Rupatadine 10 mg in adolescent and adult symptom relief of perennial allergic rhinitis

Background & objectives: This randomized, double-blind clinical trial assessed the efficacy and safety of rupatadine 10 mg administered once-daily for 4 weeks compared with placebo and ebastine 10 mg in the management of symptoms of perennial allergic rhinitis (PAR). **Methods:** We randomly assigned 223 patients to receive placebo (n = 73), ebastine 10 mg (n = 79) or rupatadine 10 mg (n = 71). The efficacy and safety population analysis included 219 patients. The efficacy assessment was based on patients' reflective assessment of the severity of symptoms in a diary card. Symptoms of allergic rhinitis included rhinorrhea, sneezing, nasal itching, nasal obstruction and ocular itching. The main variable of efficacy 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 (5TSS) and nasal symptom score (4TNSS) were measured, as well as investigators' and patients' global assessment of efficacy. **Results:** Pdmax1 was nonsignificantly lower for rupatadine 10 mg (49%) and ebastine 10 mg (51%) than for placebo (42%) at the end of the study period. Both 5TSS and 4TNSS were significantly improved for rupatadine 10 mg users compared with placebo (p = 0.019 and p = 0.025, respectively). No significant differences were seen between active treatments. All treatments were similarly safe and well tolerated, with headache (33%) and somnolence (17%) as the most often reported adverse events in all treatment groups. **Conclusions:** Symptomatic relief of PAR symptoms with rupatadine 10 mg was rapidly and effectively attained. A 4-week treatment of patients suffering from PAR with rupatadine 10 mg is as effective and well tolerated as ebastine 10 mg.

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Allergic rhinitis is an inflammatory chronic disease of the upper airways characterized by anterior or posterior rhinorrhea, sneezing, nasal obstruction and/or itching of the nose, and in most cases is also associated with ocular symptoms [1,2]. It is estimated to affect up to 40% of the population, depending on the geographical area (European lifetime prevalence ranges between 17 and 29%, depending on the country) and age of patients. Factors such as pollution have contributed to an increase of its prevalence in the last four decades [3–5]. Allergic rhinitis is considered a global health problem that affects social life, sleep, scholarization and work, and represents an increasing economic burden [1]. Even though this is the case, it is still an underdiagnosed disease [5].

The symptoms of allergic rhinitis arise as a result of inflammation induced by γ globulins' (IgE) mediated immunologic response to specific allergens and through complex interactions between effector cells, such as mast cells and basophils. A local release in the nasal mucosa of inflammatory mediators such as histamine, leukotrienes, prostaglandins and platelet activator factor (PAF) exists [6–8]. Histamine is the most important mediator in the early-phase response to allergens, and symptoms such as rhinorrhea, sneezing and itching are mediated through histamine receptors. PAF specifically induces vasodilatation and an increase in vascular permeability that may contribute to rhinorrhea and nasal congestion [8,9]. Although treatment of allergic rhinitis is based mainly on allergen avoidance and use of oral antihistamines [10,11], the finding that allergic rhinitis is driven by multiple inflammatory mechanisms has led to an increased demand for therapeutic agents with a broader spectrum of activity, beyond antagonism of H1 histamine receptors [12].

Rupatadine is a selective long-acting histamine (H1) and PAF receptor antagonist that has been approved for marketing for the treatment of allergic rhinitis and chronic urticaria in adults and adolescents [13]. Several randomized controlled trials demonstrated that 10 and 20 mg of rupatadine, given once daily, are highly efficacious in attenuating the symptoms of seasonal, perennial and persistent allergic rhinitis in adult and adolescent patients with moderate-to-severe symptoms [14–19].

The aim of this study was to assess the efficacy and safety of rupatadine 10 mg administered once daily for 4 weeks compared with ebastine 10 mg and placebo in the management of patients suffering from perennial allergic rhinitis (PAR).

Material & methods

■ Design & treatments

The study was a randomized, double-blind, parallel-group, placebo-controlled trial of rupatadine and ebastine, both at a dose of 10 mg, conducted in 29 centers in Spain. Study treatments were administered to patients suffering from PAR and were taken orally, once daily (in the morning), during a period of 4 weeks. All the medications were of identical external appearance to maintain the blinding conditions of the study.

During a screening visit, performed 1 week before treatment initiation, the investigator assessed the patients' eligibility through a physical exam, symptoms assessment, electrocardiogram and blood laboratory tests. A prick test was also performed if not carried out within 1 year of the visit. A positive prick test was defined as a wheal diameter exceeding 3 mm in size for a given nonseasonal allergen, compared with that obtained with saline solution injection or greater than that obtained with a histamine 10-mg injection.

All patients gave their written informed consent to participate in the study, which was approved by local ethics committees and the Spanish regulatory agency for health. The study was performed in accordance with The Declaration of Helsinki and its subsequent amendments.

■ Inclusion & exclusion criteria

Patients aged 12 years or over with clinical signs and symptoms compatible with PAR for at least 1 year before inclusion, and a positive prick test for nonseasonal rhinitis allergens, such as moulds or spores, dust mites and animal dander, were included in 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 to be included in the study. Women of childbearing age had to have a negative pregnancy test and had to use contraceptive measures 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.

Patients suffering from nonallergic rhinitis (e.g., vasomotor, infectious or drug-induced rhinitis) or with a negative prick test were not included. Treatment with nasal decongestants in the previous 24 h, topical antihistamines in the previous 48 h, oral antihistamines or disodium chromoglycate in the previous week, systemic or topical treatment with corticosteroids (except for topical hydrocortisone <1%) or immunosuppressants within 2 weeks were also considered as exclusion criteria. Patients under desensitization treatment had to stop therapy during the study period. Other relevant exclusion criteria included abnormal laboratory values of clinical significance, certain conditions that may interfere with response to treatment such as moderate–severe asthma treated with inhaled bronchodilators or inhaled corticosteroids over 800 mcg/day of budesonide or beclomethasone, or with over 500 mcg/day of fluticasone, obstructive nasal polyps or hypersensitivity to compounds structurally related to the study drug.

The recruitment period lasted 1 year from January 1999, so this study was undertaken before a guidance document was published, and before broad use of a new classification of allergic rhinitis was implemented [20, 101].

■ Assessment of efficacy

All patients were assessed for treatment efficacy based on the patients' subjective recording on diary cards after 2 and 4 weeks of treatment initiation. Before taking the medication, patients had to record the severity of symptoms experienced during the previous day (reflective 24-h evaluation). The investigators examined the patients' diary card at each study visit (weeks 2 and 4) to check treatment compliance, register any study discontinuation and to ask for treatment tolerability.

Symptoms of rhinitis included four nasal symptoms (rhinorrhea, sneezing, nasal itching and nasal obstruction) and one non-nasal symptom (ocular itching). The severity of symptoms was scored numerically on 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, patients' and physicians' global evaluation of efficacy was scored with a five-point categorical scale: 0 = worsened, 1 = no change, 2 = slight improvement, 3 = good improvement or 4 = excellent improvement.

The main variable of efficacy 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 one (Pdmax1). Treatment efficacy was also evaluated using

the change from baseline in the severity of total symptom score (TSS; 5TSS) and total nasal symptom score (4TNSS), defined as the sum of individual symptom scores (each symptom or nasals symptoms) at each study day. The maximum value of 5TSS from each patient was also registered (DTSSmax) throughout the study period. Finally, investigator and patient global assessment were also evaluated.

■ Assessment of safety

Treatment safety and tolerability was evaluated according to the incidence and type of adverse events spontaneously reported in the patients' diaries, or reported as an answer to the investigators' question of "Have you noticed any discomfort during these days?" at each visit. All results of blood laboratory tests and physical examinations, performed during the study as well as at the end of the study period, were considered. All adverse events were coded using the WHO Adverse Reactions Terminology dictionary and grouped by treatment.

■ Statistical analyses

It was estimated that a total of 63 patients per group were required to detect a 20% relative reduction between active treatments and placebo in the main efficacy variable (Pdmax1), with a two-sided significance level of less than 5% and a power of 80%. Recruitment was stopped after the inclusion of 223 patients because the discontinuation rate was under the initial 20% expected and statistical power guaranteed.

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, subsequent pairwise contrasts using a Bonferroni adjustment were made between the treatment groups. For quantitative (efficacy and safety) variables, mean, median, standard deviation, and maximum and minimum values were calculated. Qualitative variables were expressed as relative frequencies. The Chi-square test was used for qualitative variables and the Fisher test was used if the applicability conditions were not present. The Mantel–Haenszel Chi-square test was performed in case both variables lay on an ordinal scale.

Analysis of all efficacy and safety measures was based on intention-to-treat (ITT), including all patients who were randomized and received at least one dose of study medication. Reasons for discontinuation included treatment failure, adverse events considered severe according to the investigator criteria and lost to follow-up. Although these patients were not excluded from the efficacy analysis, only the data available were used. The first 2 weeks of analysis was not initially planned and considered exploratory. All statistical analyses were performed using the SAS® software version 6.12.

Results

■ Study population

FIGURE 1 shows the patient flow within the study. A total of 223 patients fulfilled all the inclusion criteria and none of the exclusion criteria. These patients were randomized to receive rupatadine 10 mg (71 patients), ebastine 10 mg (79 patients)
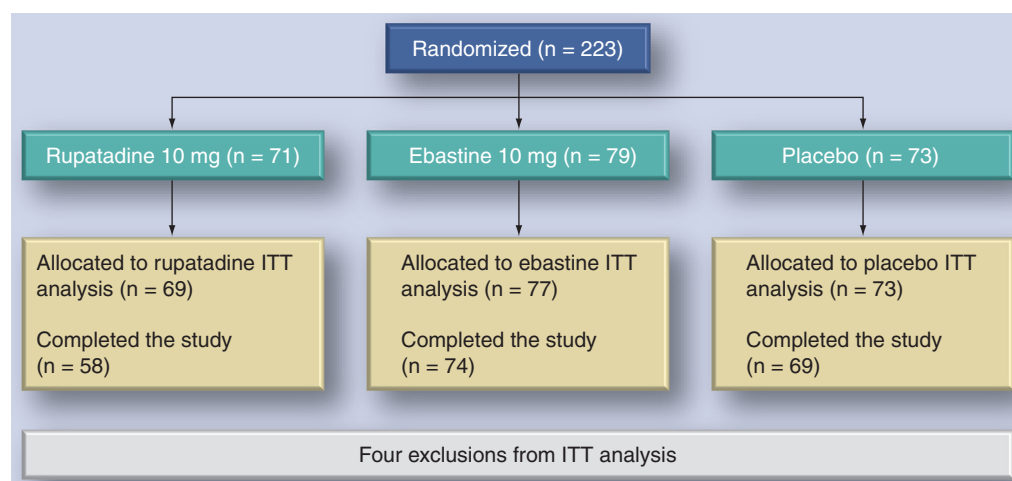
Figure 1. Patients' flow chart throughout the study conduction.
ITT: Intention-to-treat.

or placebo (73 patients). Four cases were considered to be postrandomization losses and were not considered in the analyses (two patients assigned to rupatadine did not receive medication, one patient was randomized twice to receive ebastine, and no further information was available on one patient within the ebastine group). Thus, the ITT analysis included a total of 219 patients with similar baseline rhinitis symptoms and demographic characteristics (TABLE 1). A total of 21 patients, accounting for 9% of the total, were withdrawn from the study or lost to follow-up before completion [20]. The higher incidence corresponded to the rupatadine 10-mg group (13%) for unacceptable adherence of treatment, whereas the rates for placebo (5.5%) and ebastine groups (5.1%) were very similar. Nevertheless, all these cases were included in the ITT analysis.

■ Overall efficacy

Results for the primary and secondary outcomes over the 4-week treatment period concerning the ITT population are summarized in TABLES 2 & 3. 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 one (Pdmax1), both at 2 weeks and at the end of the study period (TABLE 2), was greater for rupatadine 10 mg and ebastine 10 mg compared with placebo, but was shown to be nonsignificant. Progressive symptomatic relief became apparent since Pdmax1 values at 4 weeks were greater than those at 2 weeks, although differences between these two cutoff points did not reach statistical significance.

Reductions from baseline in 5TSS with rupatadine 10 mg and ebastine 10 mg were significantly greater than those with placebo (p = 0.019 and 0.013, respectively) at the end of the study period (4 weeks) (-5.53 ± 3.9; -5.32 ± 4 and -4.53 ± 3.8,

respectively) (TABLE 3). At 2 weeks of treatment, mean reductions from baseline were less apparent, but also greater with rupatadine 10 mg or ebastine 10 mg compared with placebo. Active treatments showed greater reductions from baseline in each of the individual symptoms in comparison with placebo that were statistically significant for rhinorrhea (ebastine 10 mg: p = 0.046), sneezing (rupatadine 10 mg: p = 0.0024; ebastine 10 mg: p = 0.0106); nasal itching (ebastine 10 mg: p = 0.0378) and ocular itching (rupatadine 10 mg: p = 0.0389) (FIGURE 2). None of the active treatments reduced nasal obstruction symptoms in a significant manner compared with placebo. Similarly, after 2 weeks of treatment, most of the individual symptom score reductions were greater with both rupatadine 10 mg and ebastine 10 mg. There were no statistically significant differences between active treatments in score reduction (total or individual symptoms) at 2 weeks, nor at the end of study period.

When the maximum daily TSS (DTSSmax) of each patient during the study period was analyzed, pairwise comparisons found significant differences between rupatadine 10 mg and placebo mean values (1.59 ± 0.7 and 1.90 ± 0.75, respectively) (p = 0.019).

Results from overall impression of efficacy showed that a greater percentage of patients and investigators considered that symptom severity did not improve or even worsened in patients taking placebo, compared with those taking any of the active treatments. More investigators considered a 'good or excellent' improvement in symptoms with rupatadine 10 mg (54%) or ebastine 10 mg (50%), in comparison with investigators that classified patients receiving placebo (42%) as having such improvement. Nevertheless, differences were only significant between rupatadine 10 mg and placebo (p = 0.03). The overall efficacy assessed by the patients also revealed a higher perception of effectiveness for active treatments than that of placebo, although these differences were not statistically significant.

■ Safety

TABLE 4 summarizes the results of the safety analysis. No differences between groups were found in the number of patients reporting at least one adverse event. Headache (n = 72; 33% of the study population) and somnolence (n = 28; 13% of the study population) were the most commonly reported adverse events in all groups of treatment. Other frequently reported adverse events were back pain (n = 13; 6%) and fatigue/asthenia (n = 11; 5%). No significant differences

Table 1. Baseline symptoms and demographic characteristics of the study population[†].

	Rupatadine (n = 69)	Ebastine (n = 77)	Placebo (n = 73)
Age (years)	27 ± 9.6	27 ± 10.2	29 ± 10.1
Male sex (n [%])	30 (43.5)	35 (45.5)	39 (53.4)
Baseline 5TSS (units)	9.64 ± 3.3	9.32 ± 3.2	9.64 ± 3.3
Baseline 4TNSS (units)	8.28 ± 2.3	7.99 ± 2.3	8.11 ± 2.4
Rhinorrhea	2.30 ± 0.7	2.00 ± 0.8	2.14 ± 0.8
Sneezing	1.91 ± 0.9	2.13 ± 0.7	1.92 ± 0.8
Nasal itching	1.84 ± 1.0	1.91 ± 0.8	2.07 ± 0.7
Nasal obstruction	2.22 ± 0.8	1.95 ± 0.9	1.99 ± 0.9
Ocular itching	1.36 ± 1.3	1.34 ± 1.1	1.53 ± 1.2

[†]Values are means ± standard deviations.
4TNSS: Total nasal symptom score; 5TSS: Total symptom score.

in the incidence of these adverse events existed between treatments. Three patients withdrew from the study due to adverse events: two in the rupatadine 10 mg group, one with a localized rash probably related to the study medication, and two patients withdrew from the study due to adverse events unrelated to the study medication. Although several laboratory values outside of the normal range were detected, none were considered as clinically relevant by the investigator. No serious adverse events were reported during the study period.

Discussion

In this clinical trial, the percentage of days with less severe symptoms (Pdmax1) was originally planned as the main variable of efficacy. In both active treatment arms (i.e., rupatadine and ebastine), patients experienced a consistent and progressive symptomatic relief; however, no statistically significant differences were detected between active treatment and placebo groups. Like many other studies in allergic rhinitis, we detected a high response to placebo and, in approximately 40% of study days, the most severe symptom score was less than or equal to one in patients receiving placebo. This fact may have compromised the statistical power needed to show differences between active treatments and placebo.

For most secondary variables of efficacy, rupatadine 10 mg showed a consistent reduction in symptom score in comparison with placebo. TSS (5TSS) throughout the entire study period was significantly lower in patients receiving any of the active treatments than in those receiving placebo. Similarly, when compared with placebo, both active groups showed greater reductions in the assessment of nasal scores (4TNSS). In addition, the analysis of individual symptoms scores revealed that patients receiving treatment with either rupatadine 10 mg or ebastine 10 mg scored better than those receiving placebo. Statistically significant differences were detected for rhinorrhea, sneezing, nasal itching and ocular itching symptoms in comparison with placebo. By contrast, none of the active treatments caused an apparent improvement in symptoms of nasal obstruction, as this symptom is the most independent of the antihistamine effects.

A sustained decrease in symptoms was seen throughout the study in patients treated with rupatadine 10 mg, suggesting that treatment maintenance beyond 4 weeks would have lead to more consistent results in efficacy, whichever variable was assessed. Visual inspection of each

Table 2. ANCOVA results of the primary efficacy variable (Pdmax1) by treatment period (intention-to-treat population).				
Condition	Rupatadine (n = 69)	Ebastine (n = 77)	Placebo (n = 73)	p-value
Pdmax1 at 2 weeks	42.3 ± 40.3	47.5 ± 38.5	36.7 ± 34.7	ns
Pdmax1 at 4 weeks	48.7± 37.9	50.8 ± 35.9	42.0 ± 34.2	ns

Values expressed as mean (± standard deviation) of reduction score from baseline adjusted for baseline score and center.
ANCOVA: Analysis of covariance; Pdmax 1: Percentage of days during the study period where the score of the most severe symptom on each day was less than or equal to one.

day's efficacy scores indicates an initial similar reduction in symptoms with active treatment and placebo; after 10 days of treatment with placebo and ebastine, slopes reached a plateau until the end of the study. Differences did not reach statistical significance, probably due to variability in the daily mean score values calculation. These results may indicate that rupatadine does not develop tolerance to symptom relief, although a 4-week follow-up period is too short to see any long-term effect. Moreover, both patients and investigators subjectively perceived the efficacy of rupatadine as being greater than that of placebo, and even ebastine.

Results obtained in this study are consistent with previous randomized controlled trials using once-daily rupatadine 10 or 20 mg, in which the medication was highly efficacious in attenuating the symptoms of allergic rhinitis in adult and adolescent patients with moderate-to-severe symptoms [14–19]. Patients with perennial symptoms tend to have less acute symptoms than patients suffering from seasonal rhinitis, leading to the impression that those patients are less responsive to treatment with antihistamines. In addition, our study points out the assessment of TSSs and their reduction from baseline values as being a more sensitive variable to detect any symptomatic improvement than the percentage of days with less severe symptoms (Pdmax1). A recent European guideline recommends the estimation of efficacy in clinical trials on this topic to be based on TSSs [101].

Treatment with rupatadine 10 mg per day during 4 weeks was a safe and well-tolerated treatment of allergic rhinitis. Headache, somnolence and asthenia were frequently reported with other second-generation antihistaminic compounds [20–22]. The incidence of somnolence for rupatadine 10 mg was slightly higher than rates found for this dosage level of the compound in previous studies. The incidence of somnolence in the placebo group (10%) also seems somewhat high. There are several explanations for this finding: firstly, all symptoms are allergic rhinitis

Table 3. ANCOVA results for mean 5TSS, 4TNSS and individual symptom scores by treatment period (intention-to-treat population)[†].

Condition	2 weeks			4 weeks		
	Placebo (n = 73)	*Rupatadine (n = 69)*	*Ebastine (n = 77)*	*Placebo (n = 73)*	*Rupatadine (n = 69)*	*Ebastine (n = 77)*
5TSS	-4.28 ± 3.8	-5.17 ± 4.3*	-5.16 ± 4.1**	-4.53 ± 3.8	-5.53 ± 3.9*	-5.32 ± 4.0*
4TNSS	-3.42 ± 3.0	-4.25 ± 3.3*	-4.27 ± 3.2**	-3.62 ± 2.9	-4.55 ± 3.0*	-4.41 ± 3.1*
Rhinorrhea	-0.77 ± 0.98	-1.02 ± 1.03*	-0.92 ± 1.03*	-0.82 ± 0.97	-1.11 ± 0.98*	-0.94 ± 1.01*
Sneezing	-0.82 ± 0.98	-1.12 ± 1.02**	-1.29 ± 0.89**	-0.86 ± 0.98	-1.19 ± 0.96**	-1.30 ± 0.84**
Nasal itching	-1.06 ± 0.84	-1.03 ± 1.12	-1.17 ± 1.02*	-1.15 ± 0.82	-1.09 ± 1.05	-1.22 ± 1.01*
Nasal obstruction	-0.71 ± 0.93	-0.99 ± 0.96	-0.83 ± 1.00	-0.74 ± 0.91	-1.06 ± 0.90	-0.89 ± 0.97
Ocular itching	-0.87 ± 1.21	-0.94 ± 1.25	0.87 ± 1.17	-0.90 ± 1.22	-0.99 ± 1.20[†]	-0.89 ± 1.15

[†]Values expressed as mean (± standard deviation) of reduction score from baseline adjusted for baseline score and center. Significant levels expressed as difference versus placebo: *p < 0.05; **p < 0.01.
4TNSS: Total nasal symptom score; 5TSS: Total symptom score; ANCOVA: Analysis of covariance.

symptoms and are indistinguishable from those caused by medication; indeed, more placebo-treated patients complained of headaches and less complained of somnolence in comparison with active treatments. Secondly, adverse event assessment was carried out through both subjective reporting in diary cards and direct questions from investigators. Finally, only two patients discontinued the study owing to treatment intolerance (one to rupatadine and one to placebo), suggesting that most adverse events were of mild or moderate intensity.

Rupatadine was compared with ebastine, a broadly used second-generation antihistamine that is effective and safe in the treatment of PAR, with a similar pattern of efficacy. Ebastine, as opposed to rupatadine, has no known anti-PAF activity. PAF has been identified as an inflammatory mediator potentially involved in allergic rhinitis through the induction of vascular leakage, which is related to symptoms such as rhinorrhea or nasal congestion [23–25], and experimental models have shown that PAF is released

secondarily to histamine's action on the nasal mucosa and plays an important role in nasal allergy [26,27]. In the clinical setting, PAF induces many of the rhinitis symptoms in the nose, including an increase in nasal airway resistance, nasal discharge and nasal hyperresponsiveness to subsequent allergen challenge [28–30]. Rupatadine has been shown to potently antagonize these inflammatory mediator receptors *in vivo* [13].

More recently, the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline document retains the clinical definition of rhinitis from previous documents, but acknowledges the existence of practical difficulties in using these definitions in some settings such as population surveys. The ARIA document also states that the classic types of seasonal and perennial rhinitis cannot be used interchangeably with the new classification, and issues a strong recommendation in favor of oral H1 antihistamine treatment in allergic rhinitis, in whichever definition is used [20]. It is important to stress that almost all studies in allergic rhinitis using available antihistamine treatments did not use ARIA classification, and substantial differences in efficacy should not be ruled out. Comparative assessment between available antihistamine drugs using persistent and intermittent allergic rhinitis classification must be considered a research target in the future.

In conclusion, the symptomatic treatment of patients suffering from PAR with rupatadine was found to be effective and safe.
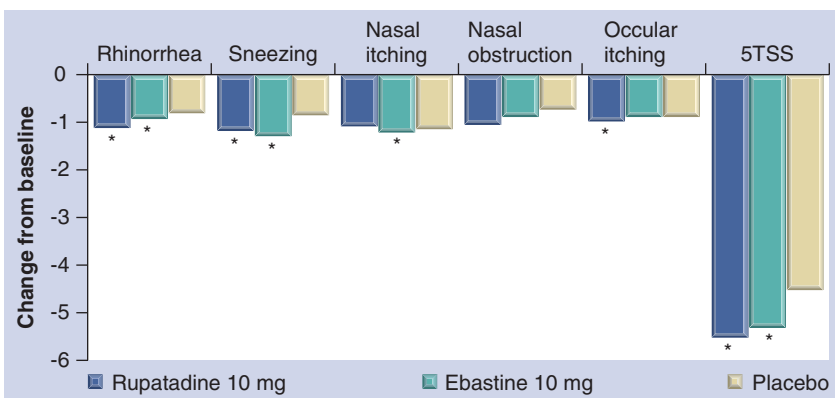
Figure 2. Change from baseline of individual symptoms and total symptom score at end of treatment (intention-to-treat population).
*p < 0.05 significative differences compared with placebo.
5TSS: Total symptom score.

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Table 4. Adverse event incidence in either treatment group (intention-to-treat population).

Adverse event (%)	Rupatadine (n = 69)	Ebastine (n = 77)	Placebo (n = 73)	Total (n = 219)
Headache	21 (30.4)	24 (31.2)	27 (37.0)	72 (32.9)
Somnolence	12 (17.4)	9 (11.7)	7 (9.6)	28 (12.8)
Back pain	3 (4.3)	5 (6.5)	5 (6.8)	13 (5.9)
Asthenia	5 (7.2)	3 (3.9)	3 (4.1)	11 (5.0)

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.

Executive summary

Epidemiology
- The prevalence of allergic rhinitis is estimated to affect up to 40% of the population, depending on the geographical area.

Therapy
- Although treatment of allergic rhinitis is based mainly on allergen avoidance and use of oral antihistamines, the finding that allergic rhinitis is driven by multiple inflammatory mechanisms has led to an increased demand for therapeutic agents with a broader spectrum of activity, beyond antagonism of H1 histamine receptors.

Results
- As in many other studies in allergic rhinitis, we detected a high responsiveness to placebo. Both active groups showed greater reductions in the assessment of nasal scores (4TNSS).
- Comparative assessment between available antihistamine drugs must be considered a research target in the future.

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