Rupatadine 10 and 20 mg are effective and safe in the treatment of perennial allergic rhinitis after 4 weeks of treatment: a randomized, double-blind, controlled trial with loratadine and placebo

Background and objectives: Allergic rhinitis is a global health concern of increasing prevalence that can impact quality of life and work and school performance of affected individuals. Antihistamines are recommended as the first-line treatment. This randomized, controlled trial aimed to investigate the effects of rupatadine in adult subjects with perennial allergic rhinitis. **Methods:** We randomly assigned 283 patients to receive placebo (n = 69), loratadine 10 mg (n = 70), rupatadine 10 mg (n = 73) or rupatadine 20 mg (n = 71). The study design was double blind and treatment was continued for 4 weeks. Subjective assessment of symptoms (reflective evaluation) was recorded by patients in a diary card. The primary end point was the percentage of days where the score of the most severe symptom was less than or equal to one (Pdmax1). Furthermore, the change from baseline in the severity of total symptom score and nasal symptom score were recorded, and the investigator and patient global assessments were evaluated. **Results:** All 283 patients were included in analyses (intention to treat); 265 (94%) patients completed the follow-up. Rupatadine 20 mg significantly improved the Pdmax1 in comparison with placebo. Significant reductions from baseline in total symptom score were achieved with rupatadine 10 mg (-4.00), rupatadine 20 mg (-3.96) and loratadine (-3.94) compared with placebo (p < 0.01). Similarly, all three active treatments significantly reduced the nasal symptom score compared with placebo. No significant differences among groups in the incidence of overall adverse events were observed and no clinically significant QTc enlargements were detected. More patients receiving rupatadine complained of somnolence compared with loratadine. **Conclusion:** Once-daily rupatadine (10 and 20 mg) is an efficacious and safe treatment for the management of patients with perennial allergic rhinitis.

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Allergic rhinitis (AR) is an inflammatory chronic disease of the upper airways characterized by anterior or posterior rhinorrhea, sneezing, nasal obstruction and/or itching of the nose. In most cases it is also associated with ocular symptoms [1,2]. AR prevalence has been increasing steadily during the past 40 years. It is estimated to affect up to 40% of the population, depending on the geographical area and age of patients [3]. Lifetime prevalence throughout European countries ranges between 17 and 29% [4,5]. Despite these figures, allergic symptoms are often underdiagnosed [5]. AR is considered a global health problem that affects social life, sleep, education and work, and accounts for an increasing economic burden [1].

Symptoms are mainly induced after allergen exposure due to IgE-mediated inflammation and complex interactions between effector cells, such as mast cells and basophils. Immunologic activation of these effector cells induces the secretion of proinflammatory mediators [6,7]. In the early-phase response to allergens, histamine is the most important mediator and symptoms such as rhinorrhea, sneezing and itching are largely mediated through histamine receptors [8]. Lipid mediators, such as leukotrienes, prostaglandins, and platelet-activating factor (PAF) are also involved. PAF specifically induces vasodilatation and an increase in vascular permeability, which may contribute to rhinorrhea and nasal congestion [9].

Both histamine and PAF have complementary activities *in vivo*, and each mediator is able to promote the release of the other [10]. Dual blockade of these mediators is likely to be an effective treatment for AR.

Rupatadine is a selective long-acting histamine (H1) and PAF receptor antagonist that has been approved for marketing in most European Community countries and Brazil for the treatment of AR and chronic urticaria in adults and adolescents at a once-daily dose of 10 mg [11]. In a study involving patients with seasonal

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AR exposed to allergens, rupatadine showed a fast onset of action and significantly decreased allergen-induced nasal and non-nasal symptoms [12]. Several randomized, controlled trials demonstrated that rupatadine 10 and 20 mg, given once daily, are highly efficacious in attenuating the symptoms of seasonal, perennial and persistent AR in adult and adolescent patients with moderate-to-severe symptoms [13–16].

The present study was conducted to evaluate the efficacy and safety of rupatadine (10 and 20 mg) given once daily in comparison with loratadine 10 mg and placebo as oral therapy in the treatment of perennial AR.

Study design & methods
■ Study design
This was a randomized, double-blind, placebo-controlled, parallel-group study, conducted in 22 centers in Poland and the Czech Republic. The study was conducted between October and March, to ensure that patients did not have seasonal symptoms. Patients suffering from perennial AR were randomized to receive rupatadine (10 mg or 20 mg), loratadine (10 mg) or placebo once daily for a period of 4 weeks. Patients took a single dose of the study medication or placebo during the morning. All the medications were of identical external appearance to maintain the blinding conditions of the study. A computer-generated randomized scheme was used to provide balanced blocks of patients numbers for each of the three treatment groups and the patients were assigned a sequential randomization number.

During a screening visit, performed 1 week before treatment initiation, the investigator assessed the patients' eligibility through a physical exam, symptom assessment, blood laboratory tests and electrocardiogram. Prick tests were performed if they had not been done within 1 year of the visit. A positive prick test was defined as a wheal diameter exceeding 3 mm for a given non-seasonal allergen, compared with that of saline solution injection or greater than that obtained with histamine 10 mg injection. Participants were provided with a diary card and admitted to the 4-week study, attending a total of three visits (baseline, 2 and 4 weeks of treatment).

All patients gave written informed consent to participate in the study, which was approved by local ethics review boards and the regulatory agencies for health in each country. The study was performed in accordance with the Declaration of Helsinki and subsequent amendments.

■ Patients inclusion & exclusion criteria
Male and female subjects aged 18–65 years, with a documented history of perennial AR symptoms for at least 1 year were recruited. This study was undertaken before the release of the updated AR and its impact on asthma (ARIA) document and broad use of new AR classification [17]. Women of child-bearing potential were required to have a negative pregnancy test at inclusion and use contraceptive methods during the study. Patients with an electrocardiogram showing QTc interval values (according to Bazzet's formula) of less than 430 ms for males or 450 ms for females were permitted to enter the study. A sum of nasal symptoms score equal to or greater than five, based on the patients' subjective assessment of their symptoms during the previous day, was required on inclusion.

Patients suffering from non-allergic rhinitis (e.g., vasomotor, infectious or drug-induced rhinitis) or with a negative prick test were excluded. Patients receiving systemic or topical medication, such as oral H1 or H2-receptor antagonists for at least 1 month, topical antihistamines for 48 h, nasal vasoconstrictors for 24 h, and/or corticosteroids, ketotifen or any immunosuppressant for 2 weeks prior to the inclusion of the study, were also excluded. Other exclusion criteria were treatment with hyposensitization therapy, or abnormal laboratory or electrocardiogram values of clinical relevance. Patients who satisfied all the inclusion criteria and none of the exclusion criteria started the study treatment.

■ Evaluation of efficacy
Assessments of efficacy were based on the patients' subjective assessment of their symptoms. Before taking the medication, patients were asked to record the severity of symptoms experienced during the previous day (reflective 24 h evaluation). Symptoms of rhinitis included four nasal symptoms (sneezing, nasal obstruction, nasal itching and rhinorrhea) and one non-nasal symptom (ocular itching). The severity of symptoms was assessed by scoring on a four-point scale (0 = absence of symptoms; 1 = some but not troublesome; 2 = frequent and annoying symptoms; 3 = continuous symptoms, interfering with sleep or daily activities).

After 4 weeks of treatment, the investigator and the patient made a global assessment of efficacy on the basis of change in symptom severity, scored on a five-point scale (0 = worse, 1 = no change, 2 = slight improvement, 3 = good improvement, 4 = excellent improvement).

The primary efficacy outcome was the percentage of days during the study period where the score of the most severe symptom on each day was less than or equal to 1 (Pdmax1). Treatment efficacy was evaluated using the change from baseline in the severity of total symptom score (five total symptom score [5TSS]) and total nasal symptom score (four nasal symptom score [4TNSS]) following a recent guidance document, issued after the study inception, that recommends these variables as a primary outcomes [101]. Total symptom score was the sum of individual symptom scores (each symptom or nasals symptoms) at each study day. Treatment efficacy was also evaluated through investigator and patient global assessment.

■ Evaluation of safety

Treatment safety and tolerability were evaluated according to the incidence and type of adverse events spontaneously reported in the patients' diaries, results of blood laboratory tests (hematology, blood chemistry), physical examinations and 12-lead electrocardiogram, before and at the end of the study period. All adverse events were coded using the WHO Adverse Reactions Terminology dictionary, and grouped by treatment.

■ Statistical analysis

The study was designed to have a statistical power of 80% to detect a relative reduction of 25% in the primary efficacy outcome between any of the rupatadine active groups compared with the placebo group, with a two-sided significance level of less than 5%. Given the specified statistical power and assuming a 10% drop-out rate, the study was planned to include a total of 280 patients.

For quantitative (efficacy and safety) variables, mean, median, standard deviation, maximum and minimum values were calculated. Qualitative variables were expressed as relative frequencies. Analysis of covariance was used to compare treatment groups for the primary (Pdmax1) and secondary outcomes. Treatment, center (as main effects) and baseline severity score (as a covariate) were taken into account, as well as any of the interactions or baseline covariates if found to be statistically significant. In case of significant results, pairwise contrasts were made between the treatment groups using Bonferroni adjustment. The χ^2-test was used for qualitative variables and the Fisher test was used if the applicability conditions were not present. The Mantel-Haenszel χ^2-test was performed in case both variables lay on an ordinal scale.

Analysis of all efficacy measures was based on intention-to-treat (ITT). ITT analysis included all patients who were randomized and received at least one dose of study medication. Treatment failure was recorded when rescue medication was needed or when unacceptable symptom severity was detected in the investigator criteria. Those patients were not excluded from the efficacy analysis. Patients with missing data or completely lost to follow-up were also included in the ITT analysis and the data available were used. All statistical tests were performed using the SAS® software version 6.12.

Results

■ Demographic characteristics

A total of 283 eligible patients fulfilled the inclusion criteria and underwent randomization to receive placebo (69 patients), loratadine (70 patients), rupatadine 10 mg (73 patients) or
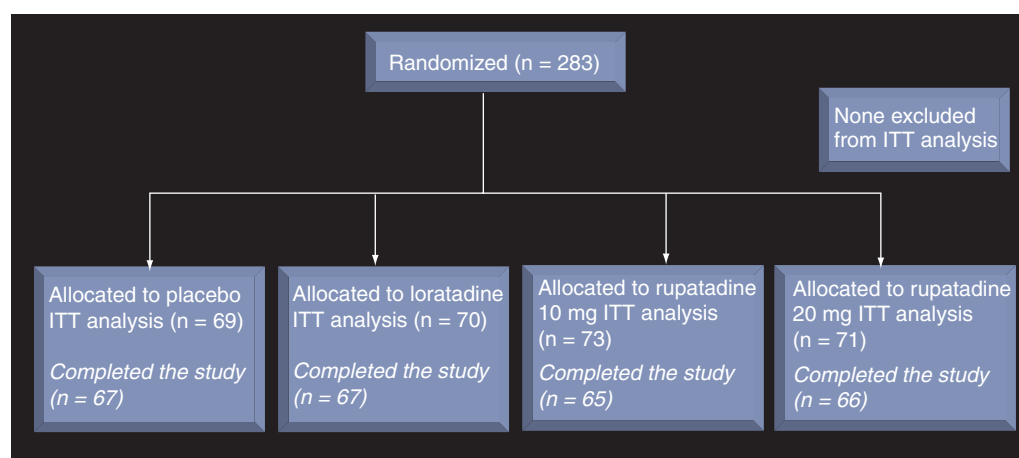

Figure 1. Participant flow.
N: Number of patients included; ITT: Intention-to-treat analysis.

rupatadine 20 mg (71 patients). All were included in the ITT population analysis. Of these, 265 (94%) completed the study (see Figure 1). There were no significant differences in the reasons for exclusion between groups.

The demographic characteristics were similar among treatment groups (see Table 1) with no statistical differences except for age. Patients in the placebo group were younger than patients who received any of the active treatments. All included patients were Caucasians. There were no statistically significant differences between groups in the baseline total and nasal symptoms severity scores.

■ Efficacy assessment

Results for the primary and secondary outcomes over the 4-week treatment period for the ITT population are summarized in Table 2. Only rupatadine 20 mg significantly improved the primary outcome (Pdmax1) in comparison with placebo at the end of the study period. The absolute difference was 15.8% (95% CI: -30.3–1.3; p = 0.025) favoring active treatment. The Pdmax1 value was 36.4% ± 4 in the placebo group, 49.9% ± 3.9 in loratadine group, 46.9% ± 3.9 in the rupatadine 10 mg group, and 52.2% ± 3.9 in the rupatadine 20 mg group. After 2 weeks of treatment, Pdmax1 values showed better results in the three active treatment groups in comparison with placebo, although none of the results were statistically significant.

Rupatadine 10 mg, rupatadine 20 mg and loratadine reduced the 5TSS scores from baseline by -4.0 ± 0.24 (p = 0.002), -3.96 ± 0.24 (p = 0.003) and -3.94 ± 0.24 (p = 0.004), respectively, all three values were significantly greater in comparison with placebo (see Table 2). In addition, all three active treatments showed significantly greater reductions from baseline in the 4TNSS (rupatadine 10 mg -3.05 + 0.21, p = 0.004; rupatadine 20 mg -3.08 + 0.21, p = 0.005 and loratadine -3.11 + 0.21, p = 0.006) in comparison with placebo. All three active treatments showed greater reductions from baseline in each of individual symptoms in

comparison with placebo, which were statistically significant for rhinorrhea (rupatadine 10 mg, p = 0.004 and loratadine p = 0.002), ocular itching (rupatadine 10 mg, p = 0.047), sneezing (rupatadine 20 mg, p = 0.004) and nasal itching (loratadine, p = 0.019) (see Figure 2).

At 14 days of treatment, changes from baseline in the 5TSS and 4TNSS scores were significantly greater in those patients taking active treatment in comparison with those who received placebo (p < 0.05). Reductions from baseline in each of the individual symptoms were also assessed in comparison with placebo and showed statistical significance in sneezing (rupatadine 10 mg and 20 mg, p = 0.039 and p = 0.004, respectively), rhinorrhea (rupatadine 10 mg, p = 0.038 and loratadine, p = 0.004) and nasal itching (loratadine, p = 0.043). Although placebo led to fewer reductions from baseline in ocular itching scores, differences between groups were not significant (see Table 2).

Concerning the results of patient and investigator overall impression of efficacy based on available data for the ITT population, a greater percentage of patients and investigators considered that symptom severity did not improve in those patients receiving placebo compared with those receiving any of the active treatments. However, differences were not statistically significant between groups in any of the assessments at 4 weeks. The investigator considered that the treatment failed in eight patients, with a similar distribution among groups.

Treatment failures were equally distributed among treatment groups (nonstatistical differences). Loratadine and placebo lead to two treatment failures each; treatment with rupatadine 10 mg was considered to fail in three patients and rupatadine 20 mg in a single patient.

■ Safety assessment

All patients who received at least one dose of the study medication were considered in the safety assessment (n = 283). No significant differences between groups in the overall incidence

Table 1. Baseline characteristics of patients.				
Characteristic	Placebo (n = 69)	Loratadine (n = 70)	Rupatadine 10 mg (n = 73)	Rupatadine 20 mg (n = 71)
Age (year)*	26.0 ± 9.7	29.6 ± 10.7	33.3 ± 11.3	28.6 ± 10.4
Male sex – n (%)	40 (58)	36 (51)	30 (41)	28 (39)
Symptoms – 5TSS	7.72 ± 1.89	7.93 ± 2.22	7.89 ± 2.11	7.92 ± 1.85
Symptoms – 4TNSS	6.96 ± 1.62	6.97 ± 1.60	6.77 ± 1.60	6.94 ± 1.48

Statistical differences between groups (p < 0.001) in Kruskal–Wallis test.
Means ± standard deviations.
4TNSS: Four nasal symptom score; 5TSS: Five total symptom score.

of adverse events existed. The most frequently reported adverse events were: headache (18%), somnolence (7%), fatigue (6%) and back pain (4%). More patients taking rupatadine 10 mg (n = 7) or rupatadine 20 mg (n = 9) reported somnolence in comparison with those taking loratadine (n = 0, p < 0.05) (see Table 3). Three patients taking placebo had somnolence during the study. Two patients showed increases in hepatic enzymes related to the study medication: one patient taking rupatadine 10 mg experienced slight and transient increase, and one patient taking placebo had an increase in hepatic enzymes that was considered a serious adverse event. One patient in each group discontinued medication owing to an adverse event at least possibly related to the study drug. Adverse events leading to discontinuation were headache in one patient taking placebo, pruritus in a patient taking loratadine, facial edema with rupatadine 10 mg and somnolence with rupatadine 20 mg.

Analysis of the 268 available electrocardiograms at the end of the study revealed several abnormal QTc values. A marked prolongation of the QTc interval (QTc > 500 ms) occurred in a single measurement at the end of the study in a patient who was taking placebo. A total of four patients experienced a QTc prolongation of more than 60 ms from baseline (one in the placebo group, one in loratadine group and two patients treated with rupatadine 20 mg). Mean QTc values in each treatment group are summarized in Table 3.

Discussion

The present study was designed to investigate the efficacy of rupatadine in comparison with that of placebo and a broadly used second-generation antihistamine compound in patients with perennial AR. The primary outcome was that the percentage of days with less severe symptoms (Pdmax1) was consistently higher with rupatadine and loratadine in comparison with placebo. However, statistically significant differences were detected for mean Pdmax1 only between rupatadine 20 mg and placebo groups (p = 0.025).

Patients with perennial symptoms tend to have less acute symptoms than those patients suffering from seasonal rhinitis. Depending on environmental factors and exposure to multiple allergenic molecules, perennial AR patients may have exacerbations or spontaneous remissions of symptoms. This may lead to the impression that patients with perennial symptoms are less

Table 2. Summary of results from primary and secondary outcomes assessment (ITT analysis).

	1–28 days					1–14 days				
	Placebo (n = 69)	Loratadine 10 mg (n = 70)	Rupatadine 10 mg (n = 73)	Rupatadine 20 mg (n = 71)		Placebo (n = 69)	Loratadine 10 mg (n = 70)	Rupatadine 10 mg (n = 73)	Rupatadine 20 mg (n = 71)	
Primary outcome										
Pdmax1	36.4 ± 4.0	49.9 ± 3.9	46.9 ± 3.9	52.2 ± 3.9 *		30.7 ± 4.1	42.2 ± 4.0	39.2 ± 4.0	45.5 ± 4.0	
Secondary outcomes										
5TSS	-2.76 ± 0.25	-3.94 ± 0.24‡	-4.00 ± 0.24‡	-3.96 ± 0.24‡		-2.39 ± 0.25	-3.55 ± 0.25‡	-3.57 ± 0.25‡	-3.56 ± 0.25‡	
4TNSS	-2.44 ± 0.21	-3.42 ± 0.21‡	-3.44 ± 0.21‡	-3.43 ± 0.21‡		-2.12 ± 0.22	-3.11 ± 0.21‡	-3.05 ± 0.21*	-3.08 ± 0.21‡	
Sneezing	-0.65 ± 0.06	-0.79 ± 0.06	-0.86 ± 0.06	-0.93 ± 0.06‡		-0.55 ± 0.06	-0.75 ± 0.06	-0.79 ± 0.06*	-0.86 ± 0.06‡	
Rhinorrhea	-0.59 ± 0.07	-0.96 ± 0.07‡	-0.93 ± 0.07‡	-0.85 ± 0.07		-0.52 ± 0.08	-0.88 ± 0.07‡	-0.81 ± 0.07*	-0.76 ± 0.07	
Nasal itching	-0.61 ± 0.07	-0.88 ± 0.08*	-0.85 ± 0.06	-0.84 ± 0.06		-0.53 ± 0.07	-0.80 ± 0.07*	-0.75 ± 0.07	-0.77 ± 0.07	
Nasal obstruction	-0.61 ± 0.08	-0.75 ± 0.08	-0.84 ± 0.08	-0.79 ± 0.08		-0.54 ± 0.08	-0.64 ± 0.08	-0.74 ± 0.08	-0.69 ± 0.08	
Ocular itching	-0.33 ± 0.06	-0.53 ± 0.06	-0.55 ± 0.06*	-0.53 ± 0.06		-0.28 ± 0.06	-0.44 ± 0.06*	-0.51 ± 0.06	-0.48 ± 0.06	

*p < 0.05 vs placebo, †p < 0.01 vs placebo.
Adjusted mean ± standard error.
4TNSS: Four nasal symptom score; 5TSS: Five total symptom score; Pdmax1: Percentage of days where the score of the most severe symptom was less than or equal to one.

Table 3. Incidence of most reported adverse events and QTc values.				
Characteristic	Placebo (n = 69)	Loratadine (n = 70)	Rupatadine 10 mg (n = 73)	Rupatadine 20 mg (n = 71)
Headache – n (%)	15 (22)	12 (17)	14 (19)	9 (13)
Somnolence – n (%)	3 (4)	0 (0)	7 (10)[*]	9 (13)[*]
Back pain – n (%)	3 (4)	2 (3)	3 (4)	3 (4)
Fatigue – n (%)	2 (3)	2 (3)	9 (12)	4 (6)
QT interval (Bazzet's correction) (ms)[‡]	281 ± 59	285 ± 52	293 ± 34	289 ± 41
[*]p < 0.05 between rupatadine groups and loratadine. Mean ± standard deviation.				

responsive to treatment with antihistamines than those with seasonal symptoms. Moreover, in our study, patients were recruited in the Czech Republic and Poland during the winter to avoid pollen allergens that could cause continuous symptoms in certain Mediterranean areas and to ensure an appropriate level of house dust mite allergens, nearly absent during the summer. In addition, a follow-up period of 4 weeks made the subjective outcome assessment based on patients' self-rating of symptoms more reliable and reduced the interference with environmental or individual factors. It should also be noted that, at 4 weeks, up to 94% of patients completed the study. In spite of these aspects, treatment with either rupatadine 10 or 20 mg or loratadine lead to greater reductions from baseline of total symptoms score (5TSS) in comparison with placebo. Similarly, all three active groups produced greater reductions in the assessment of nasal scores (4TNSS) and ocular itching at 4 weeks. These suggest that the evaluation of reductions from baseline of total symptoms is more sensitive to detect the improvement of symptoms than the percentage of days with less severe symptoms. A recent European guideline on AR suggested these two assessments be used as a primary outcome in clinical trials [17].

Symptom improvement was observed for both doses of rupatadine and loratadine at 2 weeks of treatment, and the improvement was greater at the end of treatment, with a sustained efficacy profile through the study period. This confirms the rapid mechanism of action of and may suggest that patients treated with rupatadine do not develop tolerance to the drug, although a 4-week follow-up period is too short to see any long-term effect.
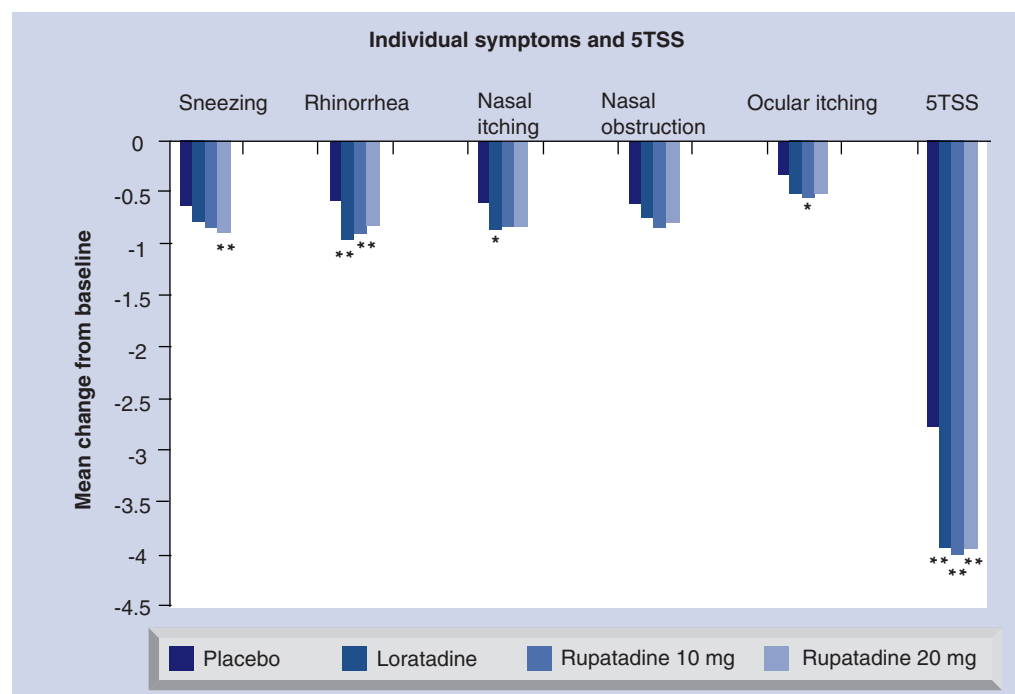

Figure 2. Change from baseline of individual symptoms and 5TSS at 4 weeks of treatment (ITT population).
[*]p < 0.05 versus placebo; [**]p < 0.01 versus placebo.
5TSS: Five total symptom score; ITT: Intention-to-treat analysis.

All active drugs showed a consistent efficacy profile compared with placebo in each individual symptom severity score, mainly in sneezing, rhinorrhea and nasal itching. By contrast, none of the active treatments caused an apparent improvement in symptoms of nasal obstruction.

There were no differences between groups in the investigators or patients' overall impression of efficacy, although the study was not powered to detect such differences in subjective assessments and some of the assessments were missing. The percentage of patients and investigators that judged the symptoms as not improving from baseline were 28 and 26% with placebo, 12 and 16% with loratadine, 19 and 14% with rupatadine 10 mg and finally 13 and 10% with rupatadine 20 mg, respectively.

Treatment with rupatadine 10 or 20 mg per day for 4 weeks was a safe and well-tolerated treatment of AR. The incidence of adverse events was low and most of them have been previously described with second-generation antihistaminic compounds. The incidence of somnolence episodes related to rupatadine was quite low and there were no statistically significant differences compared with placebo. Loratadine caused significantly less somnolence than rupatadine. There was a consistent low frequency of somnolence across studies in those patients receiving loratadine, which ranged from 0 to 3% [18,19].

There was only one serious adverse event in one patient, who was taking placebo. Importantly, no significant enlargements of QTc interval were detected during the study period. Cardiac adverse events, specifically effects on QT interval, led to the market withdrawal of astemizole and terfenadine in most countries. These results, together with previous studies with rupatadine, confer a wide safety margin [20].

Antihistamines are medications that block histamine at the receptor level (neutral antagonists or inverse agonists) [21]; however, having an additional anti-allergic property is also highly desirable [17]. Rupatadine displays a strong antagonistic activity towards both histamine H1 and PAF receptors [11] and as a consequence has a potentially dual anti-inflammatory capacity. It has also been shown *in vivo* that each of these mediators may promote the release of the other from different tissues and cells [10,22]. Loratadine has long-acting antihistamine properties with proven efficacy in the relief of AR symptoms [23] but its mechanism of action is not related to PAF antagonism.

The previous studies that have assessed rupatadine were performed before the most recent ARIA panel classification and hence the use of perennial and seasonal AR terms. Several dose-ranging placebo-controlled studies to evaluate the efficacy and safety of rupatadine showed a dose-dependent response in alleviating symptoms of seasonal [12–15,24] and persistent [16] AR. Randomized, controlled trials assessing the efficacy of loratadine in the treatment of perennial AR in adult patients were also performed under the old classification of rhinitis. Loratadine had a similar efficacy profile to that of clemastine and terfenadine in the assessment of total symptom score at 4 weeks of treatment [18,19]. Mizolastine performed better than loratadine at 2 weeks of treatment in one study where loratadine did not show significant differences to placebo in total symptom score throughout the study [25].

This 4-week study showed that both rupatadine doses were effective compared with placebo in relieving total symptoms in patients with perennial AR. Furthermore, rupatadine can be safely used up to 20 mg per day for 4 weeks to treat patients with severe-to-moderate perennial AR and results in a significant improvement in the percentage of days with less severe symptoms in comparison with placebo. Further larger studies are required to confirm the safety profile of rupatadine at 20 mg in long-term periods of treatments.

Future perspective

Since the release of the ARIA consensus document the conception of AR has changed dramatically and the previous terms of seasonal and perennial rhinitis cannot be used interchangeably with intermittent and persistent ones. In spite of this, oral H1 antihistamine treatment is recommended in both subtypes of AR. This is because almost all studies in AR using available antihistamine treatments were conducted under the old classification. There are critical differences in the mechanism of action of these drugs that may be translated to clinical practice with the adoption of ARIA classification. Comparative data between available antihistamine therapy using persistent and intermittent AR classification are needed.

Executive summary

- The aim of this double-blind, randomized study was to assess the clinical efficacy and safety of a 4-week regime of rupatadine (10 or 20 mg), loratadine (10 mg) or placebo in adult patients with perennial allergic rhinitis.
- Study population consisted of 283 eligible patients receiveding one of the study treatments daily. All were assessed using the percentage of days where the score of the most severe symptom was less than or equal to 1 (Pdmax1), total symptom score, symptom severity, investigator and patient global assessment and clinical safety.
- After 4 weeks of treatment, only rupatadine 20 mg improved the Pdmax1 in comparison with placebo; both doses of rupatadine and loratadine significantly reduced the total symptom score in comparison with placebo.
- Treatment of allergic rhinitis with rupatadine was well tolerated, although more patients taking rupatadine complained of somnolence compared with loratadine. Analysis of QTc intervals, together with previous data, demonstrated that rupatadine lacks proarrhythmic side effects.
- Rupatadine is an effective and safe second-generation antihistamine for the treatment of allergic rhinitis.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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