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Successful treatment of four types of chronic urticaria with anti-IgE omalizumab in the same patient



Urticaria is a skin disorder that is characterized by the appearance of wheals (hives), angioedema, or both.¹ Chronic urticaria (CU) is defined as wheals (with or without angioedema) that persists for 6 or more weeks, and is further classified into 2 subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).¹ In most cases of CU, a trigger cannot be identified. These cases are defined as CSU. The term *inducible urticaria* is used when a specific trigger can be linked to the development of CU. Skin lesions in inducible urticaria result from mast cell activation and mediator release. The mechanisms by which specific stimuli activate skin mast cells are not fully understood.²

The coexistence or the sequential appearance of more than 1 subtype of CU in the same subject may be observed.^{2,3} Given that symptoms from extracutaneous sites may accompany severe exacerbations of certain inducible forms of urticaria (ie, cold, cholinergic),² appropriate management is crucial. Symptomatic treatment for CU targets mast cells, either by the inhibition of mast cell activation (eg, omalizumab, cyclosporin) or by blocking the receptors of mast cell mediators (eg, H₁-antihistamines, leukotriene receptor antagonists).^{1,2} The efficacy and safety of subcutaneous omalizumab for the treatment of CU has been established in several randomized, placebo-controlled trials and confirmed in real-world clinical studies.^{4,5} Suitable treatment options are still lacking for patients with severe disabling H₁-antagonist-resistant urticaria of all subtypes.

A 35-year-old white man with 4 subtypes of CU (Table 1) presented to our referral center in November 2016. Twenty years earlier he had developed CSU, cold urticaria, symptomatic dermatographism, and cholinergic urticaria without angioedema. The diagnosis of CIndU was established by history and by the results of provocation testing, as described.² We provoked cholinergic urticaria, cold urticaria, and dermatographism, respectively, in the patient by moderate physical exercise at room temperature (appearance of small, punctate, pruritic wheals with a large surrounding red flare); an ice cube applied on the skin that resulted in the development of a wheal and redness within 10 minutes after removal; the FricTest with the longest pin that determined a positive response as a palpable wheal of 4 mm in width at 10 minutes after provocation.

Before referral, the patient had been treated with hydroxyzine, ketotifen, cyproheptadine, cinnarizine, loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine, ebastine, rupatadine, bilastine plus montelukast, and prednisone, without success. He was then prescribed cetirizine (10 mg twice daily) for 4 weeks. Despite this treatment, the patient continued to experience episodes of

CIndU, and we therefore opted for a cycle of omalizumab treatment (300 mg every 4 weeks for 24 weeks), as add-on therapy to second-generation H₁-antihistamines, according to the Italian Medicine Agency labeling information.⁶ The CSU disease activity was determined by Urticaria Activity Score⁷ (UAS7), whereas a validated CU quality of life questionnaire (CU-Q₂OL) was used to subjectively monitor the patient's response to treatment.¹ In the pretreatment period, the UAS7 score was 21/42 and the CU-Q₂OL score was 66.3/100 points, that is, a score that indicates a large negative effect on quality of life.

The patient's symptomatology related to CIndU resolved within 1 week after the first dose, whereas itching and spontaneous hives progressively decreased. The patient was entirely symptom free at week 8. Indeed, the UAS7 and CU-Q₂OL scores were measured as 0. He was not receiving H₁ antihistamine therapy. The complete control of symptoms was maintained for 2 weeks after the 6th injection, and only a mild occasional pruritus was experienced in the subsequent weeks. Twenty-four weeks after the start of omalizumab therapy, we performed all provocation tests, and the results were completely negative. At the last follow-up, 4 months after the last administration of omalizumab, the patient continues to experience episodes of mild cutaneous itching and is currently still free of symptoms related to CIndU (CU-Q₂OL score = 2.1; UAS7 score = 3). Omalizumab was well tolerated, without any adverse effects.

This is, to our knowledge, the first report of successful treatment with omalizumab of CSU, cholinergic urticaria, cold urticaria, and symptomatic dermatographism in the same patient. We observed a substantial improvement in the quality of life and rapid control of symptoms in all subtypes of CU during the 24-week anti-immunoglobulin (Ig) E therapy (6 injections at 4-week intervals of 300 mg of drug). Omalizumab is a humanized, monoclonal IgG anti-IgE antibody that binds to free IgE. Omalizumab lowers free IgE levels and causes FcεRI receptors on mast cells and basophils to be down-regulated.⁴ The efficacy of anti-IgE treatment has been shown in many disorders with complex and unclear origin, including CSU, CIndU, and angioedema.^{4,5} The pathogenesis of CSU is still debated, but its origin is probably autoimmune in a proportion of cases, and is attributable to the presence of functionally active IgG autoantibodies specific for the high-affinity IgE receptor on mast cells or basophils, FcεRI, or for IgE. Nevertheless, a subgroup of patients with CSU exhibits IgE autoantibodies against autoantigens, such as thyroperoxidase or double-stranded DNA,⁵ which might chronically activate mast cells and basophils. Passive transfer experiments have indicated the existence of a mast cell-activating IgE serum factor in some patients with symptomatic dermatographism.⁷ A pathogenic role for IgE has been

Disclosures: None.

Funding Sources: This editorial support was funded by Novartis Farma, Italy.

Table 1
Patient's Demographic and Baseline Characteristics

Parameters	Details
Age	35 years
Sex	Male
Weight	73 kg
Race	White
Time since diagnosis of CU	20 years
Total IgE level (KUA/L)	89.3
In clinic UAS ^a	5
UAS 7 ^b	21
Weekly ISS ^b	11
Weekly no. of hive score ^b	10
Presence of angioedema	No
Dermographic, cold, cholinergic test	Positive
ASST	Negative
Tests with normal results	CBC with differential; ERS; CRP; stool analysis (ova and parasites); urinalysis; hepatic and renal functions; hepatitis B and C serologies; antinuclear antibody; cryoprotein levels; serologic and skin testing for immediate hypersensitivity; TSH; antiperoxidase antibody; antimicrosomal antibody; antithyroglobulin antibody; serum protein electrophoresis; anti-toxoplasma antibody; anti- <i>Helicobacter pylori</i> antibody; C1 esterase inhibitor; C3, C4 complements; abdominal ultrasound; chest and paranasal sinuses radiography

Abbreviations: ASST, autologous serum skin test; CBC, complete blood count; CRP, C-reactive protein; CU, chronic urticaria; ESR, erythrocyte sedimentation rate; ISS, itch severity score; TSH, thyroid stimulating hormones; UAS, urticaria activity score.

^aDefined as the highest value from the day -14 visit, day -7 visit, and day 1 visit.

^bBased on data collected in the patient daily diary in the 7 days before the first treatment date.

hypothesized in cold-induced mast cell activation in patients with cold urticaria.⁸ In cholinergic urticaria, mast-cell degranulation and histamine release are thought to occur, and acetylcholine also seems to be involved.⁹ Some authors suggest that a type I hypersensitivity reaction to sweat might be causative.⁹ Possibly specific IgE to self-antigens in CSU or to autoallergens generated by exposing the skin to specific triggers could provide a rationale for the use of omalizumab.³ However, no relevant role of IgE in any of these diseases has yet been proven. Other mechanisms may be active in the suppression of urticaria by anti-IgE. Studies on additional patients will be necessary to establish a common pathomechanism between CSU and the other CIndUs.

This case shows that 4 types of CU unresponsive to antihistamine treatment in the same patient can be rapidly and successfully treated with omalizumab without side effects.

Acknowledgment

Language editing and journal styling before submission was provided by Carmen Innes, an independent medical writer, on behalf of Springer Healthcare Communications.

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Neutrophil-to-lymphocyte ratio as a novel independent predictor of severe exacerbation in patients with asthma



Severe exacerbations are well-known complications of asthma that increase the total and asthma-related health care costs¹ and decrease the quality of life of patients.² Although some exacerbation predictors have been reported,^{3,4} it is difficult to predict and

prevent severe exacerbations in a large percentage of patients affected by asthma.

The neutrophil-to-lymphocyte ratio (NLR) is a marker of chronic inflammation that is known to be inexpensive and is measured using widely available methods. The usefulness of NLR measurements has been reported in patients with many diseases.^{5–7} Only a limited number of studies have investigated NLR in patients with asthma. Zhang et al⁸ reported that NLR could predict neutrophilic asthma, whereas eosinophil-derived ratios (eg, eosinophil-to-lymphocyte ratio and eosinophil-to-neutrophil ratio) were able to predict eosinophilic asthma. In addition, it has been reported that

Disclosures: Dr Fukunaga has received lecture fees from Boehringer Ingelheim and AstraZeneca. Dr Asano has received lecture fees from Astellas Pharma, Boehringer Ingelheim, Kyorin Pharmaceutical, MSD, Novartis Pharma, and AstraZeneca. No other disclosures were reported.

Funding Sources: This study was supported in part by a Grant-in-Aid from Glaxo Smith Kline PLC.