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THERAPEUTIC HOTLINE

Mizoribine treatment for antihistamine-resistant chronic autoimmune urticaria

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ABSTRACT: Chronic autoimmune urticaria is routinely diagnosed using an autologous serum skin test. Mizoribine is a newly developed immunosuppressive agent that has low toxicity. The pharmacological effects of mizoribine are similar to those of another purine biosynthesis inhibitor, mycophenolate mofetil. A 57-year-old woman presented with recurrent wheals and was insufficiently managed with administration of antihistamines, antileukotrienes, oral corticosteroids, and cyclosporine. She was positive in the autologous serum skin test. Oral mizoribine therapy was started as a combination therapy with prednisolone. The patient achieved a dramatic improvement in symptoms and complete resolution of the urticaria a few days after adding mizoribine to her treatment. The prednisolone was tapered after the start of mizoribine treatment. Her symptoms did not flare up, and no side effects were observed. In vitro basophil histamine release assays suggested that she might have anti-IgE autoantibody-type histamine release activity. We believe that mizoribine has a therapeutic role in some patients with chronic autoimmune urticaria and may be useful for treatment of cases not responsive to classical therapy. We suggest that mizoribine might help to reduce anti-IgE autoantibody acting on the surface of basophils in chronic autoimmune urticaria.

KEYWORDS: autologous serum skin test, chronic autoimmune urticaria, mizoribine

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Letter to the editors

Chronic urticaria is defined as daily occurrence of hives for at least 6 weeks. Urticarial patients are treated with oral antihistamines (1); however, 50% do not respond to them and require corticosteroids or cyclosporin (2). Mizoribine, purine biosynthesis inhibitor, is a relatively new immunosuppressive

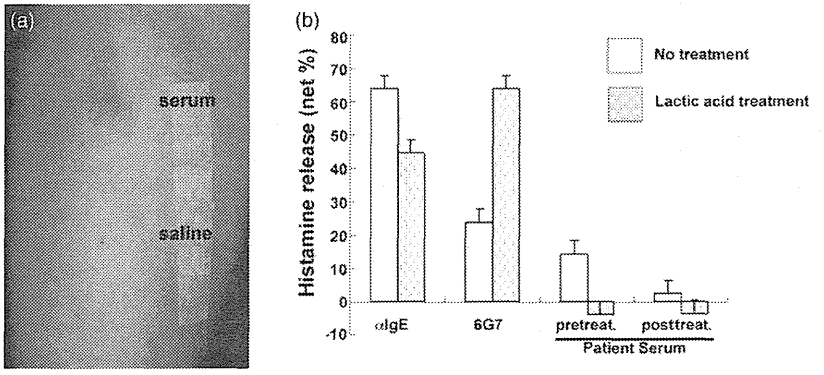

FIG. 1. (a) A positive autologous serum skin test. (b) Histamine releasing test. Histamine release (net %) is shown on the ordinate. Left columns (blind) and right columns (black dot) indicate histamine release with no treatment and with lactic acid treatment, respectively. The results for antihuman IgE autoantibody (αIgE), high-affinity IgE receptor autoantibody (6G7), the patient serum before mizoribine therapy (pretreated), and the patient serum after mizoribine therapy (posttreated) are depicted.

agent with low toxicity (3). We present a patient with antihistamine-resistant chronic autoimmune urticaria, successfully treated with mizoribine.

A 57-year-old woman presented with a 3-month history of recurrent hives. Physical examination revealed numerous wheals on the trunk and extremities. Throughout the disease course, no abnormal results were observed in C-reactive protein, antinuclear antibody, hepatitis B and C serologies, serum C1 inactivator level, serum IgE, and IgE radioallergosorbent tests. The autologous serum skin test was performed by intradermal injection of 0.05 mL of the patient's serum with saline as a negative control. Fifteen minutes after the injection, a red wheal formation of 18 × 12 mm in diameter appeared and persisted for more than 15 minutes (FIG. 1A). We diagnosed her as chronic autoimmune urticaria. She was refractory to antihistamine, leukotriene receptor antagonist, and cyclosporine. Oral prednisolone (10 mg/day) was administered combined with antihistamine (olopatadine hydrochloride, 10 mg/day), but revealed weak response. Then, mizoribine was supplemented at a dose of 150 mg/day, once after breakfast. The patient showed a dramatic improvement and complete resolution within a few days. The prednisolone was tapered in 2 weeks and seized 3 months. Mizoribine was discontinued in 6 months. After that, no recurrences or adverse effects were observed.

We carried out in vitro basophil histamine release assays to detect anti-IgE antibody and anti-high-affinity IgE receptor antibody using human donor leukocytes (FIG. 1B) (4). As positive controls, we used goat antihuman IgE antibody (Seikagaku Co. Tokyo, Japan) and a monoclonal antibody for human high-affinity IgE receptor, α-subunit (6G7, gift by Hoffmann-La Roche Company, Nutley, NJ, USA). IgE antibodies on the surface of basophils were removed by treatment with 10 mM lactic acid (pH 3.9) (5). As a result, the serum before mizoribine therapy induced histamine release from healthy donor-derived basophils, which was remarkably inversed by lactic acid treatment. A similar trend was seen by antihuman IgE autoantibody. Based on these findings, we suggest that the patient could have anti-IgE autoantibody-type histamine release activity, which was reversed after mizoribine therapy.

The present patient with chronic autoimmune urticaria, refractory to standard treatments, showed a good response to mizoribine. This is the first report to use mizoribine to treat chronic autoimmune urticaria. Some chronic autoimmune urticaria patients may have a partial or unsatisfactory response to standard therapies. In our patient, the addition of mizoribine to the antihistamine and prednisolone resulted in rapid clinical remission and allowed tapering of prednisolone. We believe that mizoribine has a potential alternative candidate for refractory chronic autoimmune urticaria.

Based on the histamine release assay, we suggest that circulating histamine-releasing factors, probably anti-IgE autoantibody, could be involved in the pathophysiology of present patient. In addition, mizoribine could reduce anti-IgE autoantibody by acting on the surface of basophils and preventing antibody-mediated cross-linking and release of mast cell mediators.

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Therapeutic effect of mizoribine on pemphigus vulgaris and pemphigus foliaceus

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ABSTRACT: We evaluated the effectiveness of mizoribine, a newly developed immunosuppressive agent, as an adjuvant therapy in the treatment of both pemphigus vulgaris and pemphigus foliaceus. Eleven pemphigus patients (eight pemphigus vulgaris and three pemphigus foliaceus) received the combination therapy of prednisolone and mizoribine. Complete remission was observed in three of the eight patients with pemphigus vulgaris and in one of the three patients with pemphigus foliaceus. The four patients with complete remission had a rapid clinical response and achieved remission at a median of 11.8 months. Partial remission was achieved in two of the three patients with pemphigus foliaceus. The median time to achieve partial remission was 16.0 months. Six (55.6%) of the 11 patients with pemphigus had complete or partial remission and were able to taper their prednisolone. The cumulative probability of having a complete remission was 64.3% at 19 months of follow-up using Kaplan–Meier analysis. The effectiveness of the additional mizoribine therapy could be attributed to its corticosteroid-sparing properties as well as its immunosuppressive effects. The serum concentration titer of mizoribine was around 1.0 μg/mL 2 hours after administration. Patients who were not improved by the additional mizoribine might require a continuously higher dose of mizoribine to achieve effective therapy.

KEYWORDS: blood concentration level, corticosteroids, immunosuppressive agent, mizoribine, pemphigus, pemphigus foliaceus, pemphigus vulgaris

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Conflict of interest disclosure: None declared.

Introduction

Pemphigus is a life-threatening autoimmune blistering disease that affects the skin and mucosa. Two main classic types of pemphigus have been identified, pemphigus vulgaris and pemphigus foliaceus, in which pathogenic IgG autoantibodies

are directed against desmosomal transmembrane glycoproteins, desmoglein (Dsg) 3 and Dsg1, respectively (1). Corticosteroids remain the primary treatment for pemphigus. However, the relatively high doses and long duration of treatment that are often required to control the disease lead to a variety of adverse effects, many of which are serious (2–4). To avoid severe side effects induced by the therapy, combinations of corticosteroids and adjuvant therapies are used, including plasmapheresis, steroid pulse therapy, intravenous immunoglobulin, and immunosuppressive agents, such as azathioprine, cyclophosphamide, cyclosporine, or mycophenolate mofetil (5,6).

Mizoribine is a newly developed immunosuppressive agent that has low toxicity (7,8). The pharmacological effects of mizoribine are similar to those of another purine biosynthesis inhibitor, mycophenolate mofetil (9,10). Mizoribine has been utilized in Japan for the treatment of several different diseases, such as renal transplantation, rheumatoid arthritis, nephrotic syndrome due to lupus nephritis, and membranous nephropathy. Some studies have reported that mizoribine is effective for patients with autoimmune bullous disease (2,11,12). The purpose of this pilot study was to evaluate the effectiveness of mizoribine as an adjuvant therapy in the treatment of both pemphigus vulgaris and pemphigus foliaceus.

Patients and methods

Patients

Eleven Japanese patients seen at the Department of Dermatology, Kurume University School of Medicine, between January 2007 and April 2009, were examined. The diagnosis of pemphigus was based on: (i) typical clinical findings of mucosal or mucocutaneous disease for pemphigus vulgaris and cutaneous findings for pemphigus foliaceus; (ii) histologic features of suprabasilar (for pemphigus vulgaris) and subcorneal (for pemphigus foliaceus) acantholysis; (iii) tissue-bound autoantibodies observed by direct immunofluorescence with IgG as the dominant immunoreactant with or without C3 deposition on epithelial cell surfaces; and (iv) circulating IgG antiepithelial antibodies that bind epithelial cell surfaces without recognizing the basement membrane zone, as demonstrated by anti-Dsg IgG antibodies by enzyme-linked immunosorbent assay. Pemphigus vulgaris was associated with positive anti-Dsg3 antibodies (with or without anti-Dsg1 antibodies) and pemphigus foliaceus was associated with negative anti-Dsg3 antibodies.

Methods

In all patients, mizoribine was administered in combination with prednisolone. Complete remission was defined as the epithelialization of all skin and mucosal lesions while the patient was receiving minimal therapy (10 mg daily of prednisolone or less) for at least 2 months. Partial remission was defined as the epithelialization of more than 50% of lesions but not of all lesions. Relapse was defined as the occurrence of new cutaneous or mucosal erosions. The persistence of old lesions as well as the appearance of numerous new lesions was regarded as relapse. The blood concentration of mizoribine 2 hours after administration was monitored.

Statistical analysis

The time to remission in patients treated with mizoribine was calculated using Kaplan–Meier analysis. All data are expressed as means ± standard deviation. The comparison of the doses of prednisolone among complete remission, partial remission, and relapse groups was calculated using post hoc test.

Results

We treated 11 patients with pemphigus, 8 of them with pemphigus vulgaris (6 men, 2 women, 53.6 ± 15.3 years) and 3 of them with pemphigus foliaceus (3 men, 56.3 ± 7.4 years) (Table 1). All 11 patients except 1 woman (patient 4) were treated with mizoribine at a dose of 150 mg daily once each morning in combination with prednisolone. Patient 4 was treated with mizoribine at 75 mg a day because of her low weight. Complete remission was observed in three of the eight patients (37.5%) with pemphigus vulgaris and in one of the three patients (33.3%) with pemphigus foliaceus (FIG. 1). Those four patients (36.4%) classified as complete remission had a rapid clinical response and achieved remission at a median of 11.8 months. Partial remission was achieved in two of the three patients (66.7%) with pemphigus foliaceus; their median time to achieve partial remission was 16.0 months. Six (55.6%) of the eleven patients with pemphigus had complete or partial remission and were able to taper their prednisolone. The cumulative probability of having a complete remission was 64.3% at 19 months of follow-up using Kaplan–Meier analysis. None of the patients had side effects severe enough

Table 1. Clinical findings and outcome in 11 patients with pemphigus

No.	Type	Age	Sex	Therapies before Miz.	Miz. dose (mg)	PSL dose (mg)	Miz. duration (months)	Outcome
1	PV	39	M	PSL, IVIg	150	12.5	19	Complete remission
2	PV	69	F	PSL	150	10.0	1	Relapse
3	PV	44	M	PSL	150	30.0	6	Complete remission
4	PV	84	F	PSL, IVIg	75	22.5	4	Complete remission
5	PV	48	M	PSL	150	10.0	1	Relapse
6	PV	43	M	PSL	150	25.0	2	Relapse
7	PV	54	M	PSL	150	10.0	1	Relapse
8	PV	48	M	PSL, plasmapheresis	150	10.0	1	Relapse
9	PF	48	M	PSL, IVIg, plasmapheresis	150	10.0	18	Partial remission
10	PF	59	M	PSL	150	30.0	18	Complete remission
11	PF	62	M	PSL	150	10.0	14	Partial remission

IVIg, intravenous immunoglobulin; Miz, mizoribine; PF, pemphigus foliaceus; PSL, prednisolone; PV, pemphigus vulgaris.

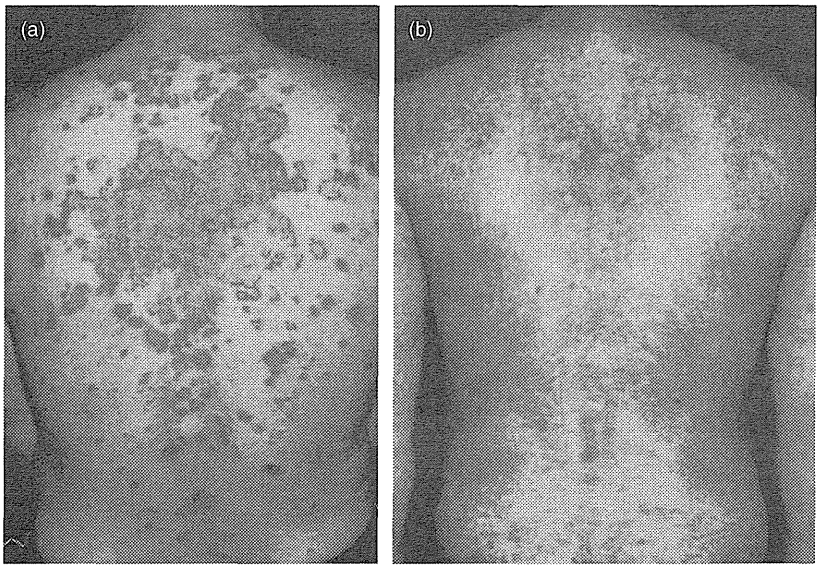

FIG. 1. (a) Examination revealed erythematous macules with crusted erosions and blisters on the posterior part of the trunk before the additional mizoribine treatment (patient 10; pemphigus foliaceus). (b) Two months after initiation of the additional mizoribine therapy, the eruption had ameliorated.

to require discontinuation of treatment. Complete responders for mizoribine treatments were not statistically on a higher dose of prednisolone assessed by post hoc test ($p = 0.073$). The serum concentration titer of mizoribine was around 1.0 μg/mL 2 hours after administration.

Discussion

The present study demonstrated that the addition of oral mizoribine therapy resulted in a rapid clinical remission in approximately one-third of patients with pemphigus. In more than one-half of pemphigus patients, mizoribine was an effective and safe adjuvant for treatment and enabled a substantial reduction in the dose and side effects of the corticosteroid therapy. The addition of mizoribine to the treatment regimen appears to have allowed tapering of the prednisolone dose and prevented a disease relapse in patients with pemphigus. The clinical findings of this limited small group-based and retrospective study suggest that the benefits of the adjuvant immunosuppressive therapy could be attributed to the corticosteroid-sparing properties as well as its immunosuppressive effects.

All three patients with pemphigus foliaceus had complete or partial remission. In contrast, the addition of mizoribine therapy was not effective for about one-half of patients with pemphigus vulgaris. In the present study, the blood concentration of mizoribine was kept around 1 μg/mL in the treated patients. It has recently been reported that 14-3-3 proteins, which are mizoribine-binding proteins, interact with the glucocorticoid receptor and may enhance the transcriptional activity of that receptor, suggesting a steroid-sparing effect of mizoribine (9). A serum mizoribine concentration of more than 2.6 μg/mL significantly enhances the interaction with the glucocorticoid receptor (13). In addition, we previously reported that when the mizoribine concentration reached around 3.0 μg/mL, there was a dramatic improvement in symptoms and there were neither flare-ups of the skin manifestations nor side effects (14,15). Patients who were not improved by the addition of mizoribine might require a continuously higher dose of mizoribine to achieve effective therapy. A larger series of patients with a longer follow-up are needed to fully assess the efficacy of this treatment.

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Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: possible association with malignancy

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