

ORIGINAL ARTICLE

Rupatadine oral solution in children with persistent allergic rhinitis: A randomized, double-blind, placebo-controlled study

Paul Potter¹, Jorge F. Maspero², Jan Vermeulen³, László Barkai⁴, Ildikó Németh⁵, Rene A. Baillieu⁶, Jesús M. Garde⁷, Josep Giralt⁸, Alejandro Doménech⁸, Iñaki Izquierdo⁸ & Antonio Nieto⁹

¹Allergy Diagnostic and Clinical Research Unit, Department of Medicine, University of Cape Town, Cape Town, South Africa; ²Fundación CIDEA, Buenos Aires, Argentina; ³Parow Research, Cape Town, South Africa; ⁴BÁZ Megyei Kórház Gyermekegészségügyi Központ, Miskolc, Hungary; ⁵Szent Erzsébet Kórház Non-profit Közhasznú Kft., Jászberény, Hungary; ⁶Centro de Alergia, Mar del Plata, Argentina; ⁷Hospital General Universitario de Elche, Elche, Alicante, Spain; ⁸Clinical Development & Medical Advice, J. Uriach & Co., Barcelona, Spain; ⁹Alergia Infantil, Hospital Materno Infantil La Fe, Valencia, Spain

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Correspondence

Alejandro Doménech, PhD, Clinical Development & Medical Advice Department, Polígon Ind. Riera de Caldes, Avinguda Camí Reial, 51-57 08184 Palau-solità i Plegamans, Barcelona, Spain.
Tel.: +34 93 863 02 87
Fax: +34 93 864 66 06
E-mail: alejandro.domenech@uriach.com

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Abstract

Background: Allergic rhinitis (AR) is one of the most common chronic diseases in childhood. No large, multicentre clinical trials in children with persistent allergic rhinitis (PER) have previously been performed. Rupatadine, a newer second-generation antihistamine, effective and safe in adults, is a promising treatment for children with AR. The aim of the present study was to evaluate the efficacy and safety of a new rupatadine oral solution in children aged 6–11 yr with PER.

Methods: A multicenter, randomized, double-blind, placebo-controlled study was carried out worldwide. Patients between 6 and 11 yr with a diagnosis of PER according to ARIA criteria were randomized to receive either rupatadine oral solution (1 mg/ml) or placebo over 6 wk. The primary efficacy end-point was the change from baseline of the total nasal symptoms score (T4SS) after 4 wk of treatment.

Results: A total of 360 patients were randomized to rupatadine (n = 180) or placebo (n = 180) treatment. Rupatadine showed statistically significant differences vs. placebo for the T4SS reduction both at 4 (-2.5 ± 1.9 vs. -3.1 ± 2.1 ; $p = 0.018$) and 6 wk (-2.7 ± 1.9 vs. -3.3 ± 2.1 ; $p = 0.048$). Rupatadine also showed a statistically better improvement in the children's quality of life compared with placebo. Adverse reactions were rare and non-serious in both treatment groups. No QTc or laboratory test abnormalities were reported.

Conclusions: Rupatadine oral solution (1 mg/ml) was significantly more effective than placebo in reducing nasal symptoms at 4 and 6 wk and was well tolerated overall. This is the first large clinical report on the efficacy of an H1 receptor antagonist in children with PER in both symptoms and quality of life.

Allergic rhinitis (AR) is one of the most common chronic diseases in childhood and adolescence and is more prevalent after 4 yr of age (1–4). Its prevalence is growing worldwide, although different trends and distribution are found in different areas (5, 6). The pathogenesis of the disease in children is similar to adult patients, but some symptoms reported by adults, such as nasal congestion, may be less evident in the paediatric setting, especially in younger pre-school children. This makes diagnosis and treatment more difficult (1, 7, 8). Considering the impact of AR in children's quality of life, the comorbidities and the risk factor which

rhinitis represents for the development of asthma (1, 9–11), the successful treatment of AR in the paediatric population is essential to decrease the burden of this disease. The ARIA guidelines state that treatment for school children is the same as in adults, but paediatric doses must be validated and special care should be taken to avoid side effects that are unique to this age group (1). The second-generation oral antihistamines are easy to administer, effective and recommended for the treatment of AR in children.

The lack of evidence-based paediatric pharmacotherapy is a well-known problem, and only a few trials have studied oral

second-generation antihistamines in children, due, in part, to practical and ethical reasons, which limit the performance of these studies in children (12). Over the last years, the European Medicines Agency (EMA) has been actively promoting the development of specific, efficacious and safe medicines for children.

Rupatadine is a newer second-generation antihistamine, with a dual mechanism of action inhibiting both H1 and PAF receptors. Rupatadine has been widely shown effective, rapid and well tolerated for the symptomatic treatment of AR and different types of urticaria in adults and adolescents (13–16). A new oral formulation of rupatadine has been recently developed for children. The objective of this study was to evaluate the efficacy and safety of rupatadine oral solution, as well as to assess the quality of life, in children aged 6–11 yr with persistent allergic rhinitis (PER).

Methods

This was a phase III double-blind, randomized, placebo-controlled, multicentre study conducted in a total of 34 centres in Argentina, South Africa, Hungary and Spain. To be enrolled in the study, children 6–11 yr weighing ≥ 16 Kg had to have a documented history of PER, according to ARIA guidelines (1), of at least 12 months prior to the selection visit. A skin prick test positive (3 mm greater than the negative control) to at least one of the following allergens was necessary: house dust mites, fungal spores and/or grass pollens. Children had to be symptomatic more than 4 days per week for more than 4 wk to the allergen to which they were positive. Results of standard laboratory blood tests and a 12-lead ECG had to be within acceptable limits, with QTc interval values after Bazett's correction within normal limits (values considered normal were <430 ms for boys and <450 ms for girls).

Children were not permitted to take the following medications: corticosteroids (any route), cromones, antihistamines, decongestants, leukotriene inhibitors, herbal remedies, systemic antibiotics, anticholinergic, ophthalmic NSAID, nasal-ophthalmic wash and/or any drug interacting with or any potential inhibitor of isoenzyme CYP3A4 (cytochrome P450).

After informed consent was signed by the patient's parent or guardian at the initial screening visit, there was a screening period of 14 days during which diary cards were completed to assess the severity of the child's AR symptoms. Daily assessments were made by the child or caregiver/guardian in a reflective manner (previous 24 h) and based on a classic 4-grade scale ranging from 0 to 3 (0, absent; 1, mild; 2, moderate; 3, severe). Children fulfilling all the inclusion and exclusion criteria as well as the symptom's severity criteria [total 4 symptom score (T4SS) ≥ 24 (max. 48) in four complete days (consecutive or not) throughout the screening period, nasal congestion individual score ≤ 6 (max. 12) and a score ≥ 2 (on a 3-point scale) in the instantaneous overall assessment of AR performed the same day of the visit] were randomized at Visit 0 (day 0) to either rupatadine oral solution 1 mg/ml or matching placebo (Fig. 1). Baseline data were obtained, and the patients were provided with the first bottle of the study medication and another diary card to assess AR symptoms for the following

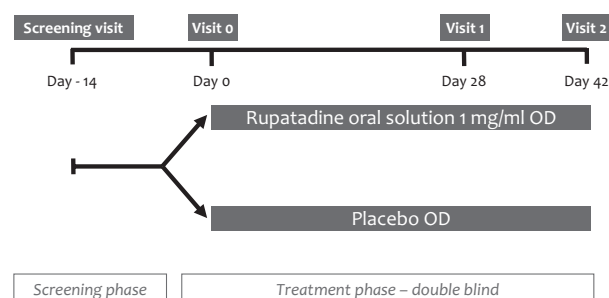


Figure 1 Study design.

28 days. At Visit 1 (day 28), patients were provided with a second bottle of study medication and a final diary card for the remaining study period, until visit 2 (day 42). Drug compliance was checked throughout the study based on returned medication, which was weighed and measured, and diary card entries. A physical examination was performed at each visit throughout the study, and adverse event/concomitant medication was also recorded.

Rupatadine oral solution 1 mg/ml was administered once daily before meals, preferably in the evening just after the symptom's assessment was performed, at doses adjusted to the patient's bodyweight: children <25 kg received 2.5 ml of rupatadine solution (equivalent to 2.5 mg of rupatadine), while children ≥ 25 kg received a dose of 5 ml (5 mg of rupatadine). This dosage was based on a previous pharmacokinetic study carried out in children age 6–11 yr, which confirmed the equivalence of these doses with those of adults in terms of systemic exposure. The use of rescue medication to relieve the unacceptable severity of any symptom was not allowed, and it was considered as a treatment failure; in that case, the patient was withdrawn from the study and treated accordingly.

The primary efficacy end-point was the average change over 28 days of the subjects' T4SS. This variable was defined as the difference between the mean of T4SS over 28-day period (patient diary card reflective 24 h assessment of all days) and the baseline T4SS. The T4SS is defined as the sum of the individual nasal symptoms score, (i) nasal congestion, (ii) sneezing, (iii) rhinorrhea and (iv) itchy nose, mouth, throat and/or ears, assessed as described above.

The main secondary efficacy end-point was the assessment of children's quality of life at baseline, 28 and 42 days of treatment by means of the Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) (9). Other efficacy end-points were the T4SS after 42 days of treatment, the T5SS after 28 and 42 days of treatment (T5SS includes the ocular symptoms – itchy, red, swollen and/or watery eyes – in addition to the nasal symptoms), the change from baseline in the daily score for each individual symptom (DSS), and the mean value of the daily T5SS (mT5SS) over the 42-day treatment period. The onset of action for rupatadine was considered as the first day in which any significant difference was observed.

The safety assessment was based on the adverse events reported by the patient, assessing mainly seriousness and

causal relationship to the study drug. Laboratory blood tests and ECGs were scheduled at baseline and after treatment completion. Physical examination and vital signs were monitored at every study visit throughout the study.

The study was designed to include a total of 366 patients (183 per treatment group) to detect, with an overall two-side alpha error of 5% and a power of 90%, a difference of 0.8 between placebo and rupatadine in the change from baseline in the T4SS during the first 28 days, assuming a common standard deviation of 2.1 and a 20% dropout. The main population for the efficacy analysis was the intention to treat (ITT) population. Differences in T4SS change between treatment groups over the 28-day treatment period (primary efficacy endpoint) were assessed by means of an analysis of covariance (ANCOVA) model.

The study was performed in accordance with Declaration of Helsinki, and the study protocol approved by the regulatory authorities and local ethics committees in each country prior to study start.

Results

The first patient was enrolled in March 2009, and the last patient completed in February 2010. Of the 180 patients randomized in each treatment group (ITT population), 164 (91.1%) in the rupatadine group and 161 (89.4%) in the placebo group completed the study, which left a dropout rate

of 8.9% and 10.6%, respectively (Fig. 2). The main demographic and baseline characteristics of the study population (ITT population) are shown in Table 1. A total of 73.3% patients in the placebo group and 72.8% in the rupatadine group presented at least one previous disorder/concomitant disease/comorbidity according to their medical history, asthma being the most frequently reported in 57.2% and 53.9% of patients in the placebo and rupatadine groups, respectively. Overall, no significant differences were found at baseline between both treatment groups. The total mean drug compliance percentage was $98.0\% \pm 8.3$ in the placebo group and $98.8\% \pm 5.3$ in the rupatadine group (Figs 1 and 2).

Efficacy

Baseline T4SS and T5SS were comparable at baseline for both treatment groups (Table 1). For the primary study end-point, the decrease of T4SS at 28 days showed statistically significant differences between placebo and rupatadine: -2.5 ± 1.9 vs. -3.1 ± 2.1 for placebo and rupatadine, respectively ($p = 0.018$), corresponding to a 34.7% vs. 43.1% decrease, respectively (Fig. 3). Statistically significant differences were also observed at 42 days for T4SS decrease: -2.7 ± 1.9 vs. -3.3 ± 2.1 ($p = 0.048$) (Fig. 3). T5SS decreased from baseline until day 42 of treatment, although the difference between placebo and rupatadine was statistically significant only at day 28: -2.8 ± 2.3 vs. -3.5 ± 2.5 , respectively ($p = 0.030$). Fig. 4

Table 1 Demographic and baseline characteristics of the ITT population

	Placebo (n = 180)	Rupatadine Sol. (n = 180)	Total (n = 360)	P-value*
Sex, N (%)				
Female	69 (38.3)	74 (41.1)	143 (39.7)	0.59
Male	111 (61.7)	106 (58.9)	217 (60.3)	
Age, mean (s.d.), [yr]	8.8 (1.7)	8.7 (1.7)	8.7 (1.7)	0.76
Age –category, N (%)				
6–8	80 (44.4)	82 (45.6)	162 (45)	0.60
9–11	99 (55)	98 (54.4)	197 (54.7)	
>11	1 (0.6)	0 (-)	1 (0.3)	
Race, N (%)				
Caucasian	88 (48.9)	84 (46.7)	172 (47.8)	0.96
Black	32 (17.8)	31 (17.2)	63 (17.5)	
Asian	19 (10.6)	20 (11.1)	39 (10.8)	
Multiracial	41 (22.8)	45 (25.0)	86 (23.9)	
Height, mean (s.d.), [m]	1.34 (0.1)	1.33 (0.1)	1.33 (0.13)	0.77
Weight, mean (s.d.), [Kg]	31.8 (9.8)	31.0 (9.3)	31.4 (9.6)	0.43
BMI, mean (s.d.), [Kg/m ²]	17.4 (3.0)	17.1 (2.8)	17.2 (2.9)	0.32
Allergen distribution†, N (%)				
Housedust mites	143 (79.4)	142 (78.8)	285 (79.2)	0.90
Fungal spores	63 (35.0)	59 (32.7)	122 (33.9)	0.66
Pollens (grass, trees)	103 (57.2)	115 (63.8)	218 (60.5)	0.20
Pets (cat, dog, feathers)	31 (17.2)	27 (15.0)	58 (16.1)	0.57
T4SS at baseline, mean (s.d.)	7.2 (1.1)	7.2 (1.1)		0.78

BMI, body mass index; s.d., standard deviation; T4SS, Total 4 Symptoms' Score.

*T-Test or Chi-square test were used for numerical [mean(s.d.)] or categorical [N(%)] variables.

†One patient may be positive for one or more allergens.

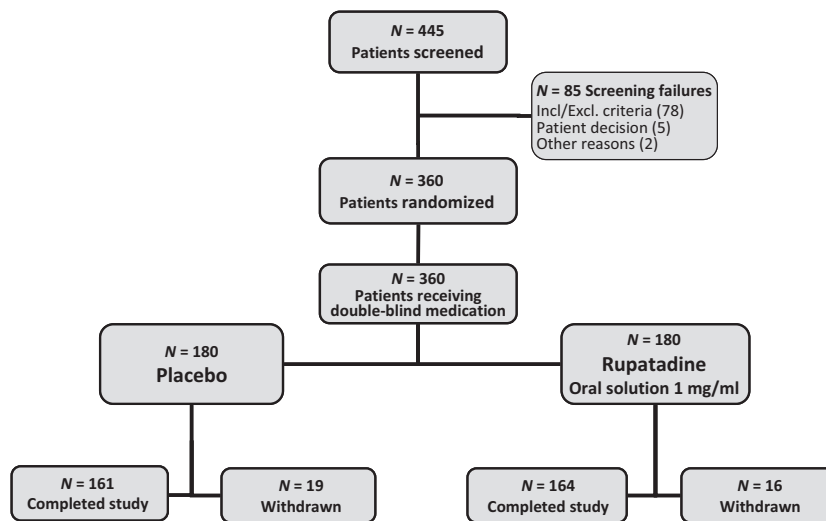


Figure 2 Disposition of patients.

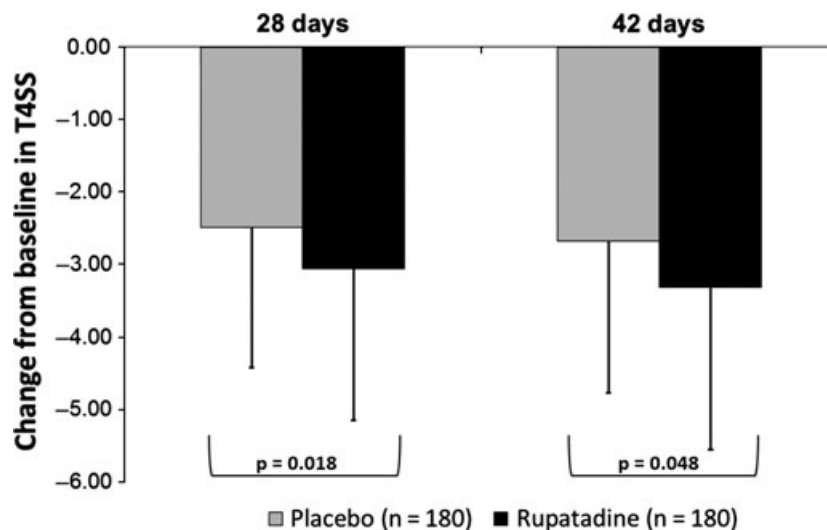


Figure 3 Change from baseline in the T4SS after 28 and 42 days of treatment with rupatadine oral solution or placebo. T4SS, total 4 nasal symptoms' score. ITT population.

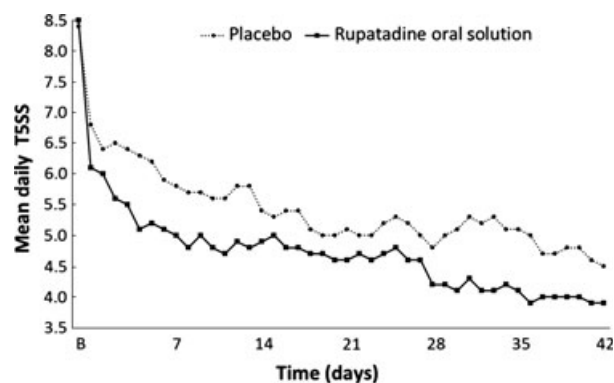


Figure 4 Mean value of the daily T5SS over the 42-day treatment period with rupatadine oral solution or placebo. ITT population.

shows the daily score of the mean T5SS throughout the 42-day treatment period; the AUCs of the T5SS evolution for both groups were calculated, with the differences between them being statistically significant (AUC of PBO group = 232.80 ± 116.46 vs. AUC RUP group = 201.84 ± 115.18 , $p = 0.012$, -test). At 12 h after the first-dose administration, significant differences between the study drug and placebo were already observed for T5SS: rupatadine reduced T5SS from 8.5 ± 1.7 to 6.1 ± 2.9 , while a decrease from 8.4 ± 1.6 to 6.8 ± 3.2 was achieved with placebo (ANOVA; $p = 0.032$ for the difference between both treatment groups) at that time point. The same statistical significance was observed for the T4SS reduction at 12 h after the first drug administration (ANOVA; $p = 0.026$ for the difference between both treatment groups). All the individual symptoms (nasal and non-nasal) scores decreased to a greater extent than placebo at 4 and 6 wk, but only rhinorrhea and itchy nose,

Figure 5 Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) score (Total and Individual domains score) after 28 days of treatment with rupatadine oral solution or placebo. * $p < 0.05$; ** $p < 0.01$ Rupatadine vs. placebo. ITT population.

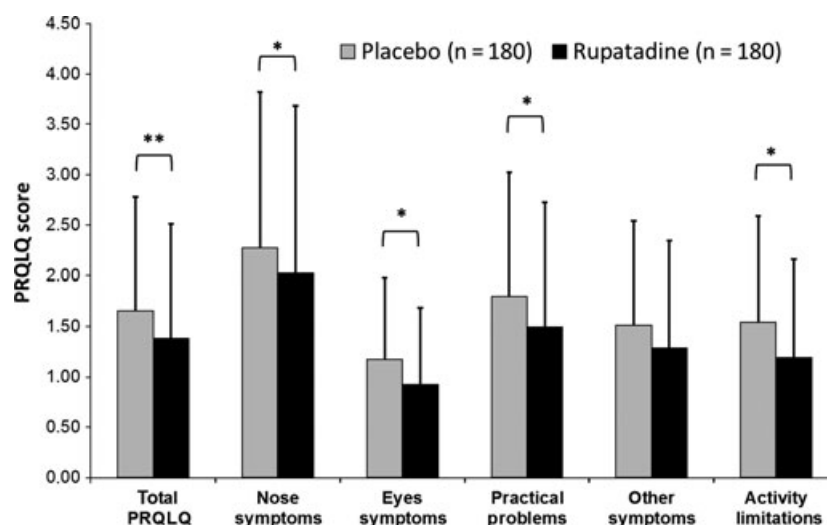


Table 2 Adverse drug reactions (considered as related by the investigator) with rupatadine paediatric oral solution 1 mg/ml or placebo

Adverse drug reaction ^a (preferred term)	Rupatadine solution (n = 180) N (%)	Placebo (n = 180) N (%)
Eosinophilia	1 (0.6)	0 (–)
Neutropenia	1 (0.6)	0 (–)
Eye pain	0 (–)	1 (0.6)
Nausea	0 (–)	1 (0.6)
Fatigue	1 (0.6)	0 (–)
Hypersensitivity	0 (–)	1 (0.6)
Influenza	1 (0.6)	0 (–)
Upper respiratory tract infection	1 (0.6)	0 (–)
Alanine amino transferase increased	0 (–)	1 (0.6)
Blood urea increased	0 (–)	1 (0.6)
Headache	1 (0.6)	3 (1.7)
Dizziness	1 (0.6)	0 (–)
Somnolence	2 (1.1)	0 (–)
Nasal congestion	0 (–)	1 (0.6)
Eczema	1 (0.6)	1 (0.6)
Night sweats	1 (0.6)	0 (–)

^aPossibly, probably or definitely related to study medication as assessed by the investigator.

mouth, throat and/or ears showed statistical significance compared with placebo (ANCOVA; $p < 0.05$ for the difference between both treatment groups, for both symptoms at 4 and 6 wk).

Quality of life

The children's quality of life (measured by means of PRQLQ) improved after 4 and 6 wk in both treatment groups. PRQLQ overall score showed statistical significant differences between rupatadine and placebo both at 4 and 6 wk. Most domains

showed also statistical significant differences between rupatadine and placebo at 4 wk of treatment (Fig. 5), while only the 'Nasal symptoms' domain achieved a statistically better score than placebo after 6 wk of treatment.

Safety

The incidence of reported adverse events with rupatadine oral solution was low. Overall, 67 (37.2%) of the 180 children treated with rupatadine reported at least one adverse event compared with 54 (30%) in those who received placebo. Headache was the most common reported adverse event, noted in 12.8% of rupatadine treated children compared with 5.6% of placebo recipients ($p < 0.001$); this event was generally mild in intensity and usually resolved on the same day that it occurred. Furthermore, most of the cases were not considered as related to the study medication by the investigator. Less-frequent treatment-emergent adverse events (all of them $< 4\%$ in either treatment group) comprised cough, abdominal pain, epistaxis, eczema and influenza.

Only a few adverse drug reactions were reported by investigators, without major differences between both treatment groups (11 in rupatadine group and 10 in placebo group) (Table 2). No serious adverse events or laboratory test abnormalities were reported. In addition, no ECG abnormalities were found in any patient.

Discussion

There is little published research on children with PER diagnosed according to the new ARIA classification and treated with second-generation H1-antihistamines. Most of the studies performed with second-generation antihistamines in children were based in the old classification of AR, into either seasonal and/or perennial AR (7, 17–20). To our knowledge, only one study was previously performed in children with PER, although it mainly aimed to evaluate the anti-inflammatory efficacy of levocetirizine measuring eosinophil-related

parameters as a primary end-point in 40 patients; clinical symptoms were assessed as secondary end-points, with results being highly affected by rescue medication intake (21). Therefore, the present study represents the first clinical evidence of the efficacy for an oral H1 receptor antagonist in children with PER.

Our study confirmed that rupatadine 1 mg/ml oral solution is effective in the reduction of nasal and non-nasal symptoms and achieves a clinical improvement, assessed by means of a reduction in the T4SS, significantly better than placebo in children with PER over a 28-day treatment period. Most of the secondary efficacy variables confirmed the results of the main study end-point both at 28 and 42 days of treatment. A loss of significance at 42 days was observed for the T5SS, which may probably be explained by statistical reasons, specifically a higher variability of the ocular symptoms compared with the rest. The efficacy shown by the oral solution of rupatadine in children confirms what has been reported for adults and adolescents (13–16), showing rupatadine as a beneficial H1 antihistamine. Previous experience in paediatric randomized controlled trials with other second-generation antihistamines have shown similar results in terms of efficacy; such is the case of cetirizine, levocetirizine and fexofenadine for perennial and seasonal rhinitis, but not yet for PER (7, 17–20).

A significant benefit in the quality of life was also shown with rupatadine in comparison with placebo both at 4 and 6 wk by means of the PRQLQ score. Quality of life improvement is currently recognized as an important aim when treating AR because the condition is known to impair, among others, social life, sleep and school/work performance (9). This can be even more relevant in children due to the impact of AR comorbidities such as eczema, asthma, conjunctivitis and otitis media, and the fact that treatment should not impair learning in school children. Additionally, as patients are very heterogeneous in their tolerance and acceptance of symptoms, one may not find a good correlation between symptoms and quality of life assessment (9). That is why the quality of life evaluation is becoming a relevant measure of the AR treatment efficacy, particularly in children. Rupatadine has been found in this study to be effective at this level too.

A marked placebo effect was observed for the main parameters, up to >30% at 4 wk. This effect was so evident that there were no differences in the treatment failures rate nor in the prohibited rescue medication consumption between both groups. This observation is not unusual because it has been previously described with other anti-H1 compounds in paediatric clinical trials (7, 17, 19). The larger placebo effect observed in children in contrast to adults could be explained, at least in part, by a more frequent use of rescue medication in the placebo group. It has been suggested that in this paediatric population, parents would treat their children with concomitant rescue medications to ease their symptoms, even though this was not recommended by the study protocol (7). However, in spite of the remarkable placebo effect, the difference between placebo and rupatadine was significant as soon as 12 h after the first treatment dose and, more importantly, remained significant both at 4 and 6 wk for the primary and other relevant secondary end-points, such as the children's quality of life.

Newer second-generation H1 antihistamines are known to cause fewer adverse effects than older first-generation H1 antihistamines in adults and children, specifically those related to CNS and cardiac safety (1, 12, 22–25). Rupatadine exhibits a safety profile in children similar to that of other second-generation antihistamines such as cetirizine, levocetirizine, desloratadine or fexofenadine (22–25) and was generally well tolerated. The overall incidence of adverse events in children aged 6–11 yr treated with rupatadine paediatric oral solution 1 mg/ml was lower than that reported in adults and adolescents with rupatadine tablets (13, 26), and almost no adverse reactions were reported with an incidence higher than 1%. Of note, the incidence of treatment-related somnolence, an important consideration from the viewpoint of reduced academic performance in school children, was very low (1.1% in the rupatadine group) and markedly lower than that observed in adults (13, 26). This finding is also consistent with the low incidence of sedation generally reported for second-generation antihistamines in the paediatric population (7, 12, 17–20, 22, 24, 25).

In conclusion, this study shows the efficacy of rupatadine oral solution in relieving the symptoms of AR in children between 6 and 11 yr, improving also their quality of life. Rupatadine was well tolerated, with a very low incidence of CNS-related adverse reactions and raising no cardiac safety concerns. This is, to our knowledge, the first comprehensive clinical report of the efficacy of a second-generation antihistamine in the treatment of PER.

Study participants

Jorge Fernando Maspero, Fundación CIDEA, Buenos Aires (Argentina); Iris Victoria Medina, Centro Médico Vitae, Buenos Aires (Argentina); René Alfredo Baillieu, Centro de Alergia Mar del Plata, Buenos Aires (Argentina); Adriana Mónica Marcipar, Instituto de Diagnóstico Médico Bioquímico de Rosario, Santa Fé (Argentina); René Maximiliano Gómez, Instituto Médico ALAS, Salta (Argentina); Mária Adonyi, Pécsi Tudományegyetem Klinikai Központ Gyermekgyógyászati Klinika, Pécs (Hungary); László Barkai, BAZ Megyei Kórház Gyermekegészségügyi Központ, Miskolc (Hungary); Márta Farkas, Heim Pál Gyermekkorház, Budapest (Hungary); Béla Nagy, Debreceni Egyetem Orvos- és Egészségtudományi Centrum Gyermekgyógyászati Intézet, Debrecen (Hungary); Ildikó Németh, Szent Erzsébet Kórház Non-profit Közhasznú Kft., Jászberény (Hungary); Zoltán Novák, Szegedi Tudományegyetem, Szeged (Hungary); Péter Pölöskey, Mohács Város Kórháza, Mohács (Hungary); Prof. Paul Potter, UCT Lung Institute, Cape Town (South Africa); Jan Vermeulen, Parow Research, Cape Town (South Africa); Solly Mahomed, Hiway Medical Centre, Durban (South Africa); Essack Mitha, Newtown Clinical Research Centre, Newtown (South Africa); Edzard Biermann, Mercantile Hospital, Port Elizabeth (South Africa); Ahmed Manjra, Hiway Medical Centre, Durban (South Africa); Johan Lombaard, Joshua Research, Bloemfontein (South Africa); Marcelle Groenewald, Military Hospital, Thaba Tshwane (South Africa); Prof. Robin Green, Pretoria Academic Hospital,

Pretoria (South Africa); Seef Pretorius, Syzygy Clinical Research Services, Lynnwood (South Africa); Carmen Vidal, Hospital Médico Quirúrgico de Conxo, Santiago de Compostela (Spain); Santiago Nevot, Hospital Sant Joan de Deu,

Manresa (Spain); Antonio Nieto, Hospital Materno Infantil La Fe, Valencia (Spain); Jesús María Garde, Hospital General Universitario de Elche, Elche (Spain).

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