Mod Rheumatol (2007) 17:33–36
DOI 10.1007/s10165-006-0533-z

ORIGINAL ARTICLE

Naomasa Yokota · Yoshiaki Kuga · Teruhisa Kanazawa
Minoru Morishita · Kensaku Tanida · Katsumi Itou

Ten years results of bucillamine in the treatment of rheumatoid arthritis

Received: August 10, 2006 / Accepted: October 10, 2006

Abstract A 10-year cohort study was performed, involving all of the 118 patients treated with bucillamine in our hospital between 1988 and 1990. Evaluation was made on the basis of erythrocyte sedimentation rate, grip strength, joint score, duration of morning stiffness, and Lansbury index consisting of the above four parameters. Eleven patients were male and 107 were female, with a mean age of 53 years (range: 20–79 years) and a mean duration of illness of 8.2 years (range: 2–31 years). Lansbury index remained significantly suppressed throughout the 10-year period of treatment. Continuous treatment was possible for 10 years in 18 patients (15%: 2 men and 16 women). Stage of disease did not advance in 14 patients. Six patients met the criteria for remission. Of all patients, 50% dropped out of treatment at 2.4 years after the start of treatment and 75% at 5 years. The 100 patients who dropped out could be roughly divided into three groups. One third of them dropped out because of lack of or attenuation of response. Another third dropped out because of referral to other medical facilities or discontinuation of visits to our hospital, and the remaining third dropped out because of adverse reactions to treatment. There was no particular trend in terms of sex, age, duration of sickness, drugs used before bucillamine, or level of activity of rheumatoid arthritis. There were no significant difference in the stage and class of the disease, and other backgrounds between 10-year treatment group and dropout group.

Key words Bucillamine · Disease-modifying antirheumatic drug (DMARD) · 10-year results

N. Yokota (✉) · Y. Kuga · T. Kanazawa · M. Morishita
Division of Rheumatic Diseases, Tokyo Metropolitan Bokutoh Hospital, 4-23-15 Kotobashi, Sumida-ku, Tokyo 130–8575, Japan
Tel. +81-3-3633-6151
e-mail: naomasanet@aol.com

K. Tanida
Department of Orthopedic Surgery, Tokyo Metropolitan Fuchu Hospital, Tokyo, Japan

K. Itou
Department of Rheumatology, Yugawara Koseinenkin Hospital, Tokyo, Japan

Introduction

Bucillamine is a disease-modifying antirheumatic drug (DMARD) with SH groups developed in Japan in 1975. Since 1987, this drug has been extensively used in Japan. A study group organized by the Ministry of Health, Labour, and Welfare (MHLW) of Japan rated bucillamine as a grade A drug (strongly recommended) on the basis of the results of development and treatment of it as well as data on clinical use of this drug in Japan collected to date.[1] However, many of the reports on which this recommendation was based were on case series, or were reviews which did not appear to have provided adequate evidence for the usefulness of this drug. The recommendation made by the same study group was therefore supplemented with the comment that it is desirable to accumulate further evidence and to evaluate it as a drug for treatment of rheumatoid arthritis (RA). Because RA tends to be progressive and chronic, it is particularly important to be certain of the long-term efficacy and tolerability of the drug when devising a plan for treatment of RA. The present study was undertaken to examine the prognosis of RA patients by means of a 10-year examination of a cohort of patients treated with bucillamine. For each patient who discontinued treatment, the reason for and time of dropout were determined. We also attempted to determine the expected role of bucillamine as a drug for the treatment of RA.

Subjects and methods

This 10-year cohort study involved all of the 118 patients treated with bucillamine at our hospital between 1988 and 1990. Evaluation was made on the basis of erythrocyte sedimentation rate, grip strength, joint score, duration of morning stiffness, and Lansbury index consisting of the above four parameters. For patients who discontinued treatment, the reason for and time of dropout were examined, including patients for whom oral drug treatment was discontinued because of adverse reactions, those for whom treatment was

discontinued because of lack or attenuation of response (group with secondary lack of response), and those for whom treatment at our hospital was discontinued because of referral to other medical facilities or discontinuation of visits to our hospital. For patients with lack or attenuated response, we considered switching to or adding DMARDs other than bucillamine as the endpoint. For statistical analysis, the paired *t*-test and Mann–Whitney *U*-test were performed on the JNP 5.0 computer program. Probability values of $P < 0.05$ were considered significant.

Results

Of the 118 patients studied, 11 were male and 107 were female, with a mean age of 53 years (range: 20–79 years) and a mean duration of illness of 8.2 years (range: 2–31 years). A total of 66 patients were naïve to DMARD therapy, while 52 patients were switched from treatment using other DMARDs, including 23 previously treated with gold sodium thiomalate (GST), 22 with d-penicillamine (D-PC), 6 with auranofine (AF), and 7 with lobenzarit disodium (CCA).

Group with continued treatment

Treatment was continued for 10 years in 18 patients (15%), including 2 men and 16 women with a mean age of 50 years (range: 26–70 years) and a mean duration of illness of 6.9 years (range: 0.2–17.5 years). The percentage of patients dropping out of bucillamine treatment was 50% at 2.4 years after the start of therapy and 75% at 5 years (Fig. 1). Ten patients were naïve to DMARD treatment, while 8 were switched from other DMARDs (D-PC in 4 cases, GST in 2 cases, and AF in 2 cases). In the 18 patients for whom bucillamine treatment was continued for 10 years, the Lansbury index remained significantly suppressed for 10 years (Fig. 2). There was no particular trend in terms of sex, age, duration of sickness, drugs used previously, or level of activity of RA. In the group with continued treatment for 10 years, 7 patients (39%) exhibited 50% or more improvement in Lansbury index, 8 (45%) exhibited less than 50% improvement, 2 exhibited no change, and 1 exhibited exacerbation. In 14 patients, stage of disease did not advance (78%, Fig. 3), and the criteria for remission was met by 6 patients. Adverse reactions to bucillamine were noted in 3 patients (17%), including 2 with proteinuria (requiring suspension of bucillamine treatment for 6 months) and 1 with eruption and itching.

Dropout group

The 100 patients who dropped out (and were accumulated chronologically) could be roughly divided into three groups. One third of them exhibited no or attenuated response to treatment. Another third were referred to other medical facilities or discontinued visiting our hospital. The remaining third exhibited adverse reactions to bucillamine. In neither disease stage nor class (according to the Steinbrocker classification) was there a significant difference between the group with continued treatment and the dropout group. There were also no significant differences in erythrocyte sedimentation rate, grip strength, joint score, duration of

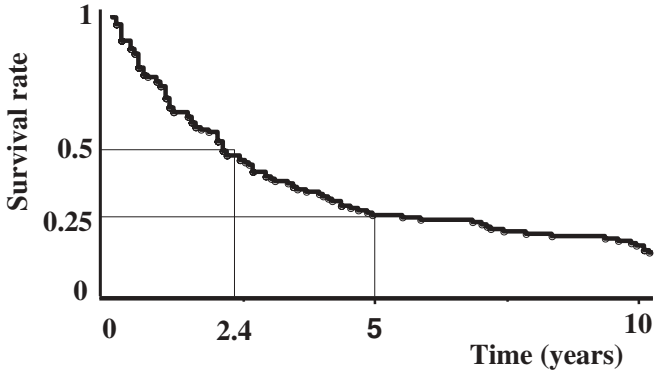

Fig. 1. Time course of change in percentage of patients with continuation of treatment (survival curve). Of all patients, 50% dropped out of treatment at 2.4 years and 75% at 5 years after the start of treatment

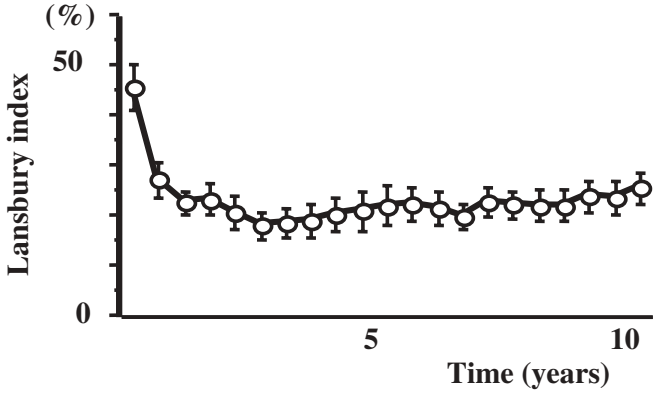

Fig. 2. Changes in Lansbury index in the group with 10-year continuation of treatment. In all of the 18 patients treated with bucillamine for 10 years, the Lansbury index was significantly suppressed for the entire 10-year period ($P < 0.05$, paired *t*-test)

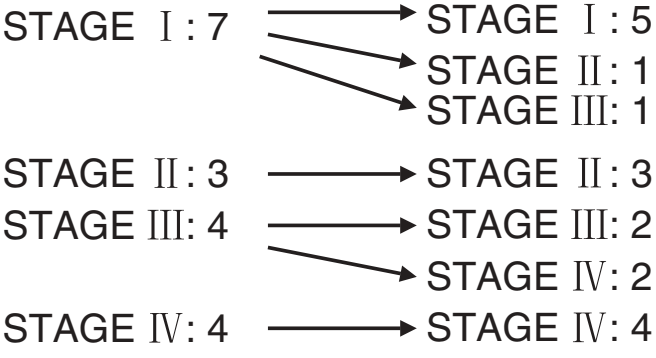

Fig. 3. Changes in disease stage in the group with 10-year continuation of treatment. Ten patients (71%) exhibited no change in disease stage, except for 4 stage IV patients

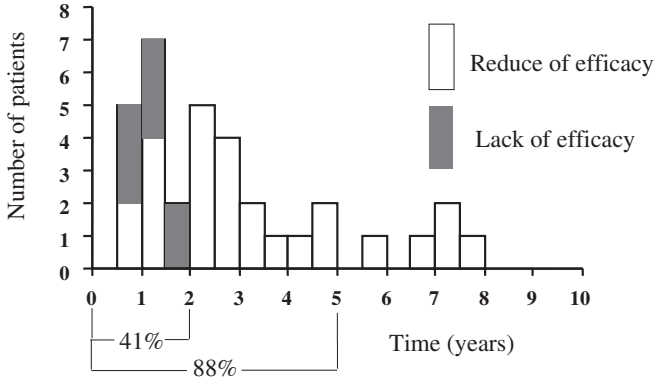

Fig. 4. Time of dropout due to lack of or attenuation of response ($n = 34$). Dropout occurred within 2 years in 41% and 5 years in 88% of the 34 cases

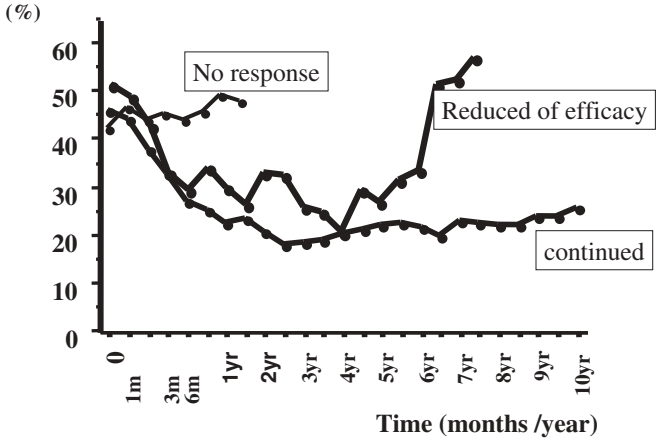

Fig. 5. Time course of change in Lansbury index (groups with continued treatment group, no response, and attenuation of response) (paired *t*-test). The group with attenuation of response exhibited significantly greater improvement in Lansbury index 2 months after the start of treatment than the group without response ($P < 0.05$). The group with continued treatment exhibited significantly greater improvement in Lansbury index 2 years after the start of treatment than the group with attenuation of response

Table 1. Background variables for the group with continued treatment ($n = 18$) and the dropout group (subdivided into the group with adverse reactions and that with no response/attenuated response) ($n = 67$)

	Continued	Discontinued	
Morning stiffness (min)	42.2	34.1	NS
Grip strength (mmHg)	142.2	114.0	NS
Joint counts	50.0	56.6	NS
ESR (1 h)	59.6	71.4	NS
Lansbury index (%)	45.8	54.1	NS
Steroid (no. of patients)	0	33	(1–7.5 mg)

There were no significant differences in any background variable (Mann–Whitney *U*-test). Oral steroid treatment was used for none of the patients in the group with 10-year continuation of treatment
ESR, erythrocyte sedimentation rate; NS, not significant

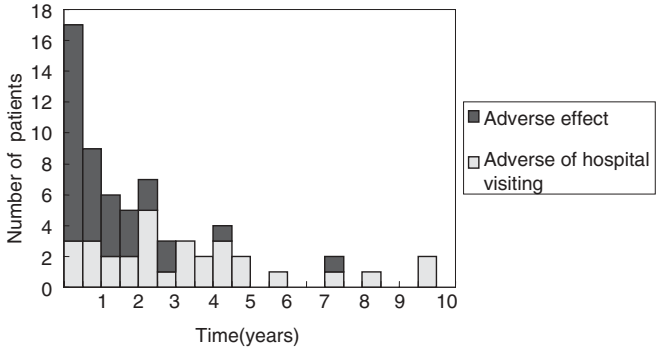

Fig. 6. Time of dropout due to referral or discontinuation of visits ($n = 34$). Dropout occurred within 5 years in 79% of the 34 cases. Time of dropout due to adverse reactions ($n = 33$). Dropout due to overall adverse reactions occurred within 6 months in 42% and within 2 years in 82% of the 33 cases. Dropout due to proteinuria occurred within 6 months in 46% and within 2 years in 79% of the 13 cases. Dropout due to disorders of the skin occurred within 6 months in 38% and within 2 years in 89% of the 11 cases

morning stiffness, or Lansbury index (Table 1). There were 34 patients (29%; 31 women and 3 men) for whom bucillamine treatment was discontinued because of no or attenuated response to treatment. Their mean age was 54.2 years and mean duration of illness 7.2 years (range: 0.3–25.4 years). For 14 patients (41%), treatment was discontinued within 2 years after initiation, while for 30 patients (88%) treatment was switched to other drugs within 5 years after initiation (Fig. 4). Attenuation of response to treatment with bucillamine sometimes appeared at 6 months of initiation. Switching to other drugs was often performed 2–5 years after the start of bucillamine treatment at our hospital. The group with attenuated responses exhibited significantly greater improvement in Lansbury index 2 months after the start of treatment than the group without response (Fig. 5). The group with continued treatment exhibited significantly greater improvement in Lansbury index 2 years after the start of treatment than the group with attenuation of response. For 33 patients (28%; 30 women and 3 men), treatment was discontinued because of referral to other medical facilities or discontinuation of visits to our hospital. The mean age of this group of patients was 49.9 years and the mean duration of illness 7.9 years (range: 0.3–31.0 years). Dropout often occurred during the first 5 years of treatment with bucillamine (Fig. 6).

Adverse reactions

There were 33 patients (30 women and 3 men) for whom treatment with bucillamine was discontinued because of adverse reactions. Their mean age was 55.8 years and mean duration of illness 11.2 years (range: 0.5–30.9 years). The most frequent adverse reaction was proteinuria (13 cases), followed by disorders of the skin (11 cases). In addition, gastrointestinal disorder (1 case), respiratory disorder (1 case), renal dysfunction (1 case), bone marrow suppression (2 cases), and other adverse reactions (4 cases) were noted. Proteinuria developed within 6 months of initiation of treatment in 46% of the patients and within 2 years in 79% of them. Disorders of the skin were observed within 6 months of treatment initiation in 38% and within 2 years in 89% of

the patients. In total, 82% of all adverse reactions appeared within 2 years after the start of treatment with bucillamine (Fig. 6).

Discussion

Bucillamine is a DMARD with SH groups developed in Japan, and is used widely in this country. However, few reports have been published concerning 5-year results of treatment with it,[2–4] and our literature search revealed no report on 10-year, long-term results of treatment with this drug. In the present study, treatment with bucillamine significantly suppressed RA activity in cases in which this drug was continued for 10 years. However, the percentage of patients for whom bucillamine treatment was continued for 10 years was lower than that reported for methotrexate (MTX) (38%).[5] The percentage of patients continuing treatment for 5 years was over 50% for only MTX but less than 50% for all other DMARDs (including bucillamine).[3] The low percentage (15%) of patients who continued bucillamine treatment for 10 years in the present study was probably due to the following factors: (1) switching to other drugs or combining bucillamine with other drugs is easy at present, when many DMARDs are available; and (2) physicians now tend to seek better control of RA.

According to the guidelines available in Japan, DMARDs of recommendation grade A include methotrexate (MTX, Rheumatrex), salazosulfapyridine (SASP), bucillamine, and leflunomide (in addition to these DMARDs, a biological preparation, infliximab, is a drug of recommendation grade A).[1] In 2002, the American College of Rheumatology (ACR) prepared new guidelines for the treatment of RA,[6] adopting a new strategy in which powerful DMARDs such as MTX should be used beginning in early stages of disease to suppress joint destruction. However, according to Wyeth, the manufacturer of MTX, the number of deaths for which a causal relationship to this drug could not be ruled out was as many as 197, during the period from March 12, 1999 (the date of launch on the market) to the end of December 2005.[7] In contrast, the number of deaths when taking bucillamine was 59 during the period from June 30, 1987 (date of launch) to the end of March 2005.[8] Thus, although the percentage of patients treated for long periods of time is not as high for bucillamine as for MTX, the mortality with bucillamine is about one tenth that for MTX. Because in Japan MTX is indicated for treatment of intractable RA resistant to treatment with other drugs, bucillamine can be considered a DMARD of first choice for use prior to initiation of treatment with MTX, with SASP.

This study suggests that it is advisable to identify patients without response at 2 months after the start of bucillamine treatment, to make the first judgment of secondary nonresponse at 6 months after the start of treatment, and to make the second judgment of secondary nonresponse at 2 years after the start of treatment. We propose the following as a realistic strategy: if adverse reactions to this drug appear or there is no or an attenuated response: switching to MTX rapidly or combination with other DMARDs (recommendation grade C)[1] or steroids can be performed, as appropriate, depending on risk factors such as age, renal function, and complications.

Conclusion

Bucillamine treatment was continued for 10 years in 18 patients (15%). In the group with continued bucillamine treatment, RA activity was significantly suppressed for 10 years. Remission was noted in 6 patients. Adverse reactions to bucillamine often appeared within 2 years after the start of treatment with it. Attenuation of response to treatment with bucillamine often appeared during the first 5 years, with a peak recorded in the second and third years.

References

1. Ministry of Health, Labour, and Welfare (MHLW) Study Group. Manual for the diagnosis and treatment of rheumatoid arthritis (revised edition) – Diagnostic manuals and evidence-based guidelines on diagnosis and treatment (in Japanese). Tokyo: Japan Rheumatism Foundation; 2004.
2. Nishimura K, Uchida S, Watanabe F. Long-term results of bucillamine in rheumatoid arthritis – Five-year results and prediction of responses at early stages of administration (in Japanese). Jpn J Inflamm 1993;13:293–9.
3. Saito M, Nagasawa T. Comparison of usefulness in the treatment of rheumatoid arthritis among DMARDs by the life table method (in Japanese). J Clin Exp Med 1998;186:139–43.
4. Mitsuhashi H, Banpa K. Long-term results of bucillamine in rheumatoid arthritis (in Japanese). Clin Rheumatol Relat Res 2001;13:268–74.
5. Weinblatt ME, Maier AL, Fraser PA, Coblyn JS. Longterm prospective study of methotrexate in rheumatoid arthritis: conclusion after 132 months of therapy. J Rheumatol 1998;25:238–42.
6. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the Management of Rheumatoid Arthritis 2002 Update. Arthritis Rheum 2002;46:328–46.
7. Wyeth KK. Information for proper use of Rheumatrex, vol. 11 (in Japanese). 2006.
8. Santen Pharmaceutical Co. Ltd. Summary of adverse reactions to Rimatil (in Japanese). 2006.