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A 12-week, placebo-controlled study of the efficacy and safety of ebastine, 10 and 20 mg once daily, in the treatment of perennial allergic rhinitis

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This double-blind, placebo-controlled, multicentre study investigated the ability of ebastine, 10 and 20 mg once daily, to control symptoms of perennial allergic rhinitis (PAR) over a 12-week period, and assessed additional benefits of the 20-mg dose. Following a 2-week baseline period, patients (12–63 years) were randomized to treatment with ebastine 10 mg (n=88) or 20 mg (n=102), or placebo (n=100). Patients scored symptom severity (0–3) twice daily, and mean changes from baseline scores showed ebastine to be significantly effective in week 1. Control of symptoms persisted over the 12 weeks, the average daily total nasal symptom score for nasal stuffiness plus nasal discharge plus sneezing plus itchy nose being reduced by both doses, with statistical significance at 20 mg (P=0.015 *vs* placebo) despite decreased usage of sodium cromoglycate rescue medications. Patient and clinician final opinions of treatment also significantly favoured ebastine, both 10 and 20 mg, over placebo. No serious adverse events occurred, and study treatments were well tolerated with a low incidence of central nervous system-related adverse events and headache. In conclusion, ebastine 10 or 20 mg once daily was rapidly effective in relieving symptoms of PAR in adult and adolescent patients; additional benefits of the 20-mg dose became apparent in the longer term.

Symptoms of allergic rhinitis – nasal discharge, sneezing, itching, and stuffiness, together with ocular itching and watering – may occur on exposure to indoor allergens such as house-dust mite and cockroach, which are present on a chronic basis and can result in perennial symptoms (1). In particular, nasal stuffiness or congestion is more pro-

Table 1. Baseline demographics and 24-h symptom severity scores. PIN (perennial index): sum of scores for nasal discharge plus sneezing plus itchy nose; TNS (total nasal symptoms): sum of scores for nasal discharge plus sneezing plus itchy nose plus nasal stuffiness. Individual symptom scores: 0=none, 1=mild, 2=moderate, 3=severe

Variable		Ebastine 10 mg	Ebastine 20 mg	Placebo
Patient no.		88	102	100
Sex	M	44	46	53
	F	44	56	47
Age (years)	Mean	26.0	25.2	25.6
	Range	12–61	12–63	12–55
Height (cm)	Mean	167.0	166.8	168.1
	Range	142–186	148–193	145–191
Weight (kg)	Mean	62.5	63.0	64.6
	Range	35–88	40–96	30–101
Baseline symptom score		*n*=88	*n*=102	*n*=100
	PIN	4.46	4.92	4.67
	TNS	6.41	6.83	6.56
	Nasal stuffiness	1.95	1.92	1.89
	Nasal discharge	1.83	1.86	1.77
	Sneezing	1.40	1.58	1.44
	Itchy nose	1.23	1.48	1.46
		n=84	*n*=97	*n*=96
	Eyes watering	0.62	0.59	0.52
	Conjunctival irritation	0.67	0.65	0.62

nounced in perennial allergic rhinitis (PAR), whereas eye itching is less severe than commonly found in seasonal allergic rhinitis (SAR) (2). Nasal discharge (watery rhinorrhoea), sneezing, and itching are brought about chiefly by the action of histamine on sensory nerve H_1-receptors, and second-generation H_1-specific antihistamines are particularly effective in controlling these symptoms. Nasal congestion, however, is often more resistant to antihistamines due to the complexity of causative factors, which, in addition to histamine and other mediators from mast cells, include the products of recruited inflammatory cells such as eosinophils and basophils (1–5). Because of this chronic allergic inflammation, topical corticosteroid treatment is the most effective means of reducing nasal congestion (1). However, H_1-specific antihistamines have also demonstrated antiallergic effects which could potentially enhance their clinical effectiveness in PAR (6).

Ebastine is a novel, nonsedating H_1-antihistamine which effectively controls SAR symptoms when administered at the standard dose of 10 mg once daily (7, 8), yet it has demonstrated significant further benefits at 20 mg once daily, in patients with relatively severe SAR (9).

Our 12-week study was undertaken to investigate the basic efficacy and safety of ebastine, 10 or 20 mg once daily, in controlling symptoms of PAR, and to assess any additional benefits of the increased dose in these patients.

Material and methods

Patients

Patients of either sex, aged 12–65 years, with a clinical diagnosis of PAR (sneezing, rhinorrhoea, and/or nasal congestion on most days) for at least 2 years, and with a documented positive (3+) skin prick test and/or IgE test (≥class 2 RAST or CAP System; Pharmacia, Uppsala, Sweden) to *Dermatophagoides pteronyssinus* and/or *D. farinae*, were recruited. Before entering the double-blind phase of study treatment, patients were required to show a minimal baseline total nasal symptom score. All patients, or, if aged under 18 years, their legal guardians freely gave their written informed consent before admittance to the trial.

Patients were excluded if they were not allergic or if they had an acute respiratory tract infection; had undergone nasal surgery within the previous 6 months; or had a history of hypersensitivity to ebastine, sodium cromoglycate, or the

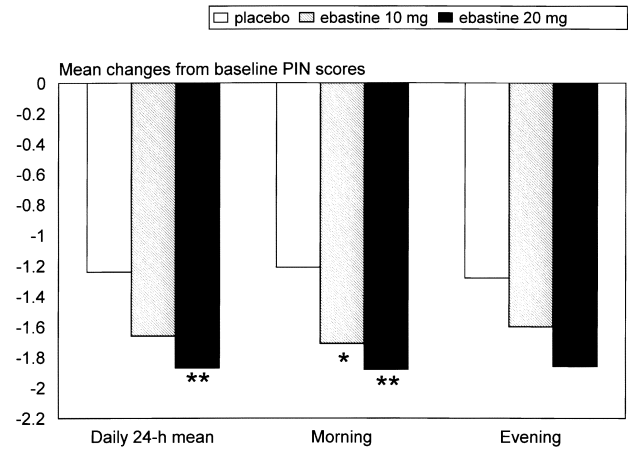

Figure 1. Improvements from baseline in daily mean (24-h), morning (second 12-h), and evening (first 12-h) perennial index (PIN) over 12-week treatment period. PIN: sum of scores for nasal discharge, sneezing, and itchy nose (maximum: 9). $*P<0.05$, $**P<0.01$ ebastine *vs* placebo during 12-week treatment.

product excipients. Furthermore, patients could not enter the study who had started immunotherapy within 6 months, or who had used astemizole within 12 weeks; depot corticosteroids within 8 weeks; ketotifen within 2 weeks; or short-acting systemic or topical corticosteroids, sodium

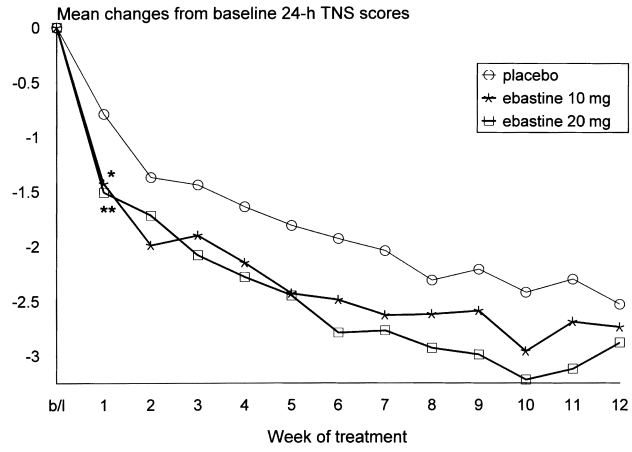

Figure 2. Weekly improvements from baseline in daily mean (24-h) total nasal symptoms (TNS) over 12-week treatment period. TNS: sum of scores for nasal discharge, sneezing, itchy nose, and nasal stuffiness (maximum: 12). $*P<0.05$, $**P<0.01$ ebastine *vs* placebo after 1 week. TNS scores were not significantly different at weeks 2–12, but overall (12-week) changes in mean TNS scores were significant for ebastine 20 mg *vs* placebo:

Group	*n*	baseline TNS	mean change ± SD	*P=vs* placebo
Placebo	97	6.56	–1.83 ± 2.17	
Ebastine 10 mg	87	6.43	–2.38 ± 2.08	0.077
Ebastine 20 mg	101	6.85	–2.57 ± 2.06	0.015*

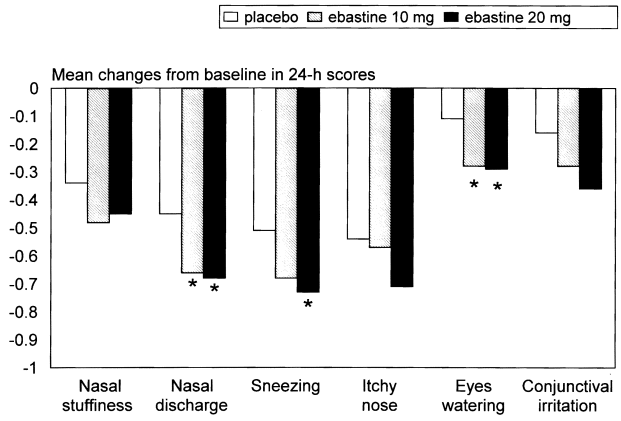

Figure 3. Mean changes in 24-h severity scores (0–3) for individual nasal and ocular rhinitis symptoms over 12-week treatment period. $*P<0.05$ ebastine *vs* placebo during 12-week treatment.

cromoglycate (4%), or nedocromil sodium within 1 week before the baseline. Also excluded were patients using any other H_1-receptor antagonists or medications which might have suppressed or exacerbated symptoms of PAR at the start of the baseline period, those with any clinically relevant disorder that might have interfered with the study, and individuals working night shift (2300–0800). Women were not admitted to the study if they were pregnant or breast-feeding, and those of child-bearing potential could participate only if protected by an effective means of contraception.

Study treatments and assessment of rhinitis severity

Patients were asked to record four nasal and two ocular rhinitis symptoms and use of medications on diary cards each morning and evening during a 2-week baseline period. Sodium cromoglycate 2% nasal spray and eye-drops were supplied as rescue medications to be used when required. The severity of symptoms of nasal stuffiness, nasal discharge, sneezing, itchy nose, eye watering, and conjunctival irritation was assessed on a four-point scale: 0=absent (no symptoms), 1=mild (symptoms present but not annoying to the patient), 2=moderate (symptoms present and annoying to the patient), 3=severe (symptoms interfered with/prevented normal daily activity). Patients with baseline total nasal symptom (TNS) scores for 2 weeks of ≥135 out of a possible 336 points were then randomized to treatment with ebastine 10 or 20 mg, or matching placebo, once daily for 12 weeks, and took one opaque capsule (containing lactose and one, two or no tablets of ebastine 10 mg, respectively) each morning, immediately after breakfast. During treatment, patients continued to keep twice-daily

records of symptom severity, use of medications, and any adverse events, and the diary cards were assessed by the investigator at monthly clinic visits. At the final visit, patients' and investigators' overall opinions of efficacy were recorded independently, on a scale from 0=greatly improved to 4=greatly worsened.

Study design

This was a double-blind, parallel-group study, completed within a 7-month period (October–May) in PAR patients recruited from 37 European centres (25 in France, six in Portugal, and six in Spain). Clinic visit assessments were made before and after a 2-week baseline period, and after 4, 8, and 12 weeks of randomized treatment. The study was conducted in accordance with the standards of the Declaration of Helsinki (Hong Kong, 1989) and Good Clinical Practice, and had the written approval of all the relevant local ethics committees.

Statistical methods

Efficacy and safety analyses were carried out on the intent-to-treat population, which included all patients who were randomized to treatment and took at least one capsule of medication. Patients withdrawing due to treatment failure were assigned worst case scores for clinical assessments and opinions, while for diary card scores, the mean of the last 3 days was carried forward for the remainder of the trial. If patients withdrew for any other reason, data were subsequently treated as missing.

Analysis of variance (ANOVA) was used to contrast diary card data in the three groups, with analysis of changes from baseline during study treatment: where significant, pairwise treatment comparisons were carried out with two two-tailed *t*-tests. Two major summary scores were considered: the *total* nasal symptom score (TNS) (sum of the scores for nasal discharge, sneezing, itchy nose, and nasal stuffiness), and a ''perennial index'' (PIN) (sum of the scores for nasal discharge, sneezing, and itchy nose), which summarized the main histamine effects anticipated in PAR. The protocol-defined primary variable was the change in mean 24-h PIN averaged over the whole 12-week treatment period. Mean overall 12-h PIN scores and weekly 24-h scores were also analysed. Changes in the TNS, the individual nasal and ocular symptoms, and use of rescue medication were compared for treatment effects on both overall (12-week average) and weekly 24-h mean scores.

Table 2. Changes in use of rescue medication (sodium cromoglycate 2% nasal spray and eye-drops) by patients with PAR during 12 weeks of study treatment with ebastine 10 or 20 mg or placebo once daily. (No statistically significant differences were found between treatments.)

	Ebastine 10 mg	Ebastine 20 mg	Placebo
Nasal spray	*n*=81	*n*=99	*n*=94
% of days used			
Baseline	29.5	37.9	42.9
Under treatment	24.4	21.7	32.7
Mean change (SD)	–5.1 (31.5)	–16.2 (37.3)	–10.1 (33.3)
Median daily use			
Baseline	0.46	0.74	0.81
Under treatment	0.31	0.32	0.49
Mean change (SD)	–0.15 (0.76)	–0.42 (1.05)	–0.32 (1.15)
Eye-drops	*n*=81	*n*=98	*n*=93
% of days used			
Baseline	8.0	10.2	12.8
Under treatment	7.6	4.8	9.1
Mean change (SD)	–0.4 (22.2)	–5.5 (22.6)	–3.8 (22.2)
Median daily use			
Baseline	0.10	0.10	0.17
Under treatment	0.06	0.07	0.05
Mean change (SD)	–0.05 (0.39)	–0.03 (0.41)	–0.11 (0.44)

Rates of withdrawal due to lack of efficacy and frequency distributions of adverse events were analysed with the chi-square test or Fisher's Exact Test, and final opinions with the Kruskal-Wallis test and the Mann-Whitney U-test. All testing was carried out at the 5% level of significance.

Results

Study population

Out of 383 patients who were screened, 290 were included in the study. Table 1 summarizes the demographic data and mean baseline symptom severity scores for each treatment group (*n*=88 ebastine 10 mg, *n*=102 ebastine 20 mg, *n*=100 placebo). Forty-two patients withdrew before completing the double-blind period, most commonly (total 19) due to treatment failure, i.e., no change/worsening of disease under study treatment: five (4/1) subjects on ebastine 10 mg; six (4/2), ebastine 20 mg; and eight (3/5), placebo. Other reasons for withdrawal were noncompliance (three, ebastine 10 mg; four, ebastine 20 mg; eight, placebo), intercurrent illness

(two, ebastine 10 mg; two, ebastine 20 mg), and other adverse events (one, ebastine 10 mg; two, ebastine 20 mg; one, placebo).

Efficacy

All groups showed a decrease in PIN symptoms over the 12-week treatment period, with significant improvements over placebo occurring in the overall 24-h (P=0.006) and morning (P=0.007) scores with 20 mg of ebastine, and for the morning score (P=0.047) with 10 mg of ebastine (Fig. 1). A statistically significant improvement over placebo was also found in the overall mean 24-h TNS score during 12-week treatment with ebastine 20 mg (P=0.015). The weekly time course of changes in mean 24-h TNS is shown in Fig. 2. Both doses of ebastine were significantly better than placebo in week 1 of treatment (seen also with PIN 24-h scores; data not given), and nasal symptoms remained less severe throughout in the ebastine-treated groups, although differences from placebo were not generally statistically significant. A slight trend favouring the higher dose of ebastine appeared after 6 weeks (Fig. 2), but there were no statistically significant differences between 10 and 20 mg.

Changes in individual symptom severity reflected the summary data, and the overall 24-h mean scores showed statistically significant improvements in nasal discharge and eye watering with both doses of ebastine *vs* placebo, and in sneezing with 20 mg of ebastine (Fig. 3). At the same time, the patients receiving ebastine 20 mg considerably reduced their use of nasal and ocular sodium cromoglycate rescue medications, although no significant treatment differences were found (Table 2).

Patients' and investigators' final opinions of treatment were significantly in favour of both ebastine 10 and 20 mg compared with placebo. The percentage of patients who considered their condition to be somewhat or greatly improved was 72% (P=0.017) for ebastine 10 mg, 84% (P<0.001) for ebastine 20 mg, and 58% for placebo. Corresponding values for investigators' opinions were 80% (P=0.004), 84% (P<0.001), and 58%. Throughout the study, no statistically significant differences occurred between the two ebastine treatments.

Safety

A total of 155 of 290 patients (53%) reported adverse events, with no statistically significant difference in incidence of events between treatment groups. The most frequent event was headache (13 patients on ebastine 10 mg, 10 on ebastine 20 mg, 13 on placebo), and somnolence was reported by less than 2% of all patients (one on ebastine 10 mg, one on ebastine 20 mg, three on placebo). Sixteen patients (5.5%) experienced events, including worsening of disease and intercurrent illness, that led to withdrawal from the study (four on ebastine 10 mg, six on ebastine 20 mg, six on placebo).

Adverse events considered by the clinician to be possibly or probably related to drug treatment were reported by 24 patients (seven on ebastine 10 mg, seven on ebastine 20 mg, 10 on placebo). Seven of these treatment-related events, none severe, led to withdrawal (one patient on ebastine 10 mg [frontal headache], three on ebastine 20 mg [nausea, headache, facial pruritus], three on placebo [dizziness, worsened rhinitis, thorax urticaria]).

Discussion

The results of this international multicentre study demonstrate that ebastine is an effective once-daily treatment for PAR at both 10- and 20-mg doses. The weekly time course of nasal symptom severity showed a rapid onset of action during week 1 of both ebastine treatments compared with placebo, and the overall mean daily reduction of nasal symptoms under treatment was also statistically significant for 20 mg, and approached significance with 10 mg of ebastine *vs* placebo. This held true for the TNS scores, including nasal stuffiness, as well as the PIN, which we took as the primary efficacy end point for investigating an H_1-antihistamine (3–5). Overall improvements in morning PIN scores (second 12-h) were statistically significant with both 10 and 20 mg of ebastine *vs* placebo, demonstrating the duration of effect of each morning dose of ebastine throughout the night, when patients' contact with indoor allergens is most likely to occur.

In contrast to SAR, nasal stuffiness or congestion is the most prominent symptom of PAR, resulting from oedema caused by a mixture of cellular products released under conditions of chronic allergic inflammation (5, 10). Our study population had a minimum 2-year diagnosis of PAR including allergy to indoor dust mites, shown by IgE or skin prick tests to *Dermatophagoides* species. This implies continuing exposure to inhaled allergens, which will result in a persistent, mast-cell-initiated eosinophilic inflammation of the nasal mucosa (11, 12), as indicated by the locally increased expression of leukocyte-endothelial adhesion molecules (VCAM-1 and ICAM-1) seen in patients with PAR (13–15). The occurrence of PAR, unlike SAR, is more

often linked with asthma, and subclinical signs of airways inflammation may persist even in the absence of symptoms (16). Congestion is unlikely to be relieved by histamine antagonists and generally requires anti-inflammatory therapy with corticosteroids; therefore, we regarded nasal stuffiness as a secondary variable in our analysis of efficacy (1). Although ebastine showed no significant effect *vs* placebo on nasal stuffiness individually, the TNS was significantly improved during treatment with 20 mg over 12 weeks. The rapid and sustained improvement in TNS during treatment with ebastine agrees with a recent study in which both 10- and 20-mg doses of ebastine reduced nasal symptoms of PAR more effectively than loratadine 10 mg from week 1 onward, additionally providing significantly better relief of nasal stuffiness over a 4-week, randomized treatment period (17). New-generation H_1-antihistamines have demonstrated certain antiallergic properties which could possibly enhance their effectiveness in treating rhinitis, although the clinical relevance of these effects remains uncertain (6, 18). At least, it is evident that H_1-antihistamine treatment can improve the quality of life of patients with PAR, a fact which seems to imply some moderation of the most troublesome symptoms (19). With the current increasing incidence of allergies worldwide (20, 21), the need is pressing for safe and effective long-term treatment options for persistent conditions such as PAR, which can seriously disrupt the normal lifestyle of patients with both emotional and socio-economic consequences (22, 23).

While ebastine doses of 10 and 20 mg once daily have also proved effective in the treatment of SAR (7, 8), the 20-mg dose has shown additional potency in controlling SAR symptoms of worse than average severity (9). Therefore, this study attempted to define any additional benefit of the 20-mg dose of ebastine in patients with PAR. No statistically significant differences occurred between the two doses of ebastine during 12 weeks of treatment, but from week 6 onward, the time course of TNS severity showed a consistent trend favouring the higher dose. In addition, ebastine 20 mg showed a generally stronger overall effect than 10 mg in comparison with placebo. Thus, mean 24-h PIN and TNS scores under treatment were reduced clinically by both 10 and 20 mg of ebastine, but only 20 mg achieved statistical significance *vs* placebo. The greater absolute efficacy of ebastine 20 mg was supported by consistent (although nonsignificant) reductions in the use of sodium cromoglycate nasal and ocular rescue medication in this treatment group. Patients' and clinicians' final opinions of treatment reflected the study findings and showed significantly greater symptomatic improvements with either dose of ebastine as compared with placebo. Again, although there was no statistical difference between the ebastine treatments, numerical trends favoured the 20-mg dose. This efficacy dose-relationship of ebastine contrasts with other H_1-antihistamines such as cetirizine, for which a 20-mg dose reportedly provides no extra benefit over 10 mg for the treatment of PAR (24), while increasing the risk of somnolence (25). The recommended adult dose of loratadine is also 10 mg once daily (26), and in 4-week studies in patients with PAR this has proved to be as effective as terfenadine, 60 mg twice daily (27), although it appeared to be inferior to ebastine at 10 or 20 mg (17). In common with loratadine, ebastine was well tolerated by PAR patients over 4 weeks, with a low incidence of CNS-related events (17). This 12-week study has confirmed the absence of dose-related antihistamine side-effects with 10 and 20 mg of ebastine, and enhances the evidence of its advantageous therapeutic index (7).

In conclusion, ebastine maintained effective control of PAR symptoms in adult and adolescent patients when administered at a dose of 10 or 20 mg once daily over a 12-week period. Efficacy trends suggested that in the longer term an additional benefit may be gained from the higher dose of ebastine, which at 20 mg showed no increased risk of somnolence or other unwanted side-effects. This flexible dosage potential should ensure a useful place for ebastine in the management of PAR.

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References

1. International Rhinitis Management Working Group (Lund VJ, Aaronson D, Bousquet J, et al.). International consensus report on the diagnosis and management of rhinitis. *Allergy* 1994;**49 Suppl 19**:1–34.
2. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax* 1991;**46**:859–901.
3. White MV, Slater JE, Kaliner MA. Histamine and asthma. *Am Rev Respir Dis* 1987;**135**: 1165–1176.
4. Brooks CD, Karl KJ, Francom SF. Profile of ragweed hay fever symptom control with terfenadine started before or after symptoms are established. *Clin Exp Allergy* 1990;**20**:21–26.
5. Howarth PH. Mediators of nasal blockage in allergic rhinitis. *Allergy* 1997;**52 Suppl 40**:12–18.
6. Canonica GW, Ciprandi G, Passalacqua G, Pesce G, Scordamaglia A, Bagnasco M. Molecular events in allergic inflammation: experimental models and possible modulation. *Allergy* 1997;**52 Suppl 34**:25–30.
7. Wiseman LR, Faulds D. Ebastine: a review of its pharmacological properties and clinical efficacy in the treatment of allergic disorders. *Drugs* 1996;**51**:260–277.
8. Storms WW. Clinical studies of the efficacy and tolerability of ebastine 10 or 20 mg once daily in the treatment of seasonal allergic rhinitis in the US. *Drugs* 1996;**52 Suppl 1**:20–25.
9. Gehanno P, Brémard-Oury C, Zeisser P. Comparison of ebastine to cetirizine in seasonal allergic rhinitis in adults. *Ann Allergy Asthma Immunol* 1996;**76**:507–512.
10. Mygind N. Pathophysiology of allergic rhinitis. *Eur Respir Rev* 1994;**4**:248–251.
11. Bousquet J, Vignola AM, Campbell AM, Michel F-B. Pathophysiology of allergic rhinitis. *Int Arch Allergy Immunol* 1996;**110**:207–218.
12. Bradding P, Feather IH, Wilson S, et al. Immunolocalization of cytokines in the nasal mucosa of normal and perennial rhinitic subjects. The mast cell as a source of IL-4, IL-5, and IL-6 in human allergic mucosal inflammation. *J Immunol* 1993;**151**:353–365.
13. Montefort S, Feather IH, Wilson SJ, Haskard DO, Lee TH, Holgate ST, Howarth PH. The expression of leukocyte-endothelial adhesion molecules is increased in perennial allergic rhinitis. *Am J Respir Cell Mol Biol* 1992;**7**:393–398.
14. Montefort S, Holgate ST, Howarth PH. Leucocyte-endothelial adhesion molecules and their role in bronchial asthma and allergic rhinitis. *Eur Respir J* 1993;**6**:1044–1054.
15. Naclerio RM. Pathophysiology of perennial allergic rhinitis. *Allergy* 1997;**52 Suppl 36**:7–13.
16. Rowe-Jones JM. The link between the nose and the lung, perennial rhinitis and asthma – is it the same disease? *Allergy* 1997;**52 Suppl 36**:20–28.
17. Davies RJ. Comparative efficacy and safety of once-daily ebastine 10 or 20 mg and loratadine 10 mg in the treatment of perennial allergic rhinitis. *Allergy* 1997;**52 Suppl 37**:168.
18. Ciprandi G, Pronzato C, Ricca V, Passalacqua G, Danzig M, Canonica GW. Loratadine treatment of rhinitis due to pollen allergy reduces epithelial ICAM-1 expression. *Clin Exp Allergy* 1997;**27**:1175–1183.
19. Bousquet J, Duchateau J, Pinnat JC, et al. Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French version of the SF-36 questionnaire. *J Allergy Clin Immunol* 1996;**98**:309–316.
20. Burkholter D, Schiffer P. The epidemiology of atopic diseases in Europe – a review. *Allergy Clin Immunol News* 1995;**7**:113–125.
21. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351**:1225–1232.
22. Juniper EF. Measuring health-related quality of life in rhinitis. *J Allergy Clin Immunol* 1997;**99**:S742–749.
23. Fireman P. Treatment of allergic rhinitis: effect on occupation productivity and work force costs. *Allergy Asthma Proc* 1997;**18**:63–67.
24. Mansmann HC, Altman RA, Berman BA, et al. Efficacy and safety of cetirizine therapy in perennial allergic rhinitis. *Ann Allergy* 1992;**68**:348–353.
25. Spencer CM, Faulds D, Peters DH. Cetirizine. A reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs* 1993;**46**:1055–1080.
26. Haria M, Fitton A, Peters DH. Loratadine. A reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs* 1994;**48**:617–637.
27. Bruttmann G, Charpin D, Germouty J, Horak F, Kunkel G, Wittmann G. Evaluation of the efficacy and safety of loratadine in perennial allergic rhinitis. *J Allergy Clin Immunol* 1989;**83**:411–416.