

Original article

Rupatadine 10 mg and ebastine 10 mg in seasonal allergic rhinitis: a comparison study

Background: The aim of this study is to establish the efficacy and safety of rupatadine vs ebastine and placebo in the treatment of seasonal allergic rhinitis (SAR). Rupatadine is a new second generation H₁-antihistamine with once-daily dosing that may provide better control of symptoms than the currently used H₁-receptor blockers because of its dual pharmacological profile (anti-PAF and anti-H₁).

Methods: In a multicentre study, 250 patients with SAR were included in a double-blind, randomized, parallel-group and placebo-controlled study. Patients received either rupatadine 10 mg, ebastine 10 mg or placebo once daily for 2 weeks. The main efficacy outcome was based on the patient's record of severity of nasal symptoms (sneezing, nasal itching, runny nose and nasal obstruction) and nonnasal symptoms (conjunctival itching, tearing and pharyngeal itching). The daily total symptom score (DTSS) was the mean of the DSS recorded for each of the seven symptoms assessed, and the mean DTSS (mDTSS) was the mean of the DTSS values for each study day.

Results: Significant differences in mDTSS were detected between rupatadine and placebo (33% lower for rupatadine group; $P = 0.005$) after 2 weeks of treatment. The TSS for rupatadine were 22% lower than for ebastine, although the differences were not statistically significant. No serious adverse events were reported during the study period.

Conclusions: Rupatadine 10 mg once daily was clearly superior to placebo in alleviating the symptoms of SAR over a 2-week period. In comparison with ebastine, rupatadine shows a trend towards a better profile as regard several secondary efficacy variables.

E. M. Guadaño¹, J. Serra-Batlles², J. Meseguer³, J. A. Castillo⁴, M. de Molina⁵, A. Valero⁶, C. Picado⁶ and Rupatadine Study Group*¹

¹Hospital Sant Pere Claver, ²Hospital General de Vic, ³Hospital General de Castelló, ⁴Cap Jaume I, ⁵Hospital de la Creu Roja de l'Hospitalet and ⁶Hospital Clínic, Department of Medicine, Universitat de Barcelona, Barcelona, Spain

*For a list of the researchers and their centres see acknowledgements.

Key words: antihistamine; ebastine; platelet-activating factor; rupatadine; seasonal allergic rhinitis; second generation.

Dr Cesar Picado
Hospital Clínic
Servicio de Neumología
C/Villarroel, 170
08036, Barcelona
Spain

Accepted for publication 31 March 2004

Allergic rhinitis is an increasingly prevalent disease in the majority of developed countries, affecting 10–20% of the general population (1–3). Allergic rhinitis was previously subdivided, based on time of exposure, into either seasonal allergic rhinitis (SAR), for which the primary cause is pollen, or perennial allergic rhinitis (PAR), caused by dust mites, animal danders, mould spores and various other antigens. As this subdivision was not entirely satisfactory, a new classification appeared recently, based on duration and severity, and subdivided into 'intermittent', intermittent allergic rhinitis (IAR) or 'persistent', persistent allergic rhinitis and 'mild' or 'moderate-severe', respectively. However, we have kept the SAR term since we do not have any additional clinical data, such as duration of symptoms or quality of life parameters that allow us to make the assumption that SAR and IAR are interchangeable clinical term. The major symptoms of allergic rhinitis include: rhinorrhoea, nasal obstruction, nasal itching and sneezing that are spontaneously reversible with treatment.

H₁-antihistamines have been the traditional first-line therapy in the treatment of allergic rhinitis (4). Rupatadine is a powerful new once-daily nonsedating H₁-antihistamine. It has also proved to inhibit platelet-activating factor (PAF) *in vitro*, in animal species and also in humans. *In vivo* studies have shown that rupatadine inhibits histamine- and PAF-induced paw oedema, increasing vascular permeability in rats and bronchoconstriction in guinea-pigs. *Ex vivo* studies reveal that orally administered rupatadine, at therapeutic doses, selectively blocks peripheral lung H₁-receptors. Rupatadine has demonstrated a potent antiallergenic activity in several type I hypersensitivity models, both *in vitro* and *in vivo* (5–6). In an *in vivo* model rupatadine is able to inhibit the wheal area in hypersensitive dog skin induced by *Ascaris suum* extract (7, 8).

Clinical experience with rupatadine in phase I, II and III clinical trials has demonstrated both its safety when given once a day at doses from 2 to 80 mg to healthy subjects, elderly people and patients, and its efficacy in

PAR and SAR at doses of 10 mg oral dose. The cardiac safety of rupatadine has been assessed in preclinical studies and in several pivotal clinical trials (9, 10).

The objective of the current study was to compare the efficacy and safety of rupatadine 10 mg *vs* a well-known second generation H₁-antihistamine such as ebastine 10 mg *vs* placebo, all administered once daily, in the treatment of SAR over a 2-week periods.

Material and methods

Patient population

The inclusion criteria were the following: patients aged 12–65 years, diagnosed with SAR due exclusively to pollen for at least 2 years, and with an acute stage of the disease (total nasal symptom score ≥ 5 -points: runny nose, itchy nose, nasal congestion, sneezing). A positive skin prick test (papule diameter > 3 mm than that produced by saline control, or greater than or equal to that obtained with 10 mg/ml histamine) was required either at inclusion or during the previous year. Eligible patients were screened for significant abnormalities by means of physical examination, haematology and serum chemistry tests and ECG. The QTc measurements were not performed over the course of the present study.

Women of child-bearing age had to show a negative pregnancy test and be committed to using contraceptive measures during the study.

Study exclusions included: (i) pregnancy or breast-feeding; (ii) history of hypersensitivity to allergens other than pollen; (iii) nonallergic rhinitis (i.e. vasomotor, infectious, drug-induced); (iv) known hypersensitivity to antihistamines, (v) any clinical disorder or concomitant illness that might interfere with the evaluation of the study's medication; (vi) nasal pathology resulting in fixed occlusion of a nostril and (vii) any treatment with immunotherapy.

Excluded medications were astemizole within the last month, ketotifen within the last 2 weeks, topical or systemic corticosteroids, immunosuppressants or any investigational drug within the last 2 weeks, any oral antihistamine or disodium cromoglycate within the last week, topical antihistamines within the last 48 h and nasal decongestants within the last 24 h. Patients with asthma were not excluded, provided they had not required treatment with drugs in the 3 months before the trial.

Study design

This was a multicentre, double-blind, randomized, parallel-group, placebo-controlled study conducted over two consecutive spring seasons (from April 1997 to June 1998), in 21 centres in Spain. Patients who consulted their doctor with symptoms of SAR expected to last for the treatment period were eligible for enrolment. The daily mean distribution of the allergen was Oleaceae: 23.3 ± 63.3 grain/m³ air; Poaceae: 13.6 ± 18.6 grain/m³ air and Urticaceae: 16.3 ± 14.6 grain/m³ air in 1997 and Oleaceae: 56 ± 14 grain/m³ air; Poaceae: 18.6 ± 28.6 grain/m³ air; Urticaceae: 10.3 ± 10 grain/m³ air in 1998.

Local ethics committees approved the protocol in accordance with national legislation. All patients gave their informed written consent before inclusion. The study was conducted in accordance with the last version of the Declaration of Helsinki.

Screened patients were randomly allocated to treatment with rupatadine 10 mg (J. Uriach & Cia, S.A. Barcelona, Spain), ebastine 10 mg (Almirall-Prodesfarma, Barcelona, Spain) or placebo. The

researcher and other on-site personnel were required to remain blinded to the study's medication, so all the products were supplied as gelatine capsules with an identical appearance, to ensure the blinding of the study. A computer-generated randomized scheme was used to provide balanced blocks of patient numbers for each of the three treatment groups and the patients were assigned a sequential randomization number. Patients were provided with diary cards and were instructed how to record their allergic symptoms every morning (before drug intake) and at bedtime.

All patients were given haematology and serum chemistry tests, and female patients were given a pregnancy test.

Efficacy evaluation

Throughout the study period patients rated the severity of their nasal (runny nose, itchy nose, nasal congestion, sneezing) and nonnasal symptoms (itchy eyes, watery eyes, itchy throat) in the morning (before drug intake) and at night in a diary card. Patients scored the severity of SAR symptoms for the previous 12 h and on a 3-point scale. This was the sum of four rating scales for the following symptoms, each being assessed on a 3-point rating scale: 0 = no symptoms (normal status), 1 = occasional mild symptoms causing discomfort, 2 = mild, frequent, distressing symptoms, 3 = severe, continuous symptoms interfering with sleep and/or work. The researchers examined the patient's diary card at each visit to check the progress of the treatment.

The main efficacy variable [mean daily total symptom score (mDTSS)] was obtained from the daily subjective assessment of the severity of each rhinitis symptom recorded by patients in their diaries. The mDTSS was calculated for all days based on the DSS, i.e. the mean of the two scores assigned to a symptom within 24 h following drug administration. The DTSS was calculated as the mean of the DSS recorded for each of the seven assessed symptoms for each day, and the mDTSS was calculated as the mean of the DTSS values over the study period.

The mDTSS was assessed both at baseline and when patients returned for medical follow-up examination.

Secondary efficacy variables were the mDSS, i.e. the mean of all the DSS calculated for given symptoms per patient for all study days; maximum value of the daily symptom score (DSSmax); maximum value of the total daily symptom score (DTSSmax).

Criteria for secondary efficacy of treatment were a daily self-assessment by the patient, who rated seven symptoms. At the end of the study each patient made an overall assessment of efficacy on a 4-point rating scale and the researcher tabulated both efficacy and tolerability. The patients' and doctors' overall evaluation of efficacy was assessed at visit 3 (day 7) and at the end of the therapy, at visit 4 (day 14). Both nasal symptoms and non-nasal symptoms (conjunctival itching, weeping and pharyngeal itching) were scored according to a scale from 0 to 3; where 0 = worsening or increased symptom severity, 1 = no change in symptom severity, 2 = improvement in symptom severity, 3 = marked improvement or disappearance of symptoms. Furthermore, the following four composite scores were calculated: TSS (sum of all seven individual scores), individual symptom score, overall impression of efficacy (assessments by both researcher and patient).

Safety evaluations

Safety and tolerability were evaluated using clinical examinations, laboratory test, reported adverse events (AE) on the patients' diary card. The AE were classified according to the World Health Organization Adverse Reaction Terminology (WHO-ART) (11)

and assessed as mild, moderate or severe and related or unrelated to treatment.

Statistical analysis

Data analysis for this study followed an amended and prospectively determined data analysis plan. An ANCOVA was applied to the symptom score variables (DSS, DTSS, mDTSS, DTSSmax) to determine the differences between treatments, centres and treatment centre interactions. We also performed an ANCOVA model including 'season' as a new factor.

Each significance test was performed at a 0.05 significant level (two-sided). The data were analysed with SPSS 7.5. The primary efficacy analysis was based on intention-to-treat analysis. Average symptom scores were analysed using an ANOVA model. The factors included in the model were treatment centre, treatment schedule, as well as treatment by centre and treatment-by-treatment schedule interactions.

The patients' and researchers' overall evaluation scores at day 14 were analysed using the Cochran–Mantel–Haenszel test stratified by centre. A Fisher's exact test would be used if the data were sparse. The overall scores were grouped into three categories: meaningful improvement, no meaningful change and meaningful deterioration.

The chi-square test was used for the presence of AE (yes/no) or the Fisher exact test if applicability conditions were not present.

A covariance analysis model was used to investigate the relationship between treatment and clinical efficacy. This model fitted the average symptom severity score with the covariate baseline TSS and factor baseline strata (equivalent to treatment schedule). According to the Bonferroni rule, a α level of 0.0016 was used to adjust for multiple comparisons.

To achieve an 80% power to detect a treatment difference of 0.3 in the main change from baseline for (mDTSS – minimum 0 and maximum 3 points – throughout the study), assuming a standard error of 0.5 and a 20% discontinuation rate, 80 patients per treatment group were needed.

Results

Demographic data

A total of 250 patients met the eligibility criteria and were randomized. Six noncompliant patients were excluded from the analysis and one was excluded because lack of baseline information data. These seven patients were equally distributed across the treatment groups. Groups were balanced for demographic characteristics and DTSS scores. No statistically significant differences were detected among the study groups at baseline (Table 1).

Overall efficacy

Efficacy was analysed by comparing changes in improvement relative to baseline in the main efficacy variable, mDTSS. The only significant reduction was found in the rupatadine treatment group (33% reduction) vs placebo (13% reduction) ($P < 0.005$). The mDTSS for rupatadine treatment was 0.16 points lower than that of the ebastine group (22% reduction), although this difference was not significant (Fig. 1).

Table 1. Patients' demographic data at baseline: all treated patients

	Rupatadine (<i>n</i> = 79)	Ebastine (<i>n</i> = 83)	Placebo (<i>n</i> = 81)
Sex			
Male	28 (35%)	37 (45%)	35 (43%)
Female	51 (65%)	46 (55%)	46 (57%)
Race			
Caucasian	78 (99%)	82 (98%)	81 (100%)
Noncaucasian	0	1 (2%)	0
Unknown (not recorded)	1 (1%)	0	0
Age (years)			
Mean ($\pm$ SD)	32 (10)	33 (10)	33 (10)
Range	17–59	18–60	18–58
Weight (kg)			
Mean ($\pm$ SD)	67 (12)	67 (12)	66 (13)
Range	40–97	50–100	43–105
Height (cm)			
Mean ($\pm$ SD)	166 (10)	166 (9)	165 (11)
Range	148–190	148–185.2	120–185
mean daily total symptom score (mDTSS) baseline			
Mean ($\pm$ SD)	1.47 (0.39)	1.70 (0.51)	1.60 (0.49)

None of the variables were statistically significant.

The group treated with rupatadine showed a higher reduction in symptom severity than placebo for all symptoms, when they were considered individually. Differences reached statistical significance in four symptoms: runny nose ($P < 0.0001$), sneezing ($P = 0.002$), nasal itching ($P = 0.02$) and weeping ($P = 0.007$). Differences between ebastine and placebo were statistically significant for only one symptom, runny nose ($P \leq 0.005$) (Fig. 1). Nasal obstruction was the symptom, which showed the smallest difference between both active treatment and placebo.

The secondary variables DTSSmax and DSSmax were calculated and compared with respect to the different treatments. The mean DTSSmax for both active treatments was significantly lower than the mean DTSSmax for the placebo group, 28% lower for the rupatadine treatment group ($P = 0.001$) and 17% lower for the ebastine treatment group ($P = 0.003$), and the mean DTSSmax for the rupatadine treatment group was 13% lower than the mean DTSSmax for the ebastine group. Mean DSSmax for four symptoms (runny nose, sneezing, itching nose and watery eyes), was significantly lower for the rupatadine treatment group compared with placebo, whereas the ebastine treatment group showed mean DTSSmax values significantly lower than the placebo group for only two symptoms (runny nose and sneezing). The DTSSmax scores for each treatment group are summarized in Fig. 2.

At day 7, according to the patients' overall impression of treatment efficacy, there was a good or excellent improvement in symptoms in 53% of patients on the placebo treatment, 80% on the ebastine treatment and 74% on the rupatadine treatment (rupatadine vs placebo, $P = 0.018$; ebastine vs placebo, $P = 0.0001$). Similarly,

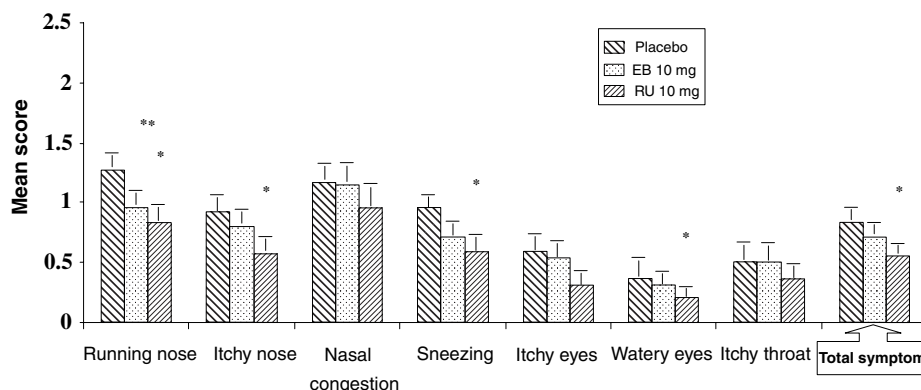


Figure 1. Summary mean daily symptom scores for each symptom during the study period. * $P < 0.05$ rupatadine 10 mg vs placebo treatment. $P < 0.05$ ebastine 10 mg vs placebo treatment.

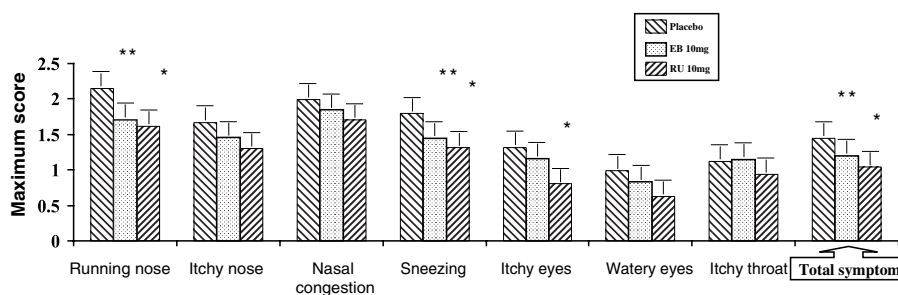


Figure 2. Summary mean maximum value of the daily symptom score (DSSmax) for each symptom during the study period. * $P < 0.05$ RU 10 mg vs placebo treatment. $P < 0.05$ EB 10 mg vs placebo treatment.

according to the researchers' overall impression of efficacy there was an excellent improvement in symptoms in 54% of patients in the placebo treatment group, 80% in the ebastine treatment group and 75% in the rupatadine treatment group (rupatadine vs placebo, $P = 0.018$; ebastine vs placebo, $P = 0.0001$). The comparison of rupatadine vs ebastine for the two measures was not significant.

At day 14, the overall impression of efficacy for patients and researchers remained greater than placebo for both active treatments as shown in Fig. 3. The primary variable was analysed using an ANCOVA that extracted sources of variation because of treatment and centre. We also included another exploratory factor 'season', in the model in order to explore the influence of differences in the levels of pollens in the two springs on the symptom severity. Although we observed a decrease in symptom severity in the second year, we could conclude that the three treatments behaved in a similar way over the two seasons, meaning they had similar efficacy profiles.

Safety results

A total of 254 AE occurred in 111 patients. Forty-six percentage were placebo-treated patients, 45% were

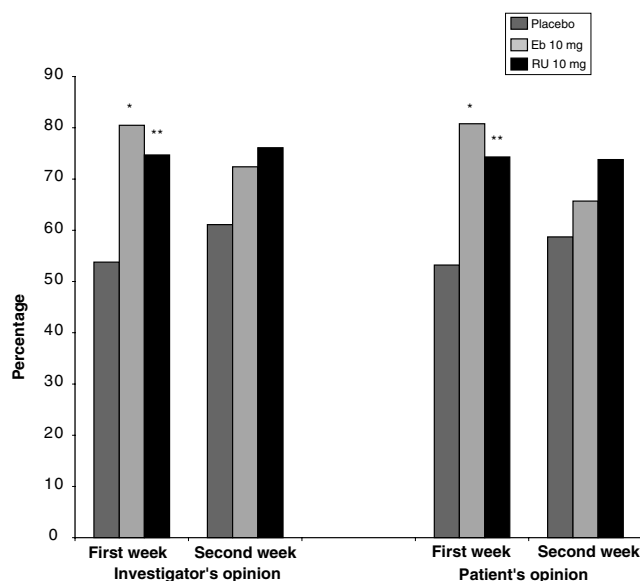


Figure 3. Overall impression of efficacy. Improvement in symptom score (%).

ebastine-treated patients and 47% were rupatadine-treated patients. None of these AE was considered serious by the researchers. These percentages did not present any

Table 2. Frequency of related adverse events

	Placebo (n = 81)	Rupatadine (n = 79)	Ebastine (n = 83)	P-value
Related adverse event (%)				
Headache	12 (14.8)	6 (7.6)	9 (10.8)	ns
Somnolence*	2 (2.4)	14 (17.7)	9 (10.8)	*
Asthenia	2 (2.4)	1 (1.3)	3 (3.6)	ns
Dizziness	—	3 (3.8)	—	ns
Abdominal pain	4 (4.3)	3 (3.7)	—	ns
Back pain	—	—	1 (1.2)	ns
Pharyngitis	—	1 (1.2)	1 (1.2)	ns
Rhinitis	—	—	1 (1.2)	ns

* $P = 0.006$; ns, nonsignificant.

significant differences. The relationship with the study's medication was considered possible in 46% (116 of 254) of the cases, probable in 63% (73 of 116), almost definite in 33% (38 of 116) and definite in 4% (five of 116). The most frequently reported treatment-related AE were: sleepiness 14 in rupatadine group, nine in the ebastine group and two in the placebo group (rupatadine vs ebastine comparison was no significant and both active treatments were significant vs placebo, $P = 0.006$). There were not significant differences between the three groups in other reported AE (headache, abdominal pain and pharyngitis). No clinically significant trends were noted during the study period in the biochemistry and haematology parameters (Table 2).

Discussion

The results of this double-blind, placebo-controlled trial demonstrated that rupatadine, a new nonsedating, once-daily antihistamine, relieved common nasal and nonnasal symptoms of SAR over a 14-day treatment. We used ebastine as a positive control to monitor the variability of the disease that is usually seen in trials of SAR. Ebastine is an effective, well-tolerated and nonsedating new generation H_1 -antihistamine, and was thus an appropriate positive standard for assessing the dose-related activity of rupatadine (12, 13).

Rupatadine reduced the symptom scores for most of the parameters more than ebastine and placebo and shows a trend towards a better profile, in comparison with ebastine, as regard primary as well as several secondary efficacy variables. The response to placebo was similar to that of earlier studies (14, 15). The fact that the placebo group had a relatively high improvement considerably reduced the observed effects of the active treatments.

Rupatadine treatment produced a higher reduction than placebo in the severity of all the symptoms evaluated, and these differences were statistically significant in sneezing, runny nose, weeping and nasal itching. The greatest difference between the rupatadine doses and placebo was in the runny nose. Otherwise, the smallest

difference (and not statistically significant) was in nasal obstruction. The marked superiority of rupatadine over placebo in alleviating the symptom of a runny nose is consistent with previously published data (16), showing that nasal discharge is one of the most histamine-dependent rhinitis symptoms. The poorer results as regard nasal obstruction concur with results of previous studies on rupatadine in seasonal rhinitis, as well as with published data showing that nasal congestion responds poorly to antihistamines (17).

The patients' and researchers' overall impression of efficacy indicated that both the rupatadine and ebastine treatments were significantly more effective than placebo during the first week of treatment but less so in the second week. This suggests that the active treatment leads to a faster and persistent resolution of the acute flare-up of disease and that this is less noticeable in the second week.

The incidence of AE with rupatadine was similar to reports on other second generation antihistamines, such as ebastine (18, 19). Most AEs were related to symptoms of the underlying allergic condition rather than to the study's medication (20).

It should be noted that at the end of each treatment week patients were actively asked to describe any adverse symptom or events that they had experienced. This could contribute to an overestimation of the AE frequency in comparison with those studies in which patients only report AEs spontaneously (19). No serious cardiac events were noted in any of the patients.

The finding of a significant increase in the incidence of sleepiness as a treatment-related AE in the rupatadine group could be linked to the fact that the drug was taken in the morning. The time of drug administration in this study differs from other similar studies, where the drug is usually taken at bedtime. In previous studies, rupatadine has shown no relevant changes in psychomotor performance in standardized tests that evaluated the effects of rupatadine 10 mg on the central and peripheral nervous system (21).

Surprisingly, Ebastine scores were not significant for the main efficacy variable compared with placebo. The results of this study indicate that treatment with rupatadine 10 mg once a day effectively improves SAR symptoms and is well-tolerated by adult and adolescent patients over a 14-day treatment period.

In order to evaluate rupatadine activity, further studies are required to investigate whether rupatadine improves the control of allergic symptoms in comparison with other second generation antihistamines.

Acknowledgments

The authors would like to thank J. Uriach & Cía (Barcelona, Spain) for their financial support to this study. This study was partially

supported by the National Scientific Research Program of the Spanish Minister of Science and Technology.

Authors gratefully acknowledge the participation of our colleagues in Spain from the Rupatadine Study Group: Dr Basomba and collaborators (Dr Alamar, Dr Campos, Dr García and Dr Hernandez) (Valencia); Dr Cadahia and collaborator (Dr Nogueiras) (Barcelona); Dr Castillo (Vilanova i la Geltrú); Dr Cerdà (Girona); Dr Alonso and collaborator (Dr Cisteró) (Barcelona); Dr López Serrano and collaborator (Dr Moreno) (Madrid); Dr Malet (Barcelona); Dr Marqués (Lleida); Dr Malek and Dr de Mateo (Castelló); Dr Pinto (L'Hospitalet); Dr Prieto and collaborators (Dr Morales and Dr Gutierrez) (Valencia); Dr Nevot and collaborator (Dr Leonart Benfill) (Manresa); Dr Pelaez and collaborators (Dr Burches, Dr Sartre and Dr Bertó) (Valencia);

Dr Casademunt (Vic); Dr Luengo (Barcelona); Dr Prieto (Barcelona); Dr Sastre and collaborator (Dr Inzúa) (Barcelona); and Dr Sierra and collaborator (Dr Plaza) (Barcelona); Dr Simón and Dr Hermida (Barcelona); Dr Granel and collaborator (Dr Olivé); Dr García and collaborators (Dr Barceló, Dr Carmona, Dr Vega, Dr Miranda, Dr Palomeque) (Málaga); Dr Morales and collaborator (Dr Castelló) (Alicante).

Also the authors would like to thank the Barcelona, Elche and Madrid Aerobiological Network for providing the pollen data. They have been obtained following the standard methods of the Aerobiological Committee of the Spanish Society of Allergology and Clinical Immunology (Sociedad Española de Alergología e Inmunología Clínica, SEAIC).

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