Mod Rheumatol (2007) 17:464–469
DOI 10.1007/s10165-007-0627-2

ORIGINAL ARTICLE

Shingo Nakayamada · Kazuyoshi Saito
Hisanori Umehara · Noriyoshi Ogawa · Takayuki Sumida
Satoshi Ito · Seiji Minota · Hiroyuki Nara
Hirobumi Kondo · Jun Okada · Tsuneyo Mimori
Hajime Yoshifuji · Hajime Sano · Naoaki Hashimoto
Susumu Sugai · Yoshiya Tanaka

Efficacy and safety of mizoribine for the treatment of Sjögren's syndrome: a multicenter open-label clinical trial

Received: February 16, 2007 / Accepted: June 22, 2007

Abstract This multicenter clinical trial was performed to evaluate the efficacy and safety of mizoribine for the treatment of Sjögren's syndrome. Fifty-nine patients with a definite diagnosis of Sjögren's syndrome received 150 mg of mizoribine daily for 16 weeks. The salivary secretion volume was determined at baseline, at weeks 8 and 16 after the start of the study treatment by the Saxon test, and clinical manifestations were assessed by the investigator and the patients using a 10-cm visual analog scale (VAS). Adverse drug reactions were reported in 18 patients, of whom 6 patients had to discontinue the study due to such adverse reactions; however, no serious adverse drug reactions definitely related to the study drug were noted. The salivary secretion volume, the rate of change in salivary secretion, the patients' own assessments of dry mouth and dry eyes, the investigators' assessment of oral sicca symptoms, and the investigators' overall assessment improved following the treatment regimen with statistical significance at week 16 after the start of treatment in comparison to the baseline values. These results suggested that mizoribine may be effective in producing a subjective and objective amelioration of the glandular symptoms in patients with Sjögren's syndrome, without observing any serious adverse effects related to this drug.

Key words Mizoribine · Sjögren's syndrome · Xerostomia

S. Nakayamada · K. Saito · Y. Tanaka (✉)
First Department of Internal Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan
Tel. +81-93-603-1611; Fax +81-93-691-9334
e-mail: tanaka@med.uoeh-u.ac.jp

H. Umehara · N. Ogawa[1]
Department of Hematology and Immunology, Kanazawa Medical University, Kahoku, Ishikawa, Japan

T. Sumida · S. Ito
Division of Clinical Immunology, Major of Advanced Biomedical Applications, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

S. Minota · H. Nara
Division of Rheumatology and Clinical Immunology, Department of Medicine, Jichi Medical School, Shimono, Japan

H. Kondo[2]
Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Japan

J. Okada
Kitasato University Health Care Center, Sagamihara, Japan

T. Mimori · H. Yoshifuji
Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan

H. Sano · N. Hashimoto
Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

S. Sugai
Kudoh Hospital, Kaga, Japan

Present address:
[1]Third Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan
[2]Kitasato Institute Medical Center Hospital, Kitamoto, Japan

Introduction

Sjögren's syndrome is an organ-specific autoimmune disease involving the salivary and lacrimal glands as the target organs. The disease is mainly characterized by dry eyes and dry mouth, and patients may also have diverse systemic lesions (extraglandular symptoms) such as interstitial pneumonia, neuropathies, and interstitial nephritis.[1,2] At the sites of the lesions, a marked periductal autoreactive lymphocyte infiltration progresses into destruction of the acini and fibrosis in the lacrimal and salivary glands.

For the treatment of Sjögren's syndrome, cevimeline hydrochloride hydrate, a muscarinic receptor (M3) agonist, first became commercially available in September 2001 in Japan, and it has since proven to be remarkably effective in the control of oral sicca symptoms. However, cevimeline has only been used for symptomatic treatment, and it cannot serve as a radical treatment for Sjögren's syndrome, which is an autoimmune disorder. In Japan and other countries,

the therapeutic use of immunosuppressive agents such as methotrexate, cyclosporine, and azathioprine as well as corticosteroids has been attempted to correct immunologic abnormalities in patients with Sjögren's syndrome, yet no efficacy with such treatments have yet been demonstrated.[1]

Mizoribine is an immunosuppressant developed in Japan, and its basic effect consists of the suppression of lymphocyte proliferation. Nakayamada et al.[3] investigated the efficacy and safety of mizoribine given at 50 mg t.i.d. for 12 months in 40 Sjögren's syndrome patients with sicca symptoms, based on the presumption that the drug might prove to be clinically useful for the treatment of Sjögren's syndrome, since an excessive activation of B cells has been strongly implicated to play a role in the pathogenesis of the disease. The results of the study showed progressive significant improvements in the salivary secretion volume as determined by the Saxon test and according to the investigators' and patients' assessments, together with a significant decrease in the serum IgG level. A biopsy-verified improvement was also noted among the patients diagnosed to demonstrate an early stage of this disease. No serious adverse effects attributable to mizoribine treatment have so far been reported.

To date, there has not been a single drug worldwide that is covered by the health insurance system for the treatment of the underlying immunologic abnormalities in Sjögren's syndrome, even though the sicca symptoms associated with this disease substantially impair the patient's activities of daily life. In view of the necessity to develop effective therapeutic agents to treat this disease and verified by clinical trials, we conducted a multicenter open-label pilot study in patients with primary Sjögren's syndrome as a first step during the period from July 2004 to May 2005 to clarify the efficacy and safety of mizoribine for the treatment of Sjögren's syndrome.

Subjects and methods

Patients

Patients enrolled in this study were all definitely diagnosed to have primary Sjögren's syndrome according to the 1999 Ministry of Health and Welfare's Diagnostic Criteria for Sjögren's Syndrome, and they presented with subjective sicca symptoms. Patients who met any of the following criteria were excluded from the study: (1) patients who had previously been treated with mizoribine, (2) patients with a total leukocyte count of 3000/mm^3 or less, (3) pregnant women or lactating mothers, women with child-bearing potential and patients wishing to become pregnant during this study, (4) patients under 20 years of age, (5) patients with concurrent rheumatoid arthritis (RA), systemic lupus erythematosus, or scleroderma, (6) patients who had received treatment with corticosteroids, immunosuppressants, or antirheumatic agents, (7) patients who had received any drugs for treatment of Sjögren's syndrome, including cevimeline hydrochloride hydrate, anetholtrithion, and pilocarpine hydrochloride within 4 weeks prior to the study treatment, and (8) patients with any concurrent serious disorders of the liver, kidney or hematopoietic organs.

The concomitant use of corticosteroids, immunosuppressants, antirheumatic agents, cevimeline hydrochloride hydrate, anetholtrithion, and pilocarpine hydrochloride was prohibited during the study period. Drugs which might affect salivary gland secretion (e.g., drugs for oral use such as artificial saliva, gargles, and troches, and other agents considered to affect salivary secretion such as expectorants, Chinese herbal medicines, and H_2 receptor antagonists) were allowed as concomitant medications, although their addition to the regimen or dosage increase was prohibited in principle during the study period.

This clinical trial was conducted at all participating study centers with prior approval of the Ethics Committee of each center. All patients were provided with detailed information regarding the objectives and procedure of the study, the characteristics of the study drug, and other relevant matters. All patients gave their informed consent in writing. During the study period, mizoribine was given at doses of 50 mg t.i.d. after meals for a period of 16 weeks.

Evaluation of efficacy and safety

The salivary secretion volume was evaluated using the Saxon test. It is preferable to familiarize the examinee with the test procedure in order to obtain more stable measurements;[4] therefore, the test was repeated twice at baseline only. Each patient was asked to make assessments of the following three variables: feelings of dry mouth, feelings of dry eyes and parotid pain, using the 10-cm Visual Analog Scale (VAS). The investigators' assessments were also performed using the VAS with respect to oral sicca symptoms, labioangular sicca symptoms, and the overall assessment. Immunoglobulins, the anti-SS-A/Ro antibody, the anti-SS-B/La antibody, rheumatoid factors, C3, C4, and CH_{50} were determined wherever feasible as immunological indicators. All the above variables were evaluated at baseline, week 8, and week 16 of the study.

Hematological tests (red blood cells, hemoglobin, hematocrit, white blood cells, and platelet count), blood biochemical tests (serum total protein, total bilirubin, blood urea nitrogen, aspartate aminotransferase; alanine aminotransferase, alkaline phosphatase, serum uric acid, serum creatinine, and lactate dehydrogenase) and urinalysis (glucose and protein) were performed at baseline, week 8, and week 16 of study treatment.

Statistical methods

A statistical analysis of the efficacy data was carried out for comparison purpose of the responses at weeks 8 and 16 of the study with the baseline values using the Wilcoxon signed rank test. The level of significance was set at 5%, two-sided. The data were also evaluated for any effects of the patient

demographic and baseline characteristics regarding the volume of salivary gland secretion using a multiple regression analysis.

Results

Patient demographic and baseline characteristics

Fifty-nine patients were enrolled in this study, of whom 48 completed the study up to week 16, while 11 patients either discontinued or dropped out of the study. The reasons for discontinuation/dropping out included adverse drug reactions/events in 7 patients, symptomatic exacerbation in 1 patient, and personal requests/decisions in 3 patients.

The patient distribution according to the demographic and baseline characteristics is presented in Table 1. There were 2 male and 57 female patients enrolled, whose median age was 59.0 years, and the median duration of illness was 0.2 years. The duration of the illness was less than 12 months for the majority of the subjects (36 patients), while it was over 10 years for 4 patients.

The baseline salivary secretion volume (median) was 0.78 g per 2 min. Patients with severe disease were frequently observed; namely, 20 patients demonstrated a baseline salivary secretion volume of 0.5 g or less and 14 patients showed a volume between 0.5 g and less than 1 g, while it exceeded 5 g in 3 patients. The Saxon test was duplicated only at baseline in 55 patients. Overall, no significant differences were noted in the measured values between the paired tests, whereas the individual patient data revealed a substantial alienation of the first and second test values in 2 patients.

The medians of the other clinical assessment variables at baseline were as follows: dry mouth, 74.0 mm; dry eyes, 66.0 mm; and parotid pain, 0.0 mm as assessed by the patient; and oral sicca symptom, 73.0 mm; labioangular sicca symptom, 69.0 mm; and overall evaluation, 68.0 mm as assessed by the investigator. The assessment of the immunoglobulin levels revealed as follows: serum IgG, 1848.0 mg/dl; IgA, 319.0 mg/dl; and IgM, 107.5 mg/dl. For the treatment of Sjögren's syndrome, cevimeline hydrochloride hydrate had previously been used by 15 patients, while anetholtrithion had been used in 1 patient.

Efficacy

Therapeutic responses over time in respect of the clinical assessment variables are presented in Fig. 1A–D for 48 patients who completed the 16-week study treatment. There was a progressive improvement over time in the salivary secretion volume and in the rate of change in the salivary secretion volume (as indicated by a percentage of the baseline value), the patients' assessments of dry mouth and dry eyes, and the investigators' assessments of oral sicca symptoms, labioangular sicca symptoms, and the overall assessment. For all these variables improvements were statistically significant at week 16 of study treatment, in comparison to the baseline values. In particular, improvements were significant from week 8 of the study onwards regarding the patients' assessment of dry mouth and the investigators' assessments. The median salivary secretion volume tended to increase at week 8 of study treatment. In comparison to the baseline level, no significant difference was noted in the salivary secretion volume at that time point, but the salivary secretion significantly increased at week 16 of treatment ($P < 0.05$). The mean salivary secretion volume was 1.51 ± 1.79 g/2 min, 1.56 ± 1.97 g/2 min, and 1.61 ± 1.93 g/2 min at week 0, 8, and 16 of the study, respectively. Regarding the patients' assessment of parotid pain, no significant change was observed because only 22 patients had this symptom at the start of study.

The changes in the salivary secretion volume over time in these 48 patients, by baseline value, are illustrated in Fig. 2. Fig. 3 shows the distribution of the patients according

Table 1. Patient demographics and baseline characteristics

Sex	Male, 2; Female, 57
Age, years (range)	59.0 (47.0–68.0)
Duration of illness, years (range)	0.2 (0.1–2.4)
Treatment history	Treatment experienced, 26 Treatment naive, 33
Salivary secretion volume (g/2 min)	0.78 (0.36–2.28)
Less than 0.5	20
0.5 to less than 1	14
1 to less than 2	8
2 to less than 4	11
4 or more	6
Dry mouth, assessed by the patient (mm)	74.0 (52.0–84.0)
Dry eyes, assessed by the patient (mm)	66.0 (47.0–81.8)
Parotid pain, assessed by the patient (mm)	0.0 (0.0–22.5)
Dry mouth, assessed by the investigator (mm)	73.0 (41.0–88.0)
Labioangular dryness, assessed by the investigator (mm)	69.0 (32.5–81.0)
Overall assessment by the investigator (mm)	68.0 (45.8–82.8)
IgG (mg/dl)	1848.0 (1528.5–2319.0)
IgA (mg/dl)	319.0 (213.0–375.0)
IgM (mg/dl)	107.5 (76.6–147.5)

Median (25th–75th percentile)

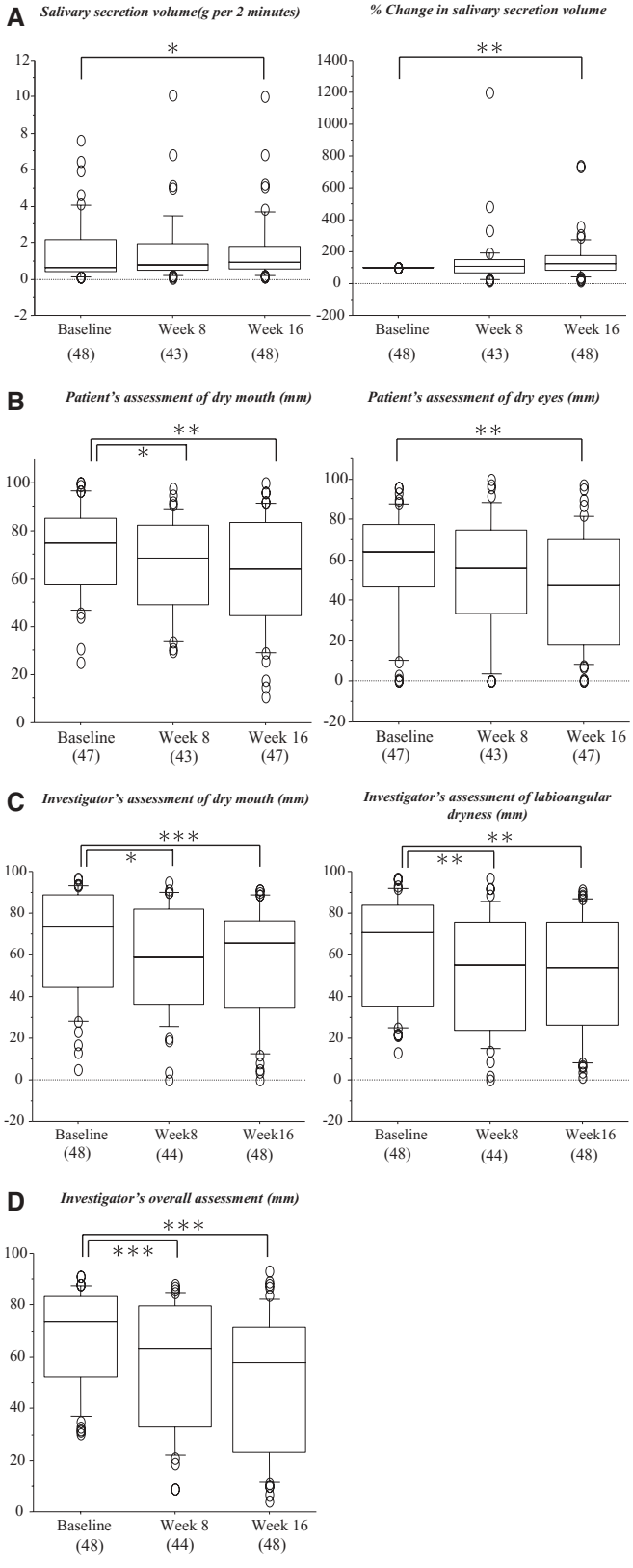

Fig. 1A–D. Time course of the clinical assessments in patients who completed the 16-week study treatment. Data are presented as box plots, where the *boxes* represent the 25th to 75th percentiles, the *lines within the boxes* represent the median, and the *lines outside the boxes* represent the 10th and 90th percentiles. The *circles* indicate outliers. A significant difference is considered to exist at the following P values: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (Wilcoxon signed rank test)

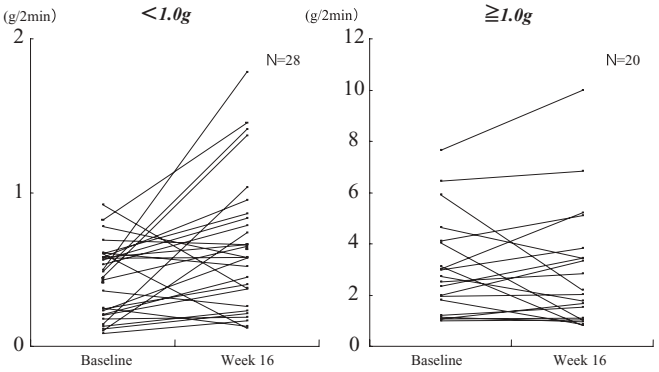

Fig. 2. Changes in salivary secretion volume over time, compared to the baseline value

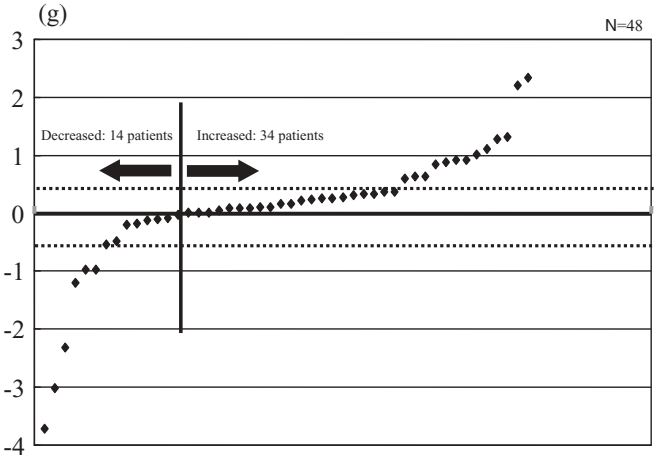

Fig. 3. Salivary secretion volume: the distribution of differences from baseline at week 16 of study treatment

to the difference in the salivary secretion volume between the baseline and the week 16 values. In comparison to the baseline value, the secretion volume decreased in 14 patients, while it increased in 34 patients; thus representing an increase in the salivary secretion in about 70% of the patients, although the degree of the increase varied from patient to patient. Nevertheless, 28 of the 48 patients were distributed within a difference range of –0.5 g to +0.5 g, and therefore the changes were not dramatic.

No significant changes were observed following the study regarding any of the immunologic parameters: immunoglobulins, the anti-SS-A/Ro antibody, the anti-SS-B/La antibody, rheumatoid factors, C3, C4, and CH_{50}. These findings may be attributable to possible differences in either the assay methods or the sensitivity between individual study centers.

The 48 patients who completed the 16-week study were analyzed for any effects of demographic and baseline characteristics on the increase in salivary secretion. The analysis was carried out using a multiple regression analysis, with a response variable of the increase in salivary gland secretion (i.e., difference in salivary secretion volume between the baseline and week 16 values) and explanatory variables

Table 2. Summary of adverse drug reactions (ADRs) noted during the study period

	n
Patients studied	59
Patients with ADRs	18
ADRs reported	29
Percentage of patients with ADRs	30.5%
Types of ADR	
Hepatic function disorder[a]	9
Blood disorders[b]	7
Gastrointestinal disorders[c]	4
Rash, pruritus	2
Increased serum uric acid	1
Others[d]	6

[a] Increased alanine aminotransferase, 4; increased aspartate aminotransferase, 2; liver function disorder, 2; increased lactate dehydrogenase, 1
[b] Decreased white blood cells, 4; decreased hemoglobin, 2; anemia, 1
[c] Nausea, vomiting, diarrhea, and abdominal pain, 1 each
[d] C3 decreased, 2; dull headache, total protein decreased, hip joint pain, and disturbance of consciousness, 1 each

including the age, duration of illness, baseline salivary secretion, the patients' assessment of dry mouth, the patients' assessment of dry eyes, the serum IgG levels, and the previous use of cevimeline. The results indicated no appreciable effect on the increase in salivary secretion by any of the variables, except for the presence or absence of a history of treatment with cevimeline. Although the effect of the previous use of cevimeline did not demonstrate a statistical significance, it did have the greatest influence among the other factors ($P = 0.0658$).

Safety

Of 59 patients enrolled in this study, 18 patients reported 29 adverse drug reactions. The pertinent data are presented in Table 2. The commonly noted adverse reactions included a hepatic function disorder, blood disorders, and gastrointestinal disorders. Of these, 8 events occurring in 6 patients led to a discontinuation of study (gastrointestinal disorders, 4; hepatic function disorder, 1 event; pruritus, 1; right hip joint pain, 1; and a disturbance of consciousness, 1). All these adverse reactions, except for pruritus, occurred within the first 4 weeks of mizoribine treatment. A disturbance of consciousness developed on Day 20 of the study in a 75-year-old female patient with concurrent hypertension whose duration of Sjögren's syndrome was 1 month. Laboratory tests revealed hyponatremia and hypokalemia, both of which resolved within about 40 days after the withdrawal of mizoribine. The patient also received trichloromethiazide concomitantly, and the use of this drug may have been related to this event.

Discussion

This multicenter open-label clinical trial was conducted in 59 patients with primary Sjögren's syndrome to assess the efficacy and safety of 16-week mizoribine therapy at a dose of 150 mg daily (50 mg t.i.d.) for the treatment of Sjögren's syndrome. The results of the study demonstrated a significant improvement in the salivary secretion volume, the rate of changes in salivary secretion volume, the patients' assessment of dry mouth and dry eyes, the investigators' assessment of oral sicca symptoms and labioangular sicca symptoms, and the investigators' overall assessment. While the patient's quality of life can be substantially impaired due to the sicca symptoms associated with Sjögren's syndrome, the present data showed an amelioration not only in the dry feeling of the mouth but also in the dry feeling of the eyes, as assessed by the patient.

In recent years, the therapeutic modalities for RA have changed considerably to a strategy of instituting antirheumatic drug therapy at an early stage of the disease to stem the progress of articular degeneration when an early diagnosis is made after onset. In patients with Sjögren's syndrome, it would therefore likewise also hold true that the spontaneous progress of the disease may be altered via a correction of the underlying immunologic abnormalities using radical therapeutic measures from the incipient stage of disease. However, the current therapy for Sjögren's syndrome primarily consists of symptomatic treatment with the use of agents aimed at the relief of sicca symptoms, such as cevimeline hydrochloride hydrate, pilocarpine hydrochloride, and others, while there have so far been few radical therapeutic modalities that have been developed to correct the underlying immunologic abnormalities. A number of attempts have heretofore been made with the use of corticosteroids, immunosuppressants, and antirheumatic agents as radical treatment for Sjögren's syndrome, but none of these have yet proven efficacious. Several clinical trials have been performed in patients with Sjögren's syndrome using biological products, which have recently been purported to have altered the therapeutic strategy for rheumatoid arthritis.

Infliximab, an anti-tumor necrosis factor-α therapeutic agent, has been demonstrated to be effective in an open-label trial conducted in 16 patients with primary Sjögren's syndrome,[5] whereas a multicenter randomized double-blind placebo-controlled trial of infliximab in 103 patients with primary Sjögren's syndrome failed to show a significant difference in the efficacy of the drug, in comparison to a placebo.[6] In another randomized double-blind placebo-controlled trial, etanercept proved not to differ from placebo in efficacy when evaluated in 28 patients with Sjögren's syndrome.[7]

Mizoribine was discovered in the culture broth of *Eupenicillium brefeldianum* isolated from soil from the island of Hachijo, Japan, and has been developed as an antifungal agent. It is currently used as an immunosuppressant for the control of graft rejection associated with renal transplants and for the treatment of lupus nephritis, rheumatoid arthritis, and primary nephrotic syndrome. Mizoribine is known to act upon the pathway of purine synthesis in cells via the specific competitive inhibition of inosine monophosphate (IMP) dehydrogenase, thereby exerting suppressive effects on T and B lymphocytes.[8,9] In patients with Sjögren's syndrome, a marked periductal autoreactive lymphocyte infil-

tration in the lacrimal and salivary glands arises, and acinar destruction and fibrosis ensue, thus leading to a diminished lacrimal and salivary gland function. These infiltrating lymphocytes largely comprise $CD4^+$ T lymphocytes at an early stage and, as the lesions progress, B lymphocytes predominate. The resultant excessive B-cell activation is accompanied by hypergammaglobulinemia, and the production of autoantibodies, such as the anti-SS-A/Ro antibody and the anti-SS-B/La antibody, has been noted. Mizoribine may therefore demonstrate a clinical efficacy in the treatment of Sjögren's syndrome since it has a suppressive effect on T- and B-lymphocyte proliferation.

Brennan et al. reported that both peripheral blood $\gamma\delta^+$ T cells and $CD5^+$ B cells, which are considered to play a role in the production of autoantibodies, were found to have increased in patients with RA and patients with primary Sjögren's syndrome, in comparison to healthy subjects.[10] In a multicenter double-blind placebo-controlled study using mizoribine for the treatment of RA (mizoribine group, 100 mg t.i.d. in 101 patients; and placebo group, 102 patients), a lymphocyte subset analysis was performed using the fluorescent double-staining technique. An analysis was performed in 8 patients in the mizoribine group and in 6 patients in the placebo group before the start and after the completion of a 16-week study treatment, and all patients in the mizoribine group exhibited a decrease in the $CD5^+$ B cell subset among the other post-treatment subset parameters.[11]

Furthermore, a recent report described an attempt to increase the blood mizoribine level by elevating the mizoribine dose level (administered at 150 mg (q.d.), 300 mg (q.d., q.o.d.), or 500 mg (q.d.) at intervals of 2–3 days) mainly in pediatric patients with lupus nephritis or nephritic syndrome. A significant improvement (increase) in the salivary secretion was therefore noted following the treatment with mizoribine in the present series, but the increase was not so dramatic. It is therefore considered to be necessary to investigate the effect of mizoribine therapy with an increased dosage in patients with Sjögren's syndrome while taking the above-mentioned findings regarding the treatment of other disorders into account.

A major problem of the sicca symptoms associated with Sjögren's syndrome is the substantial impairment in the patient's quality of life. The present study showed a substantial improvement in the patient's VAS assessment of the sicca symptoms. However, the present study was performed using an open-label design. In the case of infliximab, the open-label trial results suggested its efficacy but a randomized placebo-controlled trial failed to demonstrate its efficacy. As a result, a placebo effect thus seems to have played a role in such an open-label study. It is advisable that a placebo-controlled randomized trial should therefore be conducted to elucidate the efficacy of mizoribine for the treatment of Sjögren's syndrome.

References

1. Mavragani CP, Moutsopoulos NM, Moutsopoulos HM. The management of Sjögren's syndrome. Nat Clin Pract Rheumatol. 2006;2:252–61.
2. Fox RI. Sjögren's syndrome. Lancet. 2005;366:321–31.
3. Nakayamada S, Saito K, Nakatsuka K, Nakano K, Tokunaga M, Sawamukai N, et al. Efficacy of mizoribine treatment in patients with Sjögren's syndrome: An open trial. Mod Rheumatol 2003; 13:339–45.
4. Torikai K. Special Issue: New topics on Sjögren's syndrome. IV. Laboratory tests: 1. Saxon test, gum test, and ophthalmologic examinations (in Japanese). Prog Med 2002;22:43–6.
5. Steinfeld SD, Demols P, Appelboom T. Infliximab in primary Sjögren's syndrome: One-year followup. Arthritis Rheum 2002;46: 3301–3.
6. Mariette X, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, et al. Inefficacy of infliximab in primary Sjögren's syndrome: Results of the Randomized, Controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). Arthritis Rheum 2004;50: 1270–6.
7. Sankar V, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, et al. Etanercept in Sjögren's syndrome: A twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50:2240–5.
8. Okubo M, Chen X, Kamata K, Masaki Y, Uchiyama T. Suppressive effect of mizoribine on humoral antibody production in DBA/2 mice. Transplantation 1986;41:495–8.
9. Turka LA, Dayton J, Sinclair G, Thompson CB, Mitchell BS. Guanine ribonucleotide depletion inhibits T cell activation. J Clin Invest.1991;87:940–8.
10. Brennan F, Plater-Zyberk C, Maini RN, Feldmann M. Coordinate expansion of 'fetal type' lymphocytes ($TCR\gamma\delta^+$T and $CD5^+$B) in rheumatoid arthritis and primary Sjögren's syndrome. Clin Exp Immunol 1989;77:175–8.
11. Shiokawa Y, Honma M, Shichikawa K, Miyamoto T, Hirose J, Nobunaga T. Clinical evaluation of the immunosuppressant mizoribine for treatment of rheumatoid arthritis: a multicenter double-blind placebo-controlled trial based on basal treatment(in Japanese). J Clin Expt Med 1991;156:811–31.