The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria

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Background: H_1-antihistamines are first line treatment of chronic urticaria, but many patients do not get satisfactory relief with recommended doses. European guidelines recommend increased antihistamine doses of up to 4-fold.
Objective: To provide supportive evidence for the European guidelines.
Methods: Eighty tertiary referral patients with chronic urticaria (age range, 19-67 years) were randomized for double-blind treatment with levocetirizine or desloratadine (40/40). Treatment started at the conventional daily dose of 5 mg and then increased weekly to 10 mg, 20 mg, or 20 mg of the opposite drug if relief of symptoms was incomplete. Wheal and pruritus scores, quality of life, patient discomfort, somnolence, and safety were assessed.
Results: Thirteen patients became symptom-free at 5 mg (9 levocetirizine vs 4 desloratadine), compared with 28 subjects on the higher doses of 10 mg (8/7) and 20 mg (5/1). Of the 28 patients nonresponsive to 20 mg desloratadine, 7 became symptom-free with 20 mg levocetirizine. None of the 18 levocetirizine nonresponders benefited with 20 mg desloratadine. Increasing antihistamine doses improved quality of life but did not increase somnolence. Analysis of the effect of treatment on discomfort caused by urticaria showed great individual heterogeneity of antihistamine responsiveness: ~15% of patients were good responders, ~10% were nonresponders, and ~75% were responders to higher than conventional antihistamine doses. No serious or severe adverse effects warranting discontinuation of treatment occurred with either drug.
Conclusion: Increasing the dosage of levocetirizine and desloratadine up to 4-fold improves chronic urticaria symptoms without compromising safety in approximately three quarters of patients with difficult-to-treat chronic urticaria. (J Allergy Clin Immunol 2010;125:676-82.)

Key words: *Urticaria, levocetirizine, antihistamines, desloratadine, somnolence, quality of life*

Chronic urticaria, with or without angioedema, has traditionally been defined as daily symptoms (itching, hives and/or swelling) recurring for more than 6 weeks.[1,2] Although the condition is rarely life-threatening, it creates anxiety and embarrassment and has an impact on quality of life comparable with that of severe coronary artery disease and exceeding that associated with respiratory allergy.[3,4]

Chronic urticaria encompasses a broad spectrum of manifestations in terms of localization and number of the skin lesions, and in many cases its mechanisms remain elusive and subject to speculation. There is now a substantial body of evidence that up to 50% of patients with chronic urticaria have autoantibodies to the high-affinity receptor for IgE (FcεRI) or to the IgE molecule itself that are capable of inducing histamine release from basophils and mast cells in the skin through complement C5a generation.[5-7] In addition, in patients with or without autoantibodies, abnormalities in the blood coagulation system resulting in thrombin production[8] have been suggested. Despite the variety of suspected mechanisms, the symptoms of chronic urticaria are a result of proinflammatory mediators in the skin, among which histamine appears to be pivotal.

Because the heterogeneity of chronic urticaria and the current elusiveness of its mechanisms make a universal cure unlikely currently, it is imperative that the most effective palliative care be used. Given that histamine mediates almost all symptoms of urticaria through H_1-receptors located on nerves and endothelial cells,[1,9] the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA^2LEN)/European Dermatology Forum (EDF) guidelines[10] recommend that the first line of treatment should be with nonsedating H_1-antihistamines. Second-generation antihistamines, such as levocetirizine, desloratadine, and fexofenadine, with their long therapeutic half-life, lack of cardiotoxicity, absence of cholinergic side effects, and minimal sedation, represent a substantial therapeutic advance. Indeed, many randomized controlled trials support the use of such drugs in most forms of urticaria.[10] However, a study of 390 patients with urticaria showed that only about 44% of patients responded well to this treatment: 29% were

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Abbreviations used
ASST: Autologous serum skin test
CU-Q_2oL: Chronic urticaria quality of life questionnaire
EAACI: European Academy of Allergy and Clinical Immunology
EDF: European Dermatology Forum
GA^{2}LEN: Global Allergy and Asthma European Network
VAS: Visual analog scale

discharged asymptomatic, with another 15% showing partial relief of symptoms.[11] In practice, failure of this first-line approach often leads to the prescription of corticosteroids, which further spins the vicious circle of chronicity.

Two questions arise from the failure of antihistamines at conventional doses to bring adequate relief. The first is whether increasing the dosage of an antihistamine would increase its effectiveness. Data on this are equivocal. Two studies suggested that increasing the dose of fexofenadine from 60 mg to 240 mg twice daily did not increase the control of urticaria symptoms.[12,13] Also, with cetirizine, 1 study showed higher efficacy at twice its normally recommended dose,[14] whereas another reported an increase in efficacy in only a small proportion of patients with 3 times the recommended dose.[15] However, the EAACI/GA^{2}LEN/EDF guidelines recommended an increase in the antihistamine dose of up to 4-fold in patients not responding to the conventional posology before considering alternative treatment strategies.[10] This recommendation was based on expert opinion and experience in clinical practice and carried the caveat that up-to-date, well designed randomized controlled trials comparing the efficacy and safety of different nonsedating H_1-antihistamines in chronic urticaria are missing.

The second question that arises is whether individual patients are responsive to one antihistamine rather than other. Although this is believed to be the case by many patients and clinicians, there is no evidence to either support or refute this.

To provide evidence to answer these questions, we designed a study to assess the efficacy and safety of using up to 4 times the conventionally prescribed doses of 2 second-generation antihistamines, levocetirizine and desloratadine, in patients with difficult-to-treat chronic urticaria. The primary objective of this study was to document the added value of using 10-mg and, later, 20-mg daily doses of these preparations rather than the standard 5 mg daily. If patients were not symptom-free on 20 mg daily of one antihistamine, they were switched to receive the other. The secondary objectives were to assess the effect of treatment on the patient's perception of urticaria-related discomfort and somnolence by using visual analog scales (VASs) and their change in quality of life assessed by the chronic urticaria quality of life questionnaire (CU-Q_2oL).[16]

METHODS

Patients

The 80 patients recruited into the study (27 men and 53 women; age, 19-67 years) had been referred to the tertiary specialist centre of the Clinic of Allergy and Asthma in Sofia with difficult-to-treat chronic urticaria in that they had failed to respond to their previous prescribed treatments (Table I). All had tried standard doses of first-generation and/or second-generation H_1-antihistamines, and 58 of the 80 patients, 28 on levocetirizine and 30 on desloratadine, were receiving intermittent systemic corticosteroids up to 3 weeks before inclusion in the study. Furthermore, patients should have had at least a 6-week documented history of moderate to intense urticaria as defined in the EAACI/GA$_2$LEN/EDF guideline[1]: pruritus score $\geq$2 and wheal score $\geq$2, with symptoms at least 3 days per week without any known secondary cause. Patients with urticaria also having signs of dermographism and/or delayed pressure urticaria were still included in the study; those with history of intolerance to nonsteroidal anti-inflammatory drugs were also included but warned not to take this drug class (paracetamol was allowed instead). Subjects with pure physical or allergic urticarias, hereditary and acquired angioedema (C1 esterase inhibitor deficiency), or urticaria vasculitis were not allowed in the study. Other exclusion criteria were pregnancy and lactation; any important systemic or psychiatric chronic disease requiring drug treatment with angiotensin-converting enzyme inhibitors, antipsychotics, and antidepressants; other skin disease and habitual use of corticosteroids or leukotriene receptor antagonists for 2 months before entry into the study or occasional use of oral corticosteroids within 2 weeks before the beginning of the study; or patients with clinically significant abnormalities in electrocardiogram, hematology, and biochemistry tests.

The study was approved by the institutional review board of Alexander's University Hospital in Sofia and performed in accordance with the general principles of Good Clinical Practice and the Declaration of Helsinki as amended in Edinburgh in 2000.

Study design

This was a double-blind, randomized, 2 parallel-armed investigator initiated trial in which the primary objective was to study the effect on urticarial symptoms of increasing the dose of 2 antihistamines. The secondary aim was to assess the effect of the alternative antihistamine at the highest dose if control of their disease was had not been achieved with the initial drug treatment to which they were allocated (Fig 1). The switch to the alternative drug was a mandatory step in the trial. The study was blinded by having all drug tablets encased in identical-looking gelatin capsules prepared by a technician who was not aware of the clinical work. The schedule and the coding (in a sealed envelope) was kept by the lead investigator. Patients received capsules for 7 days + 1 spare day in a coded bottle, which they gave back at their next visit. The actual drug supply of the original marketed tablets of both drugs was from a local pharmacy.

At the screening visit, after signing an informed consent in accordance with the local law, subjects were subjected to thorough clinical evaluation by the responsible physician including a structured questionnaire. Patients were asked whether they had symptoms for the past 3 days and were asked to evaluate reflectively their urticaria-associated discomfort during the preceding week on a VAS. The spread of urticarial lesions at the time of examination was determined by the physician and marked as "wheal score": 0, none; 1, mild, <20 wheals; 2, moderate, 21 to 50 wheals; and 3, intense, >50 wheals or large confluent areas of wheals. Patients evaluated their specific quality of life related to urticaria by using the CU-Q_2oL,[16] which was translated and validated in Bulgarian. Electrocardiogram and blood tests (including a pregnancy test for all women) were performed according to the standard operating procedures of the clinic. Subjects then had a washout period of 5 days without treatment, during which they were asked to fill in a diary including 24-hour reflective symptom score (from 0, no itch and no wheals, to 3, itch at its worst with multiple wheals), facial edema, use of rescue medication (30 mg prednisone), somnolence (from 0, no somnolence, to 3, excessive somnolence), ingestion of any other drugs, and adverse events.

At visit 1, five days later, all subjective and objective assessments, including electrocardiogram, were repeated. An autologous serum skin test (ASST) was performed to stratify patients into ASST-positive or ASST-negative. Patients were then randomized to either the levocetirizine or the desloratadine arm of the study. They were then given coded bottles with capsules containing 5 mg of either levocetirizine or desloratadine and instructed how to take them once a day in the morning. The diary cards from the screening visit were collected and reviewed to clarify misunderstandings, and new diary cards for the week ahead were provided. The same assessments were performed at visit 2. Patients who had no urticarial lesions and no pruritus for the last 3 days of treatment were considered to be symptom-free and left the trial. The remaining still symptomatic patients were given