

High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: A randomized, placebo-controlled, crossover study

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Background: Increased dosing of nonsedating antihistamines is recommended by the current European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum guidelines on patients with acquired cold urticaria (ACU) who do not respond satisfactorily to the standard dose. Prospective data supporting this recommendation are scant.

Objective: We sought to assess the effects of 5 and 20 mg of desloratadine and placebo on cold-induced urticarial reactions in patients with ACU.

Methods: In this prospective, randomized, double-blind, 3-way crossover trial, patients with ACU (n = 30) received placebo, 5 mg of desloratadine, and 20 mg of desloratadine every day each for 7 days separated by 14-day washout periods. At the end of each treatment, patients underwent cold provocation with the TempTest 2.0/2.1 system, and urticarial reactions were assessed by using digital 3-dimensional time-lapse photography and thermography; the critical temperature threshold (CTT) and

critical stimulation time threshold (CSTT) were measured.

Adverse events (AEs) reported during the study were assessed. **Results:** Compared with placebo, 7 days of desloratadine at 5 and 20 mg/d significantly reduced the volume of cold-induced wheals and areas of hyperthermic skin and improved CTT and CSTT results. Desloratadine at 20 mg/d significantly reduced cold-induced wheal volume and CTT and CSTT values versus desloratadine at 5 mg/d. Desloratadine was well tolerated, with no increased rate of somnolence or other AEs with 20 mg of desloratadine.

Conclusions: Desloratadine at standard and high doses significantly improved objective signs of ACU provoked by cold exposure. Desloratadine at 4 times the standard dose significantly reduced ACU lesion severity versus 5 mg of desloratadine without an increase in AEs. This study supports current guidelines that increased desloratadine dosing might benefit patients with urticaria who do not respond to standard doses. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Urticaria, cold, chronic, objective, antihistamine, desloratadine

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Acquired cold urticaria (ACU) is a chronic physical urticaria and is associated with wheals of the skin (with or without angioedema) in response to exposure to cold temperature.^{1,2} The eliciting stimulus can consist of exposure to cold air, surfaces, or fluids. ACU has a range of severities depending on the patient and on the potency/duration of the cold stimulus. In particular, patients with ACU are potentially at risk of severe systemic anaphylactic shock-like reactions after unwitting immersion in cold water. Similarly, subjects with ACU can be at significant risk because of more localized cold stimuli, such as cold drinks, which have been recognized to cause occlusive edema of the pharynx/airway. The clinical features of ACU are due to the release of mast cell mediators in response to cold. However, the cause of the condition remains largely unknown and might be multifactorial.¹⁻³

ACU disease severity might depend to a significant extent on the degree and duration of cold exposure required to elicit wheals and itching, with patients with ACU who are sensitive to short exposures and relatively increased temperatures having a greater likelihood of encountering stimuli in their daily lives. The diagnosis of ACU has used a variety of methods to elicit

Abbreviations used

ACU:	Acquired cold urticaria
ACUSI:	Acquired Cold Urticaria Severity Index
AE:	Adverse event
AUC:	Area under the curve
CSTT:	Critical stimulation time threshold
CTT:	Critical temperature threshold
CU:	Chronic urticaria
LTWW:	Lowest temperature without wheals
SDWW:	Shortest duration without wheals

cold-induced wheals, the simplest of which is the timed application of an ice cube to the skin. More precise methods have evolved over recent years, such as the TempTest device (Emosystems, Berlin, Germany), which relies on the Peltier effect to apply a range of temperatures to defined areas of the skin, thus allowing both a temperature and time threshold to be derived.⁴

Management of ACU centers on the identification and recognition of each patient's specific temperature and exposure time thresholds and the avoidance of exposure to cold stimuli.^{1,2} Treatment of ACU relies largely on nonsedating second-generation antihistamines and the use of epinephrine and other typical measures in response to oropharyngeal edema or systemic shock. ACU lesions and symptoms are often challenging to control with antihistamines at standard doses used in allergy practice; other medication classes, such as anti-IgE, have been used with occasional success.⁵

Up-titration of dose to as high as 4 times the starting dose has been advocated in international guidelines to surmount the often relative unresponsiveness to traditional doses of antihistamines in urticaria (including ACU).^{6,7} Despite such recommendations, the evidence base supporting the efficacy and safety of this up-dosing approach is surprisingly scant. Given the availability of accurate instruments like TempTest that can reproducibly elicit wheals in patients with ACU, we hypothesized that it should be feasible to assess objectively in a placebo-controlled fashion whether increasing the dose of a second-generation antihistamine, desloratadine, from its traditional dose (5 mg every day) to a higher dose (20 mg every day) was associated with clinically meaningful changes in wheals and temperature and time thresholds in patients with ACU.

METHODS

Patients

This was a prospective, double-blind, randomized, placebo-controlled crossover study of the safety and efficacy of 5 mg of desloratadine, 20 mg of desloratadine, and placebo administered once daily for 7 days in patients with ACU. Study participants were drawn from the outpatient population at the urticaria specialty clinic of the Allergie-Centrum-Charité of the Charité-Universitätsmedizin, Berlin, Germany. Male and female patients aged 18 to 75 years with a confirmed diagnosis of ACU that was made at least 6 weeks before screening were eligible. The study (clinicaltrials.gov identifier: NCT00600847) was permitted after review by the Ethics Committee of the Berlin Region (Ethikkommission des Landes Berlin) and the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). All subjects provided written informed consent.

The baseline characteristics of the patient population in terms of ACU signs/symptoms were assessed by using the Acquired Cold Urticaria Severity Index (ACUSI; Fig 1), and information on triggering stimuli, previous medication use, and concomitant disease was also collected. At a screening visit, a cold provocation test was performed, and patients who exhibited a positive

reaction (wheal and itching) after 10 minutes of provocation at 4°C were eligible for the study. All women of childbearing potential had to use an effective means of contraception for the duration of the study. Patients were excluded if they had a history of significant gastroenterologic, neurologic, cardiac, oncologic, psychiatric, renal, or liver diseases that could have interfered with patient safety or the conduct of the study. Also excluded were those with a history of sensitivity to desloratadine, loratadine, or excipients; a current history of acute urticaria/angioedema or laryngeal edema; a current or previous history of alcohol/drug abuse; and pregnant or nursing female subjects. An adequate washout period before baseline had to be observed for antihistamines or leukotriene antagonists (7 days), oral corticosteroids (14 days), and depot/other chronic systemic corticosteroids (21 days). Alcoholic beverages were forbidden for the duration of the study. At screening, all subjects underwent a general physical examination, laboratory blood analyses, and an electrocardiogram.

Eligible patients were randomized according to a balanced experimental design: each of the 6 possible sequences of placebo and low-dose and high-dose desloratadine was applied to an equal number of patients. Each 7-day treatment period was followed by a 14-day washout period before crossing over to the next treatment group (Fig 2).

Efficacy measures

Provocation of wheals. Cold provocation was undertaken with the TempTest 2.0/2.1 system (Fig 3). This device relies on the Peltier effect in which plastic-embedded thermoelectric elements can heat/cool depending on the polarity and voltage of an electric current passing through 2 semiconductors. This permits precise and accurate delivery of different grades of heat or cold to the skin. The TempTest 2.0/2.1 system permits thermal ranges from 0°C to 42°C ($\pm 0.1^\circ\text{C}$), which are controlled through settings on a central computerized unit.

After 7 days of treatment (including the day of testing), patients were subjected to cold provocation testing with TempTest 2.1 (diameter, 1 cm) on the forearm skin. The time to development and the size of the provoked skin reaction were assessed with digital 3-dimensional time-lapse photography and thermography. The critical temperature and stimulation time thresholds were assessed after a cold provocation with TempTest 2.0 (diameter, 3 cm) on the abdominal skin. All tests were performed at a constant room temperature (mean, 21.5°C; range, 20°C–23°C).

Digital time-lapse photography and thermography.

Analysis of the test reaction was performed by using digital 3-dimensional time-lapse photography (Primos, Berlin, Germany) and thermographic imaging (Flir S60, Frankfurt, Germany) at 5-minute intervals until the skin returned to normal or a maximum duration of 90 minutes. Wheal and erythema size and duration were measured by means of planimetric analyses of digital photographs and thermographic images, and areas under the curve (AUCs) were calculated.

Urticarial stimulation thresholds. The critical temperature threshold (CTT) was defined as the highest temperature at which a wheal was induced within the test site with TempTest 2.0. The CTT was assessed at baseline by applying the TempTest 2.0 to the skin for 5 minutes at 4°C and at increasing temperatures in increments of 3°C up to 30°C (eg, 7°C, 10°C, and 13°C) to determine the lowest temperature without wheals (LTWW). Once identified, the LTWW in addition to the LTWW -1°C , -2°C , and -3°C were tested to determine the exact CTT.

The critical stimulation time threshold (CSTT) was defined as the shortest time needed to induce wheal development within the test site by means of cold provocation at 4°C. At baseline, the TempTest 2.0 was applied to the skin, and the shortest duration of provocation without wheals (SDWW) was assessed at 0.5, 2, 3.5, and 5 minutes of cold exposure. If wheals appeared before the 0.5-minute time point, then the time was recorded as 0.5 minutes. Thereafter, the CSTT was assessed by testing the SDWW and SDWW + 0.5, +1, and +1.5 minutes (maximum set at 5 minutes).

Symptom scores. The severities of itching, burning, and general subjective severity/appearance of the cold-induced ACU lesion were assessed separately 10 minutes after the end of cold provocation as absent/none (0) or present (1, mild; 2, moderate; and 3, severe).

Surname, First Name:

Date of birth:

Date:

Duration of Cold Urticaria: _____ ☐ Months ☐ Years**ACUSI (Acquired Cold Urticaria Severity Index)**Please read the following questions carefully and then mark your response with an X (☐).

1. What were the worst problems ever caused by your cold urticaria?

- ☐ hives, redness or itching
☐ deep swelling of the skin or mucous membranes / angioedema (e.g. eyes, lips, tongue)
☐ circulatory complaints / dizziness or difficulty swallowing / difficulty breathing
☐ unconsciousness / shock

2 When your urticaria was at its worst: During which season of the year did problems with outdoor activities occur because it was too cold? (not swimming)

- ☐ Only in winter (December-March)
☐ In winter, spring and autumn
☐ During all seasons

3. What is the maximum treatment that your cold urticaria has needed?

- ☐ Sufficient to avoid the cold or to wear warm clothes
☐ Antihistamines, either on demand or used continuously
☐ I needed to use my emergency medication use (cortisone or adrenaline)
☐ I had to be treated by an emergency physician

4. How often have you had complaints, when your cold urticaria was at its worst?

- ☐ rarely, about 1 or 2 times a month
☐ Occasionally, about once a week
☐ Often, several times a week
☐ daily or almost daily

5. How do you assess the overall severity of your cold urticaria:

- ☐ mild
☐ moderate
☐ severe

Surname, First Name:

Date of birth:

Date:

ACUSI Evaluation

Question 1

- ☐ 1 point
☐ 2 points
☐ 3 points
☐ 4 points

Points

Question 2

- ☐ 1 point
☐ 2 points
☐ 3 points

Points

Question 3

- ☐ 1 point
☐ 2 points
☐ 3 points
☐ 4 points

Points

Question 4

- ☐ 1 point
☐ 2 points
☐ 3 points
☐ 4 points

Points

TOTAL of 15 points

VALIDATION

Result:

- 4-7 points mild ACU ☐
 8-11 points moderate ACU ☐
 12-15 points severe ACU ☐

How did the patient judge the severity of their cold urticaria:

- ☐ mild
☐ moderate
☐ severe

FIG 1. Acquired Cold Urticaria Severity Index.**Safety**

At each study visit, patients were questioned regarding the occurrence of adverse events (AEs) over the previous week and during intervening washout periods. AEs were classified according to severity and relationship to therapy.

Statistics

All statistical analyses in the study were performed with SAS 9.1.2. (SAS Institute, Inc, Cary, NC) and SPSS 15.0 (SPSS, Inc, Chicago, Ill). The analysis of the efficacy parameters was performed in the per-protocol population, which included all patients who completed all treatment phases of the study. Demographic parameters were expressed descriptively and included the number of observations, means, SDs, medians, and ranges for continuous variables and the number of observations and respective percentages for categorical parameters. AE data and laboratory test results were tabulated according to study group and time of occurrence according to treatment/washout period.

Based on an α significance level of .05, a power of 80%, and an effect size δ value of 0.529, a total of 30 patients was considered ideal to adequately investigate the objectives of the study. The level of significance was .05 (2-sided) for all statistical tests.

The primary efficacy end point was the assessment of wheal development by means of planimetric analyses of digital photographic imaging before and after treatment with study medication (5 or 20 mg of desloratadine or placebo). Secondary end points for the study included the wheal-and-flare development by means of planimetric analyses of thermographic images and the assessment of CTT, CSTT, and urticarial symptoms in the 3 study groups. For the CTT and CSTT in patients who did not show urticarial responses during treatment, the CTT was set at 3°C, and the CSTT was set at 6 minutes.

RESULTS**Demographics and patient characteristics**

A total of 33 patients were screened, of whom 2 withdrew before visit 1 and 1 before visit 2; the remaining 30 patients completed all study visits. Therefore, the intent-to-treat population contained 31 patients, and the per-protocol population had 30 patients. Patients withdrew before visit 1 because of taking forbidden medication (corticosteroids) and identification of cardiac disease. The remaining patient dropped out after visit 1 because of noncompliance. The mean age of the study population was

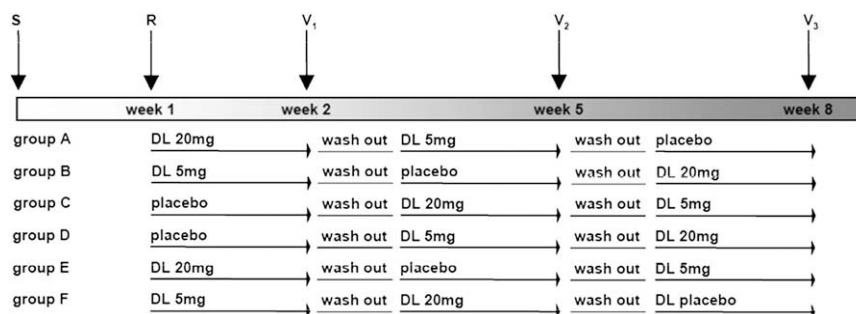


FIG 2. Study treatment group flow chart. S, Screening; R, randomization; V, visit; DL, desloratadine.



FIG 3. The TempTest 2.0/2.1 device and example of placement on the forearm for the purpose of performing cold provocation tests.

50 years (range, 18-71 years), and the population consisted of 20 female and 10 male patients. The mean duration since the diagnosis of ACU was 11.2 years. The mean blood pressure was 123/74 mm Hg (range, 100-145/60-85 mm Hg), and the mean height was 170 cm (range, 151-191 cm). Based on a mean body weight of 72 kg (range, 52-106 kg), the daily dose per kilogram for 5 mg of desloratadine was 0.07 mg, and that for 20 mg of desloratadine was 0.28 mg. The per-kilogram daily doses of desloratadine were similar for male and female subjects.

By using ACUSI, the frequencies of the worst ACU signs and symptoms previously experienced by patients were as follows: hives/redness/itching, 14 (46.7%) of 30; dizziness/difficulty swallowing/circulation disorders/dyspnea, 10 (33.3%) of 30; unconsciousness/shock, 4 (13.3%) of 30; and angioedema, 2 (6.7%) of 30. ACU occurred during all seasons in 18 (60.0%) of 30 patients; during winter, spring, and autumn in 11 (36.7%) of 30 patients; and only in the winter in 1 (3.3%) of 30 patients. At baseline, ACU severity, as determined by using the ACUSI, was mild in 8 (26.7%) of 30 patients, moderate in 16 (53.3%) of 30 patients, and severe in 6 (20.0%) of 30 patients. Patients reported the following stimuli as provoking ACU disease activity: cold (outdoors), 30 (100%) of 30; wind, 28 (93.3%) of 30; swimming, 25 (83.3%) of 40; taking a shower, 3 (10.0%) of 30; and room temperature, 2 (6.7%) of 30. The most frequent concomitant diseases were allergies (43.3%), musculoskeletal disease (33.3%), and gastrointestinal, urogenital, and cardiovascular diseases (20.0% each). Dermographism-urticaria factitia was present in 2 patients in this cohort. Previous treatments for ACU

before enrollment into the current study included antihistamines (25/30 [83.3%]) and penicillin therapy for 4 weeks (1/30 [3.3%]), whereas 5 (16.7%) of 30 patients had received no previous treatment.

Efficacy

Primary end point. The primary end point was the assessment of cold-induced wheal development before and after treatment with desloratadine (20 mg and 5 mg) and placebo for 7 days for which digital time-lapse photography was used (Fig 4, A). Five milligrams of desloratadine for 7 days was associated with a significantly lower cold-provoked wheal volume compared with placebo ($P < .001$). Similarly, treatment with 20 mg of desloratadine for 7 days was also associated with a significantly lower cold-provoked wheal volume versus placebo ($P < .001$). The effect of treatment with 20 mg of desloratadine on cold-provoked wheal volume was significantly greater than the effect of 5 mg of desloratadine ($P < .001$). Differences between the effects of 5 and 20 mg of desloratadine and placebo in terms of wheal volume were the same when volume was measured 15 minutes after cold provocation (Fig 5, A) or as an AUC over a 90-minute period after cold provocation ($P < .001$; Fig 5, B). There was no relationship between the response to therapy and the presence/absence of any particular comorbid or concomitant diseases.

Thermographic analyses. Thermographic analyses of cold-induced lesion formation (Fig 4, B) demonstrated a significantly smaller lesion area in the 5 mg of desloratadine (mean, 278.68 mm² [SD, 455.49 mm²]) and 20 mg of desloratadine (mean, 214.39 mm² [SD, 273.61 mm²]) groups compared with that seen in the placebo group (mean, 481.31 mm² [SD, 619.66 mm²]) at 15 minutes after exposure ($P \leq .01$). This was maintained over the 90-minute AUC after exposure in the placebo (mean, 2846.11 mm² [SD, 5199.48 mm²]), 5 mg of desloratadine (mean, 1638.69 mm² [SD, 3110.66 mm²]), and 20 mg of desloratadine (mean, 1088.23 mm² [SD, 1530.14 mm²]) groups ($P \leq .05$). Although the suppression of the cold-induced response was numerically greater with the 20-mg desloratadine dose compared with the 5-mg dose, this did not reach statistical significance.

CTT. Treatment with 5 mg of desloratadine was associated with a significantly improved CTT compared with placebo (mean, placebo, 20.47°C [SD, 5.30°C]; 5 mg of desloratadine, 15.17°C [SD, 7.74°C]; $P < .001$). Similarly, treatment with 20 mg of desloratadine was associated with a significantly improved CTT compared with placebo (placebo: mean, 20.47°C [SD, 5.30°C]; 20 mg of desloratadine: mean, 10.83°C [SD, 9.03°C]; $P < .001$).

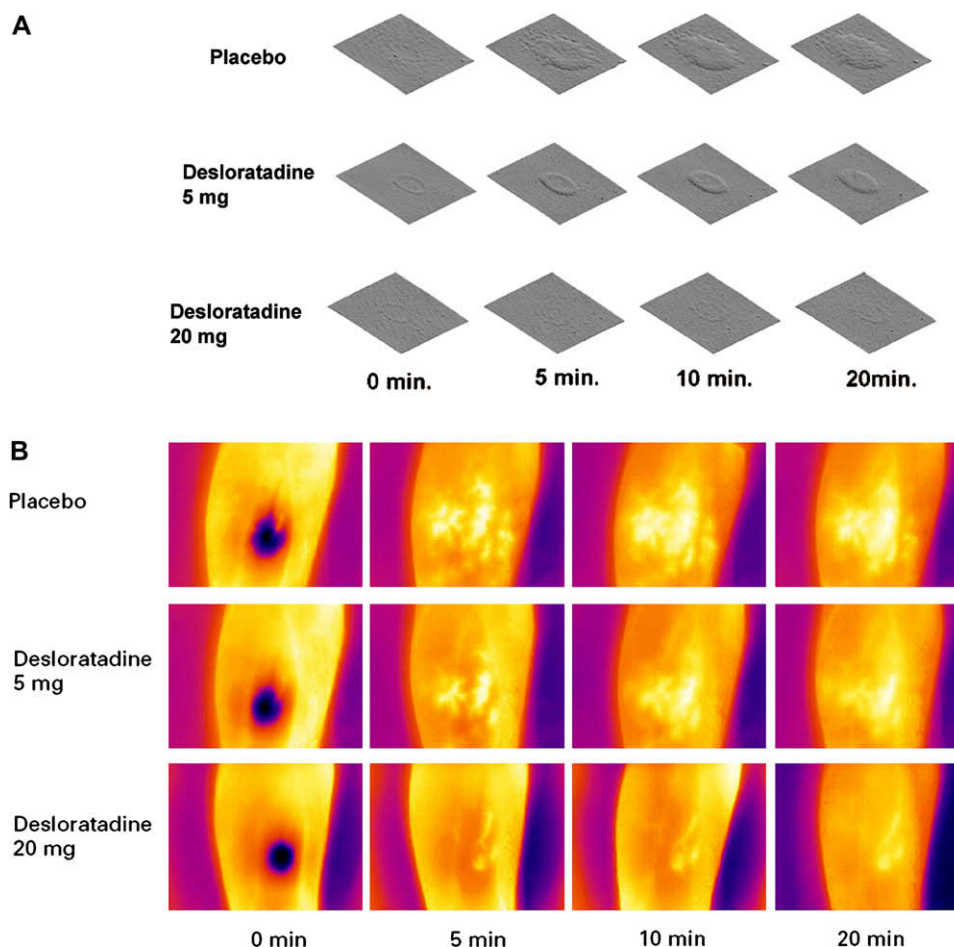


FIG 4. **A**, Representative illustration of digital 3-dimensional time-lapse photographic images of cold-induced wheal responses over time in 1 patient with ACU after treatment with placebo, 5 mg/d desloratadine, and 20 mg/d desloratadine for 7 days. **B**, Example of thermographic images of the cold-induced wheal response over 20 minutes in a patient with ACU treated with placebo, 5 mg/d desloratadine, and 20 mg/d desloratadine for 7 days.

The comparison between the 20- and 5-mg desloratadine treatments demonstrated a significantly improved CTT after high-dose therapy compared with the standard 5-mg dose ($P \leq .01$; Fig 6, A).

CSTT. Treatment with desloratadine at 5 and 20 mg led to significant increases in mean CSTT compared with placebo (placebo: mean, 1.20 minutes [SD, 1.18 minutes]; 5 mg of desloratadine: mean, 2.38 minutes [SD, 2.19 minutes]; 20 mg of desloratadine: mean, 3.87 minutes [SD, 2.33 minutes]; $P < .001$). As with the CTT above, the 20-mg desloratadine dose was associated with a significant improvement in the CSTT compared with the 5-mg dose ($P < .001$; Fig 6, B).

Symptoms. Fifteen and 7 of 30 patients treated with desloratadine 20 mg and 5 mg, respectively, reported complete protection and did not develop a wheal response after cold provocation (4°C , 5 minutes) as compared with only 1 of 30 patients treated with placebo (desloratadine 20 mg versus placebo: $P < .001$; desloratadine 5 mg versus placebo: $P < .05$; desloratadine 20 mg versus 5 mg; $P < .01$). For the presence of itching or burning, there was only a significant difference for the comparison of the 20-mg desloratadine dose and placebo for itching ($P < .001$).

Safety assessments

Twenty-five AEs were reported by 17 patients, 2 of which occurred during the placebo phase, 11 with 5 mg of desloratadine, 7 with 20 mg of desloratadine, and 5 during the washout phases. Among AEs possibly related to treatment, fatigue (primarily mild in nature) occurred in 1 patient during the placebo phase and in 3 subjects each during treatment with 5 mg of desloratadine and 20 mg of desloratadine. Somnolence/drowsiness was not reported by any patient during the study. One serious AE (gastroenteritis) occurred during a washout phase in 1 patient, for which the patient was hospitalized and recovered.

DISCUSSION

This is, to our knowledge, the first study to assess the effect of increased dosing of a nonsedating antihistamine on wheal formation in patients with ACU using an objective and precise method: the TempTest system. We found that treatment of patients with ACU for 7 days with desloratadine at its standard dose of 5 mg once daily significantly decreased the cold-induced wheal volume compared with that seen after placebo. Similarly,

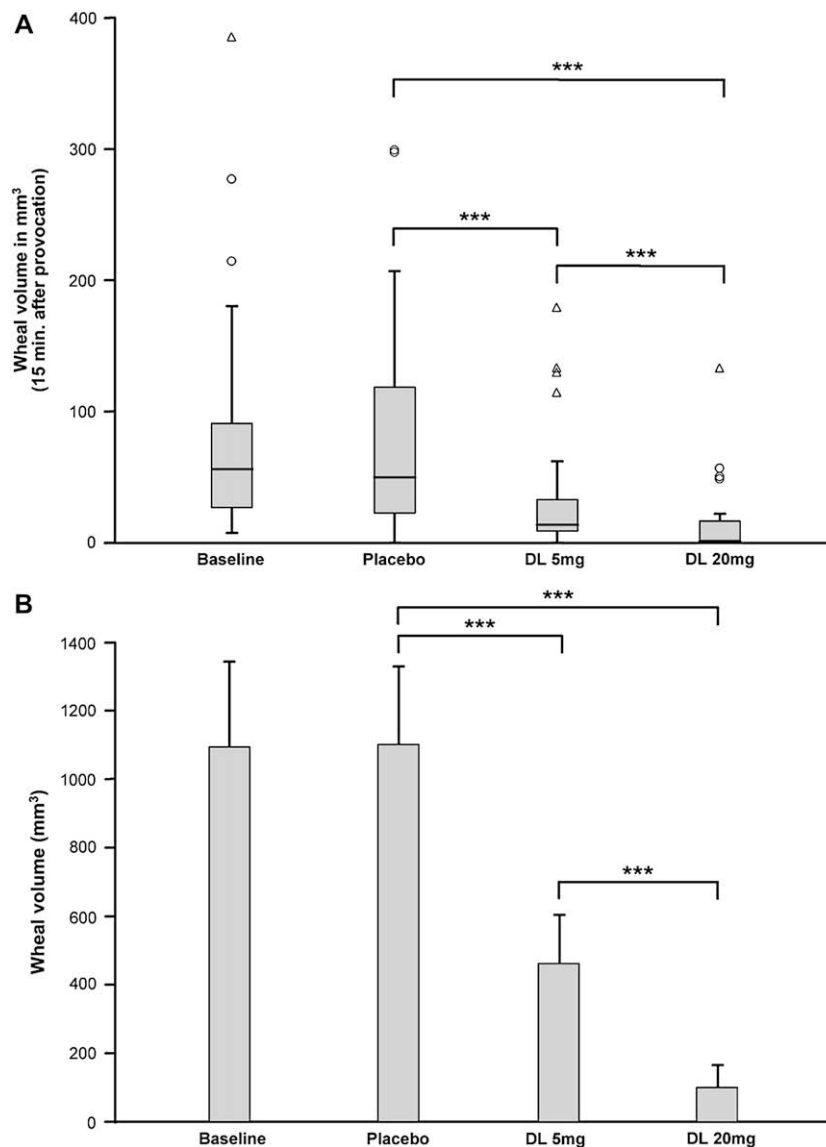


FIG 5. **A**, Box and whisker plots showing the wheal volume 15 minutes after cold provocation testing and after treatment with placebo (mean, 78.82 mm³ [SD, 81.21 mm³]), 5 mg of desloratadine (mean, 34.49 mm³ [SD, 46.03 mm³]), and 20 mg of desloratadine (mean, 13.80 mm³ [SD, 27.85 mm³]) every day for 7 days. Circles within the figures represent outliers, and triangle illustrate extreme values. **B**, Mean wheal volume AUC over 90 minutes after cold provocation after treatment with placebo (mean, 1064.55 mm³ [SD, 1200.72 mm³]), 5 mg of desloratadine (mean, 461.91 mm³ [SD, 787.21 mm³]), and 20 mg of desloratadine (mean, 158.16 mm³ [SD, 376.41 mm³]) every day for 7 days. DL, Desloratadine. *** $P \leq .001$.

5 mg of desloratadine was associated with a significantly lower area of affected skin using thermographic analyses compared with that seen after placebo. Patients were significantly less sensitive to cold temperatures and the duration of cold provocation after treatment with 5 mg of desloratadine versus placebo. Importantly, increasing the dose of desloratadine to 20 mg daily, namely 4 times the standard dose, was associated with further benefits to the patient over and above those seen at the standard dose. Twenty milligrams of desloratadine reduced cold-induced wheal volume (primary end point) significantly more than 5 mg of desloratadine and also significantly decreased the temperature and increased time thresholds at which wheals were generated. This latter effect on the urticarial thresholds suggests that the higher desloratadine dose modulated the underlying activity of the patients' ACU. Because ACU is mast cell driven, the increased desloratadine dose might have led to stabilization of

mast cells or downregulation of inflammatory signals, which has been reported previously with desloratadine in the *in vitro* setting.⁸⁻¹⁰

Although the increase in desloratadine dose led to a greater suppression of cold-induced wheals, this was not accompanied by an increase in AEs. This is an important point because the potentially negative effects on cognition/performance at higher doses might not be as well known or thoroughly investigated. In the case of desloratadine, the usual 5 mg every day is associated with a somnolence rate similar to that of placebo; even in studies at very increased doses (45 mg/d for 10 days), increases in self-reported somnolence were not noted.¹¹ Specifically, in the current study fatigue was the only potential treatment-related AE, and this occurred to the same extent (3 patients) in the standard and high-dose desloratadine groups; fatigue was reported by 1 patient during the placebo phase.

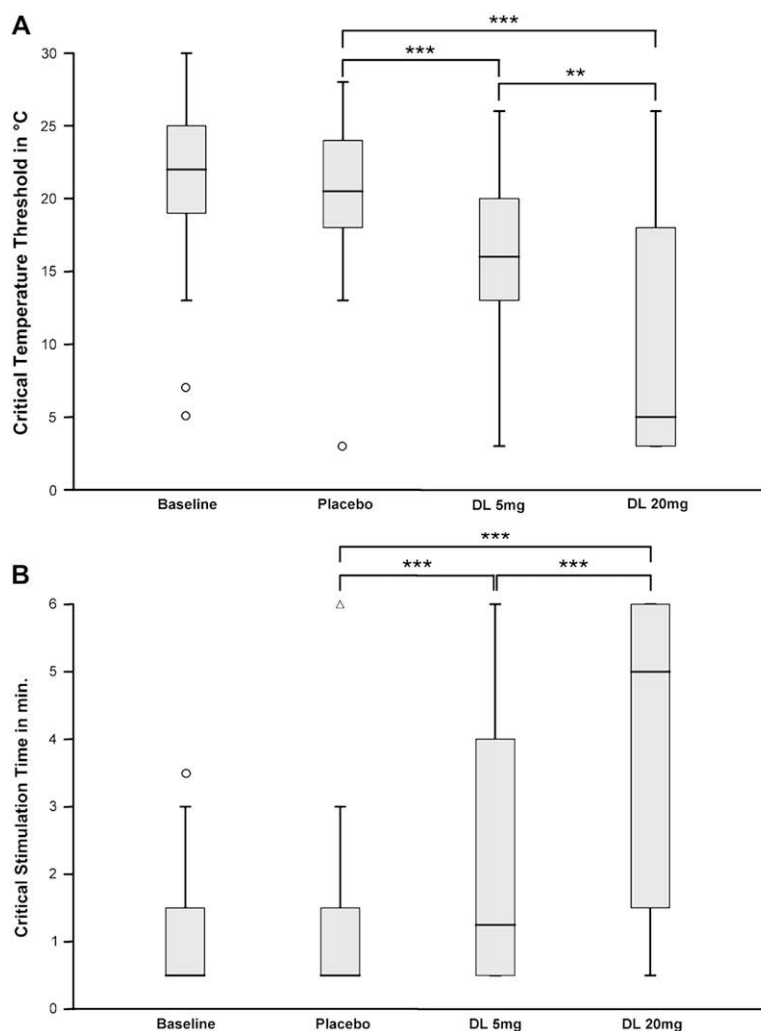


FIG 6. A, Box and whisker plots showing the CTTs elicited by using cold provocation at baseline and after treatment with placebo, 5 mg of desloratadine, and 20 mg of desloratadine every day for 7 days (assessed 10 minutes after provocation). **B,** CSTTs elicited by using cold provocation at baseline and after treatment with placebo, 5 mg of desloratadine, and 20 mg of desloratadine every day for 7 days. Circles within the figures represent outliers, and triangles illustrate extreme values. DL, Desloratadine. ** $P \leq .01$; *** $P \leq .001$ (assessed 10 minutes after provocation).

The question of the appropriate doses of nonsedating antihistamines for patients with ACU who have not responded to standard doses is an open one. This is due primarily to the fact that dose-ranging studies for nonsedating antihistamines during the clinical development phase have almost invariably been performed in subjects with allergic rhinitis. For desloratadine and many other compounds besides, there are few data regarding whether the most effective dose in patients with allergic rhinitis is also the most effective in ACU or other forms of chronic urticaria. Furthermore, although allergic rhinitis has a single pathophysiology (IgE-mediated mast cell degranulation and allergic inflammation), urticaria is a heterogeneous group of conditions that encompasses physical urticaria, chronic spontaneous urticaria, and other disease forms.^{6,7} It is not clear at this time whether the increased efficacy seen with high-dose desloratadine in the setting of ACU in the current study can be translated to patients with chronic spontaneous urticaria. Such a question remains to be studied in well-designed, prospective, randomized, multidose clinical trials, and similarly, the results obtained with desloratadine

cannot be applied to other antihistamines in the absence of similar objective evidence obtained using the same method.

Nonsedating antihistamines have been recommended by the most recent guidelines as the first-line treatment for urticaria.^{6,7} Most studies in the field have been devoted to chronic idiopathic urticaria, and 5 mg/d desloratadine has been studied in 3 multicenter, placebo-controlled trials of 6 weeks' duration in patients with chronic idiopathic urticaria and has been shown to be safe and effective in reducing pruritus and wheal size/number.¹²⁻¹⁴ Desloratadine has also demonstrated improved dermatology-specific quality-of-life measures.¹⁵ Few studies involving second-generation antihistamines have focused on physical urticaria, of which there are many types.^{2,6,7}

One previous study of desloratadine in the treatment of ACU was published by Juhlin.¹⁶ In this study the effect of 5 mg/d desloratadine for 4 days on cold-induced lesions was assessed in 12 patients with ACU. Unlike our study, that study used ice cubes applied directly to the forearm skin to induce wheals, and the times taken to produce less than 4 small wheals, 4 or more small wheals,

and confluent wheals were measured. Juhlin found that, compared with baseline values, desloratadine treatment was associated with a decrease in wheal severity and an increase of the time required to induce wheals among most patients; itching was also decreased. Interestingly, one patient benefited from an increase in desloratadine dose to 10 mg/d.¹⁶ The results of our study confirm and build on Juhlin's findings by demonstrating a significant benefit of higher-dose desloratadine across the full ACU patient population and a clearly demonstrable effect on both the time and temperature thresholds for cold-provoked wheals.

The clinical nature of ACU itself argues for the pursuit of maximal suppression of disease activity. Patients with ACU, particularly those with wheals triggered at relatively increased temperatures, can be at risk of serious complications caused by aquatic activities or ingestion of cold drinks, which might lead to anaphylactic shock or laryngeal edema and airway occlusion. The effect of higher-dose desloratadine further decreasing the CTT and increasing the CSTT above the significant effects seen at the standard desloratadine dose could therefore have clinically protective effects for many patients with ACU.

In conclusion, this is the first prospective placebo-controlled study to demonstrate, using an objective cold challenge apparatus, that 7 days of treatment with desloratadine at doses of 5 and 20 mg daily significantly decreased wheal volume/size and improved CTTs and CSTTs in patients with ACU. Furthermore, treatment with the higher dose of desloratadine was associated with a significant improvement in wheal volume and CTTs and CSTTs over and above those achieved with standard-dose desloratadine. Because use of both desloratadine doses was well tolerated, these results support the clinical utility of considering increased doses of desloratadine in patients with ACU whose symptoms are insufficiently controlled at the standard dose of 5 mg/d.

Clinical implications: In patients with ACU, increased dosing with desloratadine safely provided further objective improvements, including cold-induced 3-dimensional wheal volumes and critical temperature and time thresholds, over those achieved with standard doses.

REFERENCES

1. Siebenhaar F, Weller K, Mlynek A, Magerl M, Altrichter S, Vieira Dos Santos R, et al. Acquired cold urticaria: clinical picture and update on diagnosis and treatment. *Clin Exp Dermatol* 2007;32:241-5.
2. Wanderer AA, Hoffman HM. The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes. *Immunol Allergy Clin North Am* 2004;24:259-86.
3. Neven B, Callebaut I, Prieur AM, Feldmann J, Bodemer C, Lepore L, et al. Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood* 2004;103:2809-15.
4. Siebenhaar F, Staubach P, Metz M, Magerl M, Jung J, Maurer M. Peltier effect-based temperature challenge: an improved method for diagnosing cold urticaria. *J Allergy Clin Immunol* 2004;114:1224-5.
5. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol* 2006;117:1415-8.
6. Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM, et al. EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy* 2006;61:321-31.
7. Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM, et al. EAACI/GA2LEN/EDF guideline: definition, classification and diagnosis of urticaria. *Allergy* 2006;61:316-20.
8. Wang YH, Taché Y, Harris AG, Kreutner W, Daly AF, Wei JY. Desloratadine prevents compound 48/80-induced mast cell degranulation: visualization using a vital fluorescent dye technique. *Allergy* 2005;60:117-24.
9. Lippert U, Krüger-Krasagakes S, Möller A, Kiessling U, Czarnetzki BM. Pharmacological modulation of IL-6 and IL-8 secretion by the H1-antagonist decarboethoxy-loratadine and dexamethasone by human mast and basophilic cell lines. *Exp Dermatol* 1995;4:272-6.
10. Zhao Y, Leung PC, Woo KS, Chen GG, Wong YO, Liu SX, et al. Inhibitory effects of budesonide, desloratadine and dexamethasone on cytokine release from human mast cell line (HMC-1). *Inflamm Res* 2004;53:664-9.
11. Henz BM. The pharmacologic profile of desloratadine: a review. *Allergy* 2001;56(suppl 65):7-13.
12. Ortonne JP, Grob JJ, Auquier P, Dreyfus I. Efficacy and safety of desloratadine in adults with chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, multicenter trial. *Am J Clin Dermatol* 2007;8:37-42.
13. Monroe E, Finn A, Patel P, Guerrero R, Ratner P, Bernstein D, et al. Efficacy and safety of desloratadine 5 mg once daily in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2003;48:535-41.
14. Ring J, Hein R, Gauger A, Bronsky E, Miller B. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Int J Dermatol* 2001;40:72-6.
15. Grob JJ, Auquier P, Dreyfus I, Ortonne JP. Quality of life in adults with chronic idiopathic urticaria receiving desloratadine: a randomized, double-blind, multicenter, placebo-controlled study. *J Eur Acad Dermatol Venereol* 2008;22:87-93.
16. Juhlin L. Inhibition of cold urticaria by desloratadine. *J Dermatolog Treat* 2004;15:51-9.