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INVESTIGATIVE REPORT

# Rupatadine 20 mg and 40 mg are Effective in Reducing the Symptoms of Chronic Cold Urticaria

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**Chronic cold urticaria (ColdU) is a rare disease characterized by mast cell-mediated wheals and angioedema following cold exposure. Second-generation $H_1$-antihistamines, such as rupatadine, are the recommended first-line therapy. As of yet, the effects of rupatadine up-dosing on development of ColdU symptom have only been partially characterized. Two-centre, randomized, double-blind, 3-way crossover, placebo-controlled study in patients with a confirmed ColdU was designed to assess the effects of up-dosing of rupatadine. A total of 23 patients were randomized to receive placebo, rupatadine 20 mg/day, and rupatadine 40 mg/day for 1 week. The primary outcome was change in critical temperature thresholds and critical stimulation time thresholds after treatment. Secondary endpoints included assessment of safety and tolerability of rupatadine. Both 20 and 40 mg rupatadine were highly effective in reducing critical temperature thresholds ($p<0.001$) and critical stimulation time thresholds ($p<0.001$). In conclusion, rupatadine 20 and 40 mg significantly reduced the development of chronic cold urticaria symptom without an increase in adverse effects.** ***Key words: rupatadine; chronic cold urticarial; $H_1$-antihistamine; up-dosing.***

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Chronic cold urticaria (ColdU) is a rare, but severe and potentially life-threatening, form of chronic physical urticaria in which, in addition to urticarial wheals, angioedema and anaphylaxis may also occur after ingestion of cold foods or extended exposure to cold (1). However, patients exhibit a wide variability in terms of the risk of systemic symptoms and even life-threatening complications when untreated or undertreated. It is essential, therefore, to be able to predict the potential risk that each individual patient faces and how this may be ameliorated by therapy (2).

To assist with the diagnosis of ColdU, guidelines published by EAACI/GA²LEN/EDF/WAO[1] recommend provocation testing by applying a cold stimulus to the skin, usually the volar forearm. Traditionally, this has been done by applying an ice cube to the skin or testing with cool packs or cold-water baths (3, 4). However, while these techniques assist in diagnosis, they do not provide information about temperature and stimulation time thresholds at which patients will start to develop symptoms. This knowledge is essential in order to establish disease severity and monitor the effectiveness of treatment. The critical temperature threshold (CTT) at which a patient starts to develop symptoms may be determined by using TempTest® 3.0, a Peltier effect-based electronic device for simultaneous provocation of 12 discrete 10 $mm^2$ areas of the skin, with temperatures ranging from 4°C to 26°C and an accuracy of <2°C (5). Alternatively, the critical stimulation time threshold (CsTT) may be evaluated by exposing the skin to 4°C and assessing the development of wheals at 30-s intervals from 0.5 to 5 min.

The first-line therapy in ColdU recommended by the current EAACI/GA²LEN/EDF/WAO guidelines is symptomatic relief with second-generation H1-antihistamines. If standard doses are not effective the guidelines recommend increasing the dosage up to 4-fold in order to better control the symptoms (6). Recent data have shown that the use of high doses of second-generation antihistamines is significantly more effective in ColdU than standard dose treatment (7–9).

Rupatadine is a potent second-generation antihistamine approved for the treatment of the symptoms of allergic rhino-conjunctivitis and urticaria that has also been shown to possess anti-platelet-activating factor (PAF) activity (10, 11). Clinical trials in allergic rhini-

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tis and chronic urticaria have shown rupatadine to be well tolerated and free from untoward cardiovascular, cognitive or psychomotor effects (12, 13), all important properties for a drug to be used in higher doses.

The aim of this study was to assess the efficacy of 2-fold and 4-fold dose increments from the licensed dose of rupatadine against the development of symptoms of ColdU following provocation with TempTest® 3.0. The outcome measures were changes in CTT and CsTT.

## MATERIALS AND METHODS (see Appendix S1[2])

## RESULTS

The effects of rupatadine vs. placebo were tested in a 3-way crossover, double-blind trial (Fig. 1). Although 24 patients were enrolled in the study, one dropped out for personal reasons unrelated to the study drug. Consequently, data analysis has been performed on the remaining 23 patients. The estimation of CsTT on 40 mg rupatadine was lost for one patient due to a technical error.

### *Effect of rupatadine on critical temperature thresholds*

Fig. 2a shows the CTTs for patients having taken placebo, rupatadine 20 mg or rupatadine 40 mg for one week. The median CTT for the production of wheals for the placebo group was 14°C (range < 4°C to 24°C). The median CTT for rupatadine 20 mg and 40 mg were 10°C (range < 4°C to 24°C) and 4°C (range < 4°C to 24°C), respectively. Both of these median values were significantly ($p < 0.001$) lower than that of placebo. There was no significant difference between drug doses.

Responder analysis (Fig. 2b) shows that 7/23 (30%) and 11/22 (50%) patients were wheal-free on provocation following treatment with 20 and 40 mg rupatadine, respectively, after one week of treatment. Adding partial responders as well (patients whose CTT decreased by ≥4°C) showed responder rates of 17/23 (74%) and 18/22 (81%) for treatment with 20 and 40 mg rupatadine, respectively.

### *Effect of rupatadine on critical stimulation time thresholds*

Fig. 3a shows the CsTTs for patients having taken placebo, rupatadine 20 mg or rupatadine 40 mg for one week. The median CsTT for the production of wheals for the placebo group was 1.5 (1–>5) min. The median CsTT for rupatadine 20 and 40 mg were 3.0 (1–>5) and 5.0 (1–>5) min, respectively. Both of these median values were significantly ($p < 0.001$) greater than that of placebo. There was no significant difference between drug doses.

Responder analysis (Fig. 3b) shows that 9/23 (39%) and 11/22 (50%) patients were symptom-free on provocation following treatment with 20 and 40 mg rupatadine, respectively. Adding partial responders (patients whose CsTT increased by ≥0.5 min), showed responder rates of 15/23 (65%) and 18/22 (81%) for treatment with 20 and 40 mg rupatadine, respectively.

### *Safety assessments*

A total of 25 adverse events (AEs) were reported and distributed by treatment groups as follows: placebo ($n = 7$), rupatadine 20 mg ($n = 7$) and rupatadine 40 mg ($n = 11$). The distribution of the number of patients with at least one AE was not statistically different between treatment groups. Only one patient reported somnolence related with 40 mg dose. Few patients reported headache (2 cases with placebo, 1 with 20 mg, and 1 with 40 mg rupatadine). Other AEs, included tiredness (1 case with placebo and 2 with 40 mg), cold (2 cases with placebo, 2 with 20 mg, 1 with 40 mg) and 1 increase in liver enzymes with 40 mg. No electrocardiography (ECG) changes were seen. All of these AEs were not considered to be drug-related. All AEs resolved spontaneously and no patients withdrew from the study because of them. One serious AE (thoracic vertebra fracture) occurred in one patient during the treatment with rupatadine 40 mg, for which the patient was hospitalized and recovered. This AE was considered as not related to the study drug.

## DISCUSSION

This trial has confirmed previous studies (2, 9, 16) where rupatadine improved clinical symptoms in ColdU with doses of 20 mg and shows how also 40 mg daily for one week is highly significant compared with placebo in reducing wheal formation following cold provocation. Furthermore, the safety profile of the drug appeared excellent at both doses.

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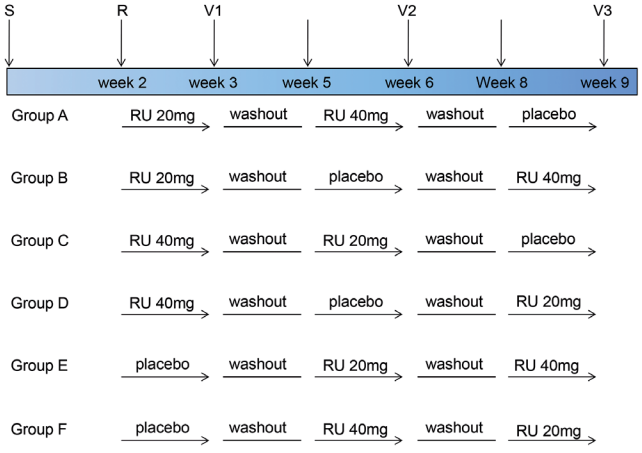


*Fig. 1.* Study design. RU: rupatadine; S: screening visit; R: randomization visit; V1, V2 and V3: visit at which critical temperature and stimulation time thresholds were determined and safety was evaluated.

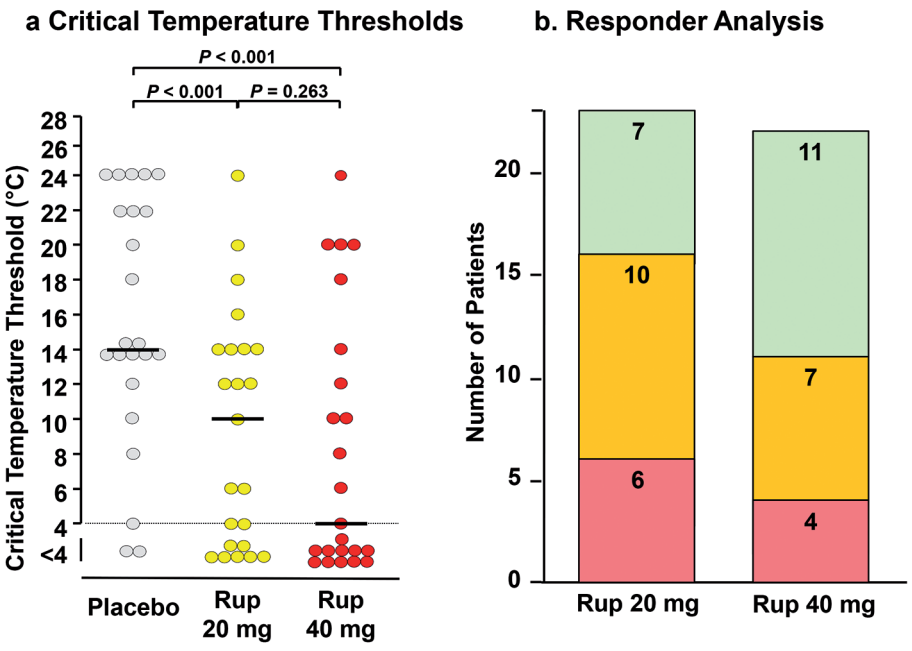


*Fig. 2.* (a) Critical temperature thresholds (CTTs) for the production of wheals following cold provocation. Horizontal lines indicate medians. The levels of significance values are for differences in the median CTTs calculated using Wilcoxon non-parametric test. (b) Rupatadine treatment protects from cold-induced wheal responses. Considering the CTT response assessed after each treatment period all patients were divided into 3 groups: complete responders (no evidence of a whealing response at 4°C, *green column*), partial responders (reduction in CTT ≥ 4°C, *orange column*) and non-responders (reduction in CTT less than 4°C, *pink column*).

This study measured provocation thresholds by 2 methods, assessment of the temperature threshold for whealing and the time taken for provocation at 4°C to induce wheals. Analysis by Spearman's rank correlation analysis showed these methods to be highly correlated ($p < 0.001$) in all treatment groups. Furthermore, the observation that treatment with 20 mg rupatadine resulted in 9/23 (39%) patients being symptom-free is not significantly different from the 11/21 (52%) symptom-free patients reported by Metz et al. (9) using an ice cube test for provocation.

The lower dose of 20 mg rupatadine was chosen because of its demonstrated greater effectiveness than the 10 mg dose in reducing chronic urticaria symptoms (13) and the effectiveness of this dose in 3 previous ColdU studies (2, 9, 16). This dose also afforded highly significant protection in this study. While not statistically significant, there were more patients partially and completely symptom-free following treatment with 40 mg rupatadine.

Three patients (13%) of 23 did not show clinical improvement on up-dosing of rupatadine. These observations are consistent with other antihistamines, such as desloratadine (4/15 non-responders) (17), rupatadine (3/21 non-responders) (9) and bilastine (1/20 non-responder) (8). While the reasons for this are not known,

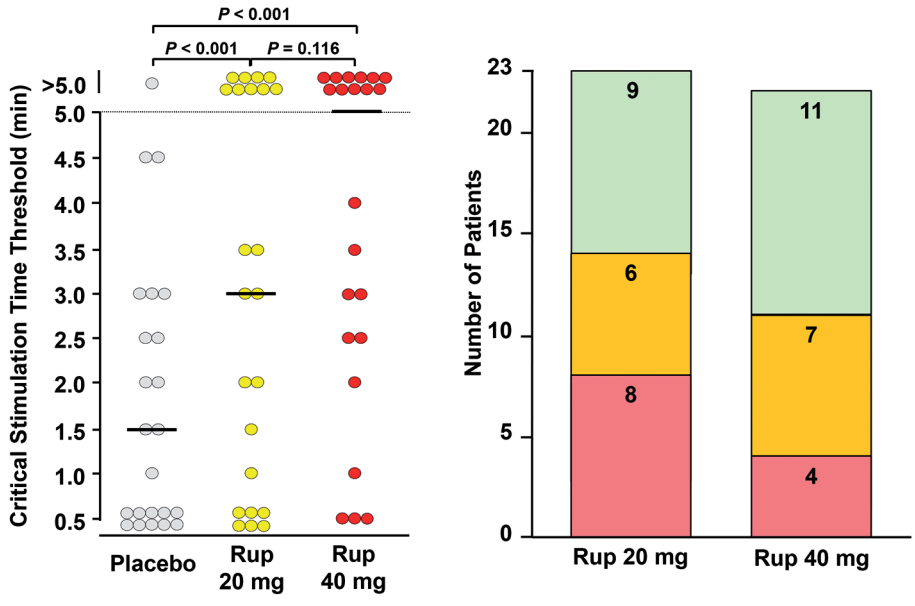


*Fig. 3.* (a) Critical stimulation time threshold (CsTTs) for the production of wheals following cold provocation. Horizontal lines indicate medians. The levels of significance values are for differences in the median CsTTs calculated using Wilcoxon non-parametric test. (b) Considering the CsTT response assessed after each treatment period all patients were divided into 3 groups: complete responders (no evidence of a whealing response after 5 min provocation with 4°C, *green column*), partial responders (reduction in CsTT ≥ 0.5 min, *orange column*) and non-responders (reduction in CsTT < 0.5 min, *pink column*).

it suggests that, as in other forms of urticaria (6), there is a subgroup ColdU patients who do not respond to H1-antihistamines. Further studies are needed to better characterize these patients.

In conclusion, this study has contributed importantly to our understanding of the use of $H_1$-antihistamines in ColdU. As we have shown, rupatadine is highly effective in reducing the symptoms of ColdU. Increasing the dose to 20 and 40 mg daily appears to increase effectiveness of the drug without showing increased sedation or an increase in other unwanted effects.

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*Conflicts of interest*. ES and II are employed by R&D department of J. Uriach & Co., S.A. The authors declare no other conflicts of interest.

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