Original article

Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study

**Background:** Chronic urticaria is one of the most common and disturbing cutaneous condition. The treatment of chronic idiopathic urticaria (CIU) is still a challenge. Antihistamines are recommended as first-line treatment. Rupatadine is a new potent non-sedative anti-H1.

**Objective:** To study rupatadine efficacy and safety for moderate to severe CIU treatment.

**Methods:** This randomized, double-blind, placebo-controlled, parallel-group, multicentre, study was designed to assess primarily mean pruritus score (MPS) reduction with rupatadine, 10 and 20 mg, administered once daily for 4 weeks. Three hundred and thirty-three patients with active episodes of moderate-to-severe CIU were included.

**Results:** A 57.5% \((P < 0.005)\) and 63.3% \((P = 0.0001)\) significative MPS reduction from baseline, was observed at week 4 with 10 and 20 mg rupatadine, respectively, compared with placebo (44.9%). Both doses of rupatadine were not significantly different at any time point, with respect to their effects on pruritus severity, number of wheals and total symptoms scores. Rupatadine 10 mg had an overall better adverse event profile.

**Conclusion:** Rupatadine 10 mg is a fast, long-acting, efficacious and safe treatment option for the management of patients with moderate-to-severe CIU.

---

Chronic urticaria is defined by spontaneous wheals lasting more than 6 weeks (1). Conventionally, if any apparent aetiology was considered, chronic urticaria was categorized as idiopathic. Chronic idiopathic urticaria (CIU) is a relatively common skin condition with a 0.5% worldwide lifelong prevalence across different populations, affecting between 0.1% and 3% people in Europe and the USA (1). Some studies show CIU accounts for nearly 75% of all cases of chronic urticaria (2). Besides being severely debilitating and disfiguring, CIU may also be potentially stigmatizing. CIU get worse the Quality of Life (QoL), primarily as a result of sleep disruption, energy loss, fatigue, social isolation and emotional/sexual disturbances (3). This condition follows a chronic course with spontaneous remission and relapses for several years (4). Chronic urticaria aetiology is often unknown (1).

There is increasing evidence for basophil- and mast cell-mediated inflammation in urticaria and angio-oedema. Histamine and other mast cell mediators [including eicosanoids, cytokines, proteases, kinins and platelet activating factor (PAF)] are involved in wheal development (1, 4). Because the symptoms of CIU, including oedema, erythema and pruritus, are primarily associated with histamine release from dermal mast cells, oral H1-receptor inverse agonists (H1 antihistamines) are the treatment of choice (4, 5).

Among specific pathological chronic urticaria triggers some pathogenic mechanisms have been suggested. In up to 50% of patients the disease could be explained by an

---

**Abbreviations:** AE, adverse event; ANOVA, analysis of variance; CIU, chronic idiopathic urticaria; DLQI, Dermatology Life Quality Index; ECG, electrocardiograph; ITT, intent-to-treat; LOCF, Last Observation Carried Forward; MedDRA, Medical Dictionary for Regulatory Activities; MNW, mean number of wheals; MPS, mean pruritus score; MTSS, mean total symptoms score; OR, odds ratio; PAF, platelet activating factor; QoL, quality of life; SAE, Serious adverse event; VAS, visual analogue scale.
underlying autoimmune mechanism involving antihigh-
affinity immunoglobulin (Ig) E receptor antibodies or less
frequently, anti-IgE antibodies. The importance of these
autoantibodies is now widely recognized (6). The associ-
ation between thyroid autoimmunity and chronic urtic-
aria has long been recognized as significant in spite of the
pathogenic mechanism is still unknown. Recently, throm-
bin generation has been suggested as relevant cause of
mast cell activation but further studies are needed (7).

A recently published International Consensus guideline
on the management of urticaria has recommended
nonsedating H1 antihistamines as first-line treatment for
chronic urticaria (8).

There is evidence that PAF and histamine have
mutually complementary activities in vivo. Each mediator
is able to promote the release of the other by different
tissues and cells (9, 10). Dual blockade of these mediators
is likely to be a more effective treatment strategy for CIU.

Rupatadine is a novel selective long-acting histamine
H1-receptor inverse agonist (H1 antihistamine), which is
currently approved as a once daily dose of 10 mg, for the
treatment of allergic rhinitis (11). Rupatadine has recently
been shown to have a higher affinity for the H1-receptor
than fexofenadine and levocetirizine (12). Although some
antihistamines have shown PAF antagonist properties
(13), these effects cannot be attributed to specific inter-
actions with PAF receptors. Rupatadine has shown both
antihistamine and anti-PAF effects through its interaction
with specific receptors and not due to physiological
antagonism (11). Studies in seasonal allergic rhinitis with
patients exposed to allergen in a controlled exposure
chamber showed that rupatadine 10 mg compared with
placebo has a fast onset of action, as indicated by
significant decrease of allergen-induced nasal and non-
nasal symptoms within 15 min of exposure to allergen
(14). Several randomized double-blind, multicentre stud-
ies demonstrated that rupatadine 10 and 20 mg once daily
are highly efficacious attenuating the symptoms of rhinitis
in adult and adolescent patients with moderate-to-severe
allergic rhinitis (15–17).

A previous dose-ranging study demonstrated that
rupatadine 10 and 20 mg once daily for 4 weeks signifi-
cantly decreased the severity of pruritus, the number of
wheals and the total symptom score in patients with CIU,
compared with placebo (18). Furthermore, both doses
investigated were well tolerated and safe, with no untoward cardiac effects.

The aim of the present study was to assess efficacy and
safety on CIU symptoms treatment and patients QoL
improvement with rupatadine, 10 and 20 mg.

Methods and materials

Patients

Male and female patients, aged 12–65 years, with a
minimum 6-week history of CIU and experiencing an
active flare (score ≥2 labelled as moderate pruritus) for at
least 3 days/week, were recruited from a total of 26
centres across Argentina, Germany, Italy, Poland,
Romania and Spain, during November 2004 to July
2005. Each patient had an ECG within normal limits, and
women of child-bearing potential tested negative for
pregnancy, at the time of inclusion. Patients receiving
systemic or topical medication, including specific H1-
receptor antagonists for at least 7 days, H2-receptor
antagonists for at least 7 days, corticosteroids for
28 days, leukotriene antagonists for 4 days and tricyclic
antidepressants for 30 days prior to inclusion were
excluded. Patients taking potential inhibitors of the
cytochrome P450 isozyme CYP3A4 were also excluded. Other exclusion criteria were acute urticaria, physical
urticaria (cholinergic, cold/heat pressure, etc.) and chro-
nic urticaria associated with some underlying disease (e.g.
Hodgkin’s disease, vasculitis, lupus erythematosus, hepati-
tis).

Study design

This was a multicentre, double-blind, randomized, pla-
cebo-controlled, parallel-group study involving five
scheduled visits. Eligible patients with a pruritus score
of ≥2 for at least three of the last 7 days were randomized
to receive either a tablet of rupatadine 10 mg, rupatadine
20 mg or placebo once daily for 6 weeks, according to a
centralized computer-generated randomization code pro-
vided by the sponsor of the study (J Uriach y Compañía,
S.A., Barcelona, Spain).

Patients’ diary cards were collected for assessment of
adverse events (AEs) and concomitant medication use,
and compliance with treatment was assessed by collecting
and counting the remaining tablets. Additionally, the
patients were provided with new diary cards and a further
20 days’ supply of study medication, and assessed for
symptom severity, overall efficacy, QoL and general
discomfort at these visits. At the end of treatment, all
patients underwent physical examination and were
assessed for ECG and blood parameters. Female patients
were assessed for pregnancy.

All patients gave written informed consent to partici-
pate in the study, which was approved by local ethics
committees/review boards of the participating centres and
performed in accordance with general principles of Good
Clinical Practice and the Declaration of Helsinki, as

Evaluation of efficacy

Efficacy was evaluated using several outcome measures.
The change from baseline in mean pruritus score (MPS)
over the 4-week treatment period was investigated as the
primary outcome measure. The change from baseline in
mean number of wheals (MNW) score, the mean of total
symptoms score (MTSS; calculated as the sum of MPS

and MNW), Dermatology Life Quality Index (DLQI; a measure of QoL) and visual analogue scale (VAS), over the 4- and 6-week treatment periods were additionally investigated as secondary outcomes. Overall efficacy was also assessed as a secondary outcome after treatment for 2, 4 and 6 weeks. An additional responder analysis for the MPS variable was conducted in order to quantify the patient’s symptoms improvement.

Pruritus severity and the number of wheals were recorded by patients in daily diary cards in the morning and at bedtime. The severity of pruritus was assessed by scoring on a 5-point scale of 0–4 with 0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying or troublesome; 3 = severe, very annoying, substantially interfering with sleep/daily activities and 4 = very severe warranting doctor visit. Similarly, the number of wheals were also scored on a 5-point scale with 0, no wheal; 1, 1–5; 2, 6–15; 3, 16–25; 4, ≥25.

The QoL of the patients was assessed using the validated self-administered DLQI (19, 20). All patients completed the DLQI by scoring each question on a 4-point scale ranging from 0 (‘not at all’) to 3 (‘very much’). Questions answered as ‘not relevant’ or unanswered were scored as 0 and in cases where two or more questions were left unanswered the questionnaire was not scored. The scores for all questions were summed and expressed as a percentage of the maximum possible score of 30, to calculate the DLQI. A high DLQI was taken to be an indicator of greater impairment in the QoL.

Global discomfort was assessed using a VAS between 0 and 100 mm, with 0 representing ‘no discomfort’ and 100 representing ‘extreme discomfort’. Patients rated their discomfort by marking along a 0–100 mm long horizontal line.

Global efficacy was assessed by the investigator at visits 1, 2 and 3 by scoring on a 5-point scale from 0 to 4 (0 = worse, 1 = no change, 2 = slight improvement, 3 = good improvement, 4 = excellent improvement), based on change in symptom severity from prestudy (visit 0).

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), clinical and physical examinations and ECG, before and at the end of the treatment period. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) V5 dictionary.

Statistical analysis

This study was powered on the basis of a preceding phase II dose-finding study, which compared the effect of treatment with rupatadine 5, 10 and 20 mg once daily for 4 weeks, vs placebo, on MPS as the primary outcome measure (18). Assuming a standard deviation of 0.95 and allowing for a loss rate of 20%, it was estimated that 300 patients (sample size of 100 per treatment group and three treatment groups) would be required with at least 80% power and at 5% significance level. Moreover, the follow-up period was extended from 4 to 6 weeks.

Analysis of all efficacy measures was conducted on the intent-to-treat (ITT) population, which included all patients who were randomized and received any study drug and for whom at least one postbaseline value was available. Analysis of safety included data from all randomized patients who received any study drug.

Differences in changes from baseline MPS, the primary outcome measure, noted between the treatment groups over the 4-week treatment period were analysed using the analysis of variance model. The significance of any difference was assessed by pairwise treatment comparison using the Fisher’s protected Least Significance Difference test. These tests were also applied to assess the significance of differences in change from baseline scores for MNW, MTSS, DLQI, VAS, and global assessment of efficacy, the secondary outcome measures, over 4 and 6-week treatment periods. Treatment-emergent AEs were compared by chi-squared test.

The statistical responder’s analyses employed a logistic model that extracted effects for centre and treatment. All statistical tests were performed using the sas® software version 8.2 for Windows (SAS Institute Inc., Cary, NC, USA) and values for \( P < 0.05 \) were considered statistically significant.

Results

Patients and baseline characteristics

Patients were enrolled between November 2004 and July 2005. The patient disposition is illustrated in Fig. 1. A total of 400 patients were screened of whom 334 patients (83.5%) were randomized to receive one of three study treatments (113 placebo, 112 rupatadine 10 mg and 109 rupatadine 20 mg). Overall, 293 (87.7%) patients completed the trial. The ITT population composed of 329 patients who were randomized and received any study drug and for whom at least one postbaseline value was available during the follow-up period was extended from 4 to 6 weeks.

The ITT population included all patients (sample size of 100 per treatment group and three treatment groups) would be required with at least 80% power and at 5% significance level. Moreover, the follow-up period was extended from 4 to 6 weeks. Analysis of all efficacy measures was conducted on the intent-to-treat (ITT) population, which included all patients who were randomized and received any study drug and for whom at least one postbaseline value was available. Analysis of safety included data from all randomized patients who received any study drug.

Differences in changes from baseline MPS, the primary outcome measure, noted between the treatment groups over the 4-week treatment period were analysed using the analysis of variance model. The significance of any difference was assessed by pairwise treatment comparison using the Fisher’s protected Least Significance Difference test. These tests were also applied to assess the significance of differences in change from baseline scores for MNW, MTSS, DLQI, VAS, and global assessment of efficacy, the secondary outcome measures, over 4 and 6-week treatment periods. Treatment-emergent AEs were compared by chi-squared test.

The statistical responder’s analyses employed a logistic model that extracted effects for centre and treatment. All statistical tests were performed using the sas® software version 8.2 for Windows (SAS Institute Inc., Cary, NC, USA) and values for \( P < 0.05 \) were considered statistically significant.

Efficacy analyses

The effect of treatment on change from baseline in MPS over the 4-week treatment period, the primary outcome measure, is illustrated in Fig. 2A. Rupatadine 10 and 20 mg significantly reduced the MPS from baseline by 1.42 (\( P < 0.005 \)) and 1.59 (\( P < 0.0001 \)), respectively, compared with a reduction of 1.13 with placebo, reflecting overall mean reductions from baseline in
pruritus severity of 57.5% for rupatadine 10 mg, 63.3% for rupatadine 20 mg and 44.5% for placebo.

Rupatadine 10 and 20 mg also reduced the MPS from baseline to a significantly greater extent than placebo over a 6-week treatment period (59.5% and 66.1%, respectively), compared with placebo (48.8%; \( P < 0.05 \) and \( P < 0.001 \), respectively; Fig. 2A). A time-dependent analysis showed that rupatadine 10 and 20 mg progressively reduced pruritus severity to a significantly greater extent than placebo from week 1 onward of treatment (Table 2).

A clear difference between 10 and 20 mg vs placebo was observed (\( P = 0.013 \) and \( P < 0.0001 \), respectively) after 24 h treatment, showing that rupatadine, at both dosages effectively relieved CIU symptoms after the first dosage, indicating a fast onset of action.

Linear trend analysis showed that the effect of rupatadine 10 and 20 mg was significant over the entire 6-week treatment period and all time points investigated, compared with placebo (\( P < 0.05 \)), but not significantly different between rupatadine 10 mg and rupatadine 20 mg at any time.

Rupatadine also led to significant improvements in the secondary outcomes, compared with placebo. The MNW was decreased to a significantly greater extent by rupatadine 10 and 20 mg (54.3% and 57.0%, respectively) than by placebo (39.7%; \( P < 0.05 \)) over a period of 4 weeks (Fig. 2B). Although the MNW scores were also decreased from baseline by 56.1% for rupatadine 10 mg and 59.2% for rupatadine 20 mg over a 6-week treatment period, these were not significantly different from the decrease of 43.5% in MNW score noted with placebo (Fig. 2B). Analysis of a time-dependent effect of rupatadine on wheals showed that the MNW was also significantly decreased by both doses of the drug from the first week of treatment, lasting up to week 4, compared with placebo (\( P < 0.05 \)). Rupatadine 10 and 20 mg were not significantly different also with respect to their effects on MNW at any time point investigated.

Assessment of the MTSS demonstrated that this was significantly reduced from baseline by 2.69 (56.3%; \( P < 0.005 \)) and 2.86 (60.3%; \( P < 0.0001 \)) over the 4-week treatment period and by 2.79 (58.4%; \( P < 0.05 \))
Rupatadine in the treatment of chronic idiopathic urticaria

showed that all scores were significantly improved after 2 weeks’ treatment with rupatadine 10 and 20 mg ($P < 0.05$ for all scores), apart from the *Leisure and Personal relationships* subdomains in rupatadine 10 mg-treated patients, compared with placebo. Time-dependent analysis demonstrated that rupatadine 10 mg progressively improved the *Symptoms and feelings*, *Daily activities* and *Work and School* subdomain scores to a greater extent than placebo after 4 and 6 weeks, although these were not significant, compared with placebo. Rupatadine 20 mg improved all the subdomain scores to a greater extent than placebo over time, with the differences being significant ($P < 0.05$ for all scores) for all scores, except for *Work and School* and *Treatment* subdomain scores after 4 weeks, and for *Personal relationships* subdomain score after 6 weeks.

Treatment with rupatadine 20 mg significantly decreased the baseline VAS score for general discomfort by 57.9% and 68.6% over the 4- and 6-week treatment periods, respectively, compared with reductions of 36.9% and 46.5% for placebo. The VAS scores were also reduced with rupatadine 10 mg from baseline by 50.6% and 60.5% over 4 and 6 weeks, although these were not significant compared with placebo.

After 2 weeks’ treatment, 27.3%, 53.7% and 57.4% of the investigators judged placebo, rupatadine 10 mg and rupatadine 20 mg, respectively, to lead to good or excellent improvement in disease symptoms. By end of treatment, the number of investigators judging good to excellent improvement in symptoms was increased to 50.9%, 63.9% and 75.0%, for placebo, rupatadine 10 mg and rupatadine 20 mg, respectively.

Concerning the analysis of responders that we conducted for the main efficacy variable (MPS), we observed that 65.5% and 73.1% of patients under treatment of rupatadine 10 and 20 mg had a pruritus symptoms reduction higher than 50% compared with 45.9% reduction in the placebo group [odds ratio (OR): 2.2 (95% CI: 1.2–3.8); $P = 0.0037$ and OR: 3.2 (95% CI: 1.8–5.6); $P < 0.0001$], respectively.

---

**Figure 2.** Effect of treatment on percentage reduction from baseline in (A) mean pruritus score, (B) mean number of wheals and (C) mean total symptom score over the 4- and 6-week treatment periods ($*P < 0.05$ vs placebo; $**P < 0.005$ vs placebo; $***P < 0.0001$ vs placebo).

<table>
<thead>
<tr>
<th>Treatment period (days)</th>
<th>Placebo</th>
<th>Rupatadine 10 mg</th>
<th>Rupatadine 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (baseline)</td>
<td></td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>−0.9 (0.67)</td>
<td>−1.19 (0.73)</td>
<td>−1.34 (0.71)</td>
</tr>
<tr>
<td>14</td>
<td>−0.96 (0.69)</td>
<td>−1.34 (0.72)</td>
<td>−1.46 (0.79)</td>
</tr>
<tr>
<td>28</td>
<td>−1.13 (0.71)</td>
<td>−1.42 (0.73)</td>
<td>−1.59 (0.79)</td>
</tr>
<tr>
<td>35</td>
<td>−1.20 (0.73)</td>
<td>−1.46 (0.75)</td>
<td>−1.62 (0.78)</td>
</tr>
<tr>
<td>42</td>
<td>−1.24 (0.74)</td>
<td>−1.47 (0.76)</td>
<td>−1.66 (0.78)</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD).

* $P < 0.05$ vs placebo, $\dagger P < 0.01$ vs placebo, $\ddagger P < 0.005$ vs placebo, $\ddagger\ddagger P < 0.0001$ vs placebo.
Safety evaluation

The incidence of AEs was found to be 24.8% for placebo-treated group, 28.6% for rupatadine 10 mg-treated group and 33.9% for rupatadine 20 mg-treated group, of which 11.5%, 11.6% and 16.5%, respectively, were found to be treatment related. The most frequently reported AEs were headache (8.0%, 4.5% and 8.3% of incidence for placebo, rupatadine 10 mg and rupatadine 20 mg, respectively) and somnolence (5.3%, 2.7% and 8.3% of incidence for placebo, rupatadine 10 mg and rupatadine 20 mg, respectively). Two SAEs (deterioration of arterial hypertension and metrorrhagia), which were not considered to be treatment related and resolved completely, were reported in the rupatadine 20 mg group. Overall, the differences in the incidence or type of AE noted in any treatment were not significant and there was no death. Comparison of the AE profiles for rupatadine 10 mg and rupatadine 20 mg; however, indicates that rupatadine 10 mg was tolerated better than rupatadine 20 mg, particularly with respect to a much lower degree of somnolence.

Discussion

This study was designed to evaluate the efficacy of rupatadine 10 and 20 mg in the treatment of CIU symptoms, by primarily assessing the change in MPS over a 4-week treatment period in patients with active CIU. The study demonstrated that rupatadine 10 and 20 mg were significantly better than placebo over the 4-week treatment period and decreased the MPS from baseline, the primary outcome, by 57.5% and 63.3%, respectively, compared with a 44.9% reduction with placebo. Moreover, the superiority of rupatadine 10 and 20 mg over placebo, in reducing the MPS, was evident from week 1 and maintained over an extended treatment period of 6 weeks. Similarly, rupatadine 10 and 20 mg were also significantly better than placebo in reducing the MNW and MTSS from week 1 onwards over 6 weeks. The two doses of rupatadine were not significantly different with respect to their efficacy in attenuating the symptoms of CIU over 4- or 6-week treatment periods and were both safe and well tolerated in this moderate-to-severe CIU patient cohort. However, rupatadine 10 mg led to nearly half the incidence of headache and about a third the incidence of somnolence, than rupatadine 20 mg. The significantly greater efficacy of rupatadine in attenuating the symptoms of CIU was reflected by a finding for greater reductions in general discomfort and improvement in the QoL from the first week of treatment. Indeed, by the end of the 6-week treatment period a larger number of the investigators (63–75%) judged there to be an overall good or excellent improvement in disease symptoms in rupatadine 10 and 20 mg-treated patients, than the number of investigators (50%) making a similar judgement for placebo-treated patients. In contrast, a greater number of investigators (11.8%) judged the symptoms to be worse by the end of 6-weeks' treatment with placebo, compared with rupatadine 10 and 20 mg (8.3% and 5.6% of investigators, respectively). Collectively, these results confirm the findings of a previous dose-finding study (17) and re-enforce the proposition that rupatadine 10 mg should be used as the preferred normal dose for the management of patients with moderate-to-severe CIU.

The findings of this study are in accordance with studies documenting the effect of other H1 antihistamines in CIU. Studies with fexofenadine have shown that fexofenadine 20–240 mg twice daily for 4 weeks, significantly reduced the MPS, MNW and MTSS from baseline as well as QoL indices in patients with moderate-to-severe CIU symptoms over the 4-week period (21, 22). Similarly, studies investigating the effect of desloratadine 5 mg once daily for 6 weeks in patients with moderate-to-severe CIU have shown that this agent was also significantly more effective than placebo in improving total symptoms/MTSS and QoL indices, compared with placebo (23, 24). Unlike these studies, however, the present study used the validated DLQI and demonstrated that rupatadine 10 and 20 mg to significantly improved most of the subdomain scores after 2 weeks, compared with placebo, suggesting that rupatadine is likely to provide rapid and meaningful overall QoL benefits in affected individuals.

The limited amount of information available on the putative mechanisms involved in the pathophysiology of chronic urticaria, and to some extent CIU, point towards the roles of histamine and PAF as important and complimentary mediators (1, 4, 9, 10). While intradermal injections of PAF and histamine cause vasodilatation and increased vascular permeability, leading to a wheal and flare response that is accompanied by pruritus (25, 26), a comparison of PAF- and histamine-induced cutaneous reactions in the skin of patients with atopic dermatitis (26) and chronic urticaria (27) suggests that the inflammatory response to these agents may be different. One study in patients with atopic dermatitis demonstrated that intradermal PAF resulted in the opening of endothelial gaps and extravasation of predominantly neutrophils, followed by eosinophils after 4 h (26). Similarly, another study in patients with chronic urticaria showed that intradermal PAF led to increased eosinophils at all injection sites, while intradermal histamine lead to increased eosinophils at only a limited number of sites (27). One study of patients with cold-induced urticaria reported that there was an association between urticaria and the release of histamine, PAF and neutrophilic chemotactic activity (NCA) in these patients (28). Collectively, these results suggest that dual blockade of the histamine and PAF receptor may provide rupatadine with an overall greater treatment advantage.
Some other pathogenic mechanisms in chronic urticaria have been evidenced and suggest that in up to 50% of patients the disease could be explained by an underlying autoimmune mechanism involving, i.e. antihigh-affinity IgE receptor antibodies and the importance of these autoantibodies is now widely recognized (6).

In the absence of a specific measure for pruritus severity, the assessment of this measure in the present study, like all other studies documenting the use of this efficacy measure in CIU, was reliant on a subjective assessment. It is nevertheless important to emphasize that the mean pruritus severity was evaluated from the patient’s perspective, and that significant decreases in this primary outcome measure, and indeed the secondary outcome measures assessing symptoms (i.e. MNW and MTSS), were detected with rupatadine treatment very early (just after 7 days of treatment) and then maintained over a period of 6 weeks.

The present study provides important information, which enlarges the currently small scientific database on treatment of patients with CIU.

It is important to mention that recent recommendations from the EAAACI/GA (2) LEN/EDF guidelines for urticaria management and diagnosis, suggest to treat the patients with new generation antihistamines, with a very low AE effect profile and good patient compliance. In addition, it is also suggested that for nonresponding patients, higher dosage (up to fourfold) should be tried (6, 29).

The responder analyses we performed may assist clinicians in evaluating the impact of rupatadine in a relevant clinical scenario, i.e. in patients with CIU previously stabilized on a second-generation antihistamine. The current results indicate that in this setting, rupatadine produce improvement of symptoms, across multiple outcomes, and thus provide a clinically important treatment benefit for patients with moderate-to-severe CIU. Based on current expert opinion, a 40–50% in symptoms reductions after 4-week treatment could be considered as a meaningful clinical response for patients suffering from CIU and are under a nonsedating anti-H1 treatment.

In particular, this study clearly demonstrates that rupatadine 10 and 20 mg are effective in providing rapid and long-lasting relief from pruritus, which is possibly the most bothersome symptom of CIU, and wheals in affected individuals. Furthermore, rupatadine appears to be efficacious in improving the QoL in these patients, which from the patient’s perspective is likely to be a major aspect of their condition.

A recent publication from Asero (30), did suggests that the proportion of patients with severe CIU that may gain a better control of their disease with high, off-label doses of antihistamines is probably small, and that most patients will eventually have to undergo more aggressive treatments. In effect this finding is in keeping with the results of the present study that did not show a marked difference between rupatadine at 10 or 20 mg/day.

In view of the finding that rupatadine 10 and 20 mg were not significantly different at any time point, with respect to their effects on pruritus severity, number of wheals and total symptom scores, but that rupatadine 10 mg has an overall better AE profile than rupatadine 20 mg, particularly with respect to headache and somnolence, it is evident that rupatadine 10 mg is the preferred dose of choice that is likely to be recommended for the management of patients with CIU.

Acknowledgments

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.

References

Gimenez-Arnau et al.


