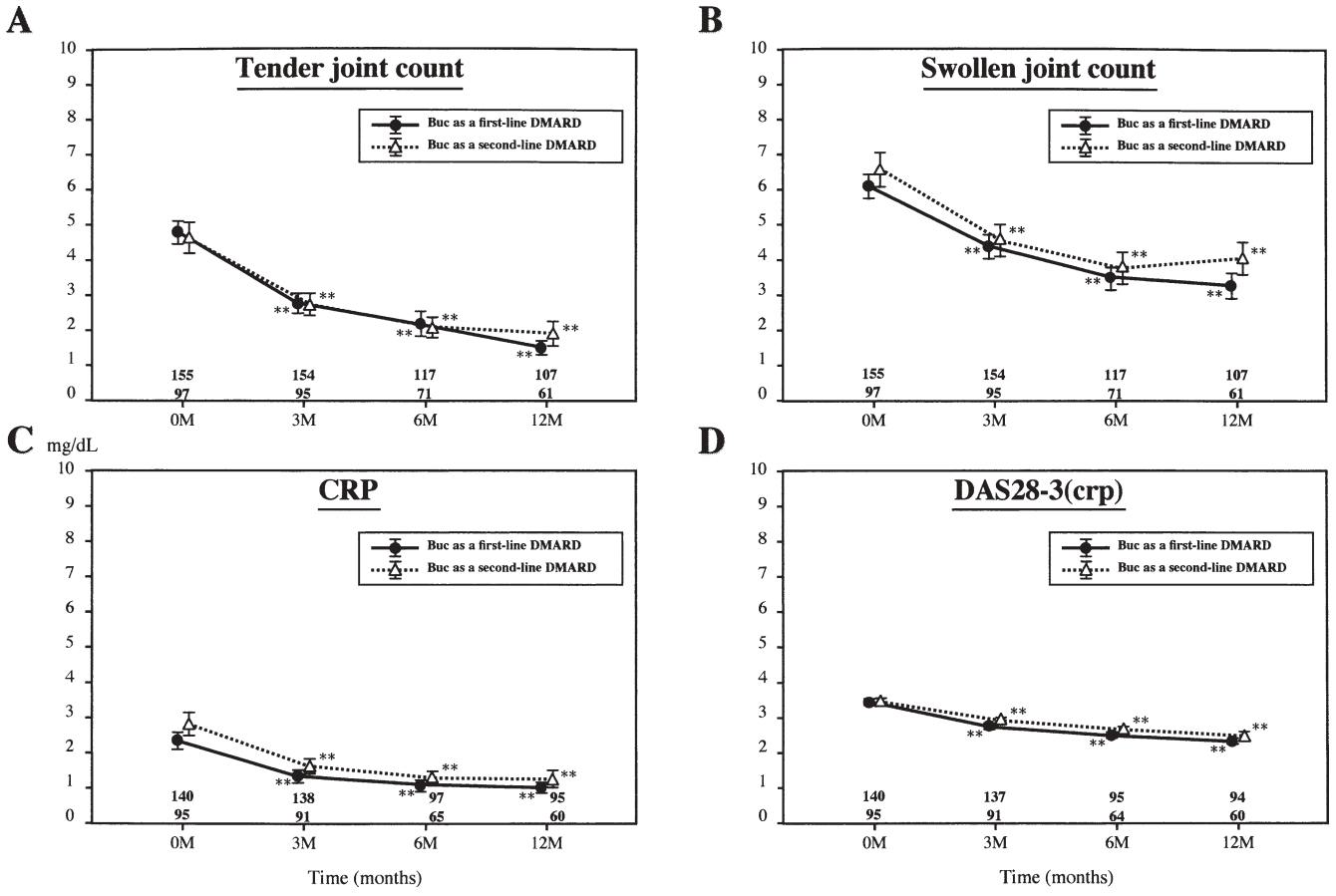

Fig. 3. Response to Buc in patients who received Buc as a first-line disease-modifying antirheumatic drug (*DMARD*) (*solid circles*) or as a second-line DMARD (*open triangles*). The *numbers below the curves* show the number of patients analyzed in each group (*upper number*, Buc as a first-line DMARD; *lower number*, Buc as a second-line DMARD). Mean ± SE, paired *t*-test; $^{**}P < 0.01$

patients after 3 and 12 months of Buc treatment, respectively, although only 3.1% and 7.6% of these patients, respectively, satisfied the criteria for a good response (Fig. 5B).

Adverse events during Buc therapy

Although no life-threatening adverse events were observed, a total of 74 adverse events developed in 71 patients receiving Buc. Skin rashes or itching were the most common complaints, accounting for 46.5% of the adverse events, followed by proteinuria (24.7%) (Fig. 6). Other adverse events included stomatitis, glossitis, an elevated transaminase level, and coughing. Notably, skin rash or itching tended to occur within 3 months of the start of Buc therapy, while proteinuria tended to develop later. One patient was admitted to hospital for 7 months after developing nephrosis while taking Buc. Bucillamine treatment was suspended, and the patient was instead given PSL (30 mg/day). The patient recovered satisfactorily.

Continuation rates for Buc treatment

The successful continuation of Buc treatment was calculated using a Kaplan–Meier analysis and was compared with that of MTX treatment.[4] After 1 year of treatment, Buc treatment had not been discontinued in 69.2% of the patients and MTX treatment had not been discontinued in 83.1% of the patients; after 3 years, the continuation rates were 31.1% and 69.1%, respectively (Fig. 7). Buc was discontinued during the first year mainly because of a lack of efficacy (25.4%) or adverse events (19.6%).

Discussion

To our knowledge, this is the first English-language report describing the efficacy and safety of Buc, compared with that of MTX, in a large number of RA patients. We could not evaluate improvements in RA activity according to the ACR improvement criteria because our study was retrospective and disease activity assessments by the patients and their physicians were not included in the medical records. Instead, changes in TJC, SJC, and CRP were used

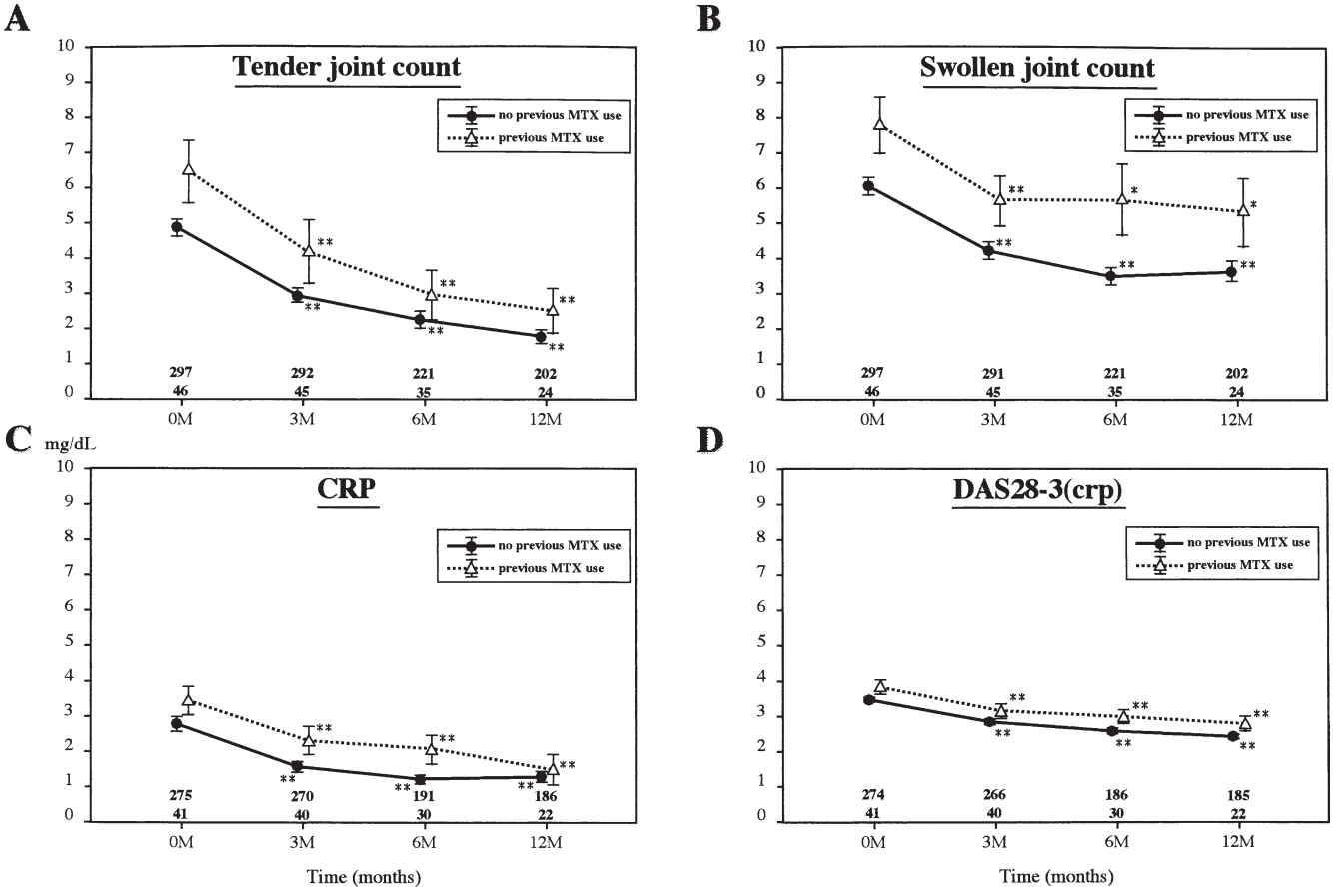

Fig. 4. Response to Buc in patients who had not previously received MTX (*solid circles*) or who had previously received MTX (*open triangles*). The *numbers below the curves* show the number of patients in each group (*upper number*, no previous MTX use; *lower number*, previous MTX use). Mean ± SE, paired *t*-test; $*P < 0.05$, $**P < 0.01$

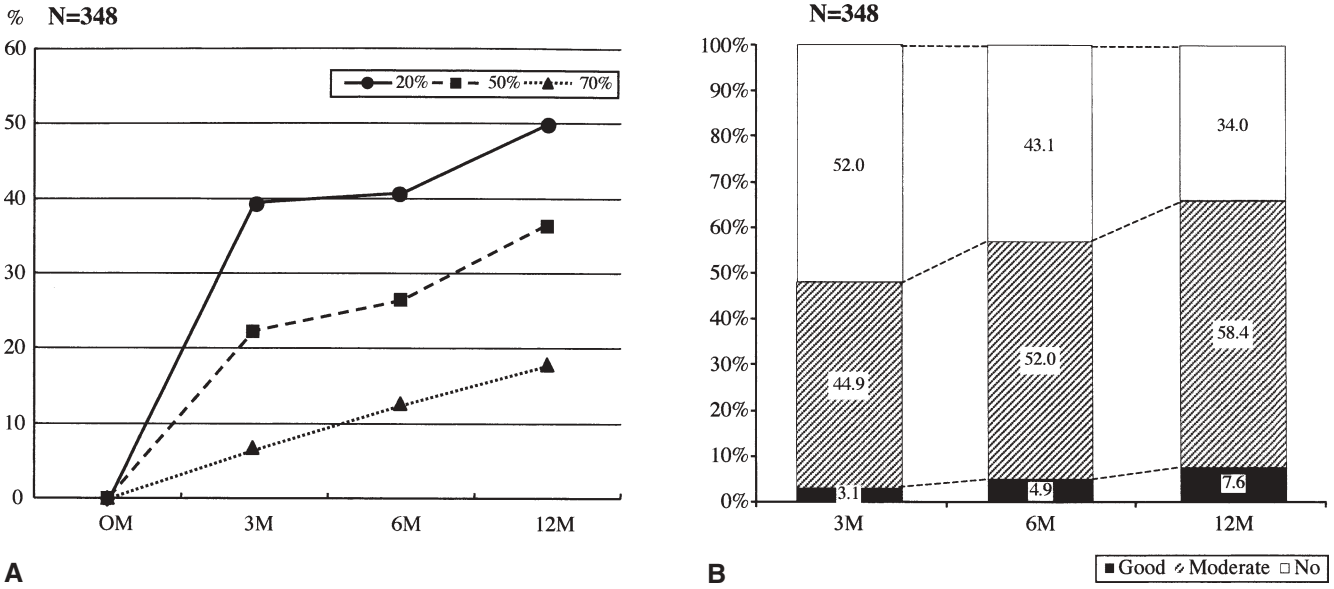

Fig. 5. A Percentage of patients who attained 20%, 50%, and 70% improvement rates in their TJC, SJC, and CRP values after treatment with Buc. The *solid circles* represent the 20% improvement rate, the *solid squares* the 50% improvement rate, and the *solid triangles* the 70% improvement rate. **B** European League Against Rheumatism responses in patients who received Buc. The *solid area* represents the percentage of good responders, the *hatched area* represents the percentage of moderate responders, and the *open area* represents the percentage of nonresponders

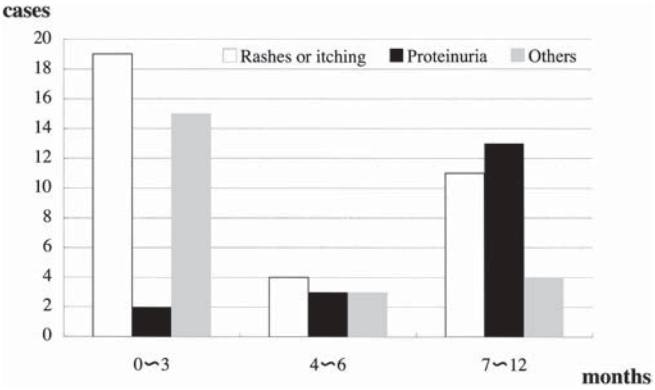

Fig. 6. Adverse events while receiving Buc. The open area represents the number of cases with rashes or itching, the *solid area* represents the number of cases with proteinuria, and the *gray area* represents the number of cases with adverse events other than rashes, itching, and proteinuria

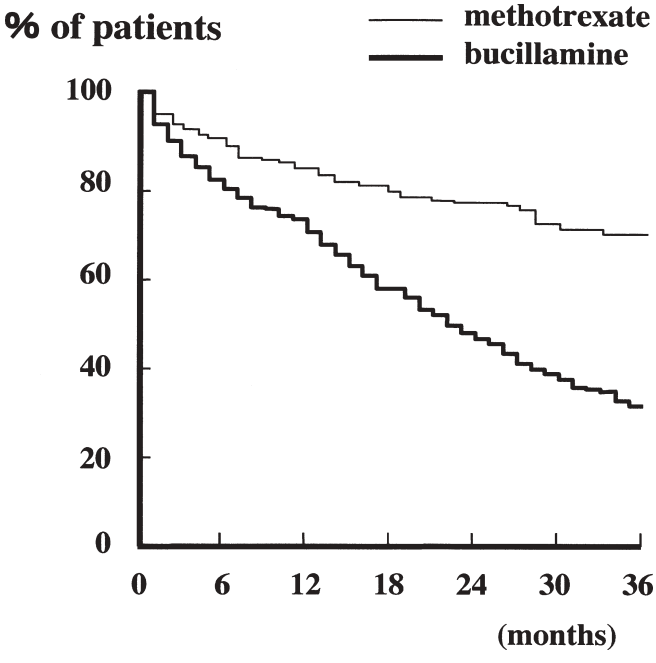

Fig. 7. Continuation rates for Buc and MTX. The *thick line* represents the continuation rate for Buc, while the *thin line* represents the continuation rate for MTX

to evaluate RA activity. We also utilized the DAS28-3(crp) values to evaluate disease activity. Radiographic improvements were not evaluated using the modified Sharp/van der Heijde scoring system for the above-mentioned reason. Recently, Ichikawa et al.[7] compared the radiographic progression of three treatment groups (MTX monotherapy, $n = 23$; Buc monotherapy, $n = 24$; and MTX–Buc combination therapy, $n = 24$) using the modified Sharp/van der Heijde scoring system. The increases in the total Sharp scores were 27.4 ± 31.2 in the MTX monotherapy group, 28.5 ± 26.2 in the Buc monotherapy group, and 12.6 ± 9.0 in the MTX–Buc combination therapy group. No statistically significant differences were found between the monotherapy groups, although the number of patients in each group was relatively small.

In the present study, significant decreases in TJC, SJC, CRP, and DAS28-3(crp) were observed in patients with RA who received Buc, regardless of whether Buc was used as a first-line or a second-line DMARD. This finding supports the use of Buc as a key DMRAD for the treatment of active, untreated RA in Japan, where the use of MTX as a first-line DMARD has not been officially approved. Moreover, Buc can probably be used as a second-line DMARD in patients who do not respond to MTX.

To avoid unnecessary delays in controlling RA, which eventually leads to joint destruction and subsequent disability, the patient's response to therapy must be evaluated as soon as possible, at least within a few months. Moreover, the first-line DMARD should not be overly toxic so that patients will not be discouraged from challenging RA. In this series, we rarely encountered patients who required hospital admission for the treatment of adverse events related to Buc therapy. Usually, Buc-related adverse events, including rashes during they early phase and proteinuria during later phases, subside within months if Buc treatment is withdrawn. Buc-induced interstitial pneumonia has also been reported;[8] however, none of the RA patients in our study developed Buc-induced interstitial pneumonia. Since Buc is an analogue of D-pc, Kim and Song[9] conducted a randomized, controlled clinical trial to compare the clinical effects and frequencies of adverse events in patients treated with D-pc or Buc. They reported that the frequency of adverse events tended to be lower in the Buc group, despite the structural similarity of Buc and D-pc. D-Penicillamine has been reported to induce autoimmune diseases,[10,11] and other DMARD-related severe adverse effects include pancytopenia, acute interstitial pneumonia, or opportunistic infections in patients treated with MTX;[12] Stevens–Johnson syndrome in patients treated with SASP;[13] and frequently fatal interstitial pneumonia in patients treated with leflunomide.[14] Therefore, the safety of Buc is relatively high among DMARDs, receiving a rank A from a subcommittee of the Japanese Ministry of Health, Labour and Welfare.

In the present study, Buc tended to be given to patients with less advanced and less active RA, compared to the patients who received MTX. Specifically, two thirds of the patients who received Buc had stage 1 or 2 Steinbrocker radiographic classifications, while only half of the patients treated with MTX treatment had Stage 1 or 2 classifications. The mean baseline DAS28-3(crp) level was also significantly higher in the MTX-treated patients than in the Buc-treated patients. Therefore, our results suggest that while MTX is a more potent DMARD than Buc, as partly reflected in Figs. 2 and 7, Buc treatment may result in an outcome as good as that achievable with MTX if these two drugs are appropriately selected according to the disease activity of RA patients. To elucidate candidates who are likely to respond to Buc therapy, we compared patients who exhibited a good response (according to the EULAR criteria) with those who did not respond to Buc. However, we did not find any demographic or characteristic features associated with a good response to Buc (data not shown).

In conclusion, our study suggests that Buc should be given to patients with moderately active RA either before or after MTX treatment, because its efficacy can be judged within 3 months and because serious adverse events are rare. Issues like the ability of Buc to prevent joint destruction and its efficacy and safety when combined with biologic agents like etanercept require further study.

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