

A. TEDESCHI

Paradoxical exacerbation of chronic urticaria by H1-antihistamines and montelukast

Unità Operativa di Allergologia e Immunologia Clinica, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Milano, Italy

KEY WORDS

Chronic urticaria, H1-antihistamines, montelukast, ciclosporin, azathioprine

SUMMARY

Histamine is the main mediator of urticaria and H1-receptor antagonists represent the treatment of choice in all patients with chronic urticaria. Leukotriene receptor antagonists as montelukast have also been used in patients with chronic urticaria unresponsive to H1-antihistamines alone. We report a patient with chronic urticaria whose disease was paradoxically exacerbated by H1-antihistamines and montelukast, and controlled by immunosuppressive drugs as ciclosporin and azathioprine. Urticaria exacerbations were caused by different molecules including either piperidine (fexofenadine, desloratadine, ebastine, rupatadine) or piperazine (hydroxyzine, cetirizine) derivatives as well as by montelukast suggesting that an IgE-mediated mechanism was not involved. A possible explanation of the observed urticaria exacerbation is that H1-antihistamines and montelukast may shift the H1 histamine receptor and the leukotriene receptor to the active conformation instead of the inactive state. The beneficial effects of ciclosporin and azathioprine confirm that immunosuppressive drugs have an important role in the treatment of refractory chronic urticaria and back the hypothesis that an autoimmune/autoreactive mechanism often underlies the disease.

Introduction

Histamine is recognized as the main mediator of urticaria, and the treatment of choice in all patients with chronic urticaria is represented by H1-receptor antagonists. In most cases chronic urticaria can be sufficiently controlled by the use of antihistamines at licensed doses or, in some cases, at higher than licensed doses, but this approach is not always effective (1-4). In these cases, all guidelines published so far recommend systemic corticosteroids as the second line treatment and immunosuppressive drugs, namely ciclosporin, as the third line treatment. In addition to the lack of effectiveness, a few cases of

multiple H1-antihistamine-induced urticaria have been reported (5-9).

We report a patient with chronic urticaria whose disease was exacerbated by H1-antihistamines and controlled only by immunosuppressive drugs including ciclosporin and azathioprine.

Case report

In the late spring 2008, a 23-year-old man was seen at the Allergy outpatient clinic because of uncontrolled chronic urticaria. He reported recurrent urticaria with angioedema

since the age of 14 and daily urticaria symptoms in the last year. He had already undergone extensive investigations for chronic urticaria, including specific IgE determination for food allergens, serological test for B and C hepatitis and human immunodeficiency virus, complement C3 and C4 fractions and C1 inhibitor, search for *Helicobacter pylori* and stool parasites, thyroid function and thyroid autoantibodies, and antinuclear antibodies. All these tests were in the normal range or negative. Total IgE level was 9 kU/L. Because of continuous urticaria, the patient was prescribed on different occasions almost all H1-antihistamines available in Italy, including cetirizine, hydroxyzine, desloratadine, fexofenadine and ebastine. In all cases the H1-antihistamines not only failed to control the disease, but provoked a severe urticaria exacerbation within one-three hours after administration. Since continuous treatment with prednisone allowed only partial relief of the disease, ciclosporin was started in the fall 2007. This led to a complete control of the disease, but only with a relatively high dosage (6 mg/kg/daily). After a six months treatment, following the detection of raised ciclosporin plasma levels, the drug was gradually tapered, and the disease relapsed. At that time the patient sought advice at our Allergy Clinic. Autologous serum and plasma skin tests were performed as described (10, 11) and gave an unequivocal positive response (at 30 min reading the diameter of the serum-induced wheal was 8 mm and the diameter of the plasma-induced wheal was 11 mm). As a negative control skin test, saline solution (0.9% weight/volume NaCl) was injected intradermally, and caused no detectable wheal at 30 min reading. Skin prick test with 10 mg/ml histamine was performed as positive control (the wheal diameter at 30 min reading was 5 mm). Positivity of autologous serum and plasma skin tests supported the autoreactive origin of urticaria, since autologous serum skin test has been considered as a screening test for histamine-releasing autoantibodies (10, 12). The patient received continuous prednisone treatment at variable doses (10-37.5 mg daily) which allowed a partial control of the disease. A further attempt to reintroduce antihistamine therapy using the recently licensed rupatadine was again followed by urticaria exacerbation within few hours from drug intake. Similarly, the addition of the leukotriene receptor antagonist, montelukast, 10 mg/day was followed by worsening of urticaria symptoms. Then, in January 2009, following a report on the efficacy of azathioprine in the management of anti-histamine resistant urticaria (3), treatment with azathioprine 100 mg daily was started. The patient experienced a gradual improvement of the

disease that allowed steroid tapering until withdrawal (June 2009). Azathioprine has been well tolerated and the patient is no longer complaining of any urticaria symptom. The dosage has been gradually reduced and now (October 2009) the patient is assuming 50 mg daily.

Discussion

The case reported is peculiar in that chronic urticaria was exacerbated by H1-antihistamines that are commonly considered as the cornerstone of the treatment strategy. A few cases of urticaria induced by H1-antihistamines have been reported and in some cases an IgE-mediated mechanism has been suspected since positive skin prick tests have been found (8-9). However, in our case an IgE-mediated mechanism is unlikely since exacerbations were caused by different molecules including either piperidine (fexofenadine, desloratadine, ebastine, rupatadine) or piperazine (hydroxyzine, cetirizine) derivatives. Furthermore, the timing of urticaria worsening (one to three hours after administration) was slower than that observed in most IgE-mediated reactions. H1-antihistamines are inverse agonists of histamine at H1 binding sites, and combine to H1 receptors to shift the equilibrium toward the inactive state, preventing H1 response (13). An interesting explanation of the paradoxical effect of H1-antihistamines has been proposed by González de Olano et al. (6) who have suggested that in rare cases antihistamines may shift the H1 histamine receptor to the active conformation instead of the inactive state, causing urticaria exacerbation. It is interesting to note that our patient also experienced urticaria worsening after montelukast administration. De-novo synthesis of sulfidoleukotrienes has been detected in chronic urticaria (14) supporting their involvement in the disease pathomechanism. The exacerbation of urticaria symptoms that occurred in our patient following montelukast administration might be explained by a shift to the active state of leukotriene receptors, as it has been hypothesized for H1 histamine receptors. Finally, the disease control that was achieved in our patient firstly with ciclosporin and then with azathioprine is not surprising since immunosuppressive drugs have been largely used in recalcitrant chronic urticaria, and quite a large experience has been collected with ciclosporin (15). Tacrolimus, micofenolate and high- and low-dose intravenous immunoglobulin are among the other treatment options that have been considered (16-19); conversely, the experience with azathioprine is limit-

ed and deserves to be expanded. In the case reported, both serum and plasma skin tests were positive supporting the autoreactive origin of chronic urticaria. In fact, autologous serum skin test has been proposed as a screening test for histamine-releasing autoantibodies (12) and has been found positive in about 50% of chronic urticaria patients whose disease is considered of autoimmune/autoreactive origin (10). Notably, a positive autologous serum skin test has been also found in about 50% of patients with multiple drug hypersensitivities and in patients with chronic urticaria and nonallergic asthma (20, 21), disorders that may be at least in part sustained by an autoimmune/autoreactive mechanism. The meaning of autologous plasma skin test still needs to be investigated but appears to be related to circulating vasoactive factors and possibly to coagulation factors (11). The favorable response to ciclosporin and azathioprine observed in our patient can be explained by the suppressive effect on the autoimmune/autoreactive mechanism involved in the disease pathophysiology. When H1-antihistamines fail to control or even worsen chronic urticaria symptoms, immunosuppressive drugs still remain a good therapeutic option that can allow achieving disease remission.

References

1. Tedeschi A, Girolomoni G, Asero R; AAITO Committee for Chronic Urticaria and Pruritus Guidelines. AAITO Position paper. Chronic urticaria: diagnostic workup and treatment. *Eur Ann Allergy Clin Immunol* 2007; 39 (7): 225-31.
2. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2) LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; 64 (10): 1427-43.
3. Lasthein Andersen S, Bindslev-Jensen C. Treatment of chronic urticaria with high dose antihistamine. Abstract Book XXV Congress of the European Academy of Allergology and Clinical Immunology, Vienna, Austria, 2006; 398 (Abstract).
4. Asero R. Chronic unremitting urticaria: is the use of antihistamines above the licensed dose effective? A preliminary study of cetirizine at licensed and above-licensed doses. *Clin Exp Dermatol* 2007; 32 (1): 34-8.
5. Demoly P, Messaad D, Benhamed S, Sahla H, Bousquet J. Hypersensitivity to H1 - antihistamines. *Allergy* 2000; 55 (7): 679-80.
6. González de Olano D, Roán Roán, de la Hoz Caballer B, Cuevas Agustín M, Hinojosa Macías M. Urticaria induced by antihistamines. *J Investig Allergol Clin Immunol* 2006; 16 (2): 144-6.
7. Inomata N, Tatewaki S, Ikezawa Z. Multiple H1-antihistamine-induced urticaria. *J Dermatol* 2009; 36 (4): 224-7.
8. Weidenger S, Mempel M, Ollert M, et al. Anaphylaxis to mizolastine. *J Allergy Clin Immunol* 2004; 114 (4): 979-81.
9. Bonanni L, Parmiani S, Sturbini S. Glottis oedema due to loratadine. *Allergy* 2004; 59 (1): 116-7.
10. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA(2)LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy* 2009; 64 (9): 1256-68.
11. Asero R, Tedeschi A, Riboldi P, Cugno M. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. *J Allergy Clin Immunol* 2006; 117 (5): 1113-7.
12. Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza Black A, Greaves MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; 140 (3): 446-52.
13. Fitzsimons CP, Monczor F, Fernández N, Shayo C, Davio C. Mepyramine, a histamine H1 receptor inverse agonist, binds preferentially to a G protein-coupled form of the receptor and sequesters G protein. *J Biol Chem* 2004; 279 (33): 34431-9.
14. Wedi B, Novacovic V, Koerner M, Kapp A. Chronic urticaria serum induces histamine release, leukotriene production, and basophil CD63 surface expression—inhibitory effects of anti-inflammatory drugs. *J Allergy Clin Immunol* 2000; 105 (3): 552-60.
15. Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000; 143 (2): 365-72.
16. Kessel A, Bamberger E, Toubi E. Tacrolimus in the treatment of severe chronic idiopathic urticaria: an open-label prospective study. *J Am Acad Dermatol* 2005; 52 (1): 145-8.
17. Shahar E, Bergman R, Guttman-Yassky E, Pollack S. Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. *Int J Dermatol* 2006; 45 (10): 1224-7.
18. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; 138 (1): 101-6.
19. Pereira C, Tavares B, Carrapatoso I, et al. Low-dose intravenous gammaglobulin in the treatment of severe autoimmune urticaria. *Eur Ann Allergy Clin Immunol* 2007; 39 (7): 237-42.
20. Colombo G, Yacoub MR, Burastero SE, et al. Multiple drug hypersensitivity: insight into the underlying mechanism and correlation with autoimmune diseases. *Eur Ann Allergy Clin Immunol* 2009; 41 (2): 50-5.
21. Tedeschi A, Cottini M, Asero R. Simultaneous occurrence of chronic autoimmune urticaria and non-allergic asthma: a common mechanism? *Eur Ann Allergy Clin Immunol* 2009; 41 (2): 56-9.