Reprinted article

A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis

on behalf of international Rupatadine study group

pp. 924 - 931
Original article

A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis

Background: With the current increasing incidence of allergies worldwide, new treatments showing efficacy and long term safety are needed for chronic conditions such as persistent allergic rhinitis (PER). New generation H1-antihistamines have demonstrated anti-allergic properties, which could possibly enhance their effectiveness in long-term periods of treatment.

Objective: To investigate the efficacy of rupatadine, in controlling symptoms of PER over a 12-week period.

Methods: A randomized, double blind, parallel-group, placebo-controlled study was carried out in patients aged older than 12 years with PER. Main inclusion criteria were: instantaneous total symptom score (i6TSS) ≥ 245, nasal obstruction score ≤ 12, and overall assessment of PER ≥ 2 as moderate during the first visit. The primary efficacy endpoint was the 12-week average change from baseline of the patients' i6TSS.

Results: In all, 736 patients were selected. Of them, 543 (73.8%) were randomized in three different groups: placebo (n = 185), cetirizine (n = 175) and rupatadine (n = 183). Rupatadine (P = 0.008) but not cetirizine (P = 0.07) statistically reduced the baseline i6TSS vs placebo (47.8%, 44.7% and 38.8%, respectively), after 12 weeks. Onset of action was observed at the first 24 h for both treatments (rupatadine vs placebo, P = 0.013; cetirizine vs placebo, P = 0.015). Furthermore, instantaneous total nasal symptoms score (iTNSS) (including nasal blockage) mean change from baseline showed a significant reduction with rupatadine 10 mg in comparison with placebo, along all treatment duration of 12 weeks. Study treatments were well tolerated.

Conclusion: Rupatadine significantly relieved symptoms of PER, providing a rapid onset of action and maintains its effects over a long period of 12-weeks.

The term 'persistent' rhinitis comes from the ARIA classification. This is based on the duration of symptoms distinguishing allergic rhinitis as 'intermittent' or 'persistent' (1). In 'persistent' symptoms occur more than 4 days per week, and more than 4 weeks. This is further classified into 'mild' or 'moderate-severe' depending on sleep disturbances, impairment of activities or how troublesome the symptoms are (1).

Abbreviations: 6TSS, instantaneous total symptoms score (including 6 symptoms); AE, adverse event; ANCOVA, analysis of covariance; ANOVA, analysis of variance; ECG, electrocardiogram; iTNSS, instantaneous total nasal symptoms score (including nasal symptoms); ITT, intent-to-treat population; MedDRA, medical dictionary for regulatory activities; OD, once daily; PAF, platelet activating factor; PER, persistent allergic rhinitis; QoL, quality of life; RQLQ, rhinoconjunctivitis quality of life questionnaire; SAE, serious adverse event.

On the other hand, H1-antihistamines are not recommended as first-line treatment in moderate-severe persistent allergic rhinitis (PER) and only scarce information of efficacy with antihistamines has been published under this new classification (2, 3).

Rupatadine is a novel, selective long-acting histamine H1 receptor inverse agonist (H1 antihistamine), which is currently approved as once daily dose of 10 mg for the treatment of allergic rhinitis and chronic urticaria (4). Although some antihistamines have shown marginal PAF antagonist properties, these effects cannot be attributed to specific interactions with PAF receptors (5). Rupatadine has shown both antihistamine and anti PAF effects through its interaction with specific receptors and not because of physiological antagonism (6).

Platelet activating factor and histamine have been shown to complement each other’s activity in vivo. Upon
release, histamine acts as a mediator of the immediate allergic response, using preformed reserves in the mastocytes. PAF, however, is synthesized de novo in response to the allergic stimulus (7). In addition, each mediator can promote the release of the other in various tissues and cells (8). According to this, it could be expected that the blockade of the effects of both histamine and PAF could produce a greater clinical efficacy than the blockade of only histamine, thus justifying the search for new chemical entities that showing this dual activity.

Rupatadine has shown to be effective in the treatment of allergic rhinitis (9–11) with a fast onset of action (12) and with a very good safety profile (13–15). Recently, rupatadine 10 mg has been approved for marketing in all European Community countries and Brazil for the treatment of allergic rhinitis as well as chronic idiopathic urticaria in adults and adolescents.

Our study was undertaken to investigate, on the basis of this recent classification, if rupatadine 10 mg is an effective once-daily treatment in comparison with placebo and cetirizine 10 mg in the management of PER patients during 12 weeks.

Patients and methods

Study design

This was a randomized, double-blind, parallel-group, placebo-controlled and multicenter study. The study lasted 12 weeks and included four visits after screening evaluation (Inclusion Visit or Visit 0 (Day 1), Visit 1 (after 4 weeks), Visit 2 (after 8 weeks) and Last Visit (after 12 weeks).

During the screening evaluation, which was conducted at least 7 days before randomization, inclusion and exclusion criteria were assessed. A 12-lead electrocardiogram, laboratory tests (haematology and chemistry) and pregnancy test were performed. After screening, patients were assigned to receive a 12-week treatment with rupatadine 10 mg od, cetirizine 10 mg od or placebo od by using a computer-generated randomized schedule provided by the sponsor of the study (J Uriach y Compañía, S.A.). All patients gave written informed consent to participate in the study, which was approved by the local ethics committees review boards of the participating centers.

Patients were provided with diary cards to collect the symptom severity with instantaneous and reflective evaluations (12 h) to cover the 12 weeks of treatment. Furthermore, overall signs and symptoms in the last 24 h were assessed by the patient and the investigator. Quality of Life Questionnaire (QoL) and adverse events were evaluated in each visit. At the end of treatment, all patients underwent physical examination and were assessed for ECG (12 leads) and blood parameters including pregnancy tests for female patients.

This study was performed in accordance with the International Conference of Harmonization (ICH) Note for Guidance on Good Clinical Practice, the Declaration of Helsinki (as amended in Edinburgh, 2000) (16).

Study population

The main criteria at the inclusion visit were: male or female aged older than 12, documented history of PER at least 12 months before the screening date with a positive prick test for one or more allergens performed on the same day or within one year before the screening visit, with clinical symptoms in the two weeks prior to the inclusion visit. Also, Total Symptoms Score (TSS) ≥ 245, the nasal obstruction score ≤ 12, and the overall assessment of PER score ≥ 2 (moderate) were determined during the inclusion visit. The results of laboratory test and ECG were within acceptable limits. Additionally, if a patient had a regular scheduled immunotherapy or with mild intermittent asthma symptoms treated with inhaled bronchodilators, the patient was allowed to continue during the study if the treatment schedule was not modified. Finally, women of childbearing potential had to have a negative pregnancy test and use contraceptive measures. Exclusion criteria included patients with nonallergic rhinitis (vasomotor, infectious, drug-induced, etc.), with obstructive nasal polyps or a significant deviation of the nasal septum according to the investigator criteria. Patients who took medication that interacted with isoenzyme CYP3A4 of cytochrome P450. Patients with psychiatric, vascular, hepatic, renal, neurological, endocrine or other systemic diseases as well as patients who according to the investigator judgment, interfered with the normal conduct of the protocol or with the interpretation of the results of the study were also excluded.

Study medication

The 10 mg rupatadine and 10 mg cetirizine tablets had the same appearance as that of the placebo tablets and were packaged identically. Tablets were distributed in sealed and coded packages. Patients were instructed to take each dose of the study medication in the morning and at the approximately same time every day. Compliance was assessed on the basis of the diary card review and tablet counts.

Evaluation of efficacy

Primary end-point was the change from baseline vs placebo in the total patient symptom-score (TSS) over 12-week treatment period (instantaneous evaluation). TSS was calculated by adding the six individual symptom scores (nasal discharge, nasal obstruction, sneezing, nasal pruritus, ocular pruritus and ocular redness) for each study day. Symptom scores were graded according to a conventional 4-point severity scale: 0, none; 1 mild (occasionally present but not troublesome); 2 moderate (frequently present and annoying) and 3, severe (continuously present and interfering with work or sleep).

All secondary assessments were based on the daily subjective scores calculated by both reflective (12 h prior) and instantaneous scores.

The overall impression of efficacy was reported by the investigator and by the patient in comparison to the baseline symptoms. This was recorded independently (on a scale from 0 = greatly improved to 4 = greatly worsened). The QoL of the patients was assessed using the validated self-administered Rhinconjonctivitis Quality of Life Questionnaire (RQLQ) (17). RQLQ involves seven domains (activities, sleep, general symptoms, practical problems, nasal symptoms, eye symptoms and emotional).

Evaluation of safety

Safety and tolerability of treatment was evaluated according to the incidence and type of Adverse Events (AEs) recorded in the
patients' diaries and evidenced by investigators. The results of routine laboratory tests (haematology, blood chemistry and urinalysis), clinical and physical examinations and ECG, before and during the study period, were also evaluated. All AEs were coded using the MedDRA (Version 6.1) dictionary.

Statistical evaluation

Descriptive statistics were used to summarize baseline characteristics by treatment group. The primary and secondary efficacy variables were analyzed using the covariance (ANCOVA) model that included the mean baseline as covariate with treatment and study centre as factors.

This study was powered on the basis of several preceding studies. Assuming a standard deviation of 2.18 in the main variable of efficacy and allowing for a loss rate of 10%, it was estimated that 510 patients (sample size of 170 per treatment group and three treatment groups) would be required with at least 80% power and 5% significance level. Statistical analyses were always performed on the Intention-To-Treat (ITT) population.

The significance of any difference was assessed by pair-wise treatment comparison using the Fisher's protected Least Significance Difference test for qualitative variables. Treatment-emergent AEs were compared by Chi-square test.

All statistical tests were performed using the SAS® software version 8.2 for Windows (SAS Institute Inc, Cary, NC, USA) and values for P values less than 0.05 were considered statistically significant.

Results

Patients and baseline characteristics

Patients were recruited from a total of 33 allergology and otorhinolaringology centres in Argentina (17), Chile (9) and Romania (7), between September 2004 and May 2005. The patient disposition is shown in Fig. 1.

A total of 736 patients were screened of whom 543 (73.7%) were randomized to receive one of three study treatments (185 placebo, 183 rupatadine 10 mg and 175 cetirizine 10 mg). There was one patient who did not present the efficacy variables and so ITT analysis was performed with 542 patients. At baseline, there were no differences between groups concerning demographic and clinical characteristics (Table 1).

Efficacy analyses

There were differences among treatments in the change from baseline i6TSS over the twelve-week treatment period (ANCOVA by treatment, country and baseline i6TSS; P = 0.025) for the ITT population (Table 2). After 12 weeks, reductions in the baseline i6TSS were 47.8% in the rupatadine 10 mg group, 44.7% in the cetirizine 10 mg group and 38.8% in the placebo group.

Figure 1. Global disposition of patients.
Rupatadine and cetirizine in persistent allergic rhinitis

Figure 2. Change from baseline in mean instantaneous Total Symptom Score (iTSS) at 4, 8 and 12 weeks of treatment period. Significant improvements at \( P < 0.05 \) and \( P < 0.01 \) levels are marked with * and **, respectively.

![Graph showing change from baseline in mean instantaneous Total Symptom Score (iTSS)](image)

Figure 3. Serial time profile over 12 weeks of the instantaneous Total Nasal Symptom Score (iTNSS) mean change from baseline. Significant improvements at \( P < 0.05 \) level were seen in both treatments (x) and only with rupatadine alone (xx) in comparison with placebo.

![Graph showing serial time profile over 12 weeks of the instantaneous Total Nasal Symptom Score (iTNSS)](image)

Table 1. Patient demographic and clinical characteristics at baseline in ITT population. iTSS: Total symptoms score was calculated by adding the 6 individual symptom score: nasal discharge, nasal obstruction, sneezing, nasal pruritus, ocular pruritus and ocular redness, NNS: nasal symptoms score was calculated by adding the 4 individual symptom score: nasal obstruction, sneezing and nasal pruritus. NNS: non nasal symptom score was only considered by adding ocular pruritus and ocular redness.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 185)</th>
<th>Rupatadine 10 mg (n = 183)</th>
<th>Cetirizine 10 mg (n = 174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)*</td>
<td>56 (30.3)</td>
<td>59 (32.2)</td>
<td>73 (42.0)</td>
</tr>
<tr>
<td>Age (years)†</td>
<td>30.13 (12.48)</td>
<td>29.58 (13.48)</td>
<td>29.18 (12.75)</td>
</tr>
<tr>
<td>Race (caucasian)*</td>
<td>184 (93.5)</td>
<td>181 (99.8)</td>
<td>173 (99.4)</td>
</tr>
<tr>
<td>Medical history</td>
<td>185 (100.0)</td>
<td>181 (99.8)</td>
<td>170 (97.7)</td>
</tr>
<tr>
<td>Physical examination (findings)*</td>
<td>44 (23.8)</td>
<td>37 (20.2)</td>
<td>31 (17.8)</td>
</tr>
<tr>
<td>iTSS†</td>
<td>Instantaneous</td>
<td>8.96 (3.25)</td>
<td>8.72 (3.20)</td>
</tr>
<tr>
<td></td>
<td>Reflective</td>
<td>10.15 (2.41)</td>
<td>9.90 (2.07)</td>
</tr>
<tr>
<td>NNS‡</td>
<td>Instantaneous</td>
<td>6.44 (2.06)</td>
<td>6.37 (1.94)</td>
</tr>
<tr>
<td></td>
<td>Reflective</td>
<td>7.31 (1.51)</td>
<td>7.22 (1.36)</td>
</tr>
<tr>
<td>TFTS AM</td>
<td>Instantaneous</td>
<td>2.53 (1.34)</td>
<td>2.36 (1.48)</td>
</tr>
<tr>
<td></td>
<td>Reflective</td>
<td>2.84 (1.31)</td>
<td>2.68 (1.26)</td>
</tr>
<tr>
<td>instantaneous‡</td>
<td>9.18 (3.40)</td>
<td>8.98 (2.96)</td>
<td>8.34 (3.22)</td>
</tr>
<tr>
<td>Nasal discharge†</td>
<td>Instantaneous</td>
<td>1.80 (0.64)</td>
<td>1.76 (0.67)</td>
</tr>
<tr>
<td></td>
<td>Reflective</td>
<td>2.03 (0.55)</td>
<td>2.01 (0.58)</td>
</tr>
</tbody>
</table>

Non-significant differences were found in any of the variables. *n (%), †mean (SD).

Table 2. Change from baseline in Total Symptom Score at 12 weeks in ITT population

<table>
<thead>
<tr>
<th>iTSS</th>
<th>Placebo (n = 185)</th>
<th>Rupatadine 10 mg (n = 183)</th>
<th>Cetirizine 10 mg (n = 174)</th>
<th>Test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Instantaneous</td>
<td>8.96 (3.25)</td>
<td>8.72 (3.20)</td>
<td>8.29 (3.21)</td>
</tr>
<tr>
<td>Reflective</td>
<td>10.15 (2.41)</td>
<td>9.90 (2.07)</td>
<td>9.69 (2.16)</td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>Instantaneous</td>
<td>5.48 (3.65)</td>
<td>4.65 (2.90)</td>
<td>4.53 (3.40)</td>
</tr>
<tr>
<td>Reflective</td>
<td>5.62 (3.02)</td>
<td>4.79 (2.95)</td>
<td>4.79 (3.48)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>Instantaneous</td>
<td>-3.48 (3.62)</td>
<td>-4.17 (3.23)</td>
<td>-3.67 (3.86)</td>
</tr>
<tr>
<td>Reflective</td>
<td>-4.53 (3.44)</td>
<td>-5.11 (2.92)</td>
<td>-4.90 (3.50)</td>
<td></td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>Instantaneous</td>
<td>-36.8%</td>
<td>-47.8%</td>
<td>-44.7%</td>
</tr>
<tr>
<td>Reflective</td>
<td>-44.6%</td>
<td>-51.5%</td>
<td>-50.6%</td>
<td></td>
</tr>
</tbody>
</table>

*ANOVA by treatment, country and baseline (baseline iTSS).

There were statistically significant differences between rupatadine 10 mg and placebo (\( P = 0.008 \)) but not between cetirizine 10 mg and placebo.

In addition at 4 (\( P < 0.01 \)) and 8 (\( P < 0.01 \)) weeks, rupatadine and cetirizine were significantly more effective than placebo in the iTSS (Fig. 2). No statistically significant difference between treatment by reflective iTSS was found.

The change from baseline of the instantaneous onset of action of the iTSS was for both treatments at the first 24h (placebo vs rupatadine 10 mg: \( P = 0.013 \) and placebo vs cetirizine 10 mg: \( P = 0.015 \)).

The change from baseline of the instantaneous total nasal symptoms score (iTNSS) (including nasal blockage) showed a significant reduction with both treatments in comparison with placebo, during all the treatment period of 12 weeks (Fig. 3). Nevertheless, rupatadine exhibited only a significant improvement in iTNSS at 6, 8, 9, 10, 11 and 12 weeks (\( P < 0.05 \)) in comparison with placebo and cetirizine.

Rupatadine also led to a significant improvement in the secondary outcomes, compared with placebo. Concerning instantaneous nasal symptoms, there were differences between placebo and rupatadine for sneezing (\( P < 0.001 \)) and nasal pruritus (\( P = 0.003 \)), and between placebo and cetirizine for the same symptoms (sneezing \( P = 0.008 \), and nasal pruritus \( P = 0.024 \)).
the rest of the symptoms, there was a clear favorable trend for both active treatments, except for nasal obstruction. There were also differences between placebo and rupatadine in the reflective nasal symptoms for sneezing (P = 0.002) and nasal pruritus (P = 0.005), and between placebo and cetirizine in the same symptoms, sneezing (P = 0.008) and nasal pruritus (P = 0.027) (Fig. 4).

Patient’s independent overall efficacy assessments in both active treatments were significantly superior to those of placebo, at 4 (P < 0.001), 8 (P = 0.002) and 12 (P = 0.006) weeks of treatment, as well as in the opinion of investigator (P = 0.002, P = 0.024 and P = 0.006 respectively). The percentage of patients who considered their condition was rated as good or excellent improvement at 12 weeks, was 70% for rupatadine, 65% for cetirizine and 57% for placebo. The corresponding values for investigators’ opinion were 55%, 64% and 62%. No statistically significant differences were found between active treatments.

There were differences between placebo and rupatadine 10 mg in the RQLQ at the 4, (P = 0.022) and 12 week (P = 0.016) of treatment (Fig. 5). The baseline RQLQ score was reduced at week 4 by 39.7% in the placebo group, and by 48.5% in rupatadine group. Cetirizine was also better than placebo (P = 0.002) with a 51.7% reduction at week 4 from the baseline RQLQ score. At week 12, the reductions were 51% for placebo, 61% for rupatadine, and 63.4% for cetirizine. Rupatadine was statistically better than placebo at 12 weeks in the following RQLQ domains: Activities (P = 0.001), Sleep disturbances (P = 0.009), and Nasal symptoms (P = 0.006). Cetirizine was also statistically better than placebo at 12 weeks in the same RQLQ domains: Activities (P = 0.004), Sleep disturbances (P = 0.048) and Nasal symptoms (P = 0.009), but also in Eye symptoms (P = 0.004).

Safety evaluation

The incidence of adverse events (AE) was 21% for the placebo group and 23% for both the rupatadine group and cetirizine group. There were no differences among treatments either (Chi-square; P = 0.820).

The most frequent adverse events reported were headache (36%, 29%, 29% of incidence for placebo, rupatadine and cetirizine); somnolence (4.3%, 10% and 8% of incidence, same groups respectively); and nasopharyngitis (10%, 6%, 9% of incidence, same groups respectively). In addition, there were no differences between treatments and placebo in any of above adverse events reported.

There were no differences in the serious adverse events (SAE) among treatment groups. The four not related SAEs reported were: a suicide attempt occurred before patient was randomized, two episodes of metrorrhagia in one patient with cetirizine 10 mg and dead retained zygote in one patient in the placebo group.

Discussion

Our study has shown in the primary outcome that rupatadine 10 mg, but not cetirizine 10 mg, was superior to placebo in improving symptoms of PER after 12 weeks of treatment. Both rupatadine and cetirizine were superior to placebo in improving the TSS including 4- and 8-weeks. Because this is a large and long-lasting study, it clearly confers a more meaningful and inherent, credible insight into the management of PER with new generation HI-antihistamine compounds.

After ARIA classification, the major change was a new subdivision of allergic rhinitis using the terms ‘intermittent’ and ‘persistent’ (4). It was shown that the previous classification of perennial rhinitis is not equivalent to the new classification of ‘persistent’, and it does not represent the same stratum of disease. In fact, PER represents about the one-third of the population with allergic rhinitis (18). In fact, a criterion to classify these patients into the group of persistent rhinitis is that
Rupatadine and cetirizine in persistent allergic rhinitis

symptoms need to be present by more than 4 days per week in at least four consecutive weeks (1). In our trial, this criterion was used in the screening period by means of a daily card with the aim to recruit patients with `persistent' allergic rhinitis according to the ARIA classification.

Rupatadine 10 mg presented a higher efficacy in all controls carried out (4, 8 and 12 weeks), which could be explained by the additional and sustained anti-inflammatory effect of rupatadine. The concept of minimal persistent inflammation implies that although these patients have been carrying allergen exposure throughout the year, these patients can still have continuous inflammation in the nose (19). Nevertheless, a significant relief in nasal obstruction was not observed for any of the active treatments when compared to placebo. In fact, nasal obstruction is unlikely to be relieved by traditional antihistamines and generally requires therapy with nasal corticosteroids, as suggested by the ARIA algorithm updated in 2007 (20).

A clear improvement in rupatadine 10 mg vs placebo was observed after 24 h of the first dose, indicating a fast onset of action of this drug in symptoms relief. This improvement was previously reported in patients with seasonal allergic rhinitis (10) where the authors suggested a faster effect than cetirizine in the control of symptoms.

It should be noted that this long-term treatment has not been assessed before for either of the treatments in PER patients. On the other hand, it is demonstrated that the instantaneous assessment is preferable to the reflective assessment for the primary and secondary variables, as the instantaneous assessment is usually more sensitive to the change in these patients.

In addition to the clinical impact of the disease, its impact in the patient's quality of life was measured by means of a validated questionnaire such as the RQLQ.

Rupatadine showed a better improvement than placebo in the total RQLQ and in most of the RQLQ dimensions (Activities, Sleep, Nasal symptoms, and Eye symptoms), indicating more important improvement in health related quality of life. All domains exceeded the predefined minimum clinically meaningful difference for baseline reductions (21), which is consistent with a significant reduction in symptoms. Rupatadine has proved to improve the overall RQLQ score from baseline ($P < 0.001$) after a 1-year follow-up (22).

This study supports the accuracy of the ARIA classification and validates the concept of persistent disease on a distinct and numerically large subset of rhinitis patients, who have enough symptoms to impair their QoL. Furthermore, a previous study tested the effect of treatment in PER; this study showed that the patients suffering from PER received long-term therapy, the treatment group showed a benefit, in terms of both QoL and a decrease in disease burden in comparison with the placebo group (2). In the same way, in our patients, a continuous treatment along 12 weeks with rupatadine has demonstrated a better control of symptom severity and suggested that this specific population of patients will probably need a prolonged treatment management.

From the safety point of view, it can be concluded that the overall incidence of related adverse events with rupatadine was similar to the incidence in patients treated with placebo and cetirizine, with no clinical differences in the physical examination or the laboratory analyses, included the ECG evaluation of QTc parameters thorough the study. These results are consistent with the outcomes of a previous 1-year tolerability clinical trial in which rupatadine 10 mg was well tolerated after 12 months of treatment in patients with PER (23).

In summary, rupatadine 10 mg is an effective and safe new antihistamine for the treatment of PER with a fast onset of action. Rupatadine provides a significant and meaningful reduction in total symptoms, and its effect is sustained after 12-weeks of treatment. In addition, treatment with rupatadine based on ARIA document appears to reduce the impact of the disease on patients' QoL.

Acknowledgments

We would like to thank Iñaki Pérez for the input in the analyses and the patients involved in this trial.

The authors thank J. Uriach y Compañía (Barcelona, Spain) for financial support for this study. This study was partially supported by the National Scientific Research Program of the Spanish Minister of Science and Technology.

References


Appendix

International Rupatadine Study Group

Argentina: Dr. Jaime Altcheh (Clinica Independencia, Buenos Aires), Dr. Luciano Napoli (Hospital Mi Pueblo, Buenos Aires), Dr. Adolfo Bodas (Centro Enfermedades Respiratorias Infantiles, Buenos Aires) Dr. German Darío Ramon (Instituto de Alergia e Immunologia del Sur, Bahía Blanca), Dr. Sara Fantin (Hospital Presidente Peron, Avellaneda, Buenos Aires), Dr. Alejandro Galgano (Policlinica Bancario, Capital Federal, Buenos Aires), Dr. Angela Gallardo (Hospital Notti, Guaymuyen, Mendoza), Dr. Tomas Herrero (Hospital Fernandez, Buenos Aires), Dr. Alejandro Malbran (in two centers: Unidad de Alergia e Immunologia; Hospital Británico Buenos Aires), Dr. Jorge Maspero (CIDEA; Buenos Aires), Dr. Silvia Melli (Hospital Churreu Vizca, Buenos Aires) Dr. Adriano Maccioni (Instituto Diagnostico Medico, Rosario, Santa Fe) Dr. Rene Maximilian Gomez (Instituto Alas, Salta) Dr. Pablo Tesolin (Hospital Italiano, Buenos Aires) Dr. Hugo Eduardo Neffen (Centro de Alergia e Immunologia, Santa Fe), Dr. Edgardo Jares (Consulturios Medicos Privados, Ramos Mejia, Buenos Aires).

Chile: Dr. Carlos Bisbal Malig (Hospital regional Rancagua, Rancagua) Dr. Ismael Zabalaga (Private
office, Santiago), Dr. Luis Guevara (Centro ORL, Rancagua), Dr. Maria Antonieta Guzman (Private Office, Providencia, Santiago) Dr. Oscar Herrera (Hospital Luis Calvo Makena, Santiago), Dr. Pedro Mardones (Clinica Servet, Santiago) Dr. Maria Angelica Perez (Hospital Exequiel Gonzalez Cortés, Santiago) Dr. Carlos Ubilla (Hospital Roberto del Rio, Santiago) Dr. Oscar Venegas (Centro de Alergias Concepcion, Concepcion), Ana Maria Agar (Clinica Alemana, Santiago).

Romania: Dr. Ioana Agache (SC Radoi mariana SRL, Brasov), Dr. Lucia Carbune (Private office, Bucharest) Dr. Dimitrie Dragomir (Children Clinical hospital 'Vidor Gomoiu'), Dr. Ioan Bradu Iamandescu, (Hospital Colentina, Bucharest) Dr. Claudia Elisabeta Nechifor (CMDTA 'N Kretzulescu', Bucharest), Dr. Sorin Perlea (National Institute of Aeronautic and Space Medecin, Bucharest), Dr. Mihaela Voiculescu (Clinical emergency Hospital, Craiova).