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ORIGINAL ARTICLE

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Efficacy of mizoribine treatment in patients with Sjögren's syndrome: an open pilot trial

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Abstract The aim of this study was to evaluate the efficacy and safety of mizoribine in patients with Sjögren's syndrome. Forty patients with sicca syndrome, whose conditions were definitely diagnosed as Sjögren's syndrome, were given mizoribine orally at a dosage of 150 mg/day for 12 months. The percentage change in salivary secretion after 3, 6, and 12 months of the therapy increased to +112.2% ($P < 0.001$), +119.9% ($P < 0.01$), and +147.3% ($P < 0.001$), respectively, compared with the baseline. Serum IgG levels decreased significantly throughout the study, and the level was 1969.4 ± 620.0 mg/dl after treatment for 12 months compared with the pretreatment value of 2094.3 ± 746.6 mg/dl ($P < 0.05$). The patient's assessment of clinical signs and symptoms on a 10-cm visual analog scale improved significantly from 7.2 ± 2.3 cm at the start of the treatment to 5.0 ± 1.9 cm after 12 months ($P < 0.001$). There was a similar improvement in the physician's assessment using the 10-cm visual analog scale: 7.1 ± 1.6 cm at the start of the treatment and 5.2 ± 1.9 cm after 12 months ($P < 0.001$). With regard to safety, no serious adverse reactions were observed. Although a controlled study would be required to clarify the efficacy of mizoribine, these preliminary observations indicate its efficacy for ameliorating glandular symptoms through improvements in immune abnormalities in patients with Sjögren's syndrome.

Key words Mizoribine · Sjögren's syndrome · Xerostomia

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Introduction

Sjögren's syndrome, a chronic autoimmune disorder, is characterized by lymphocytic infiltration of the exocrine glands and B lymphocyte hyperreactivity, resulting in xerostomia and keratoconjunctivitis sicca.[1] Clonal expansion of autoreactive T lymphocytes is thought to be involved in the pathogenesis, and their progressive infiltration leads to the destruction of acinar and ductal epithelial cells and loss of glandular parenchyma. B cell hyperreactivity and hypergammaglobulinemia are also common in Sjögren's syndrome patients, and certain autoantibodies against ribonucleoproteins (SSA/Ro and SSB/La), immunoglobulin (rheumatoid factor), and muscarinic acetylcholine receptors, which are frequently present in the sera of the patients, may play a role in the development of glandular dysfunction. Moreover, pseudomalignant or malignant lymphoproliferation of cells of the B-cell lineage may be present initially or develop later in the course of the illness, resulting in a high incidence of lymphoma.[2]

The primary objective of treatment is the alleviation of the symptoms and abnormal findings by increasing exocrine secretions, ideally by correcting and suppressing the underlying autoimmune abnormalities and exocrine adenitis. Although the efficacy of muscarinic acetylcholine receptor agonists in alleviating sicca syndrome by stimulating exocrine glands has been verified in recent years,[3] such treatment is no more than symptomatic, and cannot be employed as a drastic therapy for Sjögren's syndrome. Many types of drug, such as disease-modifying antirheumatic drugs (DMARDs) and immunosuppressants, have been tried with the aim of correcting the immunological abnormalities, but as yet there is no established pertinent treatment for the glandular symptoms. Mizoribine is an immunosuppressant that was developed in Japan and has been found to inhibit the proliferation of lymphocytes, especially B cells.[4,5] Therefore, it may be useful clinically for the treatment of Sjögren's syndrome patients in whom excessive activation of B cells has a profound pathogenetic bearing. We have examined the efficacy and safety of oral

mizoribine therapy at a dosage of 150 mg/day in 40 patients with Sjögren's syndrome presenting with sicca symptoms.

Materials and methods

Patient selection and study design

All the patients recruited for this study had Sjögren's syndrome diagnosed according to the 1999 Revised Japan–MHW Diagnostic Criteria for Sjögren's Syndrome. Patients receiving drugs for the treatment of Sjögren's syndrome, such as cevimeline hydrochloride and anetholtrithion, were admitted to the study only after a washout period of ≥4 weeks. The institution of any of the above-mentioned drugs, and of drugs that might affect salivary and/or lacrimal secretory functions, was prohibited during the study period. Treatment for a primary disease or for complications with stable doses of drugs that had been administered prior to the start of the study was allowed. Female subjects had to be neither pregnant, nursing, nor of childbearing potential. Patients with a history of liver or kidney disease, hematopoietic disorders, or who had been receiving DMARDs were excluded from the study. This was a 12-month, preliminary, single-center, open-label study to evaluate the efficacy and safety of mizoribine. We did not plan a controlled trial because it seemed to be difficult to secure sufficient patients. The study was approved by this institution's Human Subjective Research Committee, and informed consent was obtained from all the patients who enrolled. This study was also completely independent of the company, and no grant support from the company was provided.

Evaluation of treatment efficacy and safety

The therapeutic response of each patient was evaluated at monthly clinic visits over a period of at least 6 months and up to 12 months. At the start (baseline) and after treatment with mizoribine for 3, 6, and 12 months, the following parameters were determined: parotid salivary flow, measured by the Saxon test; serum levels of immunoglobulins, serum anti-SS-A/Ro and anti-SS-B/La antibody levels, and erythrocyte sedimentation rate (ESR). The global assessments of the physicians and the patients of the clinical signs and symptoms of Sjögren's syndrome, including xerophthalmia, xerostomia, parotid enlargement/pain, and arthralgia, were determined using 10-cm visual analog scales. The results of all these 3-, 6-, and 12-month assessments were compared with the baseline values.

Treatment safety was evaluated at monthly intervals up to 12 months, and was judged based on patients' complaints, clinical assessments by the physician, and the results of detailed clinical questioning.

Table 1. Patients, characteristics at baseline

Age (years)	
Mean	56.4 ± 13.5
Range	23–80
Sex	
Male	1
Female	39
Primary	32
Secondary	8
Disease duration (months)	
Mean	30.2 ± 33.3
Range	1–131
Saxon test (g/2 min)	
Mean	1.36 ± 1.49
Range	0.07–3.50
Immunoglobulins	
IgG (mg/dl)	2094.3 ± 746.6
IgA (mg/dl)	309.7 ± 92.4
IgM (mg/dl)	145.7 ± 117.7
Anti-SS-A/Ro antibody (index)	71.5 ± 67.0
Anti-SS-B/La antibody (index)	19.9 ± 35.5
Erythrocyte sedimentation rate (mm/h)	34.3 ± 25.8

Mean (± SD) are shown

Statistical analysis

The values are expressed as means ±SD, and an analysis of efficacy was carried out via intergroup comparisons of the variables/endpoints described above with the baseline values using the nonpaired Student's *t*-test. Differences at *P* values of less than 0.05 were considered to be statistically significant.

Results

Patient characteristics

Forty patients were enrolled into this study, three of whom later dropped out, one due to an adverse reaction during the 6th month of treatment. The other two failed to return after the 3rd month of study treatment and thereafter. The patients characteristics are summarized in Table 1. The group comprised 1 male and 39 females, with a mean age of 56.4 years. The average duration of illness was 30.2 months, and a considerable proportion of this population was in the early postonset stages of the disease. The disease was primary in 32 patients and secondary in 8 (rheumatoid arthritis 7, and scleroderma 1). The baseline clinical assessment variables/endpoints (mean ± SD) of the 40 patients at the start of mizoribine therapy were as follows: salivary flow rate, 1.36 ± 1.49 g/2 min; IgG, 2094.3 ± 746.6 mg/dl; IgA, 309.7 ± 92.4 mg/dl; IgM, 145.7 ± 117.7 mg/dl; anti-SS-A/Ro antibody, 71.5 ± 67.0 index; anti-SS-B/La antibody, 19.9 ± 35.5 index; ESR, 34.3 ± 25.8 mm/h; patient's assessment of clinical signs and symptoms on the 10-cm visual analog scale, 7.2 ± 2.3 cm; physician's assessment of clinical signs and symptoms on the 10-cm visual analog scale, 7.1 ± 1.6 cm. Two patients had annular erythema and one had renal tubular acidosis. The drugs used at the start of the study are shown in Table 2; these drugs were not changed during the study.

Efficacy

The relevant data for the 40 patients with Sjögren's syndrome with overt sicca symptoms after 3, 6, and 12 months of mizoribine therapy were compared with the baseline data. Salivary secretion increased significantly from 3 months of therapy onwards, with measured values of 1.76 ± 1.97 g/2 min ($P < 0.001$), 1.72 ± 1.78 g/2 min ($P < 0.01$), and 1.86 ± 1.60 g/2 min ($P < 0.01$) after 3, 6, and 12 months, respectively (Fig. 1a). After 3, 6, and 12 months, the percentage change in salivary secretion increased to +112.2% ($P < 0.001$), +119.9% ($P < 0.01$), and +147.3% ($P < 0.001$), respectively, compared with the baseline, i.e., progressive, significant increases with time (Fig. 1b). Figure 2 illustrates the changes in the other laboratory parameters with time. Significant decreases in the serum IgG levels were observed at all the assessment times, and the level was 1969.4 ± 620.0 mg/dl ($P < 0.05$) after treatment for 12 months, compared with the pretherapy value of 2094.3 ± 746.6 mg/dl. No statistically significant changes in the serum IgA or IgM levels were observed. There were no definite trends in the changes in the serum anti-SS-A/Ro and anti-SS-B/La levels per se; nor did these levels show significant changes during the study period. The ESR decreased significantly after therapy for 12 months to 28.4 ± 17.6 mm/h, compared with the baseline value of 34.3 ± 25.8 mm/h ($P < 0.001$). Marked significant improvements in the patient's assessment of clinical signs and symptoms, including xerophthalmic symptoms, on the 10-cm visual analog scale compared with the baseline value (7.2 ± 2.3 cm) were noted after 3, 6, and 12 months of therapy: 5.2 ± 2.3 cm ($P < 0.001$), 5.2 ± 2.6 cm ($P < 0.001$), and 5.0 ± 1.9 cm ($P < 0.001$), respectively (Fig. 3a). There were similar improvements in the physician's assessment using the 10-cm visual analog scale: 7.1 ± 1.6 cm at the baseline visit, and 5.9 ± 1.8 cm ($P < 0.001$), 5.3 ± 2.0 cm ($P < 0.001$), and 5.2 ± 1.9 cm ($P < 0.001$) after 3, 6, and 12 months, respectively (Fig. 3b). The annular erythema found in two patients disappeared after 1 month, and the renal tubular acidosis in one patient improved after 6 months.

Table 2. Drug treatment at entry

Drug	Number of patients
Prednisolone (5 mg/day)	2
Tear substitutes	13
NSAIDs	14
Antihypertensive drugs	4
Antacids	5
Proton pump inhibitors	2

NSAIDs, nonsteroidal anti-inflammatory drugs

Adverse effects

The study treatment was discontinued owing to an adverse reaction in only one of the 40 patients enrolled; this patient was withdrawn from the study after 6 months of therapy because of liver dysfunction. The adverse events noted in this study are listed in Table 3. A total of 11 adverse events in 11/40 patients (27.5%) were reported during the study, the most frequent being liver dysfunction (5 events in 5/40 patients, 12.5%). All these hepatic events and the other adverse events were mild or had an ambiguous causal relationship with the study medication, and therefore did not interfere with continuation of the therapy.

Case report

In this investigation, a labial minor salivary gland biopsy was precluded from the study program because of its invasive nature. However, on completion of the study, a biopsy

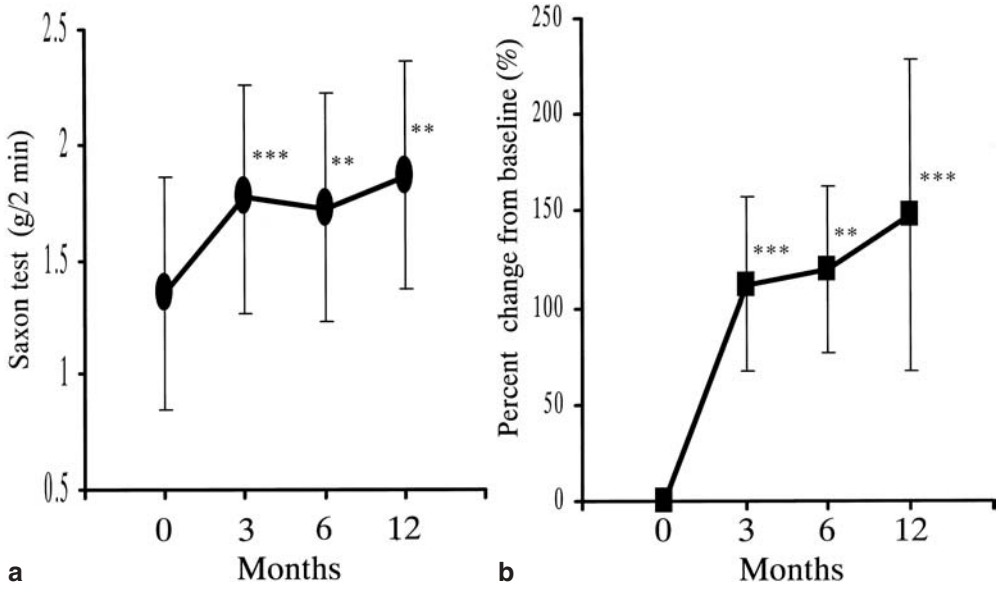

Fig. 1. Parotid salivary flow. **a** Mean values of the Saxon test. **b** Percentage change in the Saxon test from baseline. Data are mean ±SD. ** $P < 0.01$; *** $P < 0.001$ (versus baseline)

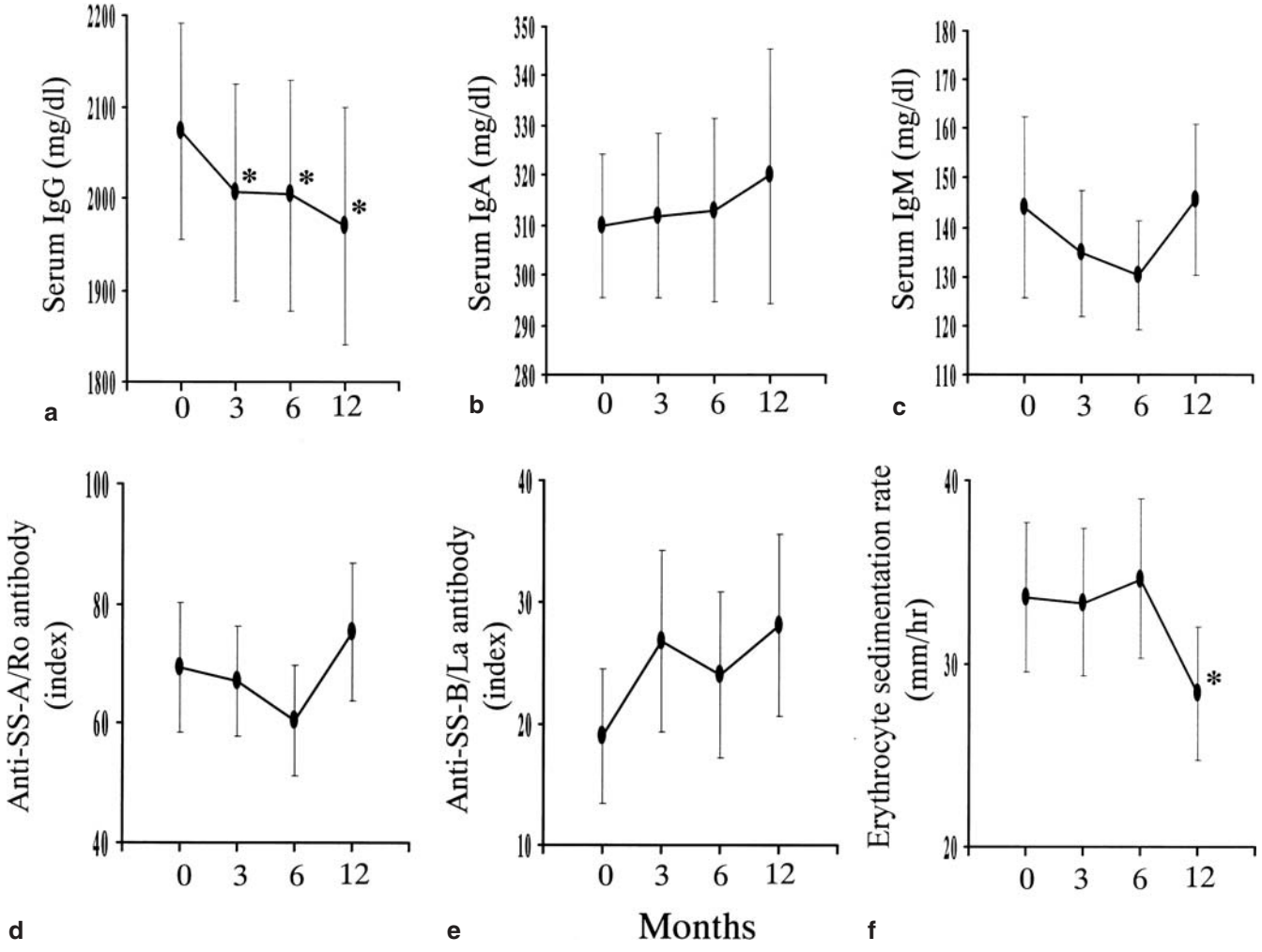

Fig. 2. Laboratory measurements. **a** IgG; **b** IgA; **c** IgM; **d** anti-SS-A/Ro antibody; **e** anti-SS-B/La antibody; **f** erythrocyte sedimentation rate. Data are mean ±SD. * $P < 0.05$ (versus baseline)

Table 3. Adverse effects reported during the study

Adverse effects	No. (%)
Liver dysfunction	5 (12.5)
Increase in ALP	1 (2.5)
Hypertension	1 (2.5)
Pneumonia	1 (2.5)
Cytopenia	1 (2.5)
Skin eruption	1 (2.5)
Proteinuria	1 (2.5)
Total number of patients	11 (27.5)

ALP, alkaline phosphatase

was performed on one patient, who consented to the procedure. The patient, a 40-year-old woman, was first seen at this hospital in November 2000 with the chief complaints of dryness of the mouth and eyes, general fatigue, and polyarthralgia. A diagnosis of primary Sjögren's syndrome was made on the grounds of positive anti-SS-A/Ro antibodies, decreased salivary secretion, and the histopathological findings from the minor salivary glands. She gave her informed consent, was enrolled in the study, and started on mizoribine at a dose level of 150 mg/day. A marked improvement in her symptoms of dryness of the eyes and mouth and polyarthralgia became evident from 1 month after the initiation of the study medication onwards, and her salivary flow rate increased markedly with time from 2.22 g/2 min at the start to 2.60, 3.50, and 3.74 g/2 min after 3, 6, and 12 months of treatment, respectively. The quantity of tears secreted, measured by the Schirmer test, also increased markedly from the baseline values of 15 and 10 mm for the right and left eyes, respectively, to 25 and 31 mm, respectively, after 6 months of treatment. A second lip biopsy was performed on completion of the 12-month treatment period, again with the patient's consent. This revealed a substantial improvement in the marked periductal lymphocytic infiltration and acinar atrophy that were evident prior to mizoribine therapy, and the microscopic features of the glands were essentially normal (Fig. 4).

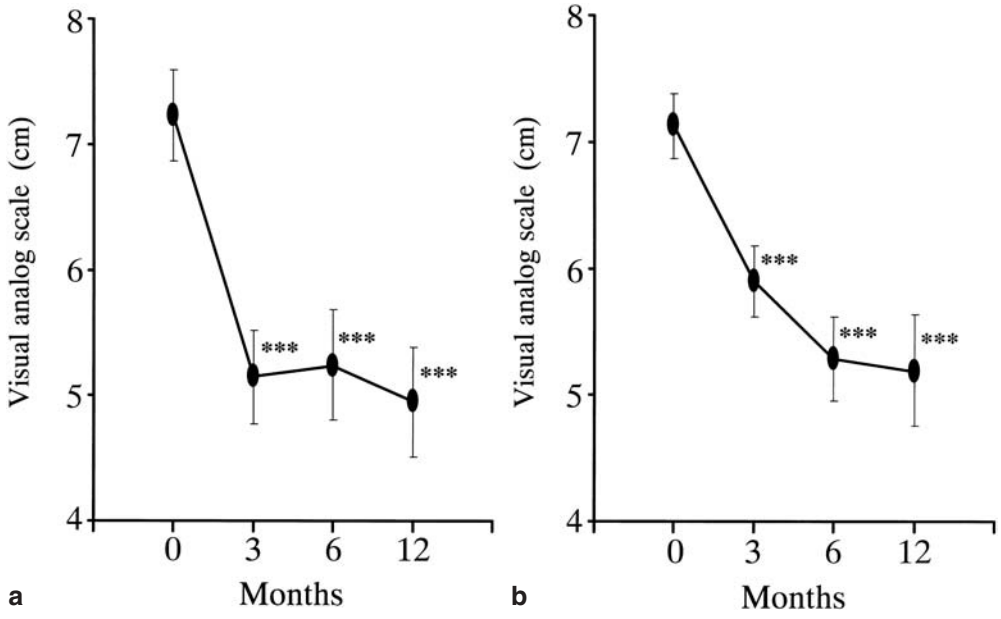

Fig. 3. Global assessments of the clinical signs and symptoms of Sjögren's syndrome determined using a 10-cm visual analog scale. **a** Patient's assessments; **b** physician's assessments. Data are mean ±SD. *** $P < 0.001$ (versus baseline)

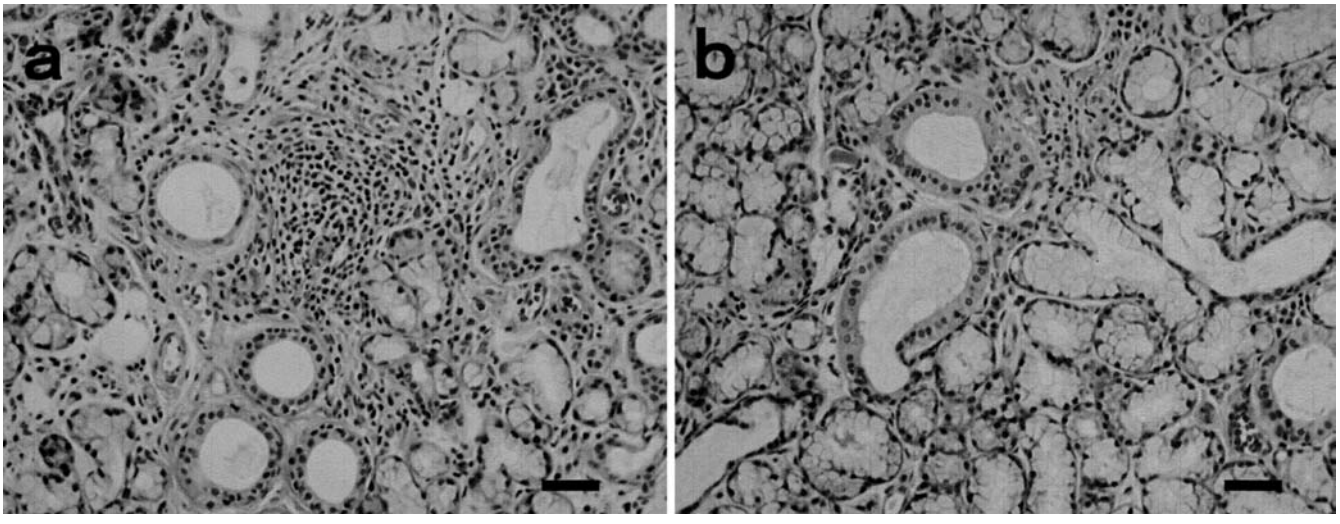

Fig. 4. Histopathological findings from the minor salivary glands (H&E staining). **a** Before treatment, showing a substantial improvement in the marked periductal lymphocytic infiltration and acinar atrophy. **b** After 12 months of treatment. The microscopic features of the glands were essentially normal. *Bar* 50 μm

Discussion

Forty patients with Sjögren's syndrome presenting with sicca symptoms were treated with oral mizoribine at 150 mg/day. First, the salivary secretion rate, measured by the Saxon test, increased significantly with time to +112.2%, +119.9%, and +147.3% of the baseline value after treatment for 3, 6, and 12 months, respectively. Second, the serum IgG level was found to have decreased significantly after treatment for 3 months, and remained significantly lower than the baseline level up to the end of the 12-month study. Third, significant improvements in both the physician's and patient's assessments (obtained using 10-cm visual analog scales) of the clinical signs and symptoms with time were observed. Fourth, no serious adverse effects were encountered, and there were no safety concerns.

There is no specific treatment for this syndrome, and the general aim of conventional therapy is symptomatic relief. DMARDs, corticosteroids, and immunosuppressants have been tried with the aim of correcting the immunological abnormalities in Sjögren's syndrome. Fox et al.[6] assessed the efficacy of medium-dose steroid therapy in patients with primary Sjögren's syndrome in a 6-month double-blind study. They observed no significant improvements in lacrimal or salivary secretory function in three groups of eight

patients receiving oral prednisolone at 30 mg every other day, piroxicam at 20 mg daily, or a placebo. Significant improvements in the IgG and IgA levels and erythrocyte sedimentation rate occurred in the oral prednisolone group, but these parameters returned to baseline levels within 4 months of completion of the course of steroid medication. Miyawaki et al.[7] assessed the efficacy of low-dose steroid therapy in 20 patients with primary Sjögren's syndrome, who took low-dose prednisolone (5–15 mg/day) and were observed for 48 months whilst on this therapy. They reported an increase in salivary secretion, amelioration of subjective symptoms, and decreases in the anti-SS-A/Ro and anti-SS-B/La antibody and serum IgG levels following prednisolone therapy. Thus, opinions are divided on the effectiveness of corticosteroids for treating the glandular lesions associated with Sjögren's syndrome. Of concern in this regard, however, are the merits and demerits of long-term steroid therapy for Sjögren's syndrome in middle-aged women, who are the group most frequently affected by the disease. The current prevailing view is that adequate-dose steroid therapy should only be given to those patients with pronounced disease activity and serious extraglandular manifestations.

Drosos et al.[8] carried out a 6-month double-blind trial of cyclosporine in patients with Sjögren's syndrome. In the group receiving cyclosporine, improvements in subjective ocular and oral sicca symptoms were observed, but objective parameters, such as exocrine glandular function and the histological findings from minor salivary glands, were comparable to those in the placebo group, and the incidence of adverse reactions was comparatively high. Price et al.[9] observed no significant differences between patients receiving azathioprine or a placebo with respect to subjective sicca symptoms, quantity of exocrine secretion, histological findings from the minor salivary glands, or serum immunoglobulin levels in a 6-month study involving 12 patients with primary Sjögren's syndrome. Skopouli et al.[10] carried out a 1-year evaluation of methotrexate therapy (0.2 mg per kg per week) in 17 patients with Sjögren's syndrome, and concluded from its results that the treatment had no effect on objective or specific findings, e.g., autoantibodies, although there were improvements in subjective symptoms, such as dryness of the eyes and mouth. In a 2-year double-blind study conducted by Kruize et al.[11] treatment with chloroquine (sales of which have been discontinued in Japan) did not produce any significant improvement in exocrine glandular function, although both hypergammaglobulinemia and erythrocyte sedimentation rate elevation were mitigated compared with the placebo group.

Therefore, immunosuppressive therapies aimed at correcting the immune abnormalities associated with Sjögren's syndrome have not proven to be fully efficacious. Our rationale for examining the clinical usefulness of mizoribine for the treatment of Sjögren's syndrome was as follows. Mizoribine is an imidazole nucleoside that was discovered in fluid cultures of the mold *Eupenicillium brefeldianum*. It has purine-antimetabolite activity, and is an immunosuppressant that was developed in Japan.[12] After administration and systemic absorption, mizoribine diffuses into cells as a result of the extra- versus intracellular concentration difference and is biotransformed by adenosine kinase to activated mizoribine-5′-phosphate, which inhibits the activity of inosine 5′-monophosphate dehydrogenase in the guanosine 5′-monophosphate synthesis pathway. Mizoribine is currently used for the suppression of graft rejection in renal transplantation patients, and for the treatment of lupus nephritis and rheumatoid arthritis (RA). In lupus nephritis, although this drug had been shown to reduce proteinuria and stabilize renal function, immunological parameters such as anti-DNA antibody were not improved.[13] In RA, although the clinical symptoms such as the number of swollen and tender joints and the duration of morning stiffness significantly improved by mizoribine treatment, immunological parameters such as rheumatoid factor and serum immunoglobulins were not improved.[14] On the other hand, our results demonstrated the efficacy of this drug in improving immunological parameters, including hypergammaglobulinemia and ESR in patients with Sjögren's syndrome. Basically, mizoribine has been shown to exert a mainly inhibitory effect on both T and B lymphocytes, especially B cells. It inhibits human and mouse B-cell IgM production and proliferation, in a dose-dependent manner, in response to stimulation with lipopolysaccharides or costimulation with *Staphylococcus aureus* Cowan I (SA) and interleukin (IL)-2.[4,5] Excessive B-cell activation and autoantibody production play decisive roles in the pathogenesis of Sjögren's syndrome, as described above, and the involvement of CD40/CD40L and B-cell-attracting chemokine-1 (BCA-1) in excessive B-cell activation has been reported.[15] It has also been reported that sialoschesis does not develop in NOD-Igμ null mice, which are devoid of B cells, and that salivary secretion in these mice diminishes following injection of the IgG fraction from NOD mice or from patients with Sjögren's syndrome.[16] Furthermore, it has been reported that patients with Sjögren's syndrome have high levels of B cells expressing CD5 antigen, and mizoribine has been known to act by selectively suppressing CD5+ B cells compared with other immunosuppressants.[17–19] These findings suggest that mizoribine exerts clinical benefits by suppressing B-cell activity in patients with Sjögren's syndrome. In fact, our present investigation demonstrated the efficacy of this drug in increasing saliva production and improving hypergammaglobulinemia in patients with Sjögren's syndrome. However, mizoribine did not improve the levels of the serum anti-SS-A/Ro and anti-SS-B/La antibody. Mizoribine might also modulate T cell activation, resulting in an improvement in T cell infiltration in acinar and ductal epithelial cells. It is particularly noteworthy that treatment with this drug resulted in marked histological improvements of the minor salivary glands. Periductal lymphocytic infiltration and atrophy of the acini, which were evident prior to treatment in one patient who gave her informed consent to pre- and posttreatment lip biopsy, subsided markedly, and her histological features were essentially normal following treatment.

Since there is no established pertinent treatment for the glandular symptoms in Sjögren's syndrome, and because of the low incidence of adverse effects in comparison with

other immunosuppressants, mizoribine could be adapted as a rational therapy. However, since this study is not a randomized trial and had no placebo control group, the data can only be used to indicate the efficacy of mizoribine treatment. Furthermore, it may be necessary to exercise caution in view of the risk of the development of cancer among patients undergoing long-term continued immunosuppressive therapy, particularly as a high incidence of malignant tumors, especially B-cell lymphomas, in patients with Sjögren's syndrome has been reported.[2] No carcinogenic potential of mizoribine in laboratory animals has been documented, but patients undergoing chronic treatment with that this drug must be carefully monitored. The present results of the use of mizoribine, which targets the underlying immune abnormalities, suggest that this drug will be useful clinically as a rational therapy for Sjögren's syndrome. Thus, although this is a preliminary paper, once published, the report will prompt us to perform placebo-controlled double-blind studies in multiple centers in order to clarify its efficacy for Sjögren's syndrome.

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