Original Article

A randomized, double-blind, parallel-group study, comparing the efficacy and safety of rupatadine (20 and 10 mg), a new PAF and H_1 receptor-specific histamine antagonist, to loratadine 10 mg in the treatment of seasonal allergic rhinitis

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ABSTRACT

Background: The main objective of this randomized, double-blind, parallel-group, comparative study was to assess the efficacy and safety of rupatadine 10 mg (R10) and 20 mg (R20) administered once-daily for two weeks compared with those of loratadine 10 mg (L10) in the treatment of seasonal allergic rhinitis (SAR).
Methods: A total of 339 SAR patients were randomized to receive R20 (111 patients), R10 (112 patients) or L10 (116 patients). The main efficacy variable was the mean total daily symptom score (mTDSS) based on the daily subjective assessment of the severity of rhinitis symptoms - rhinorrhea, sneezing, nasal itching, nasal obstruction, conjunctival itching, tearing and pharyngeal itching - recorded by patients.
Results: The mTDSS was significantly lower in the groups treated with R20 (0.80 ± 0.46) and R10 (0.85 ± 0.52) than in the group treated with L10 (0.92 ± 0.51) by protocol analysis (p=0.03) but not by intention-to-treat analysis. The secondary variables used to assess efficacy (mDSS, DSSmax, CSS and TCSS) also showed significantly milder symptoms in patients treated with R20 and R10, particularly in sneezing and nasal itching. All treatments were well tolerated and no serious adverse events were recorded. Headache was the most frequent non-serious adverse event, and these did not show significant differences between treatments at similar dose levels. Somnolence was more frequent in R20 than in the other two groups.
Conclusions: The present results suggest that rupatadine 10 mg a day may be a valuable and safe alternative for the symptomatic treatment of seasonal allergic rhinitis.

Key words: Rupatadine, loratadine, rhinitis, seasonal allergic rhinitis, intermittent allergic rhinitis, platelet activating factor, antihistamine.

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Introduction

Allergic disorders show a complex nature involving the synthesis and/or release of different mediators [1, 2]. Antigenic challenge causes the release of histamine by mast cells and basophils, leading to contraction of the bronchial smooth muscles, vasodilation and an increase in vascular permeability, as well as increased mucus secretion by the respiratory epithelium cells [3-5]. Platelet-activating factor (PAF) is another important mediator in inflammatory and allergic conditions [6]. PAF is a potent chemotactic stimulus for eosinophils [7]. Moreover, PAF and histamine complement their activities *in vivo*. Histamine is released from preformed deposits in mast cells and mediates the immediate allergic response, whereas PAF is synthesized *de novo* in response to antigenic challenges and mediates the delayed allergic response [8]. Additionally, histamine and PAF can mutually promote their release by different tissues and cells.

Based on the above information, the joint blockage of histamine and PAF actions may be expected to be clinically more effective than blockage of only one. This justifies the search for new chemical entities showing such dual activity, as they are not available in the current therapeutic arsenal. Some antihistamines such as loratadine or cetirizine show a marginal PAF-antagonist properties, such as inhibition of PAF-induced eosinophil chemotaxis, but these effects cannot be attributed to a specific interaction with PAF receptors [9, 10]. Rupatadine was recently developed as a new PAF and H_1 receptor-specific histamine antagonist [11-13], and tested as a treatment for allergic disorders involving the release of histamine and PAF [14].

Phase I studies showed that rupatadine was well tolerated in the range of single 2-80 mg oral doses and 20-40 mg oral daily doses for 7 days. The inhibitory effects of rupatadine on PAF- and histamine-induced flares were significantly greater and longer compared to those of placebo [15]. Some phase II clinical studies have shown symptomatic improvement with rupatadine *versus* placebo or other antihistamines in patients suffering from allergic rhinitis [16]. Recently, rupatadine has been approved for marketing in Spain and other European countries in the treatment for allergic rhinitis [17]. The primary objective of this study was to assess the efficacy and safety of rupatadine 20 mg and 10 mg administered once-daily for two weeks compared with those of loratadine 10 mg in the treatment of seasonal allergic rhinitis (SAR), which will be most often diagnosed as intermittent allergic rhinitis under the new classification of allergic rhinitis [18].

Material and Methods

Study design

The present study was a randomized, double-blind, parallel-group, comparative trial of rupatadine 10 mg (R10), rupatadine 20 mg (R20), and loratadine 10 mg (L10), all administered to patients with a history of SAR. All medications were taken orally at breakfast, and the dose regimen was one tablet per day. Follow-up lasted for 2 weeks, which is a standard period of time used in studies on SAR therapeutics as it allows showing any effects of treatment. An inclusion visit plus two other visits at the end of each week of treatment were conducted. The comparative drug selected, loratadine, is an effective and widely used antihistamine treatment. The study was conducted in France with the participation of 45 allergologists after their local Ethics Committees had given approval, and all patients gave their written informed consent before inclusion.

Inclusion criteria

The inclusion criteria were the following: patients aged 12 to 65 years, diagnosed with SAR due exclusively to pollen for at least 2 years, and with an acute stage of the disease (nasal symptom score ≥ 5 points). A positive skin prick test (papule diameter > 3 mm than that produced by saline control, or ≥ than that obtained with 10 mg/mL histamine) was required either at inclusion or during the previous year. Women of childbearing age had to show a negative pregnancy test and be committed to use contraceptive measures during the study.

Exclusion criteria

The main exclusion criteria were the following: 1) non-allergic rhinitis or rhinitis due to hypersensitivity to allergens other than pollens; 2) hypersensitivity to loratadine or to substances relating to the study drug ingredients; 3) nasal polyps or significant nasal septum deviation; 4) acute asthma attack or treatment for asthma within the previous 3 months; 5) patient on hyposensitization therapy; 6) treatment with ketotifen within the previous 2 weeks; 7) any oral antihistamine or disodium chromoglycate taken during the previous week, or astemizole treatment during the previous month; 8) topical antihistamines taken within the previous 48 hours or nasal decongestants used within the previous 24 hours, and 9) systemic or topical treatment with corticosteroids (except for topical hydrocortisone < 1%), immunosuppressants, or any investigational drug within 2 weeks prior to inclusion.

Assessments and study variables

All patients received a diary for daily recording (every morning before dose and every night at bedtime) of the following symptoms: rhinorrhea, sneezing, nasal itching, nasal obstruction, conjunctival itching, tearing, and

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pharyngeal itching. The severity of each symptom was scored on a scale of 0-3 with 0=absent, 1=mild, 2=moderate and 3=severe. The investigators checked the patients' diary cards at each new visit (days 7 and 14) to ensure protocol compliance and to offer any advice required.

The main efficacy variable was the *mean total daily symptom score* (mTDSS). The mTDSS was based on the daily subjective assessment of the rhinitis symptom severity as recorded by patients in their diaries. The *daily symptom score* (DSS) was the mean of the two scores for each symptom within 24 hours following drug administration. The *total daily symptom score* (TDSS) was the mean of the DSS recorded for each of the 7 symptoms assessed, and the mTDSS was the mean of all TDSS values.

The secondary efficacy variables were the *mean daily symptom score* (mDSS), defined as each patient's mean of all DSS for a given symptom over the study; DSSmax (maximum value for DSS); TDSSmax (maximum value for TDSS), and Pdmax0 and Pdmax1, percentage of days when DSSS (*daily severest symptom score*) was 0 or 1, respectively. Clinical assessment by the investigator was also quantified through the *clinical score of a symptom* or CSS (score given to each symptom by the investigator at each visit) and the *total clinical score of symptoms* or TCSS (mean of the seven CSS at each visit). The patients' and physician's global evaluation of efficacy was scored on a 0-3 scale where 0=worsening, 1=no change, 2=improvement, and 3=disappearance of symptoms. The patients also recorded any adverse events (AE) or concomitant medications taken during the study. Laboratory tests from blood samples were performed at inclusion and at the final visit.

Statistical analysis

The number of patients required to show a difference of 0.25 points between treatments in the main variable mTDSS was calculated. Assuming an mTDSS standard deviation (SD) of 0.62 based on results from a previous dose-ranging study with rupatadine in the treatment of SAR (18), together with protection levels of 0.05 against type I random errors and 0.2 against type II errors, the number of patients required to show the aforementioned difference was 97 patients per group. A recruitment of 108 patients per group was planned (for a total of 324 patients) with an initially expected dropout rate of 10%. However, the dropout rate reached during the study was 15% and therefore a new sample size was calculated (347 patients).

Comparability between treatment groups for critical demographic and baseline characteristics of the patients was assessed through a chi-square test for the qualitative variables and an analysis of variance for the quantitative variables. All statistical tests were two-tailed. The alpha significance level was set at 5% and the data shown are mean ± SD. The value of each symptom score at visit 0 was taken as baseline. Efficacy variables were analyzed on both *intention to treat* (ITT) and *per protocol* (PP) populations, whereas safety was analyzed on ITT population only. The mTDSS results were compared between treatment groups using a covariance analysis

Table 1. Main demographic and baseline characteristics of the ITT population.

		R20 (n=111)	**R10** (n=112)	**L10** (n=116)	**All** (n=339)
Age (years)	Male	32.1 (9.3)	33.7 (10.7)	31.3 (11.2)	32.4 (10.5)
	Female	33.4 (11.1)	32.4 (9.3)	32.8 (13.1)	32.9 (11.2)
Sex	Male	49	58	65	172
	Female	62	54	51	167
Race (%)	Caucasian	90 (26.6)	97 (28.6)	104 (30.7)	291 (85.8)
	Non Caucasian	21 (6.2)	15 (4.4)	12 (3.5)	48 (14.2)
BMI (kg/m2)	Male	23.8 (2.9)	23.8 (3.0)	23.8 (3.3)	23.8 (3.1)
	Female	22.7 (4.6)	21.8 (3.6)	22.3 (3.3)	22.3 (3.9)
Basal mTDSS		1.75 (0.46)	1.62 (0.47)	1.66 (0.45)	1.68 (0.46)

Data shown are number of patients (SD). R20, rupatadine 20 mg; R10, rupatadine 10 mg; L10, loratadine 10 mg; BMI, body mass index; mTDSS, mean total daily symptom score. No significant differences were found.

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that included treatment, center and basal score. Overall efficacy assessments by patients and by investigators were analyzed using the Cochran-Mantel-Haenszel statistics test. Adverse events occurring during the study were coded using the WHO-ART dictionary and summarized by treatment group, with special attention given to severe and treatment-related events.

Results

Study population

Table 1 summarizes the main demographic and baseline data of patients. A total of 347 patients were initially included in the trial; eight patients did not start the treatment, so only 339 patients took at least one dose of treatment (ITT analyzed patients). The PP analysis involved 255 patients: 65 patients showing major protocol deviations and 19 patients who had withdrawn for reasons other than inefficacy or treatment-related AEs were excluded (Table 2). Table 3 shows the main reasons for withdrawal from the study. Fourteen patients included (4.1%) were less than 18 years old (5 in the R20, 3 in the R10 and 7 in the L10 group). No significant differences were found between groups in demographic characteristics, baseline symptom scores, protocol deviations, withdrawal reasons or any other population characteristics.

Efficacy

No differences were found in the ITT analysis for the main efficacy variable, mTDSS. Nevertheless, this variable showed a significant difference between groups (p=0.03) in the PP analysis, with mean mTDSS values of 0.80, 0.85 and 0.92 found in the R20, R10 and L10 groups, respectively (Figure 1).

Significant differences were also found for secondary variables. In the ITT population, R20 and R10 showed lower scores for DSSmax than L10 ($p<0.01$) (Figure 2B). The assessment by the practitioners (CSS) confirmed the improvement with rupatadine in sneezing (Figure 3A, $p=0.01$) and nasal itching (Figure 3B, $p=0.01$). The analysis of changes in TCSS between the inclusion and final visits showed differences consistent with the efficacy progression already detected (R20>R10>L10, $p=0.04$) (Figure 4). In the PP population, mDSS for sneezing showed significant lower

Table 2. Patients' disposition.

	R20	R10	L10	All
INTENTION TO TREAT POPULATION	111	112	116	339
WITH MAJOR PROTOCOL DEVIATIONS (%)	27 (24.3)	21 (18.8)	17 (14.7)	65 (19.2)
Forbidden treatment	16	12	12	40
Diary cards badly filled	7	4	1	12
Unallowed range between visits	4	3	2	9
Exclusion criteria	0	0	1	1
Treatment allocation mistake	0	1	1	2
Lack of compliance	0	1	0	1
DISCONTINUED FOR OTHER REASONS (%)*	7 (6.3)	5 (4.5)	7 (6.0)	19 (5.6)
PER PROTOCOL POPULATION (%)	77 (69.4)	86 (76.8)	92 (79.3)	255 (75.2)

* Other than adverse events related to the treatment or absence of response to treatment. Data shown are number of patients (%). R20, rupatadine 20 mg; R10, rupatadine 10 mg; L10, loratadine 10 mg.

Table 3. Reason for withdrawal.

	R20 (n=111)	R10 (n=112)	L10 (n=116)	All (n=339)
Patient's decision	5 (4.5)	5 (4.5)	6 (5.2)	16 (4.7)
Major protocol deviation	3 (2.7)	1 (0.9)	3 (2.6)	7 (2.1)
Adverse event	4 (3.6)	5 (4.5)	2 (1.7)	11 (3.2)
No response to treatment	5 (4.5)	4 (3.6)	7 (6.0)	16 (4.7)
Other	0 (0.0)	1 (0.9)	1 (0.9)	2 (0.6)
Total	**17 (15.3)**	**16 (14.3)**	**19 (16.4)**	**52 (15.3)**

Data shown are number of patients (%). R20, rupatadine 20 mg; R10, rupatadine 10 mg; L10, loratadine 10 mg. No significant differences were found.

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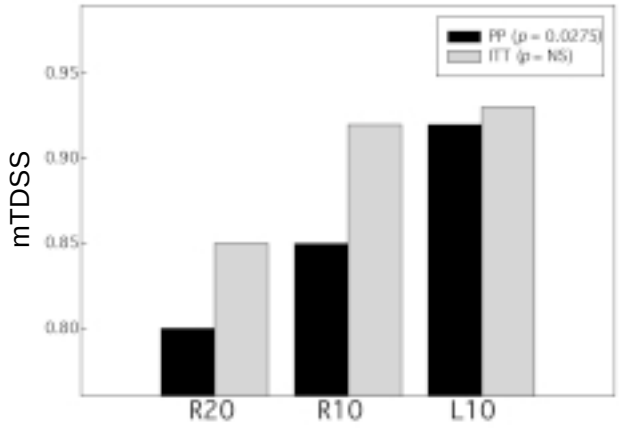

Figure 1. Mean total daily symptom score (mTDSS) in the intention to treat (ITT) and per protocol (PP) populations. R20, rupatadine 20 mg; R10, rupatadine 10 mg; L10, loratadine 10 mg. Data shown are means.

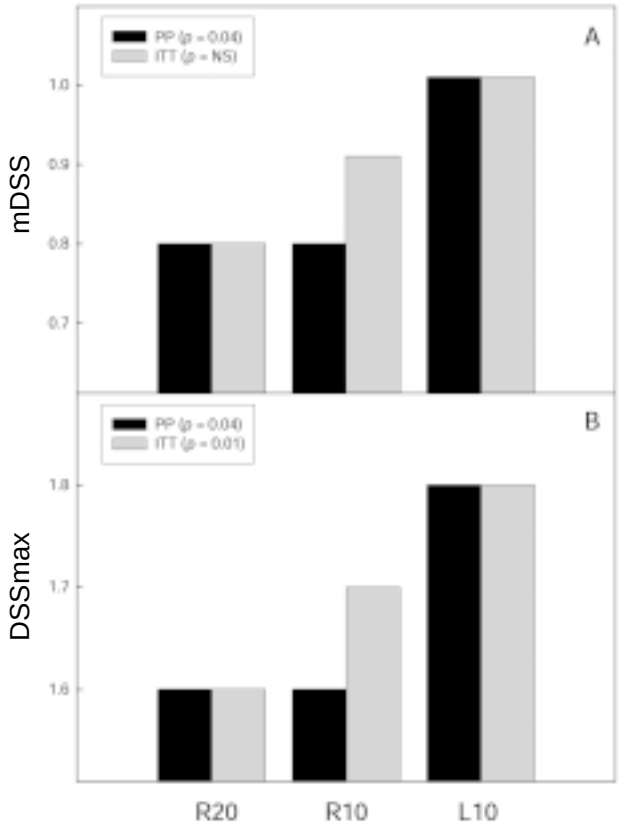

Figure 2. Changes in the mean daily symptom score (mDSS) (**A**), and maximum value of the daily score of a symptom (DSSmax) (**B**) for sneezing in ITT and PP populations. R20, rupatadine 20 mg; R10, rupatadine 10 mg; L10, loratadine 10 mg. Data shown are means.

scores (p=0.04) in the R20 and R10 groups than in the L10 group (Figure 2A). DSSmax for sneezing also showed lower scores (p=0.04) for the R20 and R10 groups than for the L10 group (Figure 2B). Overall

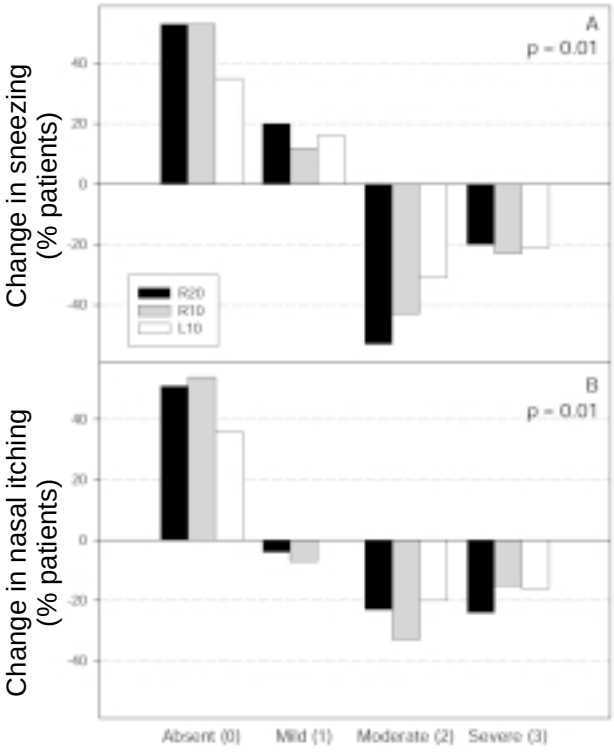

Figure 3. Changes in the clinical score of a symptom (CSS) for sneezing (A) and nasal itching (B) in the ITT population. The severity of each symptom was scored on a scale of 0-3 with 0=absent, 1=mild, 2=moderate and 3=severe. Data shown are means of percentages corresponding to each variable category. R20, rupatadine 20 mg; R10, rupatadine 10 mg; L10, loratadine 10 mg.

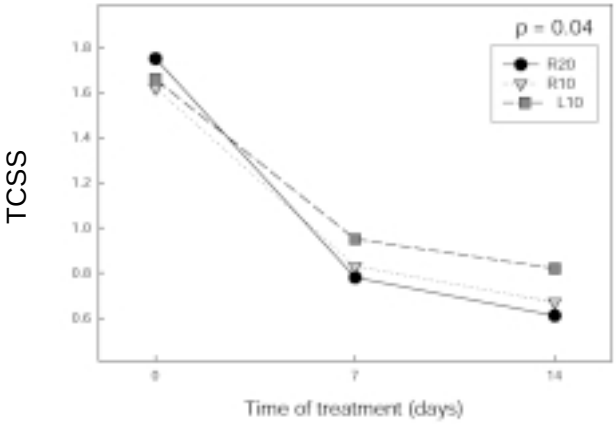

Figure 4. Changes in the total clinical score of symptoms (TCSS) in the ITT population. R20, rupatadine 20 mg; R10, rupatadine 10 mg; L10, loratadine 10 mg. Data shown are means.

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efficacy assessment showed a significant improvement by patients at the end of treatment in the PP population (p=0.05), with R10 superiority over R20 and R20 superiority over L10.

Safety

No serious adverse events were recorded during this trial. Overall, R20, R10 and L10 once-daily were found to be safe and well tolerated. The number of patients showing at least one AE were as follows: 72/111 (64.9%) in R20, 60/112 (53.6%) in R10, and 57/116 (49.1%) in L10 group. No significant differences were found between groups. Twelve AEs led to patients' withdrawal, but no significant differences were found between groups of treatment. Headache was the most frequent AE, with incidences of 23.4%, 14.3% and 12.1% in the R20, R10 and L10 groups, respectively. Other AEs found were somnolence (25%, 12.5% and 7.8%), asthenia (11.7%, 10.7% and 6.0%) and coughing (5.4%, 8.0% and 4.3%). The only significant difference in these AEs was in somnolence between R20 and the other two groups. Other AEs with an overall incidence rate lower than 5% were back pain (4.5%, 3.6% and 4.3%), dry mouth (3.6%, 1.8% and 1.7%) and pharyngitis (4.5%, 7.1% and 1.7%). No significant differences were found between groups. Finally, no relevant abnormal laboratory data were found.

Discussion

The main purpose of the study was to establish the efficacy of a recently developed histamine and PAF antagonist compound, rupatadine, relative to a gold standard such as loratadine 10 mg once daily after two weeks of treatment in the control of adult patients with SAR symptoms in the primary care setting. The results show that all treatments decreased the symptoms' severity for mTDSS, which was the primary efficacy criterion assessed. However, the study also indicates that rupatadine 20 mg was superior to rupatadine 10 mg and loratadine 10 mg in the control of symptoms, and both rupatadine dose levels proved to be better than loratadine 10 mg in the PP analysis.

Rupatadine 10 and 20 mg a day were both clinically effective, with the higher dosage causing a greater improvement in the majority of symptoms and index scores evaluated. Thus, secondary efficacy variables based on self-assessment (such as mean daily symptom scores and peak daily symptom scores) as well as based on practitioners' assessments (such as clinical symptom scores and total clinical symptom scores) revealed clear differences between treatment groups. The benefits of both rupatadine doses were mainly detected in the significant reduction of sneezing and nasal itching scores in comparison with loratadine 10 mg. Furthermore, overall efficacy assessments by patients and by practitioners at the end of treatment were also better for rupatadine doses, with R10 superiority over R20, and R20 superiority over L10.

Clinical experience to date indicates that rupatadine 10 mg is as effective as standard dosages of other second-generation antihistamine agents [19]. A pooled data analysis of different trials with rupatadine confirmed that all the doses analyzed were effective in reducing daily symptoms in SAR and PAR as compared to placebo [20].

The overall profile of adverse events reported with rupatadine was similar to that reported with other second-generation antihistamines [21]. The incidence and severity of adverse events were similar in the R10 and L10 treatment groups, without significant differences. Only somnolence showed a significant value with the higher dose of rupatadine tested (20 mg). Although the incidence of adverse events may look relatively high, most AEs were related to symptoms of the underlying allergic condition rather than to the study medication [22].

In conclusion, rupatadine 10 mg and 20 mg administered in the morning constitute an effective and well tolerated antihistamine treatment to control symptoms of intermittent or seasonal allergic rhinitis. Rupatadine 10 mg a day may be better in terms of balance between efficacy and side effect profile when compared to rupatadine 20 mg or loratadine 10 mg a day.

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