

Levocetirizine in children: evidenced efficacy and safety in a 6-week randomized seasonal allergic rhinitis trial

de Blic J, Wahn U, Billard E, Alt R, Pujazon MC. Levocetirizine in children: evidenced efficacy and safety in a 6-week randomized seasonal allergic rhinitis trial.

Pediatr Allergy Immunol 2005; 16:267–275. ©2005 Blackwell Munksgaard

Studies evaluating newer antihistamines in children are few. Levocetirizine is a potent and highly selective H₁-antihistamine with a proven efficacy in adults. Primary objective was to assess the efficacy of levocetirizine 5 mg once-daily in reducing seasonal allergic rhinitis (SAR) symptoms, as measured by Total Four Symptom Score (T4SS = sum of sneezing, rhinorrhea, nasal and ocular pruritus), over the first 2 wk of treatment. Efficacy over 4 and 6 wk of treatment, effect on nasal congestion and on health-related quality of life as measured by PRQLQ (Paediatric Rhinoconjunctivitis Quality of Life Questionnaire) were among the major secondary objectives. A double-blind, randomized, placebo-controlled study including 177 children with a documented SAR (to grass and/or weed) for at least a year and having a mean baseline T4SS ≥ 6 (out of 12). Children evaluated daily the severity of T4SS and nasal congestion on a scale from 0 (absent) to 3 (severe). PRQLQ responses were assessed on a scale from 0 (not bothered) to 6 (extremely bothered) and analysed descriptively. Global evaluation of disease evolution judged by investigators, parents and children was made on a scale from 1 (marked worsening) to 7 (marked improvement). For the primary objective, levocetirizine was statistically highly superior to placebo with a difference in adjusted means of 1.29 (95% CI: 0.66–1.92) in favour of levocetirizine ($p < 0.001$). The effect of levocetirizine was almost twice that of placebo (94.1% relative improvement over placebo). Nasal congestion was improved with levocetirizine reaching maximum difference to placebo of 0.31 ($p < 0.05$), a relative improvement over placebo of 77.5%. PRQLQ scores at week 2 improved with levocetirizine more than with placebo (0.85 vs. 0.51, respectively) remaining larger after 4 and 6 wk of treatment. In the study, 84.3%, 80.9%, 80.9% of children had their disease evolution rated as slightly-to-markedly improved by, respectively, the investigators, the parents and children themselves. Incidence of treatment-emergent adverse events was similar in both groups (33.7% with levocetirizine; 30.7% with placebo). No child in the levocetirizine group discontinued treatment because of adverse events. The 6-wk duration of this study was longer than the usual 2–4-wk duration for similar studies and shows that levocetirizine controls SAR symptoms in children over the entire pollen season.

**Jacques de Blic¹, Ulrich Wahn²,
Eric Billard³, Roger Alt⁴ and
Marie-Christine Pujazon⁵**

¹Hôpital des enfants malades, Paris, Cedex 15, France, ²Charité - Campus Virchow Klinikum, Augustenburger Platz 1, Berlin, Germany, ³Le Polygone, Chambéry, France, ⁴Avenue Jean Jaures, Strasbourg, France, ⁵Bd du Maréchal Juin, Fenouillet, France

Key words: antihistamine; levocetirizine; children; paediatric population; Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; seasonal allergic rhinitis

Dr Jacques de Blic, Hôpital des Enfants Malades, 149 rue de Sèvre, F-75730 Paris Cedex 15, France
Tel.: +33 1 44494838
Fax: +33 1 44381740
E-mail: j.deblic@nck.aphp.fr

Accepted 29 September 2004

Over the last 3 decades the prevalence of allergic rhinitis (AR) has increased dramatically and recent estimates have suggested that up to 40% of children will suffer from this illness (1). As its

prevalence peaks late in childhood (2) and as follow-up studies have shown that a high percentage of college students with AR go on to develop asthma (3), successful treatment of AR

in the paediatric population (6–12 yr of age) is of utmost importance and should be evaluated in well controlled, double-blind, randomized studies. In addition, if left untreated, AR can be detrimental to a child's physical and psychosocial well-being. At the physical level, sleep disturbance, daytime fatigue, headache, weakness, malaise and poor appetite are common. At the emotional level, there is evidence that individuals with AR are more likely to exhibit shyness, depression and anxiety (4). Allergic rhinitis can also affect a child's capacity to learn (5) and a significant number of school days are lost through the disease (6). As AR can have a profound effect on a child's quality of life (QoL), assessment of subjective health status and patient's well-being, as measured by disease and age-specific questionnaires, e.g. the Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) (7), has been recognized over the last decade as one of the primary goals of disease treatment.

Allergic rhinitis can be more difficult to treat in children than in adults, as children frequently lack the ability to verbalize their symptoms, resulting in the condition remaining undiagnosed and untreated (8). However, once diagnosed, AR in children can be successfully managed with oral antihistamines (8).

In light of the outlined importance and impact that AR can have on children's QoL, and knowing that it may be associated with and contribute to potentially serious sequelae, including asthma, sinusitis, and otitis media (9), it is surprising that few studies have attempted to evaluate the treatment success in paediatric seasonal (SAR) and/or perennial (PAR) rhinitis with the newer generation antihistamines. A Pubmed/Medline search (<http://www.ncbi.nlm.nih.gov/pubmed/>) at the time of research revealed no paediatric studies in SAR published with desloratadine and only two published with fexofenadine (10, 11). The latter were of short-term duration (2-wk treatment period) and one of them reported only safety but not efficacy of the drug (11).

Recent data (12) shows that >80% of SAR patients experience symptoms during all the 7 days in a week and >60% suffer for >5 wk a year. Also, the duration of grass pollen exposure is close to 2 months (13). Thus, a period of 2–4 wk is insufficient for making clinically relevant conclusions and studies of longer duration are needed.

Levocetirizine (Xyzal[®]) is a modern, potent (14) and highly selective H₁-antihistamine (15), with a fast onset of action (16), approved in most

European countries. Levocetirizine has been consistently shown to have superior anti-histamine potency in adults compared with a number of other available antihistamines including ebastine, fexofenadine, loratadine, mizolastine (14), and desloratadine (17).

Unlike most other antihistamines, the potency and safety of levocetirizine have been evidenced in long-term trials in adults (18). The present study was designed to assess its safety and efficacy in the treatment of SAR in a paediatric population. In order to have a better clinical understanding of the relevance of the study results, the study was designed to have a 6-wk treatment period, which may not only better reflect the usual length of the spring pollen season but may also allow for a treatment-effect assessment of inflammatory sequelae after the season. Given the effects of SAR on a child's general well-being the study included a QoL assessment using a specially developed PRQLQ (7).

Subjects and methods

The study was of a multicentre, randomized, double-blind, placebo-controlled design. It was conducted in 41 centres in France and Germany between April and September 2002. Male and female children, between the ages of 6 and 12 yr inclusive, with confirmed and documented SAR (to grass and/or weed pollen) of at least a year's duration were recruited into the study. For SAR to be diagnosed, subjects had to have a history of allergic rhinitis, pollen sensitization and presence of symptoms at inclusion. Sensitization to grass and/or weeds pollen was confirmed either by a positive skin test (wheal \geq 3 mm larger than the diluent control for prick testing or \geq 7 mm larger than the diluent control for intradermal testing) or positive RAST (Radio-Allergo-Sorbent test) (\geq Class 3 or \geq 3.5 IU/ml). These tests should have been performed during the preceding year and, if none was available, a skin test was carried during the screening visit. No other pollens were investigated.

Children were excluded from the study if they had perennial allergic rhinitis likely to change significantly the symptoms of the subject during the study; any ear, nose or throat (ENT) infection during the 2 wk preceding the baseline visit or any associated ENT disease; a temperature \geq 38.5°C at the baseline visit; the presence of any clinically significant disease or other disease that might affect the absorption, distribution, metabolism or excretion of the investigation product. Sensitization to other pollens was not an exclusion criteria.

Children were not permitted to take the following medications (days before study start): corticosteroids or desensitization in the ascending phase (30 days); ketotifen, nedocromil or cromoglycate (14 days); loratadine (10 days); leukotriene antagonists or synthesis inhibitors (7 days); other H1-antihistamines (3 days); decongestants (per o.s., nasal spray or drops) (3 days). Children were also not permitted to take these medications and other nasal or ocular topical treatment.

Asthma was not an exclusion criterion, however, no asthma treatments other than β_2 inhaled agonists were permitted during the study. Asthma diagnosis was made by recording the presence of asthma symptoms (nocturnal cough with sleep disturbance and wheezing) and the history of use of short-acting β_2 -mimetics.

The children were required to attend the clinic on five occasions (Fig. 1). At the screening visit, informed consent was obtained, baseline data recorded and a physical examination performed. Once eligibility was confirmed, the patient's parent or guardian was supplied with a daily record card (DRC). The children and/or their parents/guardians were instructed how to record daily, at bedtime and retrospectively over the preceding 24 h the patient's progress during the selection period. A disease specific quality of life questionnaire, PRQLQ (7), was completed by the investigator through subject interview at the beginning of the first visit as well as at all subsequent visits.

At the baseline visit eligibility had to be reconfirmed with the T4SS ≥ 6 during the

selection period and on the day before the visit. Use of rescue medication (one puff of sodium cromoglycate in each nostril four times a day) was permitted on request from visit 3 onwards. At the final visit, the investigator also recorded the patient/guardian's willingness to continue to use the same treatment in the future. At visit 3, a global evaluation of disease evolution was made separately by the subject, the guardian and the investigator.

Levocetirizine was supplied as a 5 mg tablet suitable for oral administration. Placebo tablets were of an identical shape, size and colour. Both treatments were supplied in securitainers given to the children and/or their parents/guardians at every visit except during visit 1. Instructions were given how to take the treatment and the children and/or their parents/guardians were asked to return the securitainers at the next visit.

Subjects were randomized to one of the two treatments. The treatment (one 5 mg tablet per day) was to be commenced on the evening of the baseline visit and to be repeated daily, in the evening, for a period of 6 wk until the evening preceding the final visit.

Assessment of efficacy, safety and tolerability

Each of the four rhinitis symptoms (sneezing, rhinorrhea, nasal pruritus and ocular pruritus) were scored daily on a scale of 0–3 (absent, mild, moderate, severe) and the total symptom score (T4SS) calculated over each treatment period. The primary efficacy variable was the mean of the T4SS evaluated daily by the children and/or their parents/guardians for the preceding 24 h over the first 2 wk of treatment. Secondary/exploratory variables included the T4SS score over other periods (including the entire 6 wk of treatment), nasal congestion score, PRQLQ and global evaluation of the illness evolution. The latter was judged by the subject, by the subject's parent or guardian and by the investigator and was based on a 7-point Likert scale. It evaluated the change in the PRQLQ domain after 2 wk of treatment and the overall scores completed at each visit.

A sensitivity analysis of the effect of rescue medication (nasal sodium cromoglycate spray) on the mean T4SS over the 6 wk of treatment was planned in order to assess whether additional medications' intake, allowed for ethical reasons, would have an effect on treatment results. This analysis excluded the data from days during which the subject was using nasal sodium cromoglycate spray (i.e. the periods of the cromoglycate rescue medication intake + 7 days following the last day of intake period).

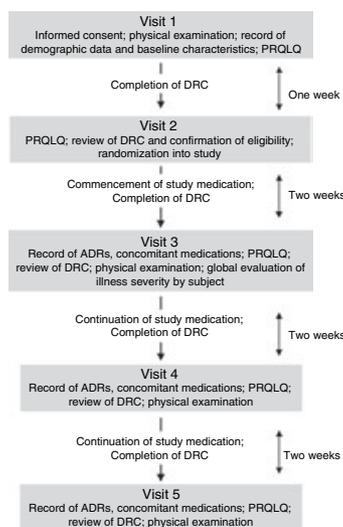


Fig. 1. Study plan. DRC, daily record card; PRQLQ, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire.

Safety and tolerability were assessed on the basis of adverse events reported by the patient, their parent or guardian or the investigator as assessed at each clinic visit and on the results of a physical examination.

Statistical methods

A sample size of 146 children by treatment group was calculated to detect a difference of 0.8 between the placebo and levocetirizine in the mean T4SS over the first 2 wk of treatment, assuming an overall alpha error of 5% and a common s.d. of 2.1, with a power of 90%. All efficacy and safety parameters were analysed using an intention-to-treat (ITT) population while the primary efficacy parameter was also analysed using a per protocol (PP) population. The ITT population included all children who were randomized and took at least one dose of study medication. The PP population included all subjects who had no major protocol deviations. The primary efficacy variable, was analysed using an analysis of covariance with treatment as factor and baseline T4SS as covariate. The treatment effect was estimated using a 95% confidence interval (CI) of the difference in the adjusted means between placebo and levocetirizine. The daily record card variables were analysed similarly to the primary efficacy variable. The secondary/exploratory variables (including assessment of disease evolution and PRQLQ) were summarized descriptively with no formal statistical analysis planned, as the population sample was not powered for them.

The study was performed in accordance with the Declaration of Helsinki and the relevant ethics committee approvals were obtained prior to study start. An informed consent form was obtained from the subjects' parents or legally acceptable representatives. Consent was also given by the child, whenever possible, before participation in the study.

Results

A total of 223 children were screened and 177 were randomized to treatment (88 to placebo and 89 to levocetirizine). This was lower than the planned number because of the issues with slow recruitment and low pollen load. The majority of the children (98.3%) were sensitized to grass pollen (a positive or a very positive RAST test or a positive skin test for grass pollen), and 37.9% were asthmatic.

The study was completed by 145 subjects (69 in the placebo group and 76 in the levocetirizine

group). The most common reason for early discontinuation was lack of efficacy, which occurred almost twice as often in the placebo group as compared to the levocetirizine group. There were no dropouts in the levocetirizine group because of side effects.

The two treatment groups were balanced with respect to demographics and baseline characteristics (Table 1). A total of 177 subjects (88 in the placebo group and 89 in the levocetirizine group) took one dose or more of trial medication and were included in the ITT population. The PP population consisted of 125 subjects (60 in the placebo group and 65 in the levocetirizine group).

Total and individual symptom scores

Both treatment groups were comparable at baseline with respect to the mean T4SS (s.d.): 7.64 (1.40) in the levocetirizine and 7.67 (1.73) in the placebo groups.

After 2 wk of treatment, levocetirizine was significantly superior to placebo [difference in adjusted means vs. placebo of 1.29 (0.66–1.92);

Table 1. Demographic and baseline characteristics of the study population

	Placebo (n = 88)	Levocetirizine 5 mg (n = 89)	Total (n = 177)
Age (yr)			
Mean (s.d.)	9.93 (1.91)	9.89 (1.85)	9.91 (1.88)
Min.–Max.	6.1–13.0	6.0–12.8	6.0–13.0
Age category (yr)			
6–8	28 (31.8%)	25 (28.1%)	53 (29.9%)
9–12	59 (67.0%)	64 (71.9%)	123 (69.5%)
≥13	1 (1.1%)	0	1 (0.6%)
Gender			
Female	34 (38.6%)	26 (29.2%)	60 (33.9%)
Male	54 (61.4%)	63 (70.8%)	117 (66.1%)
Race			
African/American	5 (5.7%)	6 (6.7%)	11 (6.2%)
Asian/pacific islander	0	4 (4.5%)	4 (2.3%)
Caucasian	82 (93.2%)	78 (87.6%)	160 (90.4%)
Other/mixed race	1 (1.1%)	1 (1.1%)	2 (1.1%)
Weight (kg)			
Mean (s.d.)	33.92 (8.33)	34.78 (9.97)	34.36 (9.19)
Min.–Max.	18.0–54.5	18.0–61.0	18.0–61.0
Height (cm)			
Mean (s.d.)	138.4 (11.4)	139.3 (12.3)	138.9 (11.8)
Min.–Max.	110–162	110–170	110–170
Medical history			
Asthma	30 (34.1%)	37 (41.6%)	67 (37.9%)
Atopic dermatitis	9 (10.2%)	11 (12.4%)	20 (11.3%)
Eczema	8 (9.1%)	12 (13.5%)	20 (11.3%)
Upper respiratory tract infection	6 (6.8%)	6 (6.7%)	12 (6.8%)
Perennial rhinitis	6 (6.8%)	5 (5.6%)	11 (6.2%)
Bronchitis	3 (3.4%)	7 (7.9%)	10 (5.6%)
Cough	4 (4.5%)	5 (5.6%)	9 (5.1%)
Varicella	0	5 (5.6%)	5 (2.8%)

$p < 0.001$] in alleviating the signs and symptoms of SAR. These were the ITT analysis results (Fig. 2) of the T4SS evaluated for the preceding 24 h over the first 2 wk of treatment (primary efficacy endpoint). This highly statistically significant difference was also reflected in the relative improvement score over placebo, which was 94.1% in favour of levocetirizine (Table 2). Levocetirizine sustained its superiority over the remainder of the study (Fig. 2 and Table 3) indicating that there was no attenuation of the treatment effect. As for alleviating the individual SAR symptoms, levocetirizine was statistically significantly superior to placebo for sneezing, rhinorrhea and nasal pruritus over the 6-wk treatment period. In almost all cases, scores improved during each of the 2-wk treatment periods of the study in both groups but response was always significantly superior in the levocetirizine group (Fig. 3). Levocetirizine was also numerically superior to placebo in alleviating ocular pruritus.

Relief of nasal congestion was observed in the levocetirizine group throughout the study

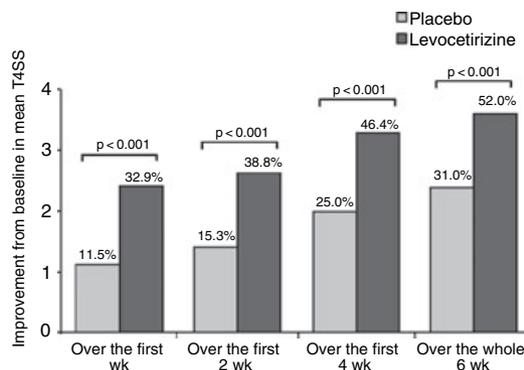


Fig. 2. Improvement from baseline in mean Total Four Symptom Score (T4SS). Data are adjusted means. Percentages are the median percent change from baseline.

Table 2. Relative improvement of the mean Total Four Symptom Score (TFSS) over the first 2 wk

Period	Treatment	n	Change from baseline	
			Adjusted mean* (s.e.)	Relative improvement† (%)
Intention-to-treat analysis over the first 2 wk	Placebo	87	1.37 (0.23)	94.1
	Levocetirizine	87	2.66 (0.23)	
Per protocol analysis over the first 2 wk	Placebo	59	1.45 (0.28)	96.4
	Levocetirizine	65	2.84 (0.27)	

*Mean adjusted for baseline score. A positive change indicates an improvement.

†Relative improvement (%) = $100 \times [(X_{\text{levocetirizine}}/X_{\text{placebo}}) - 1]$ with $X_{\text{levocetirizine}}$ is the adjusted mean for the change from baseline for levocetirizine and X_{placebo} is the adjusted mean for the change from baseline for placebo.

reaching a maximum difference to placebo of 0.31 ($p < 0.05$) during week 3, a relative improvement over placebo of 77.5%. Such an effect has been shown in other levocetirizine studies in adults and adolescents (17). This difference was maintained until week 5 (a difference to placebo of 0.30; $p < 0.05$). During the last week of the study, the difference between the treatment groups became smaller (0.13) and lost statistical significance because of the strong placebo effect (a further improvement compared with week 5 of 0.22 in the placebo group vs. a further improvement in the levocetirizine group of 0.05). The PP analysis confirmed the ITT analysis.

The sensitivity analysis for rescue medication intake showed, as expected, that the days with nasal cromoglicate use were generally associated with lower symptom scores (difference vs. non-cromoglicate days of -0.74 for placebo and -0.75 for levocetirizine). Thus, regardless of nasal cromoglicate usage, the difference and the 95% CI between the levocetirizine group and placebo group remained very similar to the original ITT analysis [1.22 (0.56–1.92); $p < 0.001$] over the entire 6 wk of treatment.

Over the first 2 wk of treatment, the investigator rated 84.3% of the children in the levocetirizine group as having an improvement in their disease evolution compared with only 54.5% in the placebo group. Similar numbers were reported by the children's parent or guardian (80.9% in the levocetirizine group compared with 60.2% in the placebo group) and by the subjects themselves (80.9% in the levocetirizine group compared with 53.4% in the placebo group) (Fig. 4).

Both treatment groups presented an improvement over baseline for each of the PRQLQ domains (nose symptoms, eye symptoms, practical problems, other symptoms and activity limitations) and for the overall score at each time point. After 2 wk of treatment, children treated with levocetirizine presented an overall score improvement over baseline larger than children under placebo (0.85 vs. 0.51, respectively). The improvement observed in the levocetirizine group after 4 and 6 wk of treatment remained larger than in the placebo group at all time points both for the overall score (1.19 and 1.55, respectively) and for the individual domains (Fig. 5).

Safety

Under a third of all children experienced at least one treatment-emergent adverse event with similar numbers in the levocetirizine group (33.7%) compared with the placebo group (30.7%).

Table 3. Difference between the placebo and levocetirizine groups in Total Four Symptom Score (T4SS) over the first 2, 4 wk and entire 6 wk of treatment (intention-to-treat population)

Period	Treatment	n	Baseline mean (s.d.)	Adjusted mean* (s.e.)	Difference vs. placebo (95% CI)	p-Value†
Over the first 2 wk	Placebo	87	7.68 (1.74)	6.27 (0.23)	1.29 (0.66–1.92)	<0.001
	Levocetirizine	87	7.61 (1.36)	4.98 (0.23)		
Over the first 4 wk	Placebo	88	7.67 (1.73)	5.69 (0.24)	1.32 (0.66–1.98)	<0.001
	Levocetirizine	88	7.65 (1.40)	4.37 (0.24)		
Over the 6 wk	Placebo	88	7.67 (1.73)	5.29 (0.24)	1.22 (0.54–1.90)	<0.001
	Levocetirizine	88	7.65 (1.40)	4.06 (0.24)		

*Mean adjusted for baseline score.

†p-Value was obtained from an ancova with baseline score as covariate and treatment as factor.

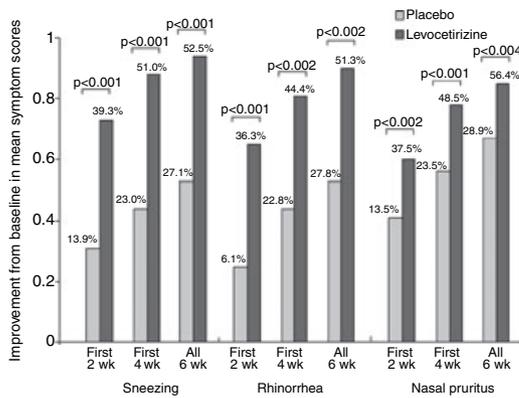


Fig. 3. Improvement from baseline in individual symptoms. Data are adjusted means. Percentages are the median percent change from baseline.

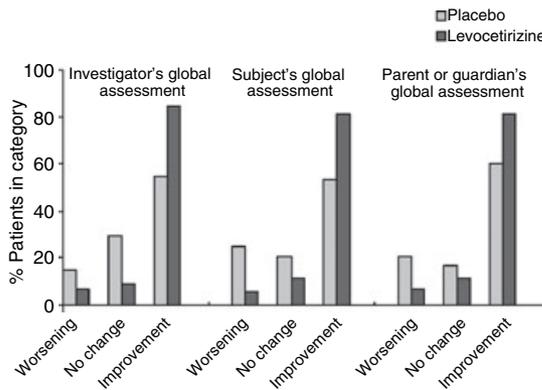


Fig. 4. Global evaluation of illness evolution over the first 2 wk of treatment as evaluated by the investigator, the subject, and the subject's parent or guardian.

Headache, bronchitis and epistaxis were the most commonly reported treatment-emergent adverse events. Headache was reported 15 times by eight subjects in the placebo group compared with five times by four subjects in the levocetirizine group while epistaxis was reported twice by one subject in the placebo group compared with five times by five subjects in the levocetirizine group. Somno-

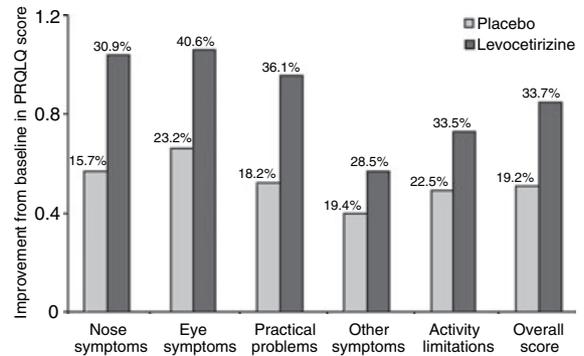


Fig. 5. Improvement from baseline in Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) score for each domain at week 2.

Table 4. Adverse drug reactions that were considered by the investigator to be treatment related*

Preferred term	placebo (n = 88) [n (%)]	Levocetirizine (n = 89) [n (%)]
Asthenia	2 (2.3)	1 (1.1)
Fatigue	0	1 (1.1)
Headache	2 (2.3)	1 (1.1)
Irritability	0	1 (1.1)
Somnolence	0	1 (1.1)
Anorexia	1 (1.1)	0

*Treatment related was defined as described by the investigator as possible, probably or highly probably related to study drug.

lence was reported by a single patient in the levocetirizine group. There were no serious adverse events reported during the study and only one child from the placebo group prematurely discontinued treatment because of an adverse event. Ten adverse events were considered by the investigator to be treatment-related, five in each group (Table 4).

Discussion

This study, designed to evaluate the treatment benefits with a new antihistamine in children with

SAR over the whole duration of the pollen season, demonstrates that once-daily levocetirizine therapy at the approved 5-mg dose is significantly more effective than placebo in relieving all the symptoms of SAR (including nasal congestion) and is also able to improve health-related quality of life after just 2 wk of treatment. Moreover, the global evaluation of illness evolution was consistently better for levocetirizine with moderate-to-marked improvements reported by > 50% of the treated children, their parent/guardian and the investigator.

In line with previous studies (16, 18), this study was able to detect a positive effect of levocetirizine on nasal congestion in children suffering from SAR. This is particularly impressive as the study included less than 100 patients per group. Other studies in a similar population (10) needed to recruit more than 450 children per group in order to observe similar effects.

These results should be interpreted in light of the observed placebo effect, which was unexpectedly large for some parameters. Patients treated with placebo saw their T4SS reduced from baseline by as much as 30% at the end of the study with some individual symptoms improving already during the first 2 wk of treatment by 13.9% for sneezing and 13.5% for nasal pruritus. Some PRQLQ domains also improved with placebo by as much as 23.2% (for eye symptoms) and 22.5% (for activity limitations). Regardless of the strong placebo performance, however, the levocetirizine treatment did achieve and maintained a significantly better control over SAR symptoms and scored better in the quality of life and disease evolution assessment variables (19, 20). Had it not been for the strong placebo effect over the last week, the effect of levocetirizine on nasal congestion could have maintained its statistically significant levels throughout the entire study period.

The positive results reported here may be explained with the potent anti-histaminic and potential anti-allergic effects of levocetirizine. Whether evaluated in the traditional weal and flare trials (17) or in nasal provocation studies (21) levocetirizine has consistently shown to be among the most potent H₁-antihistamines exceeding by a factor of 2 even the affinity to the H₁-receptor of cetirizine (22). The latter, in its recommended dosage of 10 mg, has already been shown more potent than loratadine 10 mg and fexofenadine 30 mg in paediatric pharmacodynamic studies (23, 24). In addition, levocetirizine has been shown to exhibit potent anti-allergic and anti-inflammatory effects, via its inhibitory activity on eosinophil migration (25) and through

improvement of bronchial AMP PC₂₀, a surrogate marker of inflammation (26).

The present results are relevant as the children recruited into the study had a well-established disease with an average of 4.0 yr since diagnosis. The severity of their seasonal rhinitis was moderate, and the severity scores at baseline were similar to the ones seen in another study of SAR in a paediatric population where, however, duration of disease since diagnosis was around 1 yr (10).

The 6-wk treatment duration in this study was longer than the usual treatment periods of 2–4 wk reported in SAR studies, and this was done not only in order to better cover the seasonal peak for considered allergens but also to make it possible to evaluate reliably the safety and consistent efficacy of levocetirizine in alleviating the symptoms associated with SAR. These findings indicate that levocetirizine can be safely used in children on a daily basis during the full duration of the pollen season. No other antihistamine has been studied over such a long-time period in children. Conclusions made in 2-wk studies should be interpreted with caution.

In agreement with the results of studies with levocetirizine in adults (18) there was no evidence of tachyphylaxis over the course of this paediatric study. These results may indicate that regardless of the pollen decrease towards the end of the season, active treatment with a potent antihistamine like levocetirizine maintains its significant effects because of existing histamine release and nasal inflammation throughout the whole season, even during low pollen counts.

In addition, to the best of our knowledge, there is only one study similar to the one reported here utilizing a PRQLQ with a second generation antihistamine, which showed that cetirizine, the predecessor of levocetirizine, was able to significantly improve the quality of life of children suffering from PAR (27). The study reported here is the first study that uses the PRQLQ technique as a parameter to evaluate the efficacy of a new-generation antihistamine in the treatment of SAR among children. The results of this study show that levocetirizine treatment leads to improvement in all of the domains of the PRQLQ. This improvement was observed consistently at each visit throughout the 6-wk study period.

An excellent safety profile for levocetirizine was observed during the study. No unexpected adverse events occurred in any of the groups and no clinically meaningful differences between levocetirizine and placebo were reported. This is a clinical confirmation of its safety in children

which has already been reported in studies with adults where no effects with levocetirizine on psychomotor, cognitive and memory functioning and mood (28) have been observed.

In conclusion, this study demonstrates that levocetirizine is safe and efficacious in reducing the symptoms of SAR (including nasal congestion) in children, 6–12 yr of age. It also confirms the need for continuous (throughout the pollen season) treatment of SAR in children with a potent antihistamine to ensure good overall symptom control and increased quality of life.

Acknowledgments

This study was sponsored by UCB Farchim, Bulle, Switzerland.

We thank Anne Danniau from UCB Biostatistics Department for performing the statistical analysis of the study.

References

1. US Department of Health and Human Services Agency for Healthcare Research and Quality. Management of Allergic and Nonallergic Rhinitis. 2002. Report no.: Pub. no. 02-E023.
2. SKONER DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001; 108(Suppl. 1): S2–8.
3. GREISNER WA, III, SETTIPANE RJ, SETTIPANE GA. The course of asthma parallels that of allergic rhinitis: a 23-year follow-up study of college students. *Allergy Asthma Proc* 2000; 21: 371–5.
4. BELL IR, JASNOSKI ML, KAGAN J, KING DS. Is allergic rhinitis more frequent in young adults with extreme shyness? A preliminary survey. *Psychosom Med* 1990; 52: 517–25.
5. VUURMAN EF, VAN VEGGEL LM, UITERWIJK MM, LEUTNER D, O'HANLON JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993; 71: 121–6.
6. DYKEWICZ MS, FINEMAN S. Executive summary of joint task force practice parameters on diagnosis and management of rhinitis. *Ann Allergy Asthma Immunol* 1998; 81: 463–8.
7. JUNIPER EF, HOWLAND WC, ROBERTS NB, THOMPSON AK, KING DR. Measuring quality of life in children with rhinoconjunctivitis. *J Allergy Clin Immunol* 1998; 101: 163–70.
8. FIREMAN P. Therapeutic approaches to allergic rhinitis: treating the child. *J Allergy Clin Immunol* 2000; 105: S616–21.
9. MELTZER EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 2001; 108(Suppl. 1): S45–53.
10. WAHN U, MELTZER EO, FINN AF, JR, et al. Fexofenadine is efficacious and safe in children (aged 6–11 years) with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2003; 111: 763–9.
11. GRAFT DF, BERNSTEIN DI, GOLDSOBEL A, MELTZER EO, PORTNOY J, LONG J. Safety of fexofenadine in children treated for seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2001; 87: 22–6.
12. DEMOLY P, ALLAERT FA, LECASBLE M, BOUSQUET J. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). *Allergy* 2003; 58: 672–5.
13. DVORIN DJ, LEE JJ, BELECANECH GA, GOLDSTEIN MF, DUNSKY EH. A comparative, volumetric survey of airborne pollen in Philadelphia, Pennsylvania (1991–1997) and Cherry Hill, New Jersey (1995–1997). *Ann Allergy Asthma Immunol* 2001; 87: 394–404.
14. GRANT JA, RIETHUISEN JM, MOULAERT B, DEVOS C. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and-flare response during 24 hours in healthy male subjects. *Ann Allergy Asthma Immunol* 2002; 88: 190–7.
15. GILLARD M, CHRISTOPHE B, WELS B, PECK M, MASSINGHAM R, CHATELAIN P. H1 antagonists: receptor affinity vs. selectivity. *Inflamm Res* 2003; 52(Suppl 1): S49–50.
16. DAY JH, BRISCOE MP, RAFEIRO E, RATZ JD. Comparative clinical efficacy, onset and duration of action of levocetirizine and desloratadine for symptoms of seasonal allergic rhinitis in subjects evaluated in the environmental exposure unit (EEU). *Int J Clin Pract* 2004; 58: 109–14.
17. DENHAM KJ, BOUTSILOUKI P, CLOUGH GF, CHURCH MK. Comparison of the effects of desloratadine and levocetirizine on histamine-induced wheal, flare and itch in human skin. *Inflamm Res* 2003; 52: 424–7.
18. POTTER PC. Levocetirizine is effective for symptom relief including nasal congestion in adolescent and adult (PAR) sensitized to house dust mites. *Allergy* 2003; 58: 893–9.
19. BACHERT C, BOUSQUET J, CANONICA WG, et al. Levocetirizine improves quality-of-life and reduces costs in long term treatment of persistent allergic rhinitis. *JACI* 2004; 114: 838–44.
20. BOUSQUET J, VAN CAUWENBERGE P, KHALTAEV N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108(Suppl. 5): S147–334.
21. 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: 339–43.
22. GILLARD M, VAN DER PERREN C, MOGUILVSKY N, MASSINGHAM R, CHATELAIN P. Binding characteristics of cetirizine and levocetirizine to human H1 histamine receptors: contribution of Lys(191) and Thr(194). *Mol Pharmacol* 2002; 61: 391–9.
23. SIMONS FE, JOHNSTON L, SIMONS KJ. Clinical pharmacology of the H1-receptor antagonists cetirizine and loratadine in children. *Pediatr Allergy Immunol* 2000; 11: 116–9.
24. SIMONS FE, J SEMUS M, GORITZ SS, SIMONS KJ. H1-antihistaminic activity of cetirizine and fexofenadine in allergic children. *Pediatr Allergy Immunol* 2003; 14: 207–11.
25. THOMSON L, BLAYLOCK 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: 1187–92.
26. LEE DK, BATES CE, CURRIE GP, LIPWORTH BJ. Comparative in vivo bioactivity of modern H1-antihistamines on AMP challenge in atopic asthma. *J Allergy Clin Immunol* 2003; 111: 337–41.

27. LAI DS, LUE KH, HSIEH JC, LIN KL, LEE HS. The comparison of the efficacy and safety of cetirizine, oxatomide, ketotifen, and a placebo for the treatment of childhood perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2002; 89: 589–98.
28. VERSTER JC, VOLKERTS ER, VAN OOSTERWIJCK AW, et al. Acute and subchronic effects of levocetirizine and diphenhydramine on memory functioning, psychomotor performance, and mood. *J Allergy Clin Immunol* 2003; 111: 623–7.