Allergy 2003: 58: 893–899
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ALLERGY
ISSN 0105-4538

Original article

Levocetirizine is effective for symptom relief including nasal congestion in adolescent and adult (PAR) sensitized to house dust mites

Background: Antihistamines are the most commonly prescribed class of medication for perennial allergic rhinitis (PAR). The primary objective of this study was to determine whether levocetirizine (Xyzal®), the active enantiomer of cetirizine, could achieve at least a 50% improvement in PAR symptoms compared to the placebo over the first week of treatment.
Methods: A total of 294 patients with PAR due to house dust mites were randomized in this 8-week double-blind, placebo-controlled, multicentre trial to receive either levocetirizine 5 mg/day or placebo. Mean Total Four-Symptom Scores (T4SS) (nasal pruritus, ocular pruritus, rhinorrhoea and sneezing) were compared between treatment groups over weeks 1, 4 and 6. All individual symptom scores, including nasal congestion, were also studied.
Results: Levocetirizine showed an 86% improvement in T4SS over the first week of treatment and a 47% improvement over the entire treatment period compared with placebo. Absolute changes from baseline were 3.64 and 2.47 for levocetirizine and placebo, respectively. Individual symptom scores showed statistically significant ($P \leq 0.01$) differences in favour of levocetirizine for all study timepoints. Nasal congestion was unexpectedly significantly improved ($P < 0.001$). The incidence of reported adverse events was comparable between treatment and placebo group.
Conclusions: Levocetirizine 5 mg/day is an effective and well-tolerated treatment of PAR. In addition, levocetirizine is effective for the relief of nasal congestio.

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Key words: allergic rhinitis; antihistamine; levocetirizine; nasal congestion.

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Accepted for publication 12 February 2003

Perennial allergic rhinitis (PAR) is a chronic condition that affects up to 20% of the population in the USA (1, 2) and in Europe (3), and the prevalence is increasing. The patients display a variety of symptoms that usually include nasal pruritus, ocular pruritus, rhinorrhoea sneezing and nasal congestion. The condition causes a significant reduction in the quality of life of sufferers including impaired sleep, concentration and social interaction (4). Moreover, the economic impact in terms of loss of work time and decreased employee activity is also evident (5).

Antihistamines are the most commonly prescribed class of medication for allergic rhinitis (6). They are effective in preventing and relieving sneezing, rhinorrhoea, nasal and ocular pruritus but unlike corticosteroids and decongestants they are less effective in treating nasal congestion (7–9). Recently however, desloratadine demonstrated an activity on the symptoms of nasal congestion (10).

Cetirizine, an effective H_1-receptor antagonist, is a mixture of two enantiomers: levocetirizine (*R*-enantiomer) and dextrocetirizine (*S*-enantiomer). Cetirizine has been shown to be effective in relieving the symptoms of allergic rhinitis and also significantly reduces the histamine-induced weal and flare reaction (11, 12). Further studies have revealed that it is levocetirizine, the *R*-enantiomer, that accounts for cetirizine's affinity to the H_1 receptors (13, 14).

The objective of this study was to investigate the efficacy and safety of levocetirizine (Xyzal®) 5 mg in adolescent and adult patients with PAR.

Methods

This was an 8-week randomized, double-blind, placebo-controlled, multicentre study that took place in South Africa. Patients with PAR ≥12 years of age, who had been sensitized to house dust mites as determined by a positive skin prick test or a radioallergosorbent test (RAST), were recruited from 26 centres during the winter months of 2000.

*The names of the investigators are given in the 'Acknowledgments' section.

Selection of patients was based on a positive skin test (2+) or RAST (>class 3 or 23.5 IU/ml) to house dust mites, dating less than 1 year before inclusion in the study. If these tests were not available, a skin prick test was to be performed at visit 1. Based on anamnesis, patients with seasonal allergic rhinitis that was likely to result in significant changes in the subject's symptoms during the study, were excluded.

Patients with an ear, nose and throat (ENT) infection during the 2 weeks preceding the first study visit; asthma requiring daily therapy; atopic dermatitis or urticaria treated with antihistamine or corticosteroids; vasomotor rhinitis; rhinitis medicamentosa or other debilitating conditions, were excluded.

Study sequence

Patients attended the investigator's site for a total of six visits during the total 8-week study period.

Patients entered a run-in period prior to the randomization visit, during which they recorded the frequency of their symptoms of nasal pruritus, ocular pruritus, rhinorrhoea, sneezing and nasal congestion on diary cards. Patients were provided with a questionnaire to evaluate the severity of their symptoms on a scale ranging from 0 (absent) to 3 (severe, hampering daytime activities and/or sleep). The results obtained from the diary cards and questionnaires provided the Total Four-Symptom Score (T4SS). The mean T4SS was defined as the sum of scores of nasal pruritus, ocular pruritus, rhinorrhoea and sneezing. Only patients with a mean T4SS ≥ 5 Units were assigned by randomization into the study. The severity of symptom scores for nasal congestion was not included in the T4SS scale but was measured separately.

Prohibited treatments prior to visit 1 and also at any time during the study (i.e. from visit 1 to visit 5) included: astemizole, systemic or topical corticosteroids, ketotifene, cromoglycate, topical H1 antihistamines, decongestants (oral, nasal spray or drops), desensitization in the ascending phase, nasal or ocular topical treatment, asthma treatments other than beta 2 agonists.

Patients were randomized to receive either levocetirizine 5 mg or placebo once daily at bedtime. From visits 2–5, patients continued to complete the T4SS questionnaire on daily diary cards (Fig. 1). Individual scores were recorded prior to taking the medication and were to reflect the condition over the previous 24-h period. At visit 5, patients provided a global evaluation of efficacy on a four-point scale: 'Worsening of Symptoms', 'No Change', 'Slight to Moderate Improvement' and 'Good to Excellent Improvement'.

Patient follow-up was conducted at the final visit (visit 6), 1 week after visit 5. This visit was used to assess patients' status after study drug discontinuation (Fig. 1). Adverse events (AEs) were collected during visits 2–6; blood samples were taken at visits 1 and 5 and electrocardiogram (ECG) examinations were performed at visits 1 and 3.

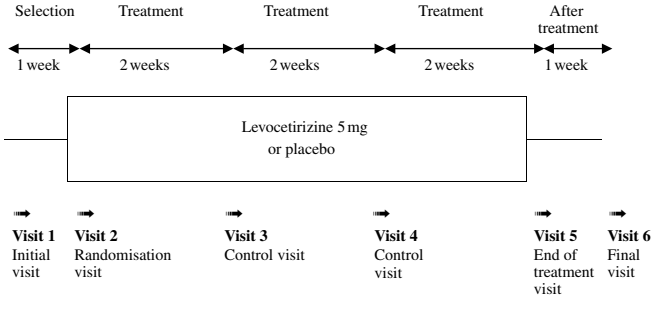

Figure 1. Schematic diagram of the study.

Primary and secondary objectives

The study was to be considered positive if two criteria were met: first, levocetirizine 5 mg had to be statistically superior (alpha error of 5%, two-sided) to placebo over the first week and over 4 weeks of treatment. Second, the point estimate of the treatment difference between levocetirizine 5 mg and placebo over the first week of treatment had to show a relative improvement from baseline over placebo of at least 50%. This relative improvement defined the clinical relevance of study results knowing that the placebo effect is generally important in allergic rhinitis trials, and symptom relief should be fast to be perceived as a significant improvement by the patient.

The secondary efficacy variables were as follows: mean T4SS scores over the total 6-week treatment period, over weeks 2–6 of study treatment; mean individual symptom scores (nasal pruritus, ocular pruritus, rhinorrhoea, and sneezing) during week 1, the first 4 weeks and over the total treatment period. The diary card and questionnaire mean scores for nasal congestion were also measured alongside each of the secondary variables.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics by treatment group. The primary and secondary efficacy variables were analysed using an analysis of covariance (ANCOVA) model that included the mean baseline as covariate with treatment and study centre as factors. Global evaluation scores were analysed using the Cochrane–Mantel–Haenszel test based on ranks. All statistical tests were two-tailed at the 5% level of significance.

It was calculated that a minimum of 125 patients per group was required (alpha error = 5%). Statistical analyses were performed on both the intention-to-treat (ITT) and per-protocol (PP, i.e. a subset of the ITT population consisting of those subjects who did not have any major protocol deviation) populations, in order to assess the impact of any possible protocol violations on the results of the study. The relative difference between the two groups was calculated as follows:

$$100 \times ([\text{change from baseline levocetirizine}/\text{change from baseline placebo}) - 1].$$

Study supplies were identical in appearance. They were provided to investigators together with coded envelopes and clear handling instructions in case of emergency.

The study was performed in accordance with the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice, the Declaration of Helsinki (Somerset West, Republic of South Africa Revision, 1996), and approved by the Ethics and Research Committee of the University of Cape Town.

Results

Of the 368 patients enrolled into the study, a total of 294 were randomized to receive either levocetirizine 5 mg once daily at bedtime ($n = 150$) or placebo ($n = 144$). Eighteen patients prematurely withdrew from the study (levocetirizine: 5 [3.3%]; placebo: 13 [9.3%]), and of these patients 10 withdrew due to lack of efficacy (levocetirizine: 2 [1.3%]; placebo: 8 [5.6%]. A patient flow diagram is shown in Fig. 2.

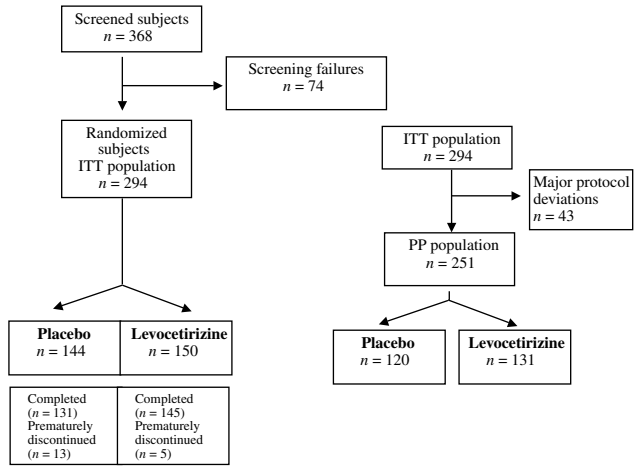

Figure 2. Patient flow diagram.

Table 1. Patient demographic characteristics (ITT population)

Demographic feature	Placebo ($n = 144$)	Levocetirizine 5 mg ($n = 150$)
Gender		
Female	80 (55.6%)	88 (58.7%)
Male	64 (44.4%)	62 (41.3%)
Ethnic origin		
White/Caucasian:	98 (68.1%)	102 (68.0%)
Other/mixed race:	24 (16.7%)	26 (17.3%)
Asian/Pacific Islander	20 (13.9%)	19 (12.7%)
Black/African-American	2 (1.4%)	3 (2.0%)
Age (years)		
Mean ± SD	28.76 ± 13.27	29.18 ± 12.61
Median	25.3	26.6
Min–max	12.6–69.6	12.3–1.4
Baseline T4SS (Units):		
Mean ± SD	7.47 ± 1.80	7.69 ± 1.82
Median	7.3	7.3
Min–max	2.7–11.6	4.5–12.0

A total of 43 patients (14.6%) were excluded from the ITT population due to major protocol deviations and composed the PP population.

The main causes of protocol deviations during the study were the use of prohibited concomitant medications (15.0%); that occurred twice as often in the placebo group compared with the levocetirizine group (20.1 *vs* 10.0%, respectively).

Patient demographics at baseline were comparable between both treatment groups and are presented in Table 1. The mean daily compliance (number of tablets effectively taken over number of tablets that were supposed to be taken) was 98.5% for the overall treatment period.

Efficacy

The mean T4SS at baseline were comparable between the two treatment groups (levocetirizine: 7.69 ± 1.82; placebo: 7.44 ± 1.80). The results of inferential ANCOVA analysis of T4SS by treatment group and treatment period are shown in Table 2. The difference between both groups at each treatment period showed a statistically significant T4SS decrease in favour of the levocetirizine group compared with the placebo group (week 1 and first 4 weeks, $P < 0.001$; total 6-week period, $P < 0.001$). The relative improvement in the levocetirizine group during week 1 of treatment was 86%. The relative improvements from baseline over placebo in the levocetirizine group during the first 4 weeks and during the total 6-week period were 56 and 47%, respectively. Statistical analyses were also performed on the PP population for the primary endpoints and these revealed similar results as shown for the ITT population (57% relative improvement over 4 weeks).

The individual symptom scores after the first week of study treatment are presented in Table 3. These results show significant improvements for levocetirizine compared with placebo for all individual symptoms ($P < 0.01$).

Interestingly, nasal congestion symptom was also significantly reduced in the levocetirizine group compared with the placebo group over all treatment period (week 1: 0.17 *vs* 0.43, $P = 0.002$; first 4 weeks: 0.27 *vs* 0.55, $P < 0.001$; total 6 weeks: 0.32 *vs* 0.59, $P < 0.001$) (Fig. 4). Nasal congestion relative improvement over the 6 weeks of treatment was 83%.

The results from the global evaluation, which took place at the follow-up visit (Visit 6), showed improvements in favour of levocetirizine compared with placebo ('Slight to Moderate Improvement' = 36% (54/150) *vs* 41% (59/144); 'Good to Excellent Improvement': 41.3% (62/150) *vs* 22.9% (33/144)).

Safety

The mean duration of treatment was 41.9 days in the levocetirizine group and 40.0 days in the placebo group. Overall, 63.9% (188/294) of patients experienced at least one AE (levocetirizine, 60.0% (90/150); placebo, 68.1% (98/144)). The most frequently reported AEs for both levocetirizine and placebo groups, respectively, included headache (34.7 *vs* 34.7%), influenza-like symptoms (16.7 *vs* 13.9%) and upper respiratory tract infections (6.7 *vs* 9.0%) (Table 4).

The most common AEs that were judged related to study treatment were headache and somnolence. One patient experienced an increase in serum glutamic pyruvic transaminase (SGPT) that was considered to be drug-related but this resolved spontaneously after 9 days. A total of three serious AEs occurred but these were not considered to be related to study treatment.

The frequency distribution of the QTc values at baseline and after treatment showed normal QTc intervals in both treatment groups. No cases of borderline or

Table 2. ANCOVA results for mean T4SS by treatment period (ITT population)

Treatment period	Treatment group	*n*	Mean* (SE)	Change from baseline adjusted mean	Difference *vs* placebo (95% CI)	*P* value†	Relative improvement‡ (%)
Week 1	Placebo	142	6.16 (0.193)	1.41			
	LCTZ 5 mg	150	4.94 (0.185)	2.63	1.22 (0.73; 1.71)	<0.001	86
First 4 weeks	Placebo	142	5.39 (0.183)	2.18			
	LCTZ 5 mg	150	4.17 (0.176)	3.40	1.22 (0.76; 1.69)	<0.001	56
Total 6 weeks	Placebo	142	5.10 (0.185)	2.47			
	LCTZ 5 mg	150	3.93 (0.177)	3.64	1.17 (0.70; 1.64)	<0.001	47

ANCOVA, analysis of covariance; LCTZ, levocetirizine. * Mean adjusted for baseline score and centre. † *P* value obtained from an ANCOVA with baseline score as covariate, centre and treatment as factors. ‡ Relative improvement with respect to placebo.

Table 3. Individual symptom scores after the first week of treatment (ITT population)

Treatment group	Mean* (SE)	Change from baseline mean	Difference *vs* placebo (95% CI)	*P* value†	Relative improvement‡ (%)
Rhinorrhoea					
Placebo	1.76 (0.060)	0.33			
LCTZ 5 mg	1.46 (0.057)	0.63	0.30 (0.15; 0.46)	<0.001	94
Nasal pruritus					
Placebo	1.48 (0.058)	0.39			
LCTZ 5 mg	1.16 (0.057)	0.71	0.32 (0.17; 0.47)	<0.001	82
Ocular pruritus					
Placebo	1.29 (0.062)	0.39			
LCTZ 5 mg	1.08 (0.060)	0.60	0.21 (0.06; 0.37)	0.008	55
Nasal congestion					
Placebo	1.76 (0.066)	0.17			
LCTZ 5 mg	1.50 (0.065)	0.43	0.26 (0.10; 0.42)	0.002	154
Sneezing					
Placebo	1.62 (0.060)	0.31	0.37 (0.22; 0.53)	<0.001	120
LCTZ 5 mg	1.25 (0.058)	0.68			

ANCOVA, analysis of covariance; LCTZ, levocetirizine. * Mean adjusted for baseline score and centre. † *P* value obtained from an ANCOVA with baseline score as covariate, centre and treatment as factors. ‡ Relative improvement with respect to placebo.

Table 4. Adverse events with an occurrence of ≥5% in either treatment group (ITT population)

Adverse event	Placebo ($n = 144$)	Levocetirizine 5 mg ($n = 150$)
Headache	50 (34.7%)	52 (34.7%)
Influenza-like symptoms	20 (13.9%)	25 (16.7%)
Pharyngitis	6 (4.2%)	13 (8.7%)
Upper respiratory tract infection	13 (9.0%)	10 (6.7%)
Somnolence	4 (2.8%)	9 (6.0%)
Sinusitis	10 (6.9%)	6 (4.0%)
Abdominal pain	9 (6.3%)	3 (2.0%)

extended QTc intervals were reported throughout study treatment.

Discussion

This multicentre study has shown that levocetirizine was effective for the treatment of patients with perennial rhinitis due to house dust mite allergy. It is generally considered that an improvement above 50% of placebo is a significant treatment effect. In the study, patients receiving levocetirizine showed an overall 86% relative improvement of major symptoms of rhinitis from baseline above placebo during the first week of treatment (Table 3). Patients in the levocetirizine group also showed highly significant ($P < 0.01$) improvements in mean T4SS for all symptoms for all treatment periods during study treatment (Fig. 4).

The results obtained from this study used a 5 mg dose, 50% less than the effective dose of cetirizine, as shown by patients' daily diary cards, mean T4SS results and individual symptom scores were significantly reduced within the first 24 h of study treatment. This improvement was maintained throughout the 6 weeks of study treatment (Table 2).

While the main criterion for inclusion was a T4SS greater than 5 Units, patients in both groups had a median of 7.3 Units at baseline. Over 4 weeks, the levocetirizine group had a median T4SS of 3.7 *vs* 5.3 for the placebo group. The rapid decrease of the levocetirizine group score was striking in this population. House dust mites are an important cause of PAR in South Africa in the Mediterranean regions and also in tropical environments of Africa, South East Asia, the USA and Australia (15). As in other Westernized countries, there has been an increase in the prevalence of sensitization to mites in recent years. In this winter study in South Africa, the allergic stimulus was constant, as demonstrated by the relatively low reduction in the T4SS score changes in the placebo population (Fig. 3). Constancy of the allergen stimulation somewhat increases the ability to demonstrate improvement in the study population allowing a better appreciation of the active treatment effect.

PAR due to mites is characterized by nasal congestion being a prominent and troublesome symptom and often intranasal steroids are required for relief of nasal congestion symptoms in PAR. Despite the fact that second generation antihistamines have been reported to

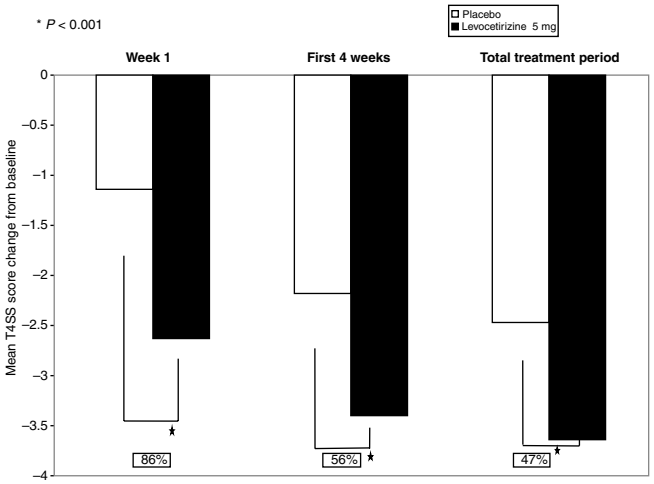

Figure 3. Mean Treatment Four-Symptom Score (T4SS) change from baseline for patients receiving levocetirizine 5 mg/day or placebo over the study duration.

be generally ineffective in nasal congestion (7–9), this study showed a statistically significant reduction of nasal congestion for levocetirizine across all treatment periods compared with placebo (Table 3, Fig. 4). The relief of congestion is comparable to that observed in another trial which used a similar symptom scoring to the current study (16). In this trial, comparing triamcinolone to loratadine, triamcinolone achieved a symptom improvement that is comparable to levocetirizine in the current trial. Relief of nasal congestion has also been reported for desloratadine using a similar scale, but the effects were evaluated on a shorter period of time (10).

In a nasal challenge setting, cetirizine but not loratadine displayed a dose-response curve of relief of nasal obstruction to histamine, that was significantly lower after treatment, compared with placebo ($P < 0.05$) (17). A study using acoustic manometry found that nasal congestion was less severe after nasal histamine challenge in 63.3% of patients treated with cetirizine (18).

The role of enantiomers in pharmacology is currently under debate. Chiral molecules can have different biological activities. For instance, both glucose enantiomers taste sweet, but only the right-handed form can be metabolized by the body. Knowing that receptors are proteins built from asymmetric aminoacids (left handed), it is not surprising that receptors show differences in affinity for stereoisomers. Levocetirizine has twice the affinity for H1 receptors as compared with cetirizine. From the dissociation kinetics curves, it is known that levocetirizine binding to the human H1 receptor is longer than cetirizine (115 *vs* 95 min) (19). In a study comparing levocetirizine to cetirizine in a histamine-induced weal and flare model, levocetirizine was found to be more active when area under the curve (AUC) were compared (14).

The mechanisms whereby an antihistamine may relieve obstruction are also of great interest. In PAR, nasal obstruction may be caused by mediators such as histamine resulting in increased vascular permeability and vasodilation in the early phase and by cellular mucosal inflammation in the late phase. Antihistamines may relieve obstruction by an inhibitory effect on vascular permeability and vasodilation in the early phase of the allergic response. However, if the antihistamine has a significant 'antiinflammatory effect', it may also reduce 'mucosal inflammation' of the late-phase reaction.

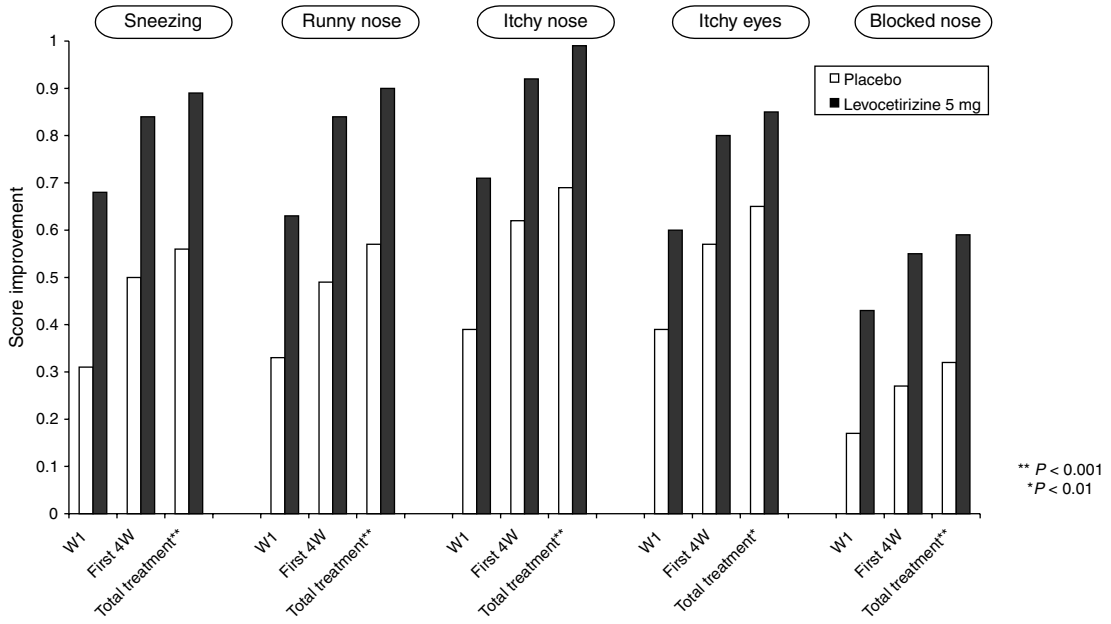

Figure 4. Individual symptom scores improvement.

Thompson et al. have observed significant anti-inflammatory effects of levocetirizine on eosinophils *in vitro* (20). *In vivo* studies are required to assess whether this effect is also seen in target organs of the allergic response (e.g. the nose). Levocetirizine has also been shown to reduce levels of sVCAM-1 and proteins during the first 6 h postchallenge in an *in vivo* skin chamber study by Michel et al. (21). Although previous studies of the antiinflammatory effects of second generation antihistamines have focussed on their effect on minimal persistent inflammation, with little clinical effect on the congestive symptoms induced by chronic nasal inflammation, it is possible that the newer generation antihistamines may be shown to have a more significant clinical effect on congestion particularly if studied over longer periods to allow time for a clinical antiinflammatory effect to become apparent.

The safety profile of levocetirizine did not reveal any prominent safety issues that could be related to the study drug. The overall incidence of adverse events was slightly higher in the placebo group than in the levocetirizine group. However, this may be attributed to the fact that influenza-like symptoms, pharyngitis, upper respiratory tract infections are common winter season ailments – the study took place during the Southern hemisphere winter season.

The results from this study are in part due to a very low dropout rate (levocetirizine, 3.3%; placebo, 9.0%) and a treatment compliance that was particularly high (98.5%). Lack of adherence is often a major cause of therapeutic failure. It has been estimated that 20–30% of patients fail to follow a curative medication regimen (22). However, in this study, the severity of symptoms and possibly the availability of free treatment for the duration of the study may have prompted a higher compliance rate.

The overall efficacy of levocetirizine in this study is promising, especially in the context of a better awareness of rhinitis comorbidities (23), associated with nasal obstruction in PAR.

In conclusion, levocetirizine 5 mg once daily is an effective and well-tolerated treatment for the symptoms of PAR caused by house dust mites. In addition, levocetirizine also significantly relieves nasal congestion, which is unusual for products of this class.

Acknowledgments

The author would like to thank M. Wajskop and V. Suznjevic for their assistance in the realization of this study. The author wishes to acknowledge the assistance of the following doctors who participated in the study as investigators: Drs M. J. Bailey, M. Bateman, W. V. Boyd, C. T. de Villiers, I. Engelbrecht, E. J. Evans, A. P. Foden, S. Furman, P. C. Grey, M. Groenwald, D. Hawarden, E. L Janari, A. Macleod, H. A. Makan, J.-M. Malan, W. E. Mans, W. W. Neethling, P. R. Nel, H. Nell, S. R. Pillay, G. Ras, J. D. Smit, H. H. Snyman, Prof. J. J Snyman, Drs J. F. Strauss, C. Tucker, B. J. van de Merwe, C. C. J. van Rensburg, F. Vawda and J. H. Vermeulen.

References

1. Bellanti JA, Wallerstedt DB. Allergic rhinitis update: epidemiology and natural history. Allergy Asthma Proc 2000;**21**:367–370.
2. Nathan RA, Meltzer EO, Selner JC, Storms W. The prevalence of allergic rhinitis in the United States. J Allergy Clin Immunol 1997;**99**:22–27.
3. Lundback B. Epidemiology of rhinitis and asthma. Clin Exp Allergy 1998;**28**(Suppl. 2):3–10.
4. Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. Ann Allergy Asthma Immunol 2000;**85**:338–347.
5. Blaiss MS. Cognitive, social, and economic costs of allergic rhinitis. Allergy Asthma Proc 2000;**21**:7–13.
6. Corren J. Allergic rhinitis: treating the adult. J Allergy Clin Immunol 2000;**105**:S610–S615.
7. White MV. The role of histamine in allergic diseases. J Allergy Clin Immunol 1990;**86**:599–605.
8. Naclerio RM. Optimizing treatment options. Clin Exp Allergy 1998; **28**(Suppl 6):54–59.
9. Bernstein DI, Creticos PS, Busse WW, Cohen R, Graft DF, Howland WC et al. Comparison of triamcinolone acetonide nasal inhaler with astemizole in the treatment of ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1996;**97**:749–755.
10. Nayak AS, Schenkel E. Desloratadine reduces nasal congestion in patients with intermittent allergic rhinitis. Allergy 2001;**56**:1077–1080.
11. Simons FE, McMillan JL, Simons KJ. A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. J Allergy Clin Immunol 1990;**86**:540–547.
12. Watson WT, Simons KJ, Chen XY, Simons FE. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. J Allergy Clin Immunol 1989;**84**: 457–464.
13. Wang DY, Hanotte F, De Vos C, Clement P. Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers. Allergy 2001;**56**: 339–343.
14. Devalia JL, De Vos C, Hanotte F, Baltes E. A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers. Allergy 2001;**56**:50–57.
15. Potter PC, Davis G, Manjra A, Luyt D. House dust mite allergy in Southern Africa historical perspective and current status. Clin Exp Allergy 1996;**26**: 132–137.
16. Schoenwetter W, Lim J. Comparison of intranasal triamcinolone acetonide with oral loratadine for the treatment of patients with seasonal allergic rhinitis. Clin Ther 1995;**17**:479–492.

17. Frossard N, Benabdesselam O, Melac M, Glasser N, Lacronique J, Pauli G. Nasal effect of cetirizine and loratadine at 24 hours in patients with allergic rhinitis. Am J Ther 1998;**5**:307–311.
18. Enzmann H, Mathe F. Acoustic rhinomanometry for evaluating the effectiveness of antihistaminics. HNO 1998;**46**:529–533.
19. Gillard M. Binding characteristics of ucb 28556 and ucb 28557 to human H1 histamine receptors: comparison with cetirizine. UCB data on file.
20. Thompson M, Baylock MG, Sexton DW, Campbell A, Walsh GM. Cetirizine and levocetirizine inhibit eotaxin-induced eosinophil transendothelial migration through human dermal or lung microvascular endothelial cells. Clin Exp Allergy 2002;**32**:1–6.
21. Michel L, Jean-Louis F, Dubertret L. Pharmacological study of levocetirizine in IgE-dependent hypersensitivity cutaneous reaction in grass pollen allergic volunteers: demonstration of mediator release and eosinophil recruitment modulation by levocetirizine. Allergy 2001; **56** (Suppl. 68): 150–151.
22. Seltzer A, Roncari I, Garfinkel P. Effect of patient education on medication compliance. Can J Psychiatry 1980;**25**:638–645.
23. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; **108** (Suppl. 5):S147–S334.