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

TABLE I. Demographic characteristics of patients

Demographic characteristics	Levocetirizine (n = 40)	Desloratadine (n = 40)	Overall (n = 80)
Age (y)			
Mean	36.4	36.7	36.5
Median	36.0	34.5	35.0
Range	19-61	19-67	19-67
Sex, no. (%)			
Male	16 (40)	11 (28)	27 (34)
Female	24 (60)	29 (72)	53 (66)
Weight (kg)			
Mean ± SEM	72.3 ± 2.7	71.7 ± 2.1	72.0 ± 1.7
Height (cm)			
Mean ± SEM	169.4 ± 1.4	170.0 ± 1.3	169.7 ± 1.0
Initial wheal score			
Mean ± SEM	2.48 ± 0.09	2.58 ± 0.10	2.53 ± 0.0
Initial pruritus score			
Mean ± SEM	2.45 ± 0.09	2.58 ± 0.10	2.51 ± 0.07
Previous treatment, no. (%)			
Second-generation AHs*	34 (85)	34 (85)	68 (85)
First-generation AHs†	14 (35)	13 (32)	27 (34)
H_2 blocker‡	1 (2.5)	2 (5.0)	3 (3.8)
Corticosteroid§	29 (72)	29 (72)	58 (72)
ASST-positive	22 (55)	25 (62)	47 (59)

AH, Antihistamine.
The initial wheal and pruritus scores were assessed using a scale from 0 to 3 as defined in Zuberbier et al.[1] There were no statistically significant differences between the demographics of patients receiving levocetirizine and desloratadine (Wilcoxon test).
*Loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine.
†Hydroxyzine, chlorpheniramine, clemastine, ketotifen, dimetindene.
‡Ranitidine.
§Intermittent courses of systemic corticosteroid.

a coded bottle with twice as many capsules as the first bottle, to be taken 10 mg per day, morning and evening throughout week 2. At visit 3, all evaluations were repeated. The symptom-free patients left the trial, and the patients remaining symptomatic were given bottles with capsules for another week to be taken 20 mg per day, 2 capsules in the morning and 2 in the evening. After evaluation at visit 4, the patients still having symptoms were crossed over to 20 mg per day, divided morning and evening, of the alternative treatment (again blind in capsules) for another (fourth) week and evaluated at visit 5.

If adverse events occurred during the treatment phase, subjects were asked about the circumstances associated with drug taken and the probability of an association with the taken medication was graded as low (0% to 33%), moderate (34% to 66%), and high (67% to 100%). Termination of the participation in the trial was envisaged if serious or severe adverse effects appeared no matter how probable their association was with the current treatment.

Statistics and representation of data

To determine sample size, this study was considered to be a 3-step therapy. If the baseline dose of 5 mg was not successful after 1 week, the dose was doubled. If this dose was not successful within in the next week, the dose was redoubled. The primary objective of the study was to estimate the effectiveness of this 3-step therapy. In such studies, an overall success rate of about 30% can be expected. To estimate this rate with a precision of ±10% at a confidence level of 95%, a minimum sample size of 80 was computed ("nQuery 70" statistical program). Using this sample size, an estimate of the cumulative success rates after 1 week and after 2 weeks with an even slightly higher precision can be expected. Furthermore, this sample size allows a difference in the means of the quantitative outcome variables between the drug groups of 0.643 SDs to be shown with a power of 80% at a significance level of 5%.

Demographic data, anthropometrical data, baseline values of the wheal and pruritus score, and previous drug history are described in the usual way, by

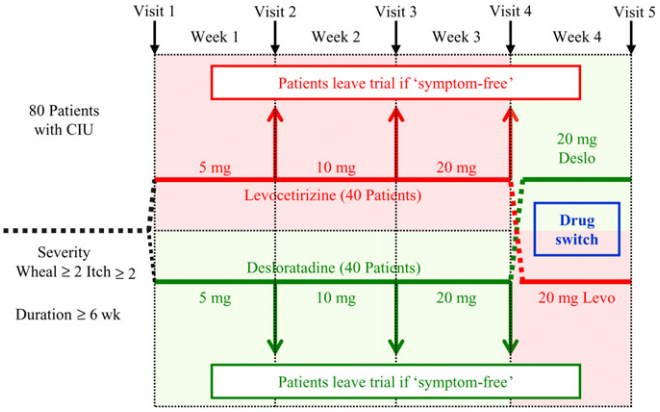

FIG 1. The study design with the treatment arms and the crossover step. *Deslo,* Desloratadine; *Levo,* levocetirizine.

absolute and relative frequencies of categorical variables and by means and SEMs of quantitative variables (Table I). Both cumulative response rates and means of quantitative outcome variables in both drug groups in the course of the study are displayed in plots. For the dose escalation part the study during the first 3 weeks, differences of response rates and differences in means of quantitative outcomes between the 2 drug groups were checked by the χ^2 test and the Mann-Whitney U test, respectively. Comparisons of the demographic data, anthropometrical data, baseline values, and quantitative outcomes at the several stages of the therapy were performed by the Wilcoxon test. Nonparametric tests were used because they are more robust and less likely to give spurious significant results than a parametric test. The success of the drug switch, the secondary objective of the study, was computed by using the Fisher exact test. A 2-tailed probability value of $P < .05$ was regarded as statistically significant.

RESULTS

Of the 80 patients randomized to treatment (intention-to-treat population), all 40 patients in the levocetirizine arm completed the study, whereas of the 40 subjects assigned to desloratadine, 3 (2 men and 1 woman) withdrew their informed consent (2 because the study interfered with their professional activities [travelling] while the third chose not to give an explanation about quitting the trial) during the second (2) and third (1) week of treatment. ASST was positive in 47 subjects (59%), 22 on levocetirizine and 25 on desloratadine.

Objective symptoms

The results of the primary objective, a comparison the number of patients who became symptom-free when receiving different doses of levocetirizine or desloratadine, are shown in Fig 2. Increasing the drug dose above the conventionally prescribed 5 mg for either drug more than doubled the success rate of treatment. There were significant differences in the number of successes in favor of higher than conventionally prescribed doses for both levocetirizine ($P < .001$) and desloratadine ($P = .002$; χ^2 test). The overall success rate of 22 patients with levocetirizine at the end of week 3 was significantly ($P < .04$) higher than the rate of 12 patients with desloratadine (Fisher exact test).

At the end of week 3, patients who were still symptomatic were switched to the opposite drug. Of 25 patients who failed to respond to 20 mg desloratadine, 7 became symptom-free on 20 mg levocetirizine, whereas the switch to desloratadine had no

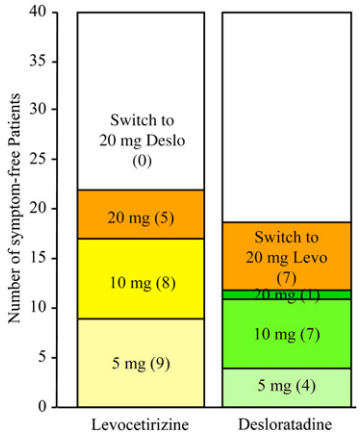

FIG 2. The number of patients whose symptoms were relieved by levocetirizine *(Levo)* or desloratadine *(Deslo)* throughout the 4 weeks of the study. The *numbers in parentheses* refer to the number of patients who were symptom free on 5 mg (week 1), 10 mg (week 2), 20 mg (week 3), or after the drug switch (week 4).

benefit in any of the 18 patients who were not symptom-free on levocetirizine ($P < .04$; Fisher exact test).

There was no significant correlation between ASST positivity and the success or failure rates of treatment with either drug.

Discomfort caused by urticaria

The analysis of the VAS scores for discomfort caused by urticaria (Fig 3) showed that patients may be divided into 3 broad groups: low-dose responders, the ~10% of patients in whom 5 mg of either levocetirizine of desloratadine caused >90% improvement (indicated by the *green arrow*); nonresponders, the ~15% of patients with <10% improvement on 20 mg of either drug (indicated by the *red arrow*); and high-dose responders, the remaining ~75% who showed increased benefit with higher antihistamine doses. The proportions of responders reporting >50% improvement in discomfort were 52%, 65%, and 74% with 5, 10, and 20 mg levocetirizine and 41%, 56%, and 63% on the same doses of desloratadine. The overall improvement with levocetirizine was significantly ($P < .003$) greater than with desloratadine (Mann-Whitney test).

Somnolence

A major concern with increasing doses of H_1-antihistamines is that of somnolence. With levocetirizine, 75% of patients showed either no change or a reduction in somnolence throughout the study (Fig 4, *A*). In fact, there was a statistically significant ($R = 0.41$; $P = .008$) Spearman rank correlation between changes in the VAS scores for somnolence and urticaria related discomfort between the start of the study and the last week in which each patient participated in the study. For desloratadine, the situation was less clear, with 55% of patients showing either no change or a reduction in somnolence throughout the study (Fig 4, *B*). There was no significant Spearman rank correlation between changes in the VAS scores for somnolence and urticaria related discomfort for desloratadine ($R = 0.06$; $P = .7$). With neither drug was somnolence significantly greater in those patients taking 20 mg per day compared with their somnolence before starting the trial (Wilcoxon test for paired data).

Quality of life

Quality of life was assessed by using the CU-Q_2oL,[16] which asks questions about pruritus, swelling, impact on life activities, sleep problems, looks and limits to obtain the patient's view of both the overall impact of chronic urticaria and the effectiveness of its treatment. The results showed that there was an increasing improvement in quality of life with increasing doses of both levocetirizine and desloratadine (Table II), with levocetirizine again showing superiority. Detailed analysis of the individual domains of this questionnaire is the subject of a separate manuscript (manuscript in preparation, DS Church et al.).

Safety

Only 17 of the 80 patients, 6 taking levocetirizine and 11 taking desloratadine, recorded adverse reactions at any time during the study. These included (each in a single patient unless stated otherwise in parentheses): hip pain, anxiety (2), nausea, and fatigue during week 0 when no drug was given; hip pain, anxiety, nausea, headache, and oral discomfort during week 1 when receiving 5 mg of drug; hip pain, nausea, headache (3), stomach ache, kidney pain, viral infection, and palpitations with no accompanying electrocardiogram change during week 2 when receiving 10 mg of drug; nausea in 1 patient only during week 3 when receiving 20 mg of drug; and nausea, viral infection (3), breathlessness during week 4 after the switch to 20 mg of the alternative drug. No reaction was serious or severe enough to cause discontinuation of treatment. There was no pattern in their appearance, and the probability for association with either drug dose or one drug in particular was low. No pathological changes appeared in the electrocardiogram during treatment with any of the medications.

DISCUSSION

This study provides evidence that in patients with difficult-to-treat chronic urticaria, increasing the daily dose of 2 second-generation antihistamines, levocetirizine and desloratadine, to up to 4 times their conventionally prescribed doses of 5 mg/d increases the control of urticaria symptoms without compromising patient safety. The number of chronic urticaria patients who became symptom-free more than doubled when administering the drugs in doses double or quadruple the conventional doses. Furthermore, the results strongly suggest that levocetirizine is the more effective of the 2 drugs in relieving whealing and itching, a conclusion supported by a previous 4-week trial in chronic urticaria[17] and wheal and flare studies comparing levocetirizine and desloratadine.[18-21] A recent study suggested that using higher doses of desloratadine in subjects with cold-induced urticaria had a beneficial effect.[22] This is in line with our results, which were, however, obtained in patients with difficult-to-treat urticaria.

Although the 80 patients recruited into the study had been deemed by their previous treating physicians to be poorly responsive to treatment, the symptoms of 13 patients, 9 on levocetirizine and 4 on desloratadine, were completely relieved by the initial 5-mg dose of drug. There are several possible reasons for this. First is the inherently variable clinical course of chronic urticaria, which would change a patient's responsiveness to therapy. Second, they were treated with less effective therapies before enrollment: 7 of the 9 responding to 5 mg levocetirizine and 3 of the 4 responding to 5 mg desloratadine had not been

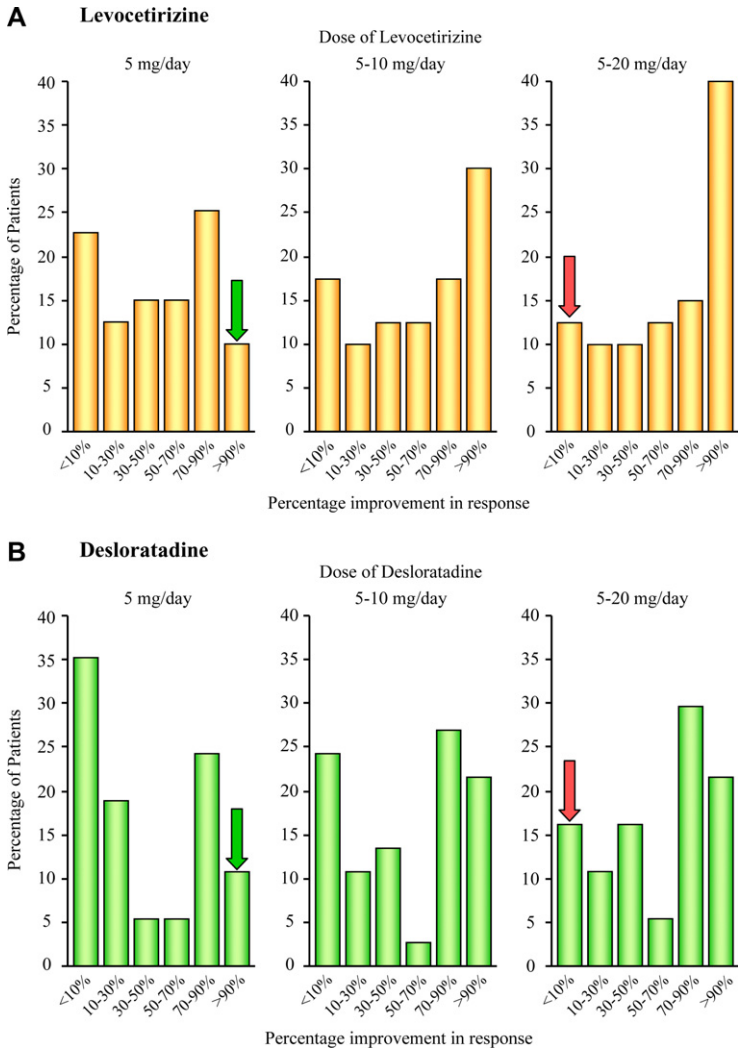

FIG 3. The cumulative percentage of patients showing differing levels of improvement of urticaria-related discomfort with increasing doses of A. levocetirizine, and B. desloratadine. The *green arrows* indicate patients with a >90% improvement on 5 mg (low-dose responders), and the *red arrows* indicate patients with <10% improvement on 20 mg (nonresponders).

treated previously with these drugs. Third, these 13 patients may belong to the less severe end of our population: 10 of these patients had not been regarded by their previous treating physician to be severe enough to receive systemic corticosteroids. Some patients were treated with less effective therapies before enrollment. The drugs taken by 8 of the 9 responding to 5 mg levocetirizine were clemastine 2 mg, chlorpyramine 75 mg, desloratadine 5 mg, dimetindene 4 mg, loratadine 10 mg (3 patients), and fexofenadine 180 mg. Only 1 patient had been taking levocetirizine 5 mg previously. The drugs taken by 3 of the 4 responding to 5 mg desloratadine were ketotifen 2 mg (2 patients) and dimetindene 4 mg + cinnarizine 50 mg + ranitidine 300 mg. Only 1 patient had been taking desloratadine 5 mg previously. The fourth possible reason is that the patients knew they were taking part in a clinical trial. This is known to have major psychological effects and improve compliance. Even placebo can have major beneficial effects in clinical trials, as exemplified by the study of Giménez-Arnau et al,[23] in which they used responder analysis to identify clinically meaningful differences in patients with chronic urticaria. In this study, placebo reduced the mean pruritus score, the mean number of wheals, and the mean urticaria activity score by more than 75% in 21%, 12%, and 14% of patients, respectively.

Our study did not find differences in the response to treatment between the 2 chronic urticaria phenotypes, with and without ASST positivity, to either drug. Because we did not use the autologous plasma skin test in our trial, we could not lend support to any of the parties involved in the recent controversy raised in this journal about the utility of ASST and autologous plasma skin test in chronic urticaria.[8,24,25]

The analysis of the VAS scores giving the patients' assessment of their discomfort caused by urticaria showed 3 broad groups: low-dose responders, made up of around 10% of the study population patients who responded well to antihistamine therapy; nonresponders, made up of around 15% of the study population who showed little or no response to investigated antihistamines even at high doses, and the remaining approximately 75% of the study group, who were defined as high-dose responders because

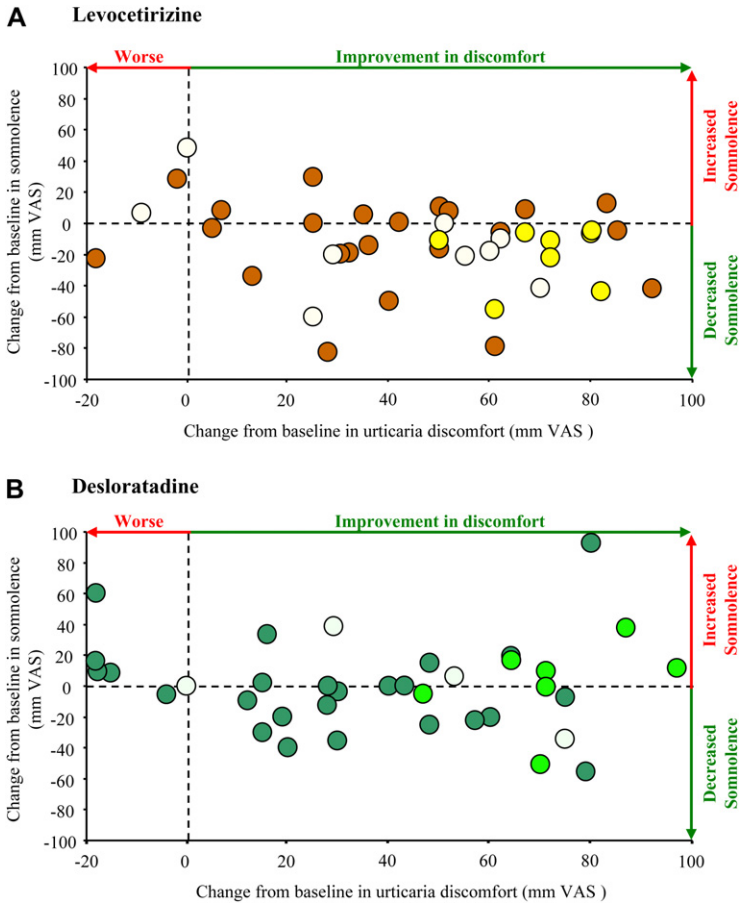

FIG 4. The relationship between somnolence and relief from urticaria discomfort for A. levocetirizine and B. desloratadine. Each point represents the change in the VAS scores of somnolence and relief from urticaria discomfort from those at the beginning of the study to those when the patients were taking the highest dose of the drug that they received. Colors of circles for levocetirizine are as follows: 5 mg, *pale yellow,* 10 mg, *mid yellow,* and 20 mg, *brown* (total, 40 patients). Colors of circles for desloratadine are as follows: 5 mg, *pale green,* 10 mg, *mid green,* and 20 mg, *dark green* (total, 38 patients).

TABLE II. Cumulative percentage of patients with an improvement in quality of life of greater than 50%

Daily dose	5 mg	10 mg	20 mg
Levocetirizine	48	58	62
Desloratadine	20	39	46

they showed increased benefit with higher doses of antihistamines. This heterogeneity of response to antihistamine therapy fits with clinical opinion. It also agrees with a previous study showing that only about 44% of patients respond to antihistamine therapy.[11] It should be emphasized at this point that the patients in our study were difficult-to-treat cases from our tertiary referral center, 72% of whom had been treated with systemic corticosteroids to alleviate the urticaria symptoms preceding their recruitment.

Perhaps the major outcome of this study was the finding that patients did not experience increased somnolence when stepping up their daily dose as opposed to an anticipated increase in somnolence on the basis of reports that all second-generation H_1-antihistamines may cause a small degree of sedation.[26] However, it does agree with a case report of a man who tolerated 50 mg per day of cetirizine for the treatment of chronic idiopathic urticaria without any sedation, somnolence, or hindrance with performing routine daily functions including driving.[27] A surprising finding was a paradoxical decrease in somnolence over time in the levocetirizine arm of the study. Two possible reasons may be suggested as an explanation. The first possibility is the relief from physical discomfort ensuing from the psychological status of the patients. The majority of sedation studies with H_1-antihistamines are performed in either healthy individuals or individuals with mild disease rather than in conditions, such as chronic urticaria, which cause sleep deprivation. Indeed, in chronic urticaria, the levels of sleep disturbance are greater than in patients with ischemic heart disease.[3] We speculate relief from urticaria-related discomfort led to a better quality of sleep with subsequent prolonged wakefulness during the day. This is supported by the finding for levocetirizine of a statistically significant ($P = .008$) Spearman rank correlation between reduction of urticaria-related discomfort and reduction of somnolence. The second possibility, which is likely to occur in parallel with the possibility explained above, is the development of tolerance to the central nervous sedative effects of the antihistamines. The development of tolerance to the central nervous system effects of both first-generation and

second-generation antihistamines after 4 to 5 days of administration has been reported repeatedly,[28-30] and the weekly stepwise increase in dosage in this study would be ideal to induce tolerance.

In conclusion, this study provides evidence that in patients with difficult-to-treat chronic urticaria, increasing the daily dose of 2 second-generation antihistamines, levocetirizine and desloratadine, to up to 4 times the conventionally prescribed doses increases the control of urticaria symptoms in approximately 75% of patients without compromising somnolence or safety. The overall comparison of levocetirizine and desloratadine in chronic urticaria showed levocetirizine to be the more effective drug in the course of treatment with 5-mg to 20-mg daily doses.

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Clinical implications: Increasing H_1-antihistamine dosage up to 4-fold improved urticarial symptoms and quality of life but did not increase somnolence in approximately three quarters of patients with difficult-to-treat chronic urticaria.

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