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Article accepted on 22/12/2006

Once-daily rupatadine improves the symptoms of chronic idiopathic urticaria: a randomised, double-blind, placebo-controlled study

This randomised, double-blind, placebo-controlled, parallel-group, international, dose-ranging study investigated the effect of treatment with rupatadine 5, 10 and 20 mg once daily for 4 weeks on symptoms and interference with daily activities and sleep in 12-65 years-old patients with moderate-to-severe chronic idiopathic urticaria (CIU). Rupatadine 10 and 20 mg significantly reduced pruritus severity by 62.05% and 71.87% respectively, from baseline, over a period of 4 weeks compared to reduction with placebo by 46.59% ($p < 0.05$). Linear trends were noted for reductions in mean number of wheals and interference with daily activities and sleep with rupatadine 10 and 20 mg over the 4-week treatment period. The two most frequently reported AEs were somnolence (2.90% for placebo, 4.29% for 5 mg-, 5.41% for 10 mg- and 21.43% for 20 mg-rupatadine-treated group) and headache (4.35% for placebo, 2.86% for 5 mg-, 4.05% for 10 mg- and 4.29% for 20 mg-rupatadine-treated group). These findings suggest that rupatadine 10 and 20 mg is a fast-acting, efficacious and safe treatment for the management of patients with moderate-to-severe CIU. Rupatadine decreased pruritus severity, in a dose- and time-dependent manner.

Key words: Chronic idiopathic urticaria, H₁ antihistamine, PAF antagonist, pruritus, rupatadine, wheals

Chronic idiopathic urticaria (CIU) is a debilitating disease which is characterised by daily, or almost daily, occurrence of wheals and pruritus, often accompanied by angioedema, for more than 6 weeks, with no obvious aetiology [1, 2]. The wheals and pruritus, which are not only physiologically bothersome but potentially stigmatizing due to their very public nature, cause disruption of sleep and daily activities and fatigue and loss of energy, resulting in decreased quality of life (QoL) for affected individuals [3, 4]. While CIU is estimated to affect between 0.1-3% of the population in Europe and the USA and account for nearly 75% of all cases of chronic urticaria [1, 5], it is thought that the world-wide lifelong prevalence for CIU is 0.5% and does not vary greatly across different populations [1]. Although it is often not possible to identify the specific cause of CIU, an increasing amount of evidence suggests that the symptoms of CIU such as oedema, erythema and pruritus are primarily elicited as a consequence of histamine released from activated dermal mast cells and basophils binding to the H₁ receptors [6]. This has consequently advocated the use of oral H₁ receptor antagonists (H₁ antihistamines) as the mainstay and only drugs licensed for therapeutic intervention for CIU [3, 6].

Rupatadine is a novel selective and long-acting (24 hour) histamine H₁ receptor and platelet-activating factor (PAF) receptor antagonist, which binds with a higher affinity to the H₁ receptor than fexofenadine and levocetirizine [7], and has a long duration (24 hours) of action, as indicated by prolonged inhibition of histamine and PAF-induced wheal

and/or flare skin reactions in healthy volunteers [8]. A recent study in patients with seasonal allergic rhinitis treated with rupatadine 10 mg showed that rupatadine also has a fast onset of action since allergen-induced nasal and non-nasal symptoms were significantly decreased within 15 minutes of exposure to allergen, compared with placebo [9]. Indeed, several randomised double-blind, multicenter studies have demonstrated that rupatadine 10 mg and 20 mg once daily is highly efficacious in attenuating the symptoms of rhinitis in adult and adolescent patients with moderate-to-severe seasonal allergic rhinitis [10-12] and perennial allergic rhinitis [8]. Rupatadine is currently approved in several European countries for the symptomatic treatment of seasonal and perennial allergic rhinitis at a daily recommended dose of 10 mg [13].

To date there is no information of the efficacy of rupatadine in the treatment of symptoms of CIU. The aims of this dose-ranging study were therefore to assess the clinical efficacy and safety of rupatadine in the improvement of symptoms and interference with daily activities and sleep in patients with CIU.

Materials and methods

Patients

Male and female patients, aged 12 to 65 years, with a documented history of clinical manifestations of CIU (urti-

carial wheals) with or without angioedema for at least three days per week over the last 6 weeks were recruited into the study, mainly during November 2003. All patients had pruritus symptom scores ≥ 2 (*i.e.* moderate symptoms classified as annoying or troublesome) for at least 3 days in the week before inclusion. At randomisation to treatment, none had been receiving specific H_1 -receptor antagonists for 3-10 days, H_2 -receptor antagonists for 2-7 days, leukotriene antagonists for 4 days, corticosteroids for 7 days and tricyclic antidepressants for 30 days for their CIU. Patients with physical urticaria (due to cold, heat, and/or sun), cholinergic urticaria, and urticaria due to any known aetiology (*e.g.* medication, insect bites, food, etc) were excluded as were patients taking any potential inhibitors of the cytochrome P450 isozyme CYP3A4.

Study design

This was a phase II dose-ranging, randomised, double-blind, placebo-controlled, parallel-group trial, conducted across France, Argentina, Hungary and Romania. Following screening, eligible patients were randomised to receive treatment with either placebo, rupatadine 5 mg, rupatadine 10 mg or rupatadine 20 mg, as a single tablet once daily for 28 days and provided with patient diaries at the start of treatment (visit 1). All patients were subsequently assessed for symptoms, efficacy of treatment, adverse events (AEs), concomitant medication and compliance after 14 days (visit 2) and 28 days (visit 3) treatment. The study protocol and the patients' informed consent were approved by local ethics committees/review boards and the study was performed in accordance with general principles of Good Clinical Practice and The Declaration of Helsinki, as amended in Edinburgh, 2000.

Evaluation of efficacy

Efficacy was assessed on the basis of change from baseline in i) mean pruritus severity (MPS) score, ii) mean number of wheals (MNW) score, iii) mean of total symptoms score (MTSS; calculated as the sum of MPS and MNW), iv) mean interference with daily activities score and v) mean interference with sleep score over the 4-week treatment period. The change from baseline in MPS was investigated as the primary outcome measure and all remaining variables as secondary outcome measures.

Patients recorded their symptoms of pruritus and the number of wheals in daily diary cards in the morning and at bedtime and scored the severity of pruritus symptoms and the number of wheals on a 5-point scale of 0-4 (*for severity of pruritus*: 0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying or troublesome; 3 = severe, very annoying, substantially interfering with sleep/daily activities; 4 = very severe warranting physician visit; *for number of wheals*: 0 = no wheals; 1 = 1 to 5; 2 = 6 to 15; 3 = 16 to 25; 4 = >25).

After 14 and 28 days treatment, the investigator and the patient additionally made a global assessment of efficacy on the basis of change in symptom severity from pre-study, scored on a 5-point scale from 0-4 (0 = worse than at pre-study, 1 = no change, 2 = slight improvement, 3 = good improvement).

Patients also assessed the impact of disease on the extent of interference with daily activities and interference with sleep by scoring on a 4-point scale of 0-3 (0 = none; 1 = mild; 2 = moderate; 3 = severe).

Evaluation of safety

Safety and tolerability of treatment was evaluated according to the incidence and type of AEs recorded in the patients' diaries, results of routine laboratory tests (haematology, blood chemistry and urinalysis) and clinical examinations, before and at the end of the treatment period. All AEs were coded using the MedDRA V5 dictionary, and grouped by treatment.

Statistical analysis

A sample size of 248 patients was calculated to detect, with 80% power and at the 5% significance, a difference > 0.5 units in the primary efficacy variable, assuming a standard deviation of 0.9 and dropouts of 20%. Differences in MPS, MNW, MTSS, global assessment of efficacy, interference with daily activities, and interference with sleep scores, between the treatments groups over the 4-week treatment period were analysed using ANOVA. The significance of any differences in these variables was assessed by pair-wise treatment comparison using the Fisher's protected Least Significance Difference (LSD) test. Treatment-emergent AEs were compared by Chi-square test to check for intolerance to higher doses. All statistical tests were performed using the SAS[®] software version 8.2 for Windows (SAS Institute Inc, Cary, NC, USA). Analysis of all efficacy parameters was carried out on intent-to-treat (ITT) basis, which included data sets of all randomised patients who received any study drug, and for whom at least one post-baseline value was available, independent of the degree of adherence to the protocol. Analysis of safety included data from all randomised patients who received any study drug.

Results

A total of 283 patients were randomised to treatment, of whom data from 277 (69 treated with placebo; 68 with rupatadine 5 mg; 73 with rupatadine 10 mg; 67 with rupatadine 20 mg) were analysed. Overall 244 completed the study according to protocol and 39 patients withdrew from the study. Of the withdrawing patients, 25 (10 in placebo group; 9 in rupatadine 5 mg group; 3 in rupatadine 10 mg group, and 3 in rupatadine 20 mg group) withdrew due to ineffective treatment, 1 due to an AE, 2 due to incorrect treatment allocation, and 11 for other or personal reasons. The demographic and clinical characteristics of the patients are shown in *table 1*. All treatment groups were similar with respect to mean age, the male to female ratio, symptoms scores and impairments in daily activity and sleep at inclusion.

Efficacy outcome measures

Change in mean pruritus score (MPS)

Over the 4-week treatment period, rupatadine 10 and 20 mg significantly reduced the MPS from baseline by 1.52 ($p < 0.05$) and 1.83 ($p < 0.001$), respectively, compared to reduction of 1.14 with placebo, reflecting significant reductions in pruritus severity of 62.7% and 72.3%, respectively, compared with 45.8% with placebo (*figure 1*). Although rupatadine 5 mg reduced the MPS by 1.31 from baseline (a

Table 1. Demographic and baseline clinical characteristics of patients in the intent-to-treat-population

	Placebo (n = 69)	Rupatadine 5 mg (n = 68)	Rupatadine 10 mg (n = 73)	Rupatadine 20 mg (n = 67)	Total (n = 277)
Age (y) mean $\pm$ SD	36.91 $\pm$ 13.44	39.31 $\pm$ 13.55	39.77 $\pm$ 11.78	36.45 $\pm$ 13.00	38.14 $\pm$ 12.96
% Female	78.26	72.06	75.34	65.67	72.92
%Caucasian	97.10	95.59	95.89	97.10	96.39
Pruritus severity score (mean $\pm$ SD)	2.49 $\pm$ 0.52	2.52 $\pm$ 0.52	2.54 $\pm$ 0.52	2.52 $\pm$ 0.53	2.49 $\pm$ 0.52
Number of wheals (mean $\pm$ SD)	2.06 $\pm$ 1.04	1.84 $\pm$ 1.07	1.95 $\pm$ 1.14	1.93 $\pm$ 1.05	1.94 $\pm$ 1.08
Interference with sleep score (mean $\pm$ SD)	1.03 $\pm$ 1.00	0.94 $\pm$ 0.93	1.11 $\pm$ 1.06	0.99 $\pm$ 0.95	1.02 $\pm$ 0.98
Interference with daily activities score (mean $\pm$ SD)	1.42 $\pm$ 1.03	1.24 $\pm$ 0.96	1.34 $\pm$ 1.07	1.33 $\pm$ 0.98	1.33 $\pm$ 1.01

reduction of 51.6%), this was not significant compared to placebo. The treatment effect of rupatadine 20 mg over the 4 week period was significantly greater compared with rupatadine 5 mg ($p < 0.001$) and rupatadine 10 mg ($p < 0.05$) (figure 1). Exploratory analyses of the time-dependent effect of rupatadine showed that rupatadine 10 mg and 20 mg progressively improved the MPS from week one onward of treatment, with rupatadine 20 mg providing significant improvements during each week

throughout the entire study, compared with placebo (table 2). Similarly, rupatadine 10 mg significantly improved the MPS for all weeks except for week 2, compared with placebo.

Rupatadine decreased pruritus severity in a dose- and time-dependent manner. Linear trend analysis showed that the trend in decreased severity was significant over the entire 4-week treatment period and all time points investigated ($p < 0.0001$ at all time points and periods).

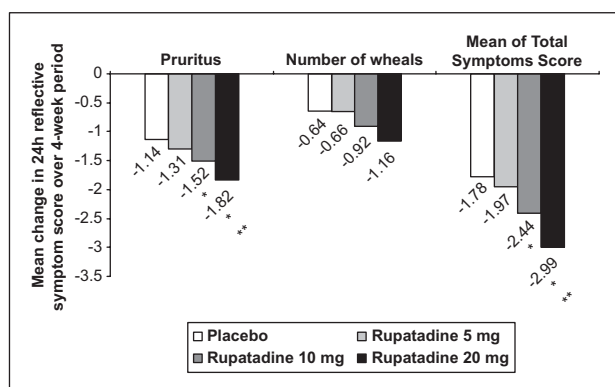


Figure 1. Effect of treatment on mean pruritus severity (MPS) score over 4-weeks treatment for all treatment groups (* $p < 0.05$ vs. placebo; ** $p < 0.001$ Rupatadine 20 mg vs. Rupatadine 5 mg).

Change in mean number of wheals (MNW)

After 4 weeks treatment, the scores for MNW were decreased from baseline by 0.64 (30.1%) for placebo, 0.66 (34.3%) for rupatadine 5 mg, 0.92 (45.2%) for rupatadine 10 mg, and 1.16 (57.8%) for rupatadine 20 mg (figure 1). The comparison between groups was not statistically significant. However, there was a tendency for a time-dependent effect of rupatadine, because assessment of changes at different time points demonstrated a linear trend for suppression of wheal at week 3 and week 4, with significant suppression in MNW by about 60% in patients treated with rupatadine 20 mg, compared with placebo ($p < 0.01$).

Change in mean total symptoms score (MTSS)

Assessment of the MTSS indicated that this was significantly reduced from baseline by 2.44 (54.8%; $p < 0.05$) and 2.99 (65.9%; $p < 0.001$) over the 4-week study period in

Table 2. Effect of treatment time on pruritus severity over the course of the study for all treatment groups

Treatment period	Mean % change in 24 hour reflective pruritus score in patients treated with			
	Placebo	Rupatadine 5 mg	Rupatadine 10 mg	Rupatadine 20 mg
Week 1	- 38.33	- 49.17*	- 55.07*	- 63.59 ^{†§¶}
Week 2	- 51.69	- 51.29	- 64.46	- 74.58 ^{†§¶}
Week 3	- 48.18	- 51.88	- 65.48*	- 75.46 ^{†§}
Week 4	- 44.96	- 53.40	- 65.72*	- 74.65 ^{†§}
Day 1 to day 14	- 45.01	- 0.23	- 59.77 [‡]	- 69.09 ^{†§¶}
Day 1 to day 21	- 46.07	- 50.78	- 61.67*	- 71.21 ^{†§¶}
4 weeks	- 45.83	- 51.56	- 62.74*	- 72.32 ^{†§¶}

* $p < 0.05$ vs placebo, [‡] $p < 0.005$ vs placebo, [†] $p < 0.0001$ vs placebo; [§] $p < 0.01$ Rupatadine 20 mg vs Rupatadine 5 mg; $p < 0.05$ Rupatadine 20 mg vs Rupatadine 10 mg.

patients treated with rupatadine 10 mg and 20 mg, respectively, compared with a reduction of 1.78 (38.6%) in placebo-treated patients (*figure 1*). Although rupatadine 5 mg reduced the MTSS by 1.97 (44.1%) from baseline over the 4-week period, this reduction was not significant compared with placebo. The effect of treatment with rupatadine 20 mg on MTSS over the 4 weeks, was also shown to be significantly greater than for rupatadine 5 mg ($p < 0.01$) (*figure 1*). Assessment of the time-dependent effects of rupatadine on MTSS demonstrated that there was a significant linear trend in the reduction of MTSS at all times in patients treated with rupatadine 20 mg ($p < 0.005$ at all time points). Similarly, a significant trend for a reduction in the MTSS by around 58% was noted in patients treated with rupatadine 10 mg during weeks 3 and 4 of treatment ($p < 0.05$ at both time points), compared with placebo.

Global assessment of efficacy

Figure 2 demonstrates the overall efficacy of treatment as assessed by the investigators and the patients over the 4-week treatment period. Approximately 20-30% of the investigators assessed symptom severity to be worse or unchanged from pre-study levels in patients treated with placebo, compared with between 5-15% of investigators who assessed it to be worse or unchanged in patients treated

with any dose of rupatadine investigated (*figure 2A*). In contrast, a significantly greater number of between 13-50% of the investigators assessed the symptom severity to be improved from pre-study with any dose of rupatadine investigated, compared with between 10-22% who assessed it to be improved with placebo ($p < 0.005$ vs rupatadine 5 mg and $p < 0.001$ vs rupatadine 10 mg and 20 mg) (*figure 2A*). Indeed, 40-50% of the investigators assessed symptom severity to be greatly improved in patients treated with rupatadine 10 mg and 20 mg, while only about 6% assessed symptoms to be worse in these treatment groups.

The patients' assessment of the global efficacy of treatment followed very similar trends, with only 5-14% of patients treated with rupatadine assessing symptom severity to be worse or unchanged from pre-study levels compared 21-28% of placebo-treated patients (*figure 2B*). Similarly, a significantly greater number of patients (13-48%) treated with any dose of rupatadine assessed symptom severity to be improved from pre-study, compared with placebo-treated patients (10-25%; $p < 0.005$ vs rupatadine 5 mg and $p < 0.001$ vs rupatadine 10 mg and 20 mg) (*figure 2B*).

The global improvement in efficacy was accompanied by clear trends in dose-dependent reductions in daily activities and sleep scores with rupatadine, although the reductions were not significantly different over the 4-weeks, compared with placebo. Linear trend analysis showed significant trends in the 10 and 20-mg treated groups compared to placebo in the reduction of daily activities over the entire 4-week treatment period and at all time points investigated ($p < 0.05$ at all time points and periods). Similarly, a trend in the 10 and 20-mg groups was observed in the reduction of sleep interference over week 3 ($p < 0.05$) and week 4 ($p < 0.05$) of treatment, but not over the entire 4-week treatment period.

Safety evaluation

A total of 214 AEs were reported during the study, of which 95 were considered to be treatment related. The two most frequently reported AEs were somnolence (2.90% for placebo, 4.29% for 5 mg-, 5.41% for 10 mg- and 21.43% for 20 mg-rupatadine-treated group) and headache (4.35% for placebo, 2.86% for 5 mg-, 4.05% for 10 mg- and 4.29% for 20 mg-rupatadine-treated group). The only reported SAE was an asymptomatic and transient increase in serum creatine kinase (CPK) at the end of the study (visit 3) in the 5-mg treatment group. The patient performed fitness sessions twice a week. One week follow-up after the study finalization showed that the patient was asymptomatic and had normal serum CPK and ECG, and neither muscular nor chest pains.

No clinically relevant AEs of rupatadine were observed on vital signs.

Overall, there were no differences between the incidence or the type of any other AEs noted in any of the rupatadine-treated groups and the placebo-treated group, and all AEs were resolved completely.

Discussion

Rupatadine 10 mg and 20 mg significantly decreased the severity of pruritus over 4-weeks treatment, the primary

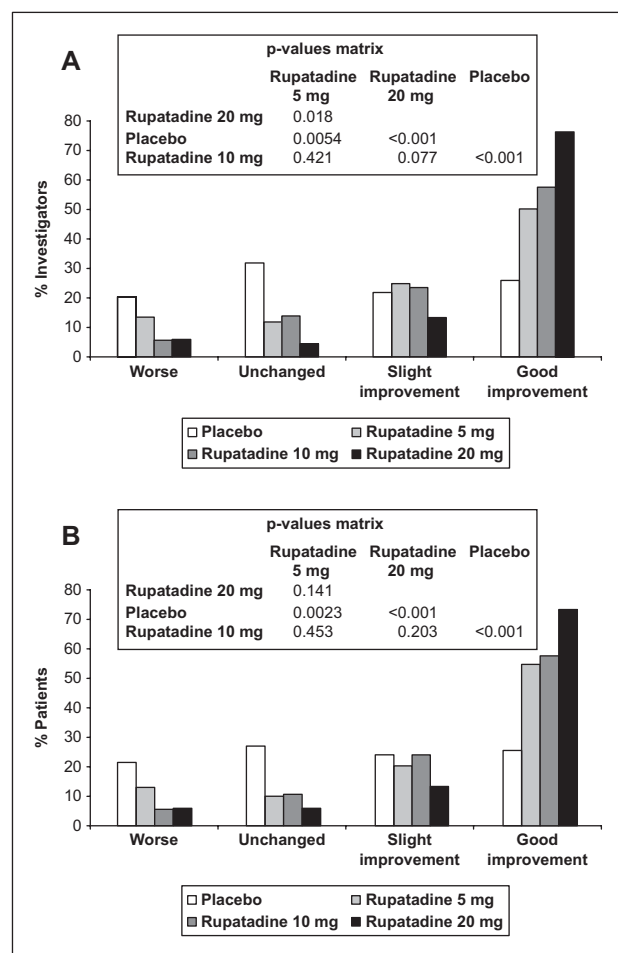


Figure 2. Investigator's (A) and patients' (B) global assessment of efficacy after 4 weeks for all treatment groups.

outcome measure of the study, by 62.7% and 72.3%, respectively, compared with 45.8% with placebo. Similarly, treatment for 4 weeks with rupatadine 10 mg and 20 mg significantly reduced the mean total symptom score from baseline by 54.8% ($p < 0.05$) and 65.9% ($p < 0.001$), compared with 38.6% with placebo, and additionally showed linear trends in wheal suppression. The pruritus severity reducing effect of rupatadine was significant from the first week of treatment and progressive over the entire study period, with increased reductions in pruritus severity being noted after each week of treatment.

A blinded global assessment of the overall efficacy of treatment showed that about 50% of the investigators and patients judged the symptoms of CIU to be greatly improved with rupatadine 10 mg and 20 mg, compared with a much small number of between 5-15% who assessed the symptoms to be either improved with placebo or to be worse from pre-study levels in rupatadine-treated patients. Indeed, the greater improvements in symptoms and overall global efficacy of rupatadine were reflected by linear trends in larger reductions in interference with daily activities and sleep, compared with placebo-treated patients. The present study also demonstrated that treatment with rupatadine 5-20 mg was well tolerated in patients with moderate-to-severe CIU.

Collectively, these results suggest that there is a linear relationship between the treatment dose and the main efficacy variable, with constant dose rises producing constant decreases in pruritus scores and that a therapeutic dose from 20- and 10 mg once daily is likely to provide fast onset of action with long-lasting improvements in both the symptoms and quality of life indices in patients with moderate-to-severe CIU.

There was a clear symptom reduction in patients under rupatadine 20 mg over time.

While several studies have shown rupatadine 10 mg once daily to be efficacious for the symptomatic treatment of moderate-to-severe allergic rhinitis [10-12] and perennial allergic rhinitis [7], this is the first study to investigate the effect of rupatadine in patients with CIU. The findings of the present study, however, are in accordance with the findings of the few documented studies that have investigated the effect of treatment in CIU and shown also fexofenadine [14, 15] and desloratadine [16, 17] to be more effective than placebo in reducing both the symptoms of CIU and interference with daily activities and sleep. One study demonstrated that, although mizolastine and cetirizine were also significantly more effective than placebo in decreasing the severity of pruritus, the effects of these agents were significant after 2 weeks treatment [18]. Whilst this difference in the onset of action noted for rupatadine and mizolastine/loratadine may possibly be explained on the basis of differences in pruritus severity scales employed in the two studies (5-point scale for rupatadine *versus* 0-100 mm visual analogue scale (VAS) for mizolastine and loratadine), it is possible that the comparatively faster onset of action (within one week) noted for rupatadine may actually be a consequence of a potentially greater anti-inflammatory effect resulting from its dual activity as a H_1 - and PAF-receptor antagonist [19]. This is particularly so in view of evidence that histamine and PAF have complementary activities *in vivo* and each mediator may promote the release of the other from different tissues and cells [20, 21]. While animal studies have suggested that PAF may possi-

bly the most potent mediator inducing cutaneous vascular leakage [22], studies investigating the effects of intradermal injections of PAF in human skin have shown that this mediator causes vasodilatation and increased vascular permeability, producing a wheal and flare response with accompanying pruritus [23, 24]. A comparison of the wheal and flare response induced by PAF and histamine has shown that PAF leads to opening of endothelial gaps and extravasation of predominantly neutrophils, suggesting that the inflammatory response to these agents is different [24]. Despite the availability of information from mechanistic studies, and the large body of evidence for the role of PAF in allergic airway diseases, there is a marked paucity of information regarding the effect of this mediator in chronic urticaria. One early study documented that cold-induced urticaria was associated with the release of histamine, PAF and neutrophilic chemotactic activity (NCA) in patients with cold-urticaria, and that suppression of urticaria with doxepin in these patients correlated only with inhibition of PAF release [25]. The data from these studies collectively suggest that blockade by rupatadine of the complementary activities of histamine and PAF, is likely to lead to an overall greater inhibitory effect of these mediators than that of the individual mediators. This in turn would manifest clinically as fast and long lasting improvements in symptoms of CIU that are of greater magnitude with rupatadine, compared with H_1 antihistamines that do not demonstrate such additional anti-PAF activity. This hypothesis, however, needs to be confirmed in well-controlled trials directly comparing the effects of rupatadine with other antihistamines in CIU patients.

It is important to mention that in this study we found a high treatment response in the placebo group and this efficacy increased over time, leading to a progressive decrease in the difference between the active treatments and the placebo group. In the same way, other studies with second generation anti-histamines have reported similar placebo response rate [14, 17]. Psychological factors seem to be frequently associated with CIU and assuming that MPS is a subjective variable evaluated from the patient's perspective, a relative high response in the placebo group should be expected.

Despite the accordance of our findings for rupatadine and other H_1 antihistamines in reducing symptoms and interference with daily activities and sleep in patients with moderate-to-severe CIU, our study is somewhat limited in that the effect of rupatadine was evaluated on a weekly basis, rather than on a daily basis in the first week of treatment, and therefore does not allow a more accurate evaluation of the onset of effect of rupatadine in this study population cohort. Although measurement of interference with daily activities and sleep were not the primary outcome measures, our study is also slightly limited in this respect, because it does not provide more details of the impact of CIU on the quality of life of patients. However, the Dermatology Life Quality Index (DLQI) [26, 27] was used in a recently completed phase III study investigating the effect of rupatadine in moderate-to-severe CIU patients. This study demonstrated that rupatadine 10 mg and 20 mg significantly decreased the DLQI scores in these patients, compared with placebo, with greatest improvements noted for daily activities and symptoms/feelings [28].

Conclusion

The current dose-finding study provides important information with respect to use of rupatadine as a novel treatment option for CIU. The study clearly shows that rupatadine 10 mg and 20 mg provides rapid and long-lasting relief from pruritus, possibly the most bothersome symptom of CIU, in affected individuals. Importantly, from the patient's perspective, rupatadine appears to be a highly efficacious therapy that alleviates the symptoms of their disease and the interference in daily activities and sleep, associated with these symptoms. In particular, the information on the effect of rupatadine on interference with sleep is important because sleep problems have been shown to be associated with impaired QoL in chronic illnesses such as clinical depression, congestive heart failure, diabetes, asthma, hypertension, back problems and arthritis [29]. In view of the dual antagonism of the H₁ and PAF receptors, rupatadine 10 mg is likely to be equally, or possibly more, effective than some of the currently available treatments and therefore indicated for the management of patients with CIU. ■

Acknowledgements. The authors thank J.Uriach y Compañía (Barcelona, Spain) for financial support for this study. This study was partially supported by the National Scientific Research Program of the Spanish Minister of Science and Technology.

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