

THERAPEUTIC HOTLINE

Mizoribine treatment for antihistamine-resistant chronic autoimmune urticaria

TAKASHI HASHIMOTO^{*,1}, TAMIHIRO KAWAKAMI^{†,1}, NORITO ISHII^{*},
KAORI ISHII[‡], TADASHI KARASHIMA^{*}, TAKEKUNI NAKAMA^{*},
DAISUKE TSURUTA^{*}, TERUKI DAINICHI^{*}, MICHIIHIRO HIDE[‡] &
TAKAHIRO HAMADA^{*}

**Department of Dermatology, Kurume University School of Medicine and Kurume University Institute of Cutaneous Cell Biology, Kurume, Japan, †Department of Dermatology, St. Marianna University School of Medicine, Kawasaki, Japan, and ‡Department of Dermatology, Hiroshima University, Hiroshima, Japan*

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

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

Address correspondence and reprint requests to: Takashi Hashimoto, MD, Department of Dermatology, Kurume University School of Medicine and Kurume University Institute of Cutaneous Cell Biology, 67 Asahimachi, Kurume, Fukuoka 830-0011, Japan, or email: hashimoto@med.kurume-u.ac.jp.

¹Co-first authors.

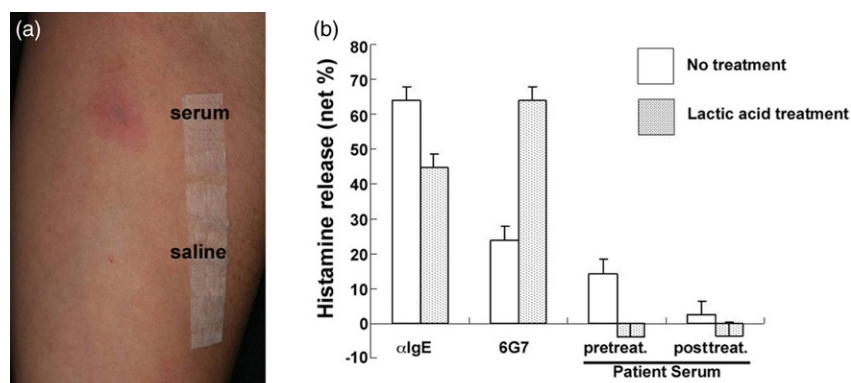


FIG. 1. (a) A positive autologous serum skin test. (b) Histamine releasing test. Histamine release (net %) is shown on the ordinate. Left columns (blind) and right columns (black dot) indicate histamine release with no treatment and with lactic acid treatment, respectively. The results for antihuman IgE autoantibody (α IgE), 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 reversed 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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