Refractory Chronic Urticaria Treated Effectively with the Protease Inhibitors Nafamostat Mesilate and Camostat Mesilate

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Chronic urticaria (CU) is characterized by the spontaneous recurrent appearance of wheals and pruritus, which seriously impairs patients' quality of life (QoL) (1, 2). Patients with refractory CU are treated with leukotriene receptor antagonists, glucocorticoids and/or other immunomodulatory agents in addition to antihistamines (3, 4). Nevertheless, there remain a number of patients who are unsatisfactorily treated even with these medications, either due to insufficient efficacy or to the occurrence of side-effects.

Nafamostat mesilate (NM) and camostat mesilate (CM) are newly synthesized protease inhibitors. They inhibit broad serine proteases, including trypsin, kallikrein, complements ($C1r^-$, $C1s^-$), and coagulation/fibrinolytic factors (thrombin, plasmin) (5, 6). Moreover, NM could inhibit the activation of mast cells and the production of inflammatory cytokines (7, 8). Serine proteases have been suggested to be involved in the pathogenesis of CU, in addition to mast cell activation and production of inflammatory cytokines (9, 10).

We describe here two patients with refractory CU who were treated effectively with NM and CM.

CASE REPORTS

Case 1. A 58-year-old man had had severe CU without angioedema for 2 years. No apparent abnormalities were found in the physical examination, complete blood count, biochemical blood examinations, and markers of inflammation and coagulation. Dermal injection of autologous serum did not induce a significant skin reaction. Skin biopsy did not show leukocytoclastic vasculitis. The patient had been treated with various antihistamines, leukotriene receptor antagonists, glucocorticoids and immunosuppressants, but none of them resulted in a significant reduction in symptoms. He experienced unbearable wheals and pruritus, and stopped his job as a truck driver.

Taking account of impaired QoL, and with informed consent from the patient, we began intravenous administration of NM at a dose of 0.040 mg/kg/h. The wheals and pruritus disappeared in a few hours, and did not re-emerge during the continuous intravenous infusion of NM. However, when infusion of NM was interrupted, urticarial activity returned to the level of pre-treatment within 10 h. Subsequent subcutaneous injection of 5000 units heparin twice a day and oral administration of 600 mg/day CM did not improve the symptoms.

Levels of plasma histamine before and after the administration of NM were 0.051 ng/ml and 0.032 ng/ml, respectively. Wheal and flare reaction induced by the histamine skin prick test had been strongly inhibited even before NM infusion by orally administered antihistamines.

Case 2. A 35-year-old woman had severe CU without angioedema. She sometimes experienced a slight fever around 37ºC and arthralgia, but we found no apparent abnormality in clinical examinations, including complete blood count, general biochemical blood examinations and markers of inflammation and coagulation such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and D-dimer. The autologous serum skin test was positive, and skin biopsy did not show leukocytoclastic vasculitis. The level of plasma histamine was 0.22 ng/ml. For 20 years she had experienced unbearable wheals and pruritus with an exacerbation during menstruation, despite treatments with various antihistamines, leukotriene receptor antagonists, glucocorticoids and immunosuppressants.

Following informed consent, we administered intravenous NM at a dose of 0.030 mg/kg/h (40 mg/day), which resulted in immediate disappearance of wheals and pruritus in 2 h (Period 1 in Fig. 1). However, a half-dose reduction of NM to 0.015 mg/kg/h (20 mg/day) restored urticaria to the pre-treatment level approximately 7 h later (Period 2 in Fig. 1). She then received an intermittent drip of NM at the initial concentration (0.030 mg/kg/h) twice a day (Period 3 in Fig. 1). Both wheals and pruritus disappeared completely within 2 h during infusions, and a few thumb-tip sized or smaller erythemas appeared a few hours after the end of each drip. Moreover, administration of CM at 600 mg/day resulted in a slight improvement of her symptoms. Based on her informed consent, we increased the dose of CM to 1200 mg/day, which eventually resulted in complete relief from wheals and pruritus for 2 months (her best months during the past 20 years), allowing us to reduce the dose of glucocorticoids, without exacerbation during menstruation. A reduction of CM to 900 mg/day led to an exacerbation, and an increase again

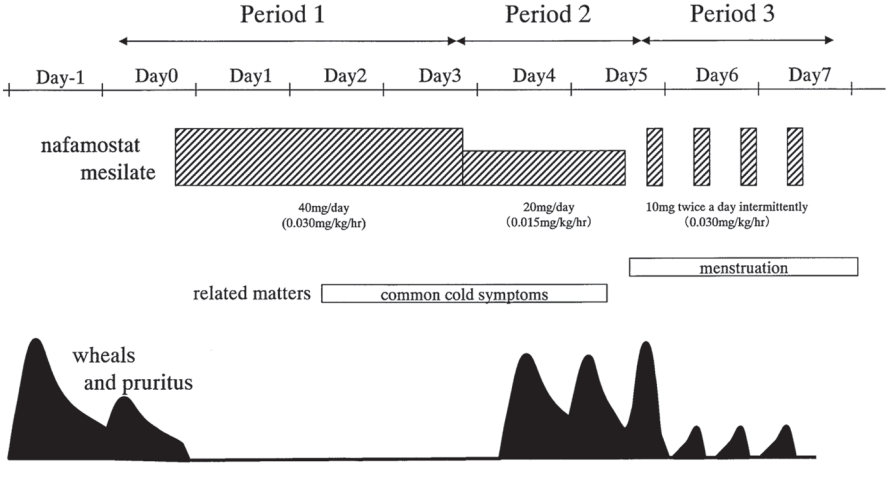

Fig. 1. Time course of clinical symptoms during the infusion of nafamostat mesilate in case 2.

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to 1200 mg/day resulted in disappearance of the symptoms for the following 6 months. During CM therapy, the patient's abdomen enlarged, her hands and feet become heavy, and her stool frequency increased, but these side-effects were all tolerable and it was possible for her to continue with therapy.

DISCUSSION

We have reported here that two cases of severe CU were treated effectively with NM and CM, newly synthesized protease inhibitors, without serious adverse events. The beneficial effect of a protease inhibitor in the treatment of urticaria and angioedema was first shown by Juhlin & Michaëlsson using aprotinin (11). Berova et al. (12) subsequently treated 20 patients with CU with aprotinin in a double-blind study, 17 of whom showed a complete cure or improvement. However, this treatment has not been accepted widely in spite of its high efficacy for patients with CU, because of the high occurrence of allergic adverse reactions (13).

NM immediately improves urticarial symptoms, but needs to be administered intravenously and is not suitable as a treatment for patients in outpatient clinics. On the other hand, CM can be administered orally and relieve a patient from urticaria as maintenance therapy, but a dose higher than the manufacturer's recommendation (600 mg/day) is required to suppress urticarial symptoms and was effective for only one of the two cases in this report.

The clinical effects of NM on CU appear to depend on its blood concentration rather than the total amount of administration. In our cases, NM at doses of 0.030 mg/kg/h or higher resulted in a significant improvement in wheals and pruritus, while the administration of 0.015 mg/kg/h NM was not enough to exert this effect. In case 2, two methods of administration of the same dose of NM (20 mg/day) resulted in different degrees of clinical efficacy. An intermittent drip of 0.030 mg/kg/h was more effective than a continuous infusion of its half dose (0.015 mg/kg/h).

Considering that the half-life of NM in blood is as short as 24 min, and the symptoms of urticaria recurred a few hours after the interruption of NM infusion, the direct target of NM may be very closely associated with the release of mediators, including histamine, from mast cells. In the cases described here we cannot prove the influence of NM on histamine release from mast cells or on subsequent skin reactions, because levels of plasma histamine and skin reaction to histamine were low even before the administration of NM. However, it has been reported that NM may inhibit the activation of mast cells (7, 8) and the production of inflammatory cytokines, such as IL-1β, IL-6 and TNF-α (7), which may be involved in the pathogenesis of CU. Moreover, the complement and coagulation cascades have been reported to be involved in the pathogenesis of CU (9, 10), although clinical markers of these cascades in our cases were within their normal ranges. The protease inhibitors NM and CM inhibit the complement and coagulation factors, such as $C1r^-$, $C1s^-$, plasmin and thrombin (5, 6). Thus, NM and CM may prevent the development of symptoms of CU by either inhibiting the activation of complement, coagulation pathways, and/or release of mediators, including histamine, from skin mast cells.

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