

Rupatadine and its effects on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticaria

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Background: Patients with acquired cold urticaria (ACU) show itchy wheals during cold exposure. This disturbing condition involves histamine and platelet-activating factor in its pathogenesis. Rupatadine is a dual antagonist of both histamine and platelet-activating factor.

Objective: To assess rupatadine efficacy in preventing reactions to cold challenge in patients with ACU.

Methods: A crossover, randomized, double-blind, placebo-controlled study in which 21 patients with ACU received rupatadine, 20 mg/d, or placebo for 1 week each is presented. The main outcome was the critical stimulation time threshold (CSTT) determined by ice cube challenge. Secondary outcomes included CSTT and the critical temperature threshold assessed by a cold provocation device (TempTest 3.0), as well as scores for wheal reactions, pruritus, burning sensations, and subjective complaints after cold challenge.

Results: After rupatadine treatment, 11 (52%) of 21 patients exhibited a complete response (ie, no urticaria lesions after ice cube provocation). A significant improvement in CSTT compared with placebo was observed after ice cube and TempTest 3.0 challenge ($P = .03$ and $P = .004$, respectively). A significant reduction of critical temperature threshold ($P < .001$) and reduced scores for cold provocation-induced wheal reactions ($P = .01$), pruritus ($P = .005$), burning sensation ($P = .03$), and subjective complaints ($P = .03$) after rupatadine treatment were also found. Mild fatigue ($n = 4$), somnolence ($n = 1$), and moderate headache ($n = 1$) were reported during active treatment.

Conclusion: Rupatadine, 20 mg/d, shows high efficacy and is well tolerated in the treatment of ACU symptoms.

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INTRODUCTION

Acquired cold urticaria (ACU) is characterized by the immediate appearance of itchy wheals and angioedema in response to cold exposure or cooling of the skin.^{1–4} Patients with ACU are at risk of systemic symptoms and even life-threatening complications^{2,3,5,6} and, therefore, must be advised against

exposing large skin areas to cold (eg, by swimming in cold water).^{1,4,6} Acquired cold urticaria also has important occupational and employment implications.⁷ Acquired cold urticaria is rather evenly distributed by sex (55% women) and age (mean [SD] age, 41 ± 16 years), at least in the Berlin, Germany, population, according to the only scientific epidemiologic study available.⁸ Diagnosis is made on the basis of the history and cold challenge test results.^{1–4,9} Acquired cold urticaria often lasts for several years^{1,3,8} and can have a substantial impact on patients' quality of life, necessitating effective treatment.³ As with all physical urticarias, avoidance of the triggering factor (cooling of the skin) is a basic part of managing ACU.^{2,3} In most patients, ACU is idiopathic.^{1,2,10} Its pathogenesis remains mostly unclear, but it is known that mast cell degranulation releases histamine and other mediators, thus causing the wheal-and-flare reaction.^{2,3,6,10}

Platelet-activating factor (PAF)¹¹ is a mediator implicated in many inflammatory conditions, including ACU. The intradermal injection of PAF leads to a dose-dependent, biphasic, wheal-and-flare response.¹² Platelet-activating factor triggers the binding of neutrophils to endothelial cells, which may be part of an inflammatory response.¹³ A classic experimental study¹⁴ showed an association between PAF and edema in patients with ACU.

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Rupatadine (J. Uriach & Co, SA, Barcelona, Spain) is a new molecule with dual-affinity binding for both histamine H₁ and PAF receptors, with anti-inflammatory properties as well.^{15–17} The pharmacologic parameters of rupatadine¹⁸ and the safety profile at high doses were reviewed in detail previously.^{19–21} Rupatadine is indicated for the treatment of allergic rhinitis²² and chronic urticaria.^{23,24}

The present study assesses the efficacy of 20 mg of rupatadine compared with placebo for effects on wheal trigger thresholds (stimulation time and temperature) and protection from ACU symptom development using conventional (ice cube testing) and novel and more accurate cold provocation techniques.

METHODS

Study Design

The study was designed as a randomized, double-blind, cross-over, placebo-controlled study of efficacy and safety of rupatadine, 20 mg, vs placebo, administered once daily for 7 days in patients who had ACU. Rupatadine in a 20-mg dose has been demonstrated to be significantly better than that in a 10-mg dose for reducing chronic urticaria symptoms²³ and improving life quality in such patients.²⁴

Patients enrolled were scheduled to start the study 2 weeks after the initial enrollment screening. At the next visit (day 0), all baseline assessments were made and the patient received his or her first set of pills. Patients took the first assigned treatment daily for 1 week (days 1–7) and then underwent the outcome evaluation for that treatment (day 7). There was then a 2-week washout period (days 8–21) and a study visit (day 21). A 14-day washout period between treatments guarantees an anti-H₁ blanching period for those patients who were initially actively treated. Patients then took the second assigned treatment daily for 1 week (days 22–28) and then underwent the outcome evaluation for that treatment (day 28). Two weeks later (day 42), a final discharge study visit occurred to evaluate any possible adverse events. Compliance was monitored by counting the returned unused tablets.

The study protocol was approved by the institutional review boards of both participating study centers. After proper elucidation, each patient provided written informed consent to participate in the study. The study was conducted in compliance with the Declaration of Helsinki and applicable local and European laws and regulations.

Patient Enrollment

The baseline severity of the ACU symptoms was determined using the Acquired Cold Urticaria Severity Index (ACUSI).²⁵ The ACUSI is composed of 4 questions regarding the severity of ACU, resulting in a score ranging from 4 to 15. Scores of 4 to 7, 8 to 11, and 12 to 15 points indicate low, middle, and high ACU severity, respectively.

The main inclusion criterion was ACU of more than 6 weeks' duration, confirmed at a screening visit by a positive ice cube test result. 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. A history of hypersensitivity or an allergic reaction to rupatadine or any other antihistamine compounds was also excluded. Washout periods before the beginning of the study were 7 days for antihistamines or leukotriene antagonists, 14 days for oral corticosteroids, and 21 days for depot corticosteroids and long-term systemic corticosteroids.

Outcome Measures

The main outcome was the critical stimulation time threshold (CSTT) after a standard ice cube challenge.^{1,4} Four melting ice cubes with a contact surface area of 80 mm² were placed on the patients' volar forearm and then removed one by one at 0.5, 2.0, 3.5, and 5.0 minutes. Ten minutes after all ice cubes were removed, the resulting wheals were scored on a scale of 0 to 5, where 0 indicates no wheal; 1, numerous small noncoalescent wheals; 2, a large, regular, slightly edematous coalescent wheal; 3, a large and moderately edematous wheal; 4, a large, regular, significantly edematous wheal without pseudopodia; and 5, a large, very edematous wheal with pseudopodia.²⁶ The lowest of the 4 time points (0.5, 2.0, 3.5, and 5.0 minutes) at which a wheal scored as 2 or higher was chosen as the CSTT. If the patient showed no wheal rated as 2 or higher from the 5-minute ice cube 10 minutes after its removal, the test outcome was coded as negative and a CSTT of 6 minutes was documented.

Secondary outcome measures are also reported as follows. First, the CSTT was evaluated with an instrument (TempTest 3.0; Emosystems, Berlin, Germany)^{3,9,25,27} at baseline and at the end of each treatment phase exposing the skin to 4°C for 0.1, 0.3, 0.5, 0.7, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, and 5.0 minutes. Second, critical temperature thresholds (CTTs) were evaluated at baseline and at the end of each treatment phase using the same test set at 2°C intervals from 4°C to 26°C. The device's 12 cold probes were placed on the patient's stomach beneath the navel, and the patient was challenged for 5 minutes. Fifteen minutes later, the resulting wheals were evaluated with the same scale as previously described (ie, 0 to 5). The highest temperature at which a wheal reaction scored as 2 or higher was observed was recorded as the CTT. In patients who did not develop a score 2 wheal at the lowest temperature tested (4°C), the CTT was documented as 3°C. Third, whealing reactions to 5-minute ice cube testing were scored as above (0–5) by the treating physician. Patients rated itch, burning, and subjective complaints as follows: 0, absent; 1, mild; 2, moderate; and 3, severe. During the follow-up visits, the patients were explicitly asked if they had experienced any adverse events.

Data Analysis

Data entry was performed independently by 2 separate people, and any inconsistencies were audited. Analyses of efficacy parameters were performed in the per-protocol population, which included all patients who completed the study. Demographic variables and baseline clinical characteristics are presented de-

scriptively. Comparisons between the treatment sequences for baseline characteristics were analyzed using the Mann-Whitney test for continuous variables and χ^2 or Fisher exact tests for categorical variables. Nonparametric methods based on ranks were used in the statistical analysis of the 2-period crossover outcome. The appropriate nonparametric rank tests were applied to evaluate the presence of carryover, period, and treatment effects for all primary and secondary efficacy variables. Because no carryover effect was observed, a Wilcoxon rank sum test was performed to analyze the treatment effect. Safety data are presented descriptively. All statistical analyses were performed using computer software (SAS 9.1.2; SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Characteristics

Twenty-four participants were drawn from the outpatient population of the Department of Dermatology and Allergy, Allergie-Centrum-Charité-Universitätsmedizin, Berlin, Ger-

many, and from the Department of Dermatology, Hospital del Mar, Universitat Autònoma, Barcelona, Spain. Three patients did not meet all the inclusion criteria. The remaining 21 patients (16 women; mean [SD] age, 41.1 [13.9] years) presented an ACU disease activity as evaluated by using ACUSI ranging from mild (3 patients [14%]) to moderate (14 patients [67%]) to severe (4 patients [19%]). The recruitment period was completed from October to December 2008. All 21 patients were compliant for both treatments. No patients reported use of any of the medications listed in the exclusion criteria during the study.

Rupatadine Improves ACU Thresholds

Rupatadine treatment, 20 mg, markedly improved CSTTs as evaluated by ice cube testing (Fig 1A and B). Specifically, rupatadine, 20 mg, increased the shortest time of ice cube application sufficient to induce a large, regular, slightly edematous coalescent wheal by a median of 1.5 minutes compared with a median increase of 0 minutes with placebo

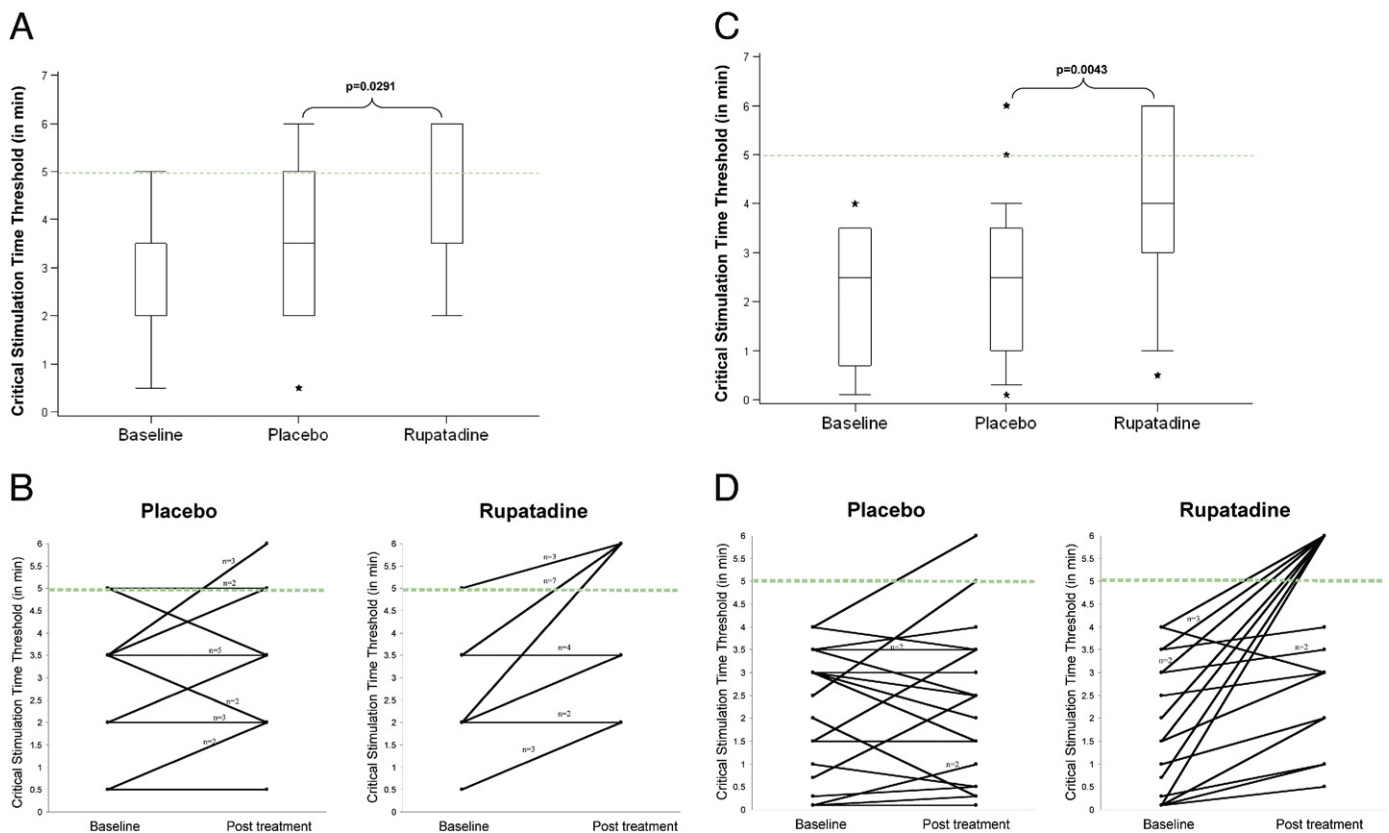


Figure 1. Rupatadine improves stimulation time thresholds in patients with acquired cold urticaria. The critical stimulation time thresholds (CSTTs) were evaluated by the ice cube test (A and B) and the TempTest 3.0 (C and D) before (baseline) and after treatment with placebo or rupatadine, 20 mg, for 7 days. A and C, The solid line inside the box indicates the median; the lower end of the box, the 25th percentile score; the upper end of the box, the 75th percentile score; the lower whisker line, the 10th percentile score; and the upper whisker line, the 90th percentile score. Data points that are outside this percentile range are represented with asterisks. B and D, Changes of CSTTs in individual patients. The broken line represents the maximum stimulation time used (ie, 5 minutes). In those patients who did not show a positive reaction to cold stimulation for this stimulation time, CSTTs were recorded as 6 minutes.

($P = .03$) (Fig 1A). After rupatadine treatment, 11 (52%) of the patients showed a complete response (ie, no wheal development) after 5-minute ice cube exposure compared with only 3 (14%) of the placebo-treated patients (Fig 1B).

Critical stimulation time thresholds were also markedly improved after treatment with rupatadine, 20 mg, using a commercially available instrument (TempTest 3.0) (Fig 1C and D). Critical stimulation time thresholds increased by 1.9 and 0 minutes after rupatadine, 20 mg, and placebo treatment, respectively ($P = .004$) (Fig 1C). Significantly more patients showed complete protection from wheal development induced by the 5-minute test challenge (TempTest 3.0) after rupatadine, 20 mg, treatment (10 patients [48%]) than placebo treatment (1 patient [5%]).

Rupatadine, 20 mg/d, significantly reduced CTTs as evaluated by the instrument (TempTest 3.0) (by 8°C in median), whereas placebo treatment did not (change vs baseline, 0°C in median; $P < .001$) (Fig 2A and B). Of the 21 patients, 11 (52%) treated with rupatadine, 20 mg, but only 1 (5%) treated with placebo showed complete protection (ie, no induction of urticaria) when challenged with the instrument (TempTest 3.0) at the coldest temperature tested (4°C).

Rupatadine Reduces ACU Symptoms

When we evaluated the size and characteristics of wheal reactions to a 5-minute 4°C ice cube provocation before and after treatment, we found that rupatadine, 20 mg, prevented whealing and reduced the size and score value of wheals, whereas placebo treatment did not ($P = .01$) (Fig 3). Also, rupatadine, 20 mg, treatment significantly reduced the ACU symptoms of pruritus and burning as well as the overall subjective complaints after cold challenge, compared with placebo treatment (Fig 4). Notably, pruritus and subjective complaints, which were present in virtually all patients after the baseline cold challenge, became absent in two thirds of rupatadine-treated patients, but only in 14% of placebo-treated patients (pruritus, $P = .005$; subjective complaints, $P = .03$). Burning, which was less frequently reported after the baseline challenge, was unchanged after placebo treatment, whereas 86% of rupatadine-treated patients reported its absence after cold provocation ($P = .03$).

Safety Evaluation

Adverse events were reported in both the placebo group ($n = 2$) and the rupatadine group ($n = 6$). These included fatigue (rupatadine group, $n = 4$), headache (placebo group, $n = 2$; rupatadine group, $n = 1$), and somnolence (rupatadine group, $n = 1$). All adverse events resolved spontaneously, and no patient withdrew from the study because of them. No serious adverse events occurred during the treatment phase of the study.

DISCUSSION

This study shows that rupatadine, 20 mg/d, is effective and safe in the management of patients with ACU. Rupatadine markedly improved ACU thresholds (ie, critical time and temperature) and symptoms. Most notably, rupatadine treat-

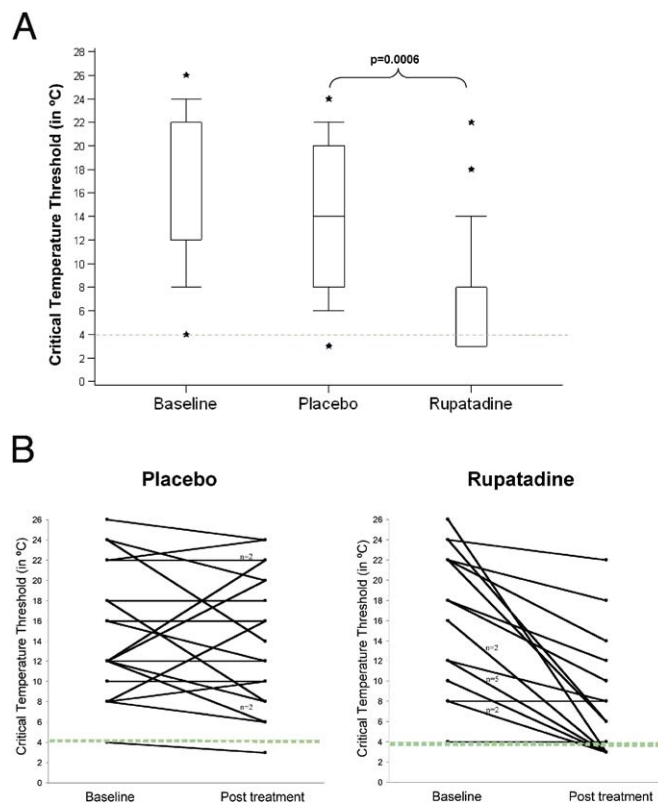


Figure 2. Rupatadine improves temperature thresholds in patients with acquired cold urticaria. Critical temperature thresholds (CTTs) were evaluated by TempTest 3.0 testing before (baseline) and after treatment with placebo or rupatadine, 20 mg, for 7 days. A, The solid line inside the box indicates the median; the lower end of the box, the 25th percentile score; the upper end of the box, the 75th percentile score; the lower whisker line, the 10th percentile score; and the upper whisker line, the 90th percentile score. Data points that are outside this percentile range are represented with asterisks. B, Changes of CTTs in individual patients. The broken line represents the lowest temperature used for stimulation (ie, 4°C). In those patients who did not show a positive reaction to cold stimulation at this temperature, CTTs were recorded as 3°C.

ment resulted in complete protection from cold-induced urticaria symptoms in more than half of all treated patients.

A daily dose of 20 mg of rupatadine was used based on our previous experience with the drug in treating chronic spontaneous urticaria. Although 10 mg could also be effective in patients with ACU, 20 mg of rupatadine has been demonstrated to be significantly better in reducing chronic urticaria symptoms²² and improving life quality, as evaluated by the Dermatology Life Quality Index in these patients.²³ The responder rates from the pooled data for these 2 previous studies^{22,23} showed that rupatadine, 20 mg/d, significantly reduced the “mean pruritus score” and the “urticaria activity score” in the 75% responder patients vs rupatadine, 10 mg/d.²⁶ The need to increase anti-H₁ doses for effectively controlling symptoms in patients with ACU has previously been shown by Siebenhaar et al.²⁵

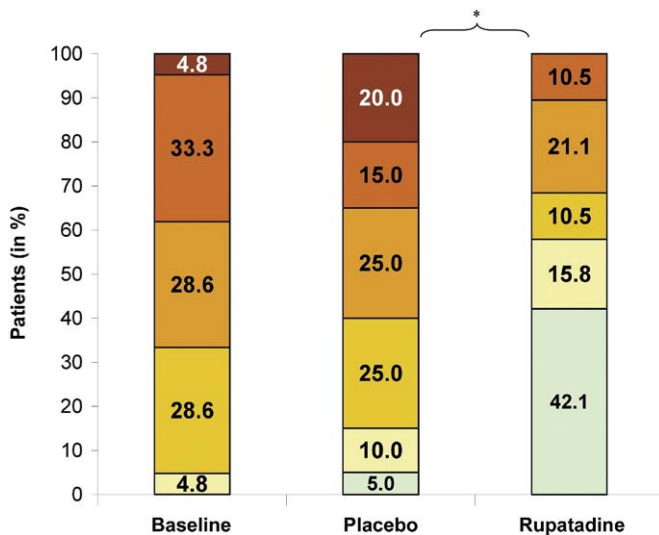


Figure 3. Rupatadine treatment protects from cold-induced wheal responses. Wheal responses to 5-minute ice cube tests performed before and after treatment with placebo or rupatadine, 20 mg, for 7 days were evaluated using the following score: 0, no wheal; 1, numerous small noncoalescent wheals; 2, a large, regular, slightly edematous coalescent wheal; 3, a large and moderately edematous wheal; 4, a large, regular, significantly edematous wheal without pseudopodia; and 5, a large, very edematous wheal with pseudopodia. The percentage of patients for each score value is given inside the corresponding bar segment. The asterisk indicates $P < .05$.

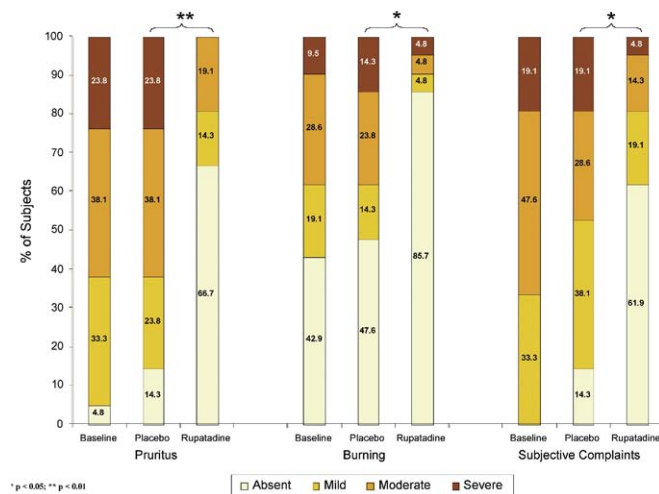


Figure 4. Rupatadine treatment protects from cold-induced pruritus, burning, and subjective complaints. The presence and intensity of pruritus, burning, and subjective complaints after a 5-minute ice cube test performed before or after treatment with placebo or rupatadine, 20 mg, for 7 days were scored as absent, mild, moderate, or severe. The percentage of patients is given inside the corresponding bar segment. The asterisk indicates $P < .05$; double asterisk, $P < .01$.

A significant improvement of the CSTT with rupatadine has been demonstrated using the standardized cold provocation test (ie, the ice cube test). This significant improvement

was also accurately evaluated with the recent version of a Peltier element-based cold provocation device (TempTest 3.0).⁹ This tool allowed us to also define in each individual patient the baseline of the critical temperature sufficient to induce a wheal (ie, CTT) and to evaluate the reduction of the CTT after active treatment. An accurate measurement of CTTs in both study centers was demonstrated.

The ACU prognosis and behavior in the daily life of each patient can be different depending on environmental factors. The diagnostic provocation test and the effective threshold assessments allow for a standardization of the evaluation of the efficacy of a treatment. Based on these observations, we can recommend the use of this device (TempTest 3.0) for further controlled trials. This test also appears to be ideally suited to implement the recommendation of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) guidelines,²⁷ and a recent position paper on the classification and diagnosis of physical urticarias,²⁸ in which threshold testing in all patients with ACU (eg, to monitor the activity and course of ACU and the response to treatment) is suggested.

Our results confirm that nonsedating second-generation antihistamines are effective in the treatment of ACU,²⁹ which supports the recent EAACI/GA²LEN/EDF/WAO guidelines on the management of urticaria recommendation to use second-generation antihistamines as the first-line treatment for patients with ACU.²⁷ Although older antihistamines have also been demonstrated to be helpful in cold urticaria management, the efficacy and safety profile of the second-generation antihistamines supports them as first-choice drugs.³⁰

As of yet, we cannot directly compare the efficacy of rupatadine with that of other second-generation antihistamines shown to be protective in patients with ACU. Previous studies with other nonsedating antihistamines in patients with ACU differ from our present trial in patient characteristics (including severity and duration of diseases), the cold provocation techniques used, and/or the efficacy parameters reported. A direct comparison of the efficacy and safety of rupatadine and other second-generation antihistamines would require a head-to-head comparison using the same efficacy readout (eg, reduction in CTTs or CSTTs) in the same patient population. However, looking only at complete responder rates, patients with ACU show similar responses when treated with rupatadine, 20 mg, or other nonsedating antihistamines, such as cetirizine, ebastine, or desloratadine. In our trial, 11 (52%) of 21 patients treated with rupatadine were complete responders. Previously, 5 of 12 patients with ACU were shown to no longer develop a wheal reaction to a 12-minute ice cube challenge 4 hours after a single 10-mg dose of cetirizine,³¹ and similar results were reported for a case series of 12 pediatric patients with ACU demonstrating that 7 of them were treated successfully with cetirizine.³² A well-designed, double-blind, crossover trial of 22 patients with ACU found that 20 mg of ebastine prevented a wheal reaction

after a 5-minute 4°C ice pack challenge in 18 patients in the ebastine arm compared with only 5 in the placebo arm.³³ Recently, a double-blind, crossover, placebo-controlled study involving 30 patients with ACU found that 5 and 20 mg of desloratadine (4 times the standard dose) provided complete protection in 7 and 15 patients, respectively.²⁵ Taken together, rupatadine, 20 mg (twice the standard dose), and other second-generation antihistamines at high doses can provide complete control of cold-induced symptoms in at least half of the treated patients with ACU.

The hypothesis that the efficacy of rupatadine in ACU treatment could be explained by its dual action on H₁ and PAF receptors needs to be confirmed, and experimental studies are required.³⁴ Both histamine and PAF have been shown to importantly contribute to the induction of ACU symptoms.¹⁴ Interestingly, PAF is involved mainly in the chemotaxis of neutrophils and eosinophils,³⁵ and it promotes binding of neutrophils to endothelial cells.¹³ Platelet-activating factor can also stimulate further histamine release from mast cells.³⁶ It would be interesting to clarify the exact role of blocking PAF receptor-mediated responses in the prevention of symptoms in patients with ACU or other inducible types of urticaria. Controlled trials comparing an H₁ antihistamine with rupatadine (H₁ antihistamine and PAF antagonist) in the same patients should be performed to address this question.

The results of this study with rupatadine cannot be extrapolated to other nonsedating antihistamines. Although we expect all nonsedating antihistamines to work well in patients with ACU because of the prominent role of H₁ receptor activation in the pathogenesis of the disease, different second-generation antihistamines exhibit different efficacy and safety profiles when used by patients with urticaria, especially when used in higher than standard doses.

In this study, rupatadine, 20 mg/d, improved exposure time thresholds, critical temperature thresholds, and symptom control compared with placebo treatment. Taken together, treatment with rupatadine, 20 mg/d, should be effective and well tolerated in the management of patients with ACU in their daily lives.

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