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ORIGINAL ARTICLE

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Efficacy profile of bucillamine in rheumatoid arthritis patients in a large observational cohort study, IORRA

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Abstract Bucillamine (Buc) is a disease-modifying antirheumatic drug (DMARD) developed in Japan, which has been used as one of the first-line DMARDs for the treatment of rheumatoid arthritis (RA) in Japan. However, direct comparison of this drug with standard DMARDs including sulfasalazine (SASP) and methotrexate (MTX) has been scarcely reported. We therefore tried to evaluate the clinical efficacy of Buc by analyzing the database from the long-term observational cohort study IORRA (previously known as J-ARAMIS). The cross-sectional analysis revealed that responses to Buc treatment were better in males, patients with shorter duration of illness, and those who were rheumatoid factor-negative. In the longitudinal analysis, although there was no marked difference among the baseline variables of patients with Buc, SASP, and MTX, the percentage of patients exhibiting moderate or good response to treatment, as rated using the European League Against Rheumatism improvement criteria, was higher in the Buc group (41.0%) than in the MTX (32.6%) and SASP groups (25.6%). These data support Buc as a candidate for being a first-line drug for the treatment of patients with RA.

Key words Bucillamine · Disease Activity Score (DAS) · Disease-modifying antirheumatic drug (DMARD) · Institute of Rheumatology Rheumatoid Arthritis (IORRA) · Rheumatoid arthritis

Introduction

The etiology of rheumatoid arthritis (RA) has not yet been fully determined. However, considerable knowledge has been accumulated on the features of this disease, enabling the development of various types of drugs for the treatment of RA and changes in the strategy of drug treatment of RA.

Traditional drug treatments for RA were aimed at achieving temporary improvement in the quality of life (QOL) of patients by alleviating pain and other symptoms with nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids.[1] In the past, no drugs capable of significantly modifying the natural history of RA were available, and in the absence of such drugs the best treatment for RA was to alleviate the complaints of individual patients and to maintain their QOL. However, following the recent introduction of disease-modifying antirheumatic drugs (DMARDs), it has become possible to delay or prevent the destruction of bone and joints and to actively modify the natural history of RA. The aim of drug treatment of RA thus now encompasses not only temporary improvement of QOL but also long-term (10- or 20-year) improvement and preservation of QOL.[2,3] This paradigm shift in therapeutic strategy is also affecting routine clinical care for RA patients.

Bucillamine (Buc) is a DMARD developed in Japan.[4,5] It is a cysteine derivative possessing two SH-groups,[6,7] and is believed to exert antirheumatic effects by suppressing the formation of IgM in B cells,[7,8] the formation of matrix metalloproteinase (MMP)-3, the differentiation of osteoclasts,[9] and other mechanisms. It was first marketed in Japan in 1987 and is now in wide use, with the number of prescriptions for it issued in the year 2005 (ca. 100000) as large as that for methotrexate (MTX).[10,11] However, as with many other drugs developed in Japan, it is unclear whether adequate clinical evidence of its efficacy has been obtained. The present study was undertaken to analyze the database for the long-term observational cohort study, IORRA (previously known as J-ARAMIS) currently ongoing at the Institute of Rheumatology, Tokyo Women's Medical University,[12,13] with the goal of evaluating the clinical efficacy of bucillamine and its effects on the responses of patients to other means of treatment.

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Subjects and methods

IORRA/J-ARAMIS

The IORRA (Institute of Rheumatology Rheumatoid Arthritis) study is a long-term observational prospective cohort study begun in October 2000 at the Institute of Rheumatology, Tokyo Women's Medical University. It was initially called the J-ARAMIS (Japanese Arthritis Rheumatism and Aging Medical Information System) study, but in April 2006 was renamed IORRA. It involves all patients with RA receiving care as outpatients at the above-noted institute. For each patient, a survey composed of three domains (background variables, physician's evaluation, and laboratory test data) is conducted twice a year, to create a database. The study was begun in October 2000. As of May 2006, data collection for 6 full years had been completed. Information on about 8000 patients has been collected, with a rate of patient survey form collection of over 98% for each survey.

Cross-sectional analysis of patients treated with bucillamine

Of the patients enrolled in the 8th IORRA survey in April 2004, 871 (153 males and 718 females) had been receiving Buc therapy for 3 months or more as of April 2004. These 871 cases were divided by Disease Activity Score (DAS28) into a remission group (DAS28 < 2.6), low-activity group (2.6 < DAS28 < 3.2), moderate-activity group (3.2 < DAS28 < 5.1), and high-activity group (DAS28 > 5.1). Background variables were compared between two of these four groups, i.e., the remission group (213 cases), which included many patients responding well to Buc therapy, and the high-activity group (78 cases), which included many patients resistant to Buc therapy. We thus attempted to identify background variables determining responses to Buc therapy.

Longitudinal analysis of responses to Buc, MTX, and SASP in patients without previous treatment with DMARDs

Based on the results of the cross-sectional analysis, we conducted a longitudinal analysis of the background variables and responses to treatment of patients treated for the first time with one of the three DMARDs (Buc, MTX, and SASP) for 3 months or longer, with the goal of avoiding effects of treatment with multiple DMARDs. Of the RA patients enrolled in the 7th IORRA survey in October 2003 and the 8th IORRA survey in April 2004, those meeting both of the following requirements were subjected to this analysis: (1) patients who began to receive treatment with Buc, SASP, or MTX between October 2003 and April 2004 without any previous history of DMARD therapy, and (2) patients who had been receiving one of these three drugs for 3 months or longer as of April 2004. This analysis included 313 patients, including 85 patients for whom Buc therapy was initiated (23 males and 62 females), 81 patients for whom SASP therapy was initiated (16 males and 65 females), and 147 patients for whom MTX therapy was initiated (26 males and 121 females). The following background variables (as of October 2003) were compared as pretreatment background variables among the three groups: sex (male-to-female ratio), age, duration of illness, HAQ (Health Assessment Questionnaire), number of painful/swollen joints, overall visual analog score (VAS), DAS28, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and steroid dosage. Evaluation of the efficacy of DMARDs included 78 patients in the Buc group (20 males and 58 females), 78 in the SASP group (16 males and 62 females), and 138 in the MTX group (23 males and 115 females). Disease activity was assessed using the DAS28. Based on DAS28 scores in October 2003 and April 2004, responses to treatment were rated using the European League Against Rheumatism (EULAR) three-category scale (good, moderate, or no response) as described before.[14]

Statistical analysis

The Mann–Whitney test was used for intergroup comparison of background variables in the cross-sectional analysis. In the longitudinal analysis, background variables in each group as of October 2003 were analyzed using the Mann–Whitney test, Fisher's exact test, and Kruskal–Wallis test. Intergroup comparisons of responses to treatment employed the chi-square test and Fisher's exact test.

Results

Cross-sectional analysis of patients treated with bucillamine

Figure 1 shows the results of dividing the 871 patients by DAS28 score as of April 2004 into the remission group, low-activity group, moderate-activity group, and high-activity group. Table 1 shows the results of comparison of background variables between the remission group (213 cases) and high-activity group (78 cases) with the goal of identifying factors associated with responses to Buc therapy. There was no significant difference in mean age between these two groups. However, the remission group had a significantly higher percentage of males, a significantly shorter duration of illness, a significantly lower rate of RF-positivity, a significant lower mean RF level, and a significantly lower percentage of patients undergoing combined drug therapy (Buc + other drugs) than the high-activity group. The DMARD most frequently used for combined drug therapy was MTX, and combination with SASP was second most frequent. The percentage of patients undergoing combined DMARD + steroid therapy and the mean dose level of steroid were significantly lower in the remission group than in the high-activity group.

Table 1. Cross-sectional analysis of background variables between the remission group (213 patients) and high-activity group (78 patients) in April 2004 with the goal of identifying factors associated with responses to Buc therapy

	Remission group (DAS28 < 2.6)	High-activity group (DAS28 > 5.1)	*P* value
No. of patients	213	78	
Male/female ratio	59:154	11:67	0.02
Age (years)	57.7 ± 12.4	59.2 ± 11.0	0.258
Duration of disease (years)	10.6 ± 8.8	12.3 ± 7.2	0.011
Positive serum test for RF (%)	59.2	92.3	<0.001
RF (IU/ml)	84.6 ± 156.2	181.6 ± 243.4	<0.001
Combination with other DMARD (%)	24.4	67.9	<0.001
Combination with MTX (%)	16.0	44.9	<0.001
Combination with SASP (%)	6.1	20.5	0.001
Combination with GST (%)	0.9	9.0	0.002
Combination with prednisolone (%)	29.6	60.3	<0.001
Prednisolone (mg)	1.3 ± 2.3	3.3 ± 3.2	<0.001

DAS, disease activity score; RF, rheumatoid factor; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; SASP, sulfasalazine; GST, glutathione *S*-transferase

Table 2. Cross-sectional analysis of background variables between the patients treated with bucillamine alone in the remission group (161 patients) and in high-activity group (25 patients) in April 2004

	Remission group (DAS28 < 2.6)	High-activity group (DAS28 > 5.1)	*P* value
No. of patients	161	25	
Male/female ratio	42:119	1:24	0.011
Age (years)	56.4 ± 12.6	57.0 ± 12.2	0.697
Duration of disease (years)	9.9 ± 9.0	11.6 ± 7.4	0.118
Positive serum test for RF (%)	58.4	88.0	0.004
RF (IU/ml)	64.4 ± 115.8	106.9 ± 124.0	0.001
Combination with prednisolone (%)	24.2	52.0	0.007
Prednisolone (mg)	0.9 ± 1.9	2.5 ± 2.9	0.001

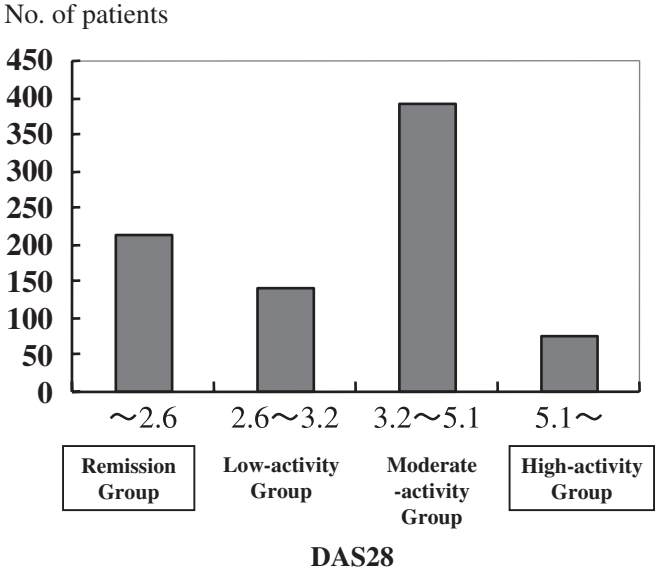

Fig. 1. Distribution of Disease Activity Score (*DAS28*) for 871 patients treated with bucillamine in April 2004. These patients were divided into the remission group, low-activity group, moderate-activity group, and high-activity group, depending on individual DAS28 scores

Because this analysis revealed a significantly higher percentage of patients receiving two or more DMARDs in the high-activity group, we performed a similar comparison of background variables between the remission group and the high-activity group confining to patients treated with Buc alone. Table 2 summarizes the results of this comparison between the remission group (161 cases) and the high-activity group (25 cases). When analysis was confined to patients treated with Buc alone, there were no significant inter-group differences in mean age or duration of illness, but the remission group included a significantly higher percentage of males (remission group: 35.2%, high-activity group: 4.1%), a significantly lower rate of RF-positivity, and a significantly lower mean RF level. The percentage of patients undergoing combined Buc + steroid therapy and the mean steroid dose level were significantly lower in the remission group. Thus, the overall findings of analysis of patients treated with Buc alone were identical to those of analysis of all patients.

Table 3. Summary of the background variables as of October 2003 in the Buc, SASP and MTX group in longitudinal analysis of responses to Buc, SASP and MTX in patients without previous treatment with DMARDs

	Buc (n = 85)	SASP (n = 81)	P value	MTX (n = 147)	P value
Dose (mean ± SD, mg)	153.1 ± 61.2	807.5 ± 382.9		5.23 ± 2.07	
Duration (months) [Median (25%, 75%)]	6 (6, 6)	6 (6, 6)		6 (4, 6)	
Male/female	23:62	16:65	0.279	26:121	0.098
Age (years)	59.1 ± 12.5	57.4 ± 12.8	0.452	57.9 ± 13.5	0.625
Duration of disease (years)	10.1 ± 7.7	10.2 ± 9.2	0.678	10.1 ± 9.8	0.39
HAQ	0.73 ± 0.69	0.60 ± 0.65	0.284	0.77 ± 0.62	0.414
TJC	2.9 ± 4.1	2.2 ± 2.9	0.794	2.5 ± 3.2	0.799
SJC	3.2 ± 4.5	2.3 ± 2.9	0.354	2.8 ± 2.8	0.385
Total VAS (mm)	36.5 ± 26.6	29.4 ± 24.2	0.085	40.1 ± 25.8	0.34
DAS28	3.9 ± 1.3	3.6 ± 1.1	0.204	4.1 ± 1.0	0.399
CRP (mg/dl)	1.6 ± 1.9	1.4 ± 1.7	0.539	1.9 ± 1.8	0.032
ESR (mm/h)	36.7 ± 25.8	34.4 ± 23.0	0.703	41.1 ± 25.0	0.112
RF (IU/ml)	88.0 ± 475.1	156.2 ± 350.1	0.529	105.2 ± 161.5	0.409
Prednisolone (mg)	2.7 ± 2.6	2.7 ± 3.3	0.869	2.6 ± 2.6	0.962

Buc, bucillamine; SASP, sulfasalazine; HAQ, Health Assessment Questionnaire; TJC, tender joint score; VAS, visual analog score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

Table 4. Percentage of patients in each group in each EULAR category of response (Good, Moderate or No response) on the basis of DAS28 scores in October 2003 and April 2004

	No. of patients (M/F)	Response (%)		
		Good	Moderate	No response
Buc	78 (20/58)	14.1	26.9	59.0*
SASP	78 (16/62)	7.7	17.9	73.4
MTX	138 (23/115)	9.4**	23.2	67.4

* P = 0.119 vs SASP, P = 0.403 vs MTX
** P = 0.397 vs Moderate, P = 0.397 vs No response

Longitudinal analysis of responses to Buc, MTX, and SASP in patients without previous treatment with DMARDs

Table 3 summarizes the background variables as of October 2003 in the Buc, SASP, and MTX groups. There were no significant differences between the Buc and SASP groups in sex (male-to-female ratio), age, duration of illness, HAQ, number of painful/swollen joints, overall VAS, DAS28, CRP, ESR, RF level, or steroid dosage. C-reactive protein was significantly higher in the MTX than in the Buc group (Buc: 1.6 ± 1.9 mg/dl, MTX: 1.9 ± 1.8 mg/dl, P = 0.032), but there were no significant intergroup differences in any other variables.

Table 4 compares responses to treatment among the DMARD treatment groups, and shows the percentages of cases in each group in each EULAR category of response (good, moderate, or no response) on the basis of DAS28 scores in October 2003 and April 2004. The percentages of patients rated good was 14.1% in the Buc group, 7.7% in the SASP group, and 9.4% in the MTX group, suggesting that treatment with Buc is more likely to result in remission than treatment with any other DMARD tested. The percentages of cases rated moderate were 26.9%, 17.9%, and 23.3% in the Buc, SASP, and MTX groups, respectively. The total percentages of cases rated good and moderate were 41.0%, 25.6%, and 32.6%, respectively, in these three groups.

Discussion

As noted, the cross-sectional analysis revealed that responses to Buc treatment were better in males, patients with shorter duration of illness, and those who were RF-negative. When Buc was used in such cases, combination of Buc with other DMARDs or steroid was usually not necessary. In the longitudinal analysis, comparison of background variables at the start of DMARD therapy revealed no marked differences among the Buc, SASP, and MTX groups. However, the percentage of patients exhibiting moderate or good response to treatment, as rated using the EULAR response criteria, was higher in the Buc group (41.0%) than in the MTX (32.6%) and SASP groups (25.6%). The mean dose levels of Buc, SASP, and MTX were 153.1 ± 61.2 mg/day, 807.5 ± 382.9 mg/day, and 5.23 ± 2.07 mg/week for the patients included in the longitudinal analysis, and identical to the dose levels of these drugs usually used clinically in Japan.[11] The reason the efficacy of MTX and SASP was lower in this study than that reported from Western countries is probably related to the lower doses of these DMARDs that are allowed to be prescribed in Japan.

Since its launch on the Japanese market in 1987, Buc has been used as a first-line DMARD for the treatment of RA. The Guidelines on Treatment Based on EBM (Evidence-Based Medicine), prepared by a study group of the Japanese Ministry of Health, Labour and Welfare, also list Buc as a drug whose use is strongly recommended.

Because Buc has been marketed only in Japan and Korea, no direct comparison of this drug with other DMARDs often used in Western countries (e.g., SASP and MTX) had been reported until a few years ago. Recently, however, clinical studies comparing Buc with MTX or

SASP have begun to be reported.[10,11,15] Ichikawa et al. compared the responses to Buc or MTX monotherapy and combined Buc + MTX therapy in patients with early-stage RA. They reported that Buc monotherapy was as effective as MTX monotherapy, and that the rate of response to combined Buc + MTX therapy was significantly higher than that to Buc or MTX monotherapy.[15] Nagashima et al. determined the percentage of cases in which Buc therapy was continued, and on the basis of their findings concluded that Buc can be considered a well-balanced DMARD.[11] The results of the present study endorse those of these previous reports. Buc can thus be considered a first-line drug for the treatment of early-stage RA.

The IORRA database, which was examined in the present study, is composed of the data from a cohort made up of RA patients undergoing routine management at the Institute of Rheumatology, Tokyo Women's Medical University. Randomized control trials (RCTs) permit collection of data with the highest evidence level. However, it is difficult to extrapolate the results of an RCT involving only a narrow range of patients to routine clinical management. The importance of cohort studies in determining strategies of management of RA has recently been emphasized.[16] When conducting cohort studies, close attention must be paid to biases. Because the IORRA is a cohort from only one facility (Institute of Rheumatology, Tokyo Women's Medical University), facility-related biases may need to be taken into account in interpreting the results of this survey. However, patient selection bias appeared to be minimal in this study, because almost all outpatients seen at this facility were enrolled in the study. This cohort can therefore be considered appropriate for the present type of study, which involved stratification of patients within a cohort.[13]

The present study revealed the usefulness of Buc in patients without previous history of DMARD therapy. Furthermore, analysis revealed several background variables that may determine the responses of individual patients to Buc. If the validity of these background variables as factors determining responses to this drug can be established in a prospective cohort study, it will be possible to establish findings that can contribute to advancing treatment of RA patients towards the goal of remission of this disease. Further study is now in progress to investigate the usefulness of this DMARD by the retention rate using life table analysis.

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