Original Article

# Rupatadine 10 mg and cetirizine 10 mg in seasonal allergic rhinitis: A randomised, double-blind parallel study

C. Martínez-Cócera[1], M. De Molina[2], E. Martí-Guadaño[3], J. Pola[4], J. Conde[5], J. Borja[6], I. Pérez[6] , E. Arnaiz[6], I. Izquierdo[6], on behalf of the Spanish Rupatadine Rhinitis Study Group*

[1] Allergology Department. Hospital Clínico San Carlos. Madrid.
[2] Allergology Department. Hospital de la Creu Roja. L'Hospitalet de Llobregat. Barcelona.
[3] Allergology Department. Hospital Sant Pere Claver. Barcelona.
[4] Policlínica Sagasta. Zaragoza.
[5] Hospital Virgen de la Macarena. Sevilla.
[6] Clinical Research & Development Unit. J. Uriach y Compañía, S.A. Palau-solità i Plegamans. Barcelona
*Members listed at the end of paper

**Summary.** This randomised, double-blind, parallel-group, multicentre clinical trial evaluated the efficacy and safety of rupatadine, a new antihistamine with antiplatelet-activating factor (PAF) activity, and cetirizine in the treatment of patients with seasonal allergic rhinitis (SAR). A total 249 patients were randomised to receive rupatadine 10 mg once daily (127 patients) or cetirizine 10 mg (122 patients) for two weeks. The main efficacy variable was the mean total daily symptom score (mTDSS) and was based on the daily subjective assessment of the severity of each rhinitis symptom - nasal (runny nose, sneezing, nasal itching and nasal obstruction) and non-nasal (conjunctival itching, tearing, and pharyngeal itching) - recorded by patients in their diaries. The mTDSS was 0.7 for both treatment groups (intention to treat analysis). In the investigator's global evaluation of efficacy at the seventh day, 93.3% and 83.7% patients in the rupatadine and cetirizine groups, respectively, showed some or great improvement ($p = 0.022$) . In the per protocol analysis ($n = 181$), runny nose at the seventh day of treatment was absent or mild in 81.1% of patients in the rupatadine group and in 68.6% of patients in the cetirizine group ($p = 0.029$). In any case statistical significance was not maintained at the second week.
Overall, all treatments were well tolerated. Adverse events (AEs) were similar in both treatment groups, i.e. headache, somnolence and fatigue/asthenia as the most often reported. Somnolence was reported in 9.6% and 8.5% of patients treated with rupatadine or cetirizine, respectively. The most reported AEs (67%) were mild in intensity. Our results suggest that rupatadine 10 mg may be a valuable and safe alternative for the symptomatic treatment of SAR.

**Key words:** Rupatadine, cetirizine, seasonal allergic rhinitis, platelet-activating factor antihistamine drugs.

## Introduction

Allergic rhinitis (AR) represents a global health issue affecting between 10% to 25% of the world population, with increasing prevalence over the last decade, and it is a significant cause of morbidity [1]. Several mediators such as histamine, cysteinyl leukotrienes, prostaglandins and kinins play an active role in the pathophysiology of AR and probably contribute to that of other upper and lower airway associated diseases such as asthma, rhinosinusitis and otitis media with effusion [2]. Platelet-activating factor (PAF) is an important mediator of AR as can be concluded from the effectiveness of the PAF antagonist ABT-491 in rat and guinea pig models of AR [3, 4]. The biological properties of this mediator include vasodilation and an increase in vascular permeability that may contribute to the appearance of rhinorrhea and nasal congestion [5, 6]. Both PAF and its metabolite, lyso-PAF, have been detected in the nasal fluids and plasma of patients with rhinitis [7, 8]. Moreover, PAF and histamine are known to complement each other *in vivo*; histamine is a mediator of early response, and it is released from preformed reservoirs in mast cells, whereas PAF is mainly synthesized de novo [9, 10]. Furthermore, each of these mediators is able to promote the release of the other in some tissues and cells [11]. Thus it seems reasonable to infer that the blockade of both PAF and histamine receptors could be of better clinical efficacy than the blockade of only one of them in the treatment of AR. Although some antihistamines have shown marginal PAF antagonist properties, these effects cannot be attributed to specific interaction with PAF receptors [12, 13]. Rupatadine is a novel compound that shows both antihistamine and anti PAF effects through its interaction with specific receptors and not due to physiological antagonism [14]. In addition, rupatadine has potentially beneficial effects such as inhibition of mast cell degranulation, neutrophil and eosinophil migration, and cytokine release [15]. The safety and efficacy of rupatadine (mostly 10 and 20 mg once daily) in the treatment of SAR and perennial allergic rhinitis (PAR) has been evaluated in phase II and phase III clinical trials. In both clinical entities, rupatadine provided better efficacy than placebo and similar efficacy as well known antihistamines such as ebastine and loratadine (16-20). The dose of 10 mg once daily showed the most favourable risk/benefit balance.

Cetirizine is a specific and long-acting histamine H1 - receptor antagonist. It has marked antiallergic properties and inhibits eosinophil chemotaxis during the allergic response, and has shown efficacy and safety in the treatment of patients with SAR and PAR [21].

The aim of this study was to assess the efficacy and safety of rupatadine, in comparison with those of cetirizine, in the treatment of patients with SAR.

## Methods

### Study Design

The study was a randomised, double-blind, parallel and multicentre clinical trial. Eligible patients were assigned to receive treatment with rupatadine 10 mg or cetirizine 10 mg tablets both administered orally once daily in the morning during two weeks. A computer-generated randomisation scheme was used and the patients were assigned to a sequential randomisation number. Tablets were capsulated in two-piece hard gelatine capsules, Dbcaps®, for double-blind clinical trials, in order to mask the treatments and preserve the double-blind conditions. Treatments considered exclusion criteria (see below) were not allowed during the study. J. Uriach & Compañía, S.A. (Barcelona, Spain) provided all study medications. Patients were visited in basal conditions (day -1) and at days $7 \pm 3$ and $14 \pm 3$ in order to be evaluated for efficacy and safety (see below) and to check treatment compliance. Laboratory blood tests were performed at days -1 and $14 \pm 3$.

A total 26 Spanish allergology centers participated in the study after their local Ethics Committees had given their approval, and after all patients (or a parent/guardian for minors) gave their written informed consent before admittance to the trial. The study was conducted in accordance with applicable Good Clinical Practice and International Conference on Harmonization Guidelines under the principles of the 1996 World Medical Assembly Declaration of Helsinki and subsequent revisions.

### Inclusion criteria

Male and female patients aged 12 to 65 years, diagnosed as suffering SAR caused exclusively by pollen for at least 2 previous years, and with an acute state of the disease (nasal symptom score $\geq 5$ points) were elegible if they presented a positive skin prick test (diameter of the papule > 3 mm than saline solution control, or $\geq$ than histamine 10 mg/ml) at inclusion or within one year before inclusion. Women of childbearing potential had to show a negative pregnancy test at study entry and commit themselves to use contraceptive measures during the study.

### Exclusion criteria

Patients were ineligible for the study if they showed: 1) rhinitis due to hypersensitivity to allergens other than pollens (e.g., mites) or non-allergic rhinitis; 2) known hypersensitivity to cetirizine, to compounds structurally related to the study drugs or to any other component

 

included; 3) nasal polyps or significant deviation of nasal septum; 4) asthma attack or treatments for asthma in the last 3 months; 5) immunotherapy if the patients had to receive this therapy during the time of the study, 6) treatment with topical antihistamines in the previous 48 hours, nasal decongestants in the previous 24 hours, oral antihistamines (other than astemizole) or disodium chromoglycate in the previous week, astemizole in the previous month, ketotifen in the two previous weeks, and systemic or topical treatment with corticosteroids (except for topical hydrocortisone < 1%), immunosuppressants, or any investigational drug within 2 weeks prior to inclusion and 7) patients with out of normal range values in any of the following laboratory blood tests: complete blood count, blood glucose, ionogram, AST, ALT, total bilirrubin, total proteins, urea, creatinine, total cholesterol and triglycerides.

## Assessments of study variables

In the visit prior to study initiation treatment (day -1) all patients received a diary card for daily recording of symptoms severity. Every morning (before taking the medication) and every night (at bedtime) patients noted the severity of the following symptoms: nasal (runny nose, sneezing, nasal itching and nasal obstruction), and non-nasal (conjunctival itching, tearing, and pharyngeal itching). The severity of symptoms was scored numerically on a 0 - 3 scale, in which 0 = absent, 1 = mild (occasionally present but not troublesome), 2 = moderate (frequently present and annoying), or 3 = severe (continuously present and interfering with work or sleep). 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), based on the daily subjective assessment of the severity of each symptom of rhinitis recorded by the patients in their diaries. The mTDSS was calculated for all study days based on the daily symptom score ( DSS ), i.e. the mean of the two scores assigned to a symptom within 24 hours following drug administration. Daily total symptom score (DTSS) was the mean of the DSS recorded for each of the 7 assessed symptoms, and the mTDSS was the mean of all the DTSS values for each study day.

The following secondary efficacy variables were assessed: mean daily symptom score ( mDSS ), defined as each patient's mean of all DSS calculated for a given symptom over study days; maximum value for DSS (DSSmax ) and maximum value for TDSS ( TDSSmax ). From the daily severest symptom score (DSSS), i.e. the score of the most severe symptom on each study day, the percentage of days when DSSS was 0 (Pdmax0) and the percentage of days when DSSS was 0 or 1 (Pdmax1) were also calculated.

Clinical assessment by the investigator was also quantified by means of clinical score of a symptom at each visit (CSS) and total clinical score of a symptom (TCSS). Moreover, the patients' and investigator's global evaluation of efficacy was done. It was scored numerically on a scale in which 0 = greatly worsened, 1 = no change, 2 = somewhat improved, and 3 = greatly improved.

Adverse events (AEs) reported by patients or observed by investigators were recorded. Patients recorded any concomitant medication throughout the study period.

## Statistical analysis

The number of patients required to detect a difference of 0.25 points between treatments in the mTDSS was calculated. Based on the results of a previous dose-ranging study with rupatadine in the treatment of seasonal rhinitis (data on file), and assuming a standard deviation (SD) of 0.62, and protection levels of 0.05 and 0.2 against type I and type II errors, respectively, the number of patients required to detect the expected difference was 97 per group. A dropout rate of 10% was expected, and therefore it was planned to recruit 108 patients per treatment group.

The main efficacy as well as safety analysis were performed on an intention-to-treat (ITT) basis (i.e., the analysis included all patients receiving at least one dose of the study medication). In addition, a per protocol (PP) analysis was performed in patients that completed the study without major protocol deviations. All statistical analyses were performed using the SPSS statistical software and a = 0.05 was set as the significance level. Main efficacy variable as well as symptom score variables were analyzed using analysis of covariance (ANCOVA) to determine differences between treatments, between centers, and interaction between treatments and centers. We also included a "season" factor in the model in order to explore the influence of possible differences in the pollen levels on the symptom severity. Baseline symptom scores recorded by the patient in the daily card were used as covariates for analysis adjustments. The residuals from the model were investigated in order to detect any inequality of variances or non-normality. Whenever the required assumptions were not held, a rank transformation was applied. ANCOVA would be performed using the ranks for the primary variable, which would allow for the covariates to be included in the model. However, if the required assumptions were still not held and no other suitable transformations were found, then non-parametric tests (e.g. Mann-Whitney-U test) were considered. Similar tests were applied to assess the secondary variables. For the categorical variables the Chi-square test was used (or the Fisher's exact test, if applicability conditions were not fulfilled). The incidence of related AEs, as categorized by the

WHOART preferred terms, was compared between treatment groups using the Chi-square test. All abnormal laboratory findings considered to be clinically significant were recorded as AEs.

## Results

### Study population

The disposition of patients during the study is shown in Figure 1. This study was conducted over two consecutive spring seasons (from March 1998 through June 1999), in 26 centres in Spain. Patients who consulted their doctor with symptoms of SAR expected to last for the treatment period were eligible for enrolment.

A total 249 patients were randomised (127 to rupatadine and 122 to cetirizine). Eight patients (three in the rupatadine group and five in the cetirizine group) received no dose of the study medication. Thus 124 patients in the rupatadine group and 117 in the cetirizine group were evaluable for ITT analysis. From those, 18 patients in the rupatadine group and 19 patients in the cetirizine group discontinued the study prematurely. Reasons for early discontinuation are shown in Figure 1.

Main baseline data of patients are summarized in Table 1. There were no differences between treatment groups with regard to sex distribution, age, body weight or baseline scores of DTSS.

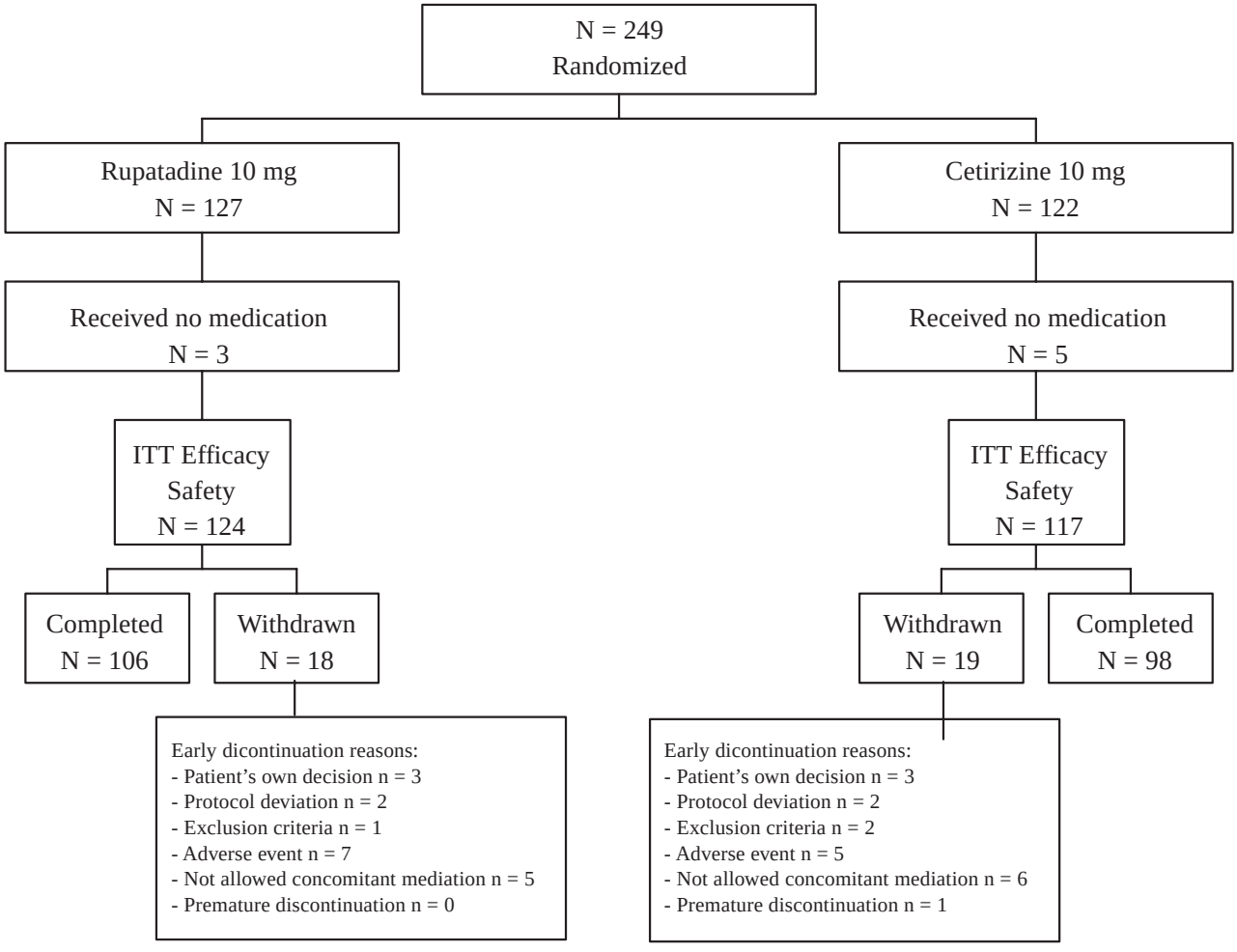


*Figure 1*. Flow-chart of the study population.

 

*Table 1.* Baseline characteristics of patients.

| | **Rupatadine** (n = 124) | **Cetirizine** (n = 117) | **All** (n = 241) |
|---|---|---|---|
| **Gender** | | | |
| Male | 58 (46.8%) | 60 (51.3%) | 118 (49%) |
| Female | 66 (53.2%) | 57 (48.7%) | 123 (51%) |
| **Race** | | | |
| Caucasian | 121 (97.6%) | 116 (99.0%) | 237 (99.3%) |
| Non-Caucasian | 3 (2.4%) | 1 (0.9%) | 4 (1.7%) |
| **Age** (years) | | | |
| Mean (SD) | 31.3 (10.5) | 30.6 (9.0) | 31 (9.8) |
| Range | 16-65 | 14-56 | 14-56 |
| **Weight** (kg) | | | |
| Mean (SD) | 69.4 (16.1) | 70.6 (14.4) | 70.0 (15.3) |
| Range | 44-165 | 48-135 | 48-165 |
| **Height** (cm) | | | |
| Mean (SD) | 167.7 (10.1) | 169.7 (10.3) | 168.7 (10.2) |
| Range | 149-196 | 150-198 | 149-196.2 |
| **Baseline TDSS** | | | |
| Mean (SD) | 1.6 (0.5) | 1.4 (0.6) | 1.5 (0.5) |
| Range | 0.3-2.7 | 0.5-2.7 | 0.3-2.7 |
| **Symptom severity** | | | |
| Mean (SD) | | | |
| Runny nose | 1.9 (0.8) | 2 (0.7) | 1.9 (0.8) |
| Sneezing | 2 (0.7) | 1.9 (0.7) | 1.9 (0.7) |
| Nasal itching | 2 (0.8) | 1.8 (0.8) | 1.9 (0.8) |
| Nasal obstruction | 1.8 (0.9) | 1.5 (0.9) | 1.6 (0.9) |
| Conjuctival itching | 1.6 (1) | 1.5 (1) | 1.5 (1) |
| Tearing | 1.1 (0.9) | 0.8 (0.9) | 0.9 (0.9) |
| Pharyngeal itching | 1.1 (1) | 0.9 (1.1) | 0.9 (1.1) |

No significant differences were found.

*Table 2.* Results of efficacy (ITT population) during the whole study period (2 weeks). Primary variable: mTDSS, mean total daily symptom score. Secondary variables: mDSS, mean daily symptom score; DSSmax, maximum value of the daily score of a symptom, TDSSmax, maximum value of the total daily symptom score; Pdmax0, percentage of days when DSSS was 0 and Pdmax1, percentage of days when DSSS was 0 or 1.

| | **Rupatadine** (n = 124) | | **Cetirizine** (n = 117) | |
|---|---|---|---|---|
| | **Baseline** | **Whole study period** | **Baseline** | **Whole study period** |
| **mTDSS** | 1.6 ± 0.5* | 0.7 ± 0.4** | 1.4 ± 0.6* | 0.7 ± 0.4** |
| **mDSS** | | | | |
| Runny nose | 1.9 ± 0.8 | 1.0 ± 0.6 | 2.0 ± 0.7 | 1.0 ± 0.7 |
| Sneezing | 2.1 ± 0.7 | 0.6 ± 0.5 | 1.9 ± 0.7 | 0.7 ± 0.5 |
| Nasal itching | 2.0 ± 0.8 | 0.8 ± 0.6 | 1.8 ± 0.7 | 0.8 ± 0.5 |
| Nasal obstruction | 1.8 ± 0.9 | 1.2 ± 0.8 | 1.5 ± 0.9 | 1.1 ± 0.8 |
| Conjunctival itching | 1.6 ± 1.0 | 0.6 ± 0.6 | 1.5 ± 1.0 | 0.6 ± 0.6 |
| Tearing | 1.1 ± 0.9 | 0.3 ± 0.5 | 0.8 ± 0.9 | 0.3 ± 0.5 |
| Pharyngeal itching | 1.1 ± 1.0 | 0.5 ± 0.7 | 0.9 ± 1.1 | 0.5 ± 0.6 |
| **DSSmax** | | | | |
| Runny nose | 1.9 ± 0.8 | 1.8 ± 0.7 | 2.0 ± 0.7 | 1.9 ± 0.8 |
| Sneezing | 2.1 ± 0.7 | 1.4 ± 0.7 | 1.9 ± 0.7 | 1.5 ± 0.7 |
| Nasal itching | 2.0 ± 0.8 | 1.6 ± 0.8 | 1.8 ± 0.7 | 1.6 ± 0.7 |
| Nasal obstruction | 1.8 ± 0.9 | 2.0 ± 0.8 | 1.5 ± 0.9 | 1.9 ± 0.8 |
| Conjuctival itching | 1.6 ± 1.0 | 1.3 ± 0.9 | 1.5 ± 1.0 | 1.3 ± 0.9 |
| Tearing | 1.1 ± 0.9 | 0.8 ± 0.9 | 0.8 ± 0.9 | 0.8 ± 0.8 |
| Pharyngeal itching | 1.1 ± 1.0 | 1.0 ± 0.9 | 0.9 ± 1.1 | 1.1 ± 1.0 |
| **TDSSmax** | 1.6 ± 0.5 | 1.2 ± 0.6 | 1.4 ± 0.6 | 1.3 ± 0.6 |
| **Pdmax 1** | | 38.0 ± 36.0 | | 40.6 ± 37.2 |
| **Pdmax 0** | | 5.9 ± 16.6 | | 5.7 ± 14.6 |

Data show are mean ± SD. No significant differences were found

* Mean of Total Symptoms Score corresponding to day 1
** $p < 0.0001$ from the baseline (paired t-test).

## Overall efficacy

Efficacy results are shown in Table 2. Mean changes in Total Symptoms Score were -0.87 and -0.65 in rupatadine and cetirizine groups, respectively. No differences between groups were found concerning either the primary efficacy variable, mTDSS, or mDSS, DSSmax, TDSSmax, Pdmax0 and Pdmax1. In the investigator's global evaluation of efficacy at seventh day 93.3% and 83.7% patients in the rupatadine and cetirizine groups, respectively, showed some or great improvement ($p = 0.022$) (Figure 2). In the per protocol analysis (n = 181) runny nose at seventh day of treatment was absent or mild in 81.1% of patients in the rupatadine group and in 68.6% of patients in the cetirizine group ($p = 0.029$). In any case statistical significance was not maintained at two weeks.

No interaction between season and treatment was observed: no heterogeneity was detected concerning the effect of treatments in the mTDSS along the two seasons ($p = 0.67$).

## Safety

The safety analysis included all patients who had been administered study medications at least once (n=241). No differences between treatments were found in the number of patients reporting related (possible, probable or definitive) AEs: 49 (39.5%) and 50 (42.7%) patients with rupatadine and cetirizine, respectively. No significant differences between treatments were found concerning the overall incidence of AEs. Most reported AEs (67%) were mild in terms of intensity. Most frequent related AEs were headache (15.3% rupatadine; 19.7% cetirizine), fatigue/asthenia (10.5% rupatadine; 6.8%, cetirizine) and somnolence (9.6% rupatadine; 8.5% cetirizine). No significant differences between treatments were found in the incidence of those AEs.

 

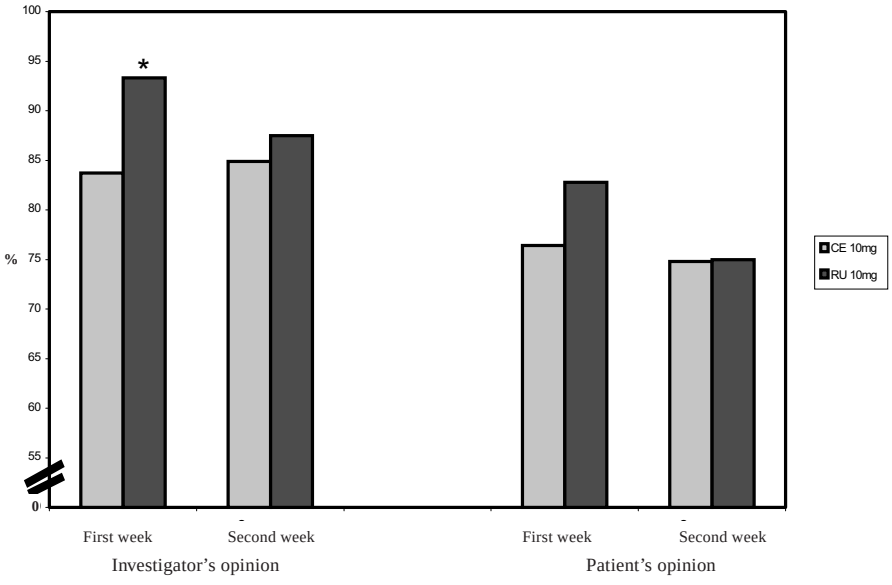


*Figure 2*. Global evaluation of efficacy. Patients with somewhat or greatly improvement in symptom score (%).

* p = 0.022, Chi-square test

## Discussion

The ideal therapeutic agent for managing the symptoms of SAR should be one that effectively addresses the pathophysiology of both the early-phase reaction (EPR) and the late-phase reaction (LPR) [22]. Such a drug must antagonise histamine at the H1-receptor sites and reduce the cardinal symptoms of SAR including nasal pruritus, sneezing, rhinorrhea and nasal congestion. Nevertheless, as other chemical mediators are released through mast cell degranulation, this ideal drug must counter these effects as well [23,24]. Preclinical studies showed that rupatadine is characterised by this mixed pharmacological profile [14], however, we found no differences between rupatadine and cetirizine after 2 weeks of therapy in patients with SAR as reflected by the absence of significant differences in the primary efficacy variable assessed (mTDSS).

Differences were found in the variable investigator's global evaluation of efficacy and runny nose in both cases at seventh day, thus suggesting a possible faster effect of rupatadine. This suggests that rupatadine leads to a faster and persistent resolution of the acute flare-up of the disease during the first week of treatment in comparison with cetirizine and that effect is less noticeable in the second week of therapy.

Therefore, the overall results of efficacy show a similar efficacy profile of rupatadine and cetirizine in the relief of the SAR symptoms. In fact, comparisons of second-generation H1-antihistamines in SAR have, in general, not found any major clinical differences over 1-2 week study periods [25]. The question about the clinical role of the PAF receptors blockade in the treatment of patients with SAR remains unanswered at this moment.

Both treatments were well tolerated and safe to use in patients with SAR. AEs with rupatadine were reported with a frequency similar to cetirizine and the AEs profile in all treatment groups was the one expected from an antihistamine therapy against SAR symptoms: e.g., headache or somnolence [26,27].

In conclusion, our results suggest that rupatadine at a daily dose of 10 mg is a valuable and safe therapeutic drug for the symptomatic treatment of SAR.

## Acknowledgements

This study was partially supported by the National Scientific Research Program of the Spanish Ministry of Science and Technology.

## The Spanish Rupatadine Study Group

Martínez Cócera C, Cabrera M, Chamorro M, Cimarra M, (Hospital Clínico San Carlos. Madrid); Navarro A, Ortas JC, (Hospital El Tomillar, Dos Hermanas. Sevilla); Conde J, Hernández M, Delgado J, Sánchez H, (Hospital Virgen de la Macarena. Sevilla); Subiza FC, Borau C, (Clínica Dr. Subiza. Madrid), Molina M, Pinto E, (Hospital de la Creu Roja. L'Hospitalet de Llobregat. Barcelona); Sierra JI, (Hospital Sant Joan de Deu. Esplugues de Llobregat. Barcelona); Reguero, Terradas S, Justicia JL, (Hospital Universitario San Cecilio. Granada); Florido JF, Sáez B, (Hospital Ciudad de Jaén. Jaén); Feo F, Galindo PA, Borja J, (Complejo Hosp del Carmen. Ciudad Real); Cobo R, Hernández FJ, Jiménez S, (Hospital San Pedro de Alcántara. Cáceres); Lorente F,

Dávila I, (Hospital Universitario. Salamanca); Mur MP, (Hospital Santa Bárbara. Puertollano. Ciudad Real); Pola J, Zapata C, (Policlínica Sagasta. Zaragoza); Duce F, Domínguez C, Colas C, Fraj J, Lezaun A, (Hospital Clínico Lozano Blesa. Zaragoza); Laguna R, Chivato T, Galván JM, (Hospital del Aire. Madrid); De la Hoz B, Alfaya T, González E, Losada E, Pulido C, Pérez I, (Hospital Ramon y Cajal. Madrid); Martínez F, ( Hospital General. Albacete); Hernández J, Pagán JA, (Hospital Virgen Arrixaca. Murcia); Luna I, Bravo M, González R, (Hospital Xeral. Vigo); Vidal C, Armisén M, (Hospital Provincial de Conxo. Santiago de Compostela); Boquete M, Carvallada F, (Complejo Hospitalario Xeral Calde. Lugo); Álvarez, (Hospital General de Galicia. Santiago de Compostela); Soto MT, (Hospital Provincial. Pontevedra); Raga E, Ruvira N, Serra JP, (Clínica Platón. Barcelona); Martí-Guadaño E, Hermida E, (Hospital Sant Pere Claver. Barcelona).

## References

1. Salib R J, Drake-Lee A, Howart P H. Allergic rhinitis: past, present and the future. Clin Otolaryngol 2003; 28: 291-293.
2. Baroody F M. Allergic rhinitis: broader disease effects and implications for management . Otolaryngol Head Neck Surg 2003; 185: 616-631.
3. Albert D H, Malo P E, Tapang P, Shaughnessy T K, Morgan D W, Wegner C D, Curtin M L, Sheppard G S, Xu L. Davidsen S K, Summers J B, Carter G W. The role of platelet-activating factor (PAF) and the efficacy of ABT-491, a highly potent and selective PAF antagonist, in experimental allergic rhinitis. J Pharmacol Exp Ther 1998; 284: 83-88.
4. Albert D H, Tapang P, Morgan D W, Curtin M L, Sheppard G S, Davidsen S K, Summers J B, Carter G W. ABT-491, a highly potent and selective PAF antagonist, inhibits nasal vascular permeability associated with experimental allergic rhinitis in Brown Norway rats. Inflam Res 1997; 46 (Suppl2): S133-S134.
5. Yamada Y, Yokota M. Roles of plasma platelet-activating factor acetylhydrolase in allergic, inflammatory and atherosclerotic diseases. Jpn Circ J 1998; 62: 328-335.
6. Evans T W, Rogers D F, Aursudkij B, Chung K F, Barnes P J. Inflammatory mediators involved in antigen-induced airway microvascular leakage in guinea pigs. Am Rev Respir Dis 1988; 138: 395-399.
7. Labrakis-Lazanas K, Lazanas M, Koussissis M, Tournis S, Demopoulos J. Evidence of PAF-acether metabolic pathway activation in antigen challenge of upper respiratory airwais. Am Rev Respir Dis 1989; 140: 142-147.
8. Shirasaki H, Asakura K. Detection of platelet-activating factor in nasal lavage fluid from patients with pollinosis and experimental animals with nasal allergy. Nippon Jibiinkoka Gakkai Kaiko 1990; 93: 420-427.
9. Sciberras D G, Bolognese J A, Goldemberg M M, James I, Baber N S. Platelet-activating factor induced inflammatory responses in the skin. Prostaglandins 1988; 35: 833.
10. Snyder F. Metabolic processing of PAF. Clin Rev Allergy 1994; 12: 309-327.
11. Prescott S M, Zimmerman G A, McIntyre T M. The production of platelet-activating factor by cultured human endothelial cells: Regulation and function. In: Snyder F, ed. Platelet-Activating Factor and Related Lipid Mediators. New York, Plenum Press, 1987; 323-240.
12. Townley R G, Okada Ch. Use of cetirizine to investigate non-H1 effects of second-generation antihistamines. Ann Allergy 1992; 68: 190-196.
13. Eda R, Sigiyama H, Hopp R J, Bewtra A K, Townley R J. Effect of loratadine on human eosinophil function in vitro. Ann Allergy 1993; 71: 373-378.
14. Merlos M, Giral M, Balsa D, Ferrando R, Queralt M, Puigdemont A, García-Rafanell J, Forn J. Rupatadine, a new potent, orally active dual antagonist of histamine and platelet-activating factor (PAF). J Pharmacol Exp Ther 1997; 280: 114-121.
15. Queralt M, Brazis P, Merlos M, de Mora F, Puigdemont A. In vitro inhibitory effect of rupatadine on histamine and TNF-α release from dispersed canine skin mast cells and the human cell line HMC-1. Inflam Res 2000; 49: 355-360.
16. Izquierdo I, Lurigados C, Perez I, Forn J. Rupatadine exhibits a better profile than ebastine in patients with seasonal allergic rhinitis. Allergy 2001;56(Suppl 68):200.
17. Izquierdo I, Paredes I, Lurigados C, Sospedra E, Cooper M, Thomas H. A dose ranging study of rupatadine fumarate in patients with seasonal allergic rhinitis. Allergy 2000;55(Suppl 63):275.
18. Merlos M. Rupatadine, a new nonsedating antihistamine and PAF antagonist. Methods Find Exp Clin Pharmacol 2002;24(Suppl A):37.
19. Izquierdo I, Merlos M, García-Rafanell J. Rupatadine. A new selective histamine H1 receptor and platelet-activating factor (PAF) antagonist. A review of pharmacological profile and clinical management of allergic rhinitis. Drugs of Today 2003; 39: 451-468.
20. Saint Martin F, Dumur JP, Pérez I , Izquierdo I. A randomised, double-blind, parallel-group study, comparing the efficacy and safety of rupatadine, a new PAF and H1 receptor-specific histamine antagonist, to loratadine 10 mg in the treatment of seasonal allergic rhinitis. J Invest Allergol Clin Inmunol 2003; 14: 34-40.
21. Spencer C M, Faulds D, Peters D H. Cetirizine. A reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. Drugs 1993; 46: 1055-1080.
22. Prenner BM. The evolution of pharmacotherapy for rhinitis and urticaria. Allergy Asthma Proc 2001;22(5):277-80.
23. Spector S. Ideal pharmacotherapy for allergic rhinitis. J Allergy Clin Immunol 1999;103:S386-7.
24. Horak F. Clinical advantages of dual activity in allergic rhinitis. Allergy 2000;55(Suppl 64):34-9.
25. Howart P. Antihistamines in rhinoconjuntivitis. In: F E R Simons (Ed). Histamine and H1-antihistamines in allergic disease. 2nd ed. New York: Marcel Dekker, Ink. 2002; pp. 179-220.
26. Slater JW, Zechnich AD, Haxby DG. Second-generation antihistamines: a comparative review. Drugs 1999;57:31-47.
27. Estelle F, Simons R. H1-receptor antagonists: safety issues. Ann Allergy Asthma Immunol 1999;83:481-8.

Dr. Iñaki Izquierdo

J Uriach y Compañía, S.A.
Poligon Industrial Riera de Caldes
Avinguda Cami Reial, 51-57
08184 Palau-Solità i Plegamants
Barcelona, Spain
Phone: 34 902 47 15 11
Fax: 34 938 64 66 06
e-mail: clin-izquierdo@uriach.com

 