
Efficacy comparison of levocetirizine vs montelukast in ragweed sensitized patients

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Background: To date, no adequate data are available on direct comparison of the efficacy of levocetirizine, a recently approved histamine₁-antihistamine, with that of a leukotriene antagonist in the treatment of seasonal allergic rhinitis (SAR) symptoms.

Objective: To compare the efficacy of therapeutic doses of 5 mg of levocetirizine and 10 mg of montelukast in ragweed sensitized patients.

Methods: A randomized, double-blind, placebo-controlled, parallel-group study was conducted between July and October 2006. Symptomatic patients with SAR were exposed to ragweed pollen under controlled conditions in an environmental exposure chamber for 4 to 5 hours after treatment with 5 mg of levocetirizine, 10 mg of montelukast, or matched placebo on 2 consecutive days. The mean change from baseline in pollen-induced rhinitis symptoms, expressed as a major symptoms complex (MSC) score (sum of scores for rhinorrhea, itchy nose, sniffles, nose blows, sneezes, and watery eyes), in period 1 (first 5 hours after first drug intake) was the primary efficacy outcome.

Results: A total of 611 patients were screened, of whom 403 were randomized to receive treatment (102 placebo, 152 levocetirizine, and 149 montelukast). The MSC score in period 1 was progressively decreased to a significantly greater extent in the levocetirizine group compared with the montelukast and placebo groups (adjusted mean differences, -2.18 [95% confidence interval, -3.35 to -1.01 ; $P < .001$] and -2.22 [95% confidence interval, -3.51 to -0.92 ; $P < .001$] for levocetirizine vs montelukast and vs placebo, respectively). The effect of 10 mg of montelukast was not significantly different compared with placebo. Levocetirizine also achieved a significantly faster onset of action within 2.5 hours of administration. Both products were well tolerated.

Conclusions: This study in an environmental exposure chamber confirms the therapeutic efficacy of 5 mg of levocetirizine in improving symptoms of SAR, which was superior to 10 mg of montelukast.

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INTRODUCTION

National and international treatment guidelines for allergic rhinitis have indicated oral antihistamines to be the mainstay of pharmacotherapy and recommend these drugs as first-line treatment.^{1–5} Levocetirizine, the latest commercially available oral histamine₁-antihistamine in the United States, was efficacious and well tolerated in randomized, double-blind, placebo-controlled clinical trials in children and adult patients with seasonal allergic rhinitis (SAR)^{6,7} and perennial allergic rhinitis^{8,9} and improved the quality of life of these individuals during a 6-month treatment period compared with placebo.¹⁰

Montelukast, a leukotriene antagonist used for the treatment of asthma symptoms,¹¹ is also approved for the treatment of symptoms associated with allergic rhinitis; it has been shown to be effective in clinical trials in patients with SAR^{12–15} and is recommended as a treatment option for allergic rhinitis.^{1–3} To our knowledge, no study has directly compared the efficacy of montelukast with levocetirizine in

patients with SAR. The objective of this study was to compare the efficacy of a therapeutic dose of levocetirizine with that of a therapeutic dose of montelukast in ragweed sensitized patients with SAR exposed to ragweed pollen under controlled conditions in an environmental exposure chamber (EEC).

METHODS

Patients

Male and female patients 18 years and older with a clinical history of SAR due to ragweed for the last 2 consecutive years were recruited into the study. All patients were required to have a positive skin test result to ragweed pollen and a minimum total symptoms complex (TSC) score of 18 after exposure to ragweed pollen in the EEC. Patients who required asthma medication other than occasional use of an inhaled short-acting β_2 -agonist and immunotherapy injections within 48 hours of a pollen exposure visit were excluded, as were patients with clinically significant nasal anatomical deformities, a history of chronic sinusitis or experience of an acute episode of sinusitis or a respiratory infection within 30 days of exposure to ragweed pollen in the EEC, or any clinically significant disease or abnormal function test results. Patients who were pregnant or breastfeeding were also excluded.

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The study was approved by an independent ethics committee and institutional review board of the participating center and performed in accordance with the International Conference on Harmonization notes for Guidance on Good Clinical Practice, the principles of Declaration of Helsinki, and all applicable local laws and regulations.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study. During study phase 1 (screening visit), each patient who provided written informed consent was evaluated for demographic characteristics and medical history. The patient underwent a physical examination and evaluation of vital signs. Hypersensitivity to ragweed pollen was confirmed by a positive skin test result in any patient without documentation of skin prick tests and reactivity to specific allergens within the last 12 months. During study phase 2, each patient was primed by exposure to a mean (SD) of 3,500 (500) grains/m³ of ragweed pollen on 1 or more occasions in the EEC (maximum of 6 exposures for a minimum of 90 minutes and a maximum of 3 hours each) and their response to pollen exposure evaluated in the absence of any medication. During exposure, the patient rated the severity of rhinitis symptoms every 30 minutes until a minimum TSC score of 18 was obtained during the combined 3 half-hourly postpollen evaluations in the EEC or until 3 hours of exposure had elapsed.

Eligible patients with TSC scores of 18 or more during at least 1 priming session proceeded to study phase 3, during which they were randomized to double-blind treatment for 2 consecutive days with overencapsulated tablets of 5 mg of levocetirizine, 10 mg of montelukast, or matched placebo, the pharmacokinetic profiles of which were shown not to be modified by overencapsulation. The patients were exposed to pollen in the EEC on each day (Fig 1). On day 1, patients were exposed to a mean (SD) of 3,500 (500) grains/m³ of pollen for 2 hours before treatment (period 1), during which they noted and scored rhinitis symptoms every 30 minutes. Only patients who demonstrated baseline TSC scores of 18 or more proceeded to treatment and posttreatment exposure to pollen. At the end of exposure, patients were followed up for 1 hour in a pollen-free area, where they noted any adverse events (AEs). The procedure was repeated on day 2, during which the baseline symptoms were scored more than 1.5 hours before treatment (period 2) and then again for an additional 4.5 hours (period 3) of pollen exposure. At the end of exposure, patients were evaluated for global satisfaction and willingness to take the same medication during the next pollen season, before being followed up for 1 hour in a pollen-free area.

Efficacy Measurements

The primary objective of this study was to compare the efficacy of 5 mg of levocetirizine and 10 mg of montelukast, as measured by the mean change from baseline in ragweed

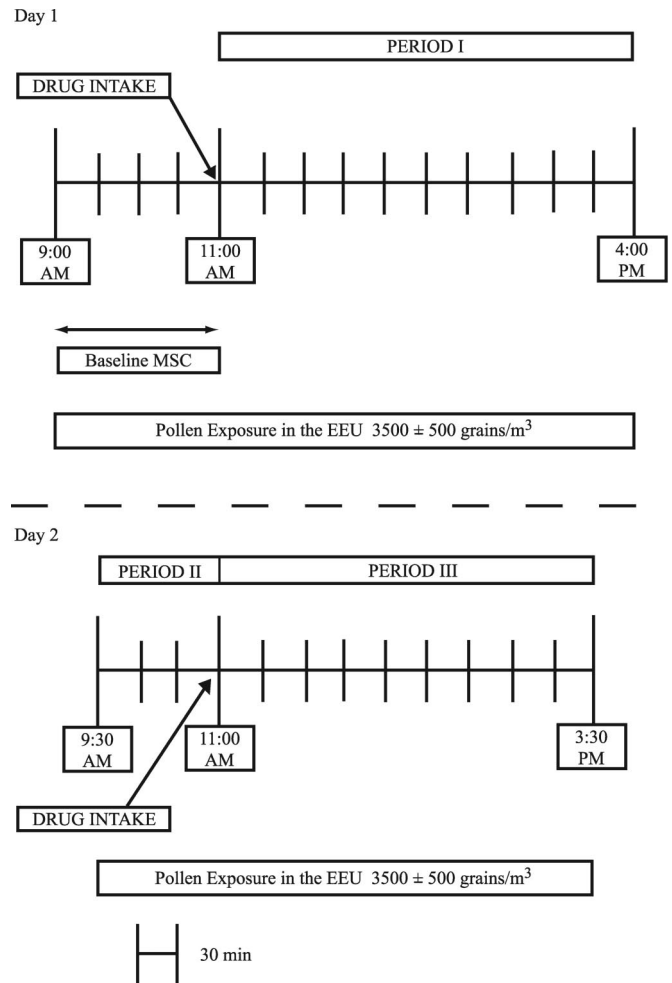


Figure 1. Schematic diagram of phase 3 of the study: pollen challenges in the environmental exposure chamber.

pollen-induced rhinitis symptoms (expressed as a major symptoms complex [MSC] score) during period 1. Comparison of the effects of 5 mg of levocetirizine, 10 mg of montelukast, and placebo on change from baseline in pollen-induced rhinitis MSC, TSC, TSC plus nasal congestion (NC), and individual symptom scores during the study were secondary objectives. Evaluation of the time of the onset of action of 5 mg of levocetirizine and 10 mg of montelukast, the time to first feeling of improvement by the patient, global satisfaction with treatment, and the patient's willingness to take the same medication during the next pollen season were also investigated as secondary objectives.

Rhinitis Symptom Scores

Patients evaluated the severity of runny nose (right and left), itchy nose (right and left), sniffles, postnasal drip, watery eyes, itchy eyes and ears, itchy throat, and cough on a 6-point scale of 0 to 5. Similarly, the severity of NC was rated on a

5-point scale of 0 to 4, and the numbers of nose blows and sneezes were rated on 9-point scale of 0 to 8.

The MSC score was calculated by combining individual scores for the 6 dominant symptoms of runny nose (mean value of right and left), itchy nose (mean value of right and left), sniffles, nose blows, sneezes, and watery eyes and ranged from 0 to 36. The TSC score was calculated as the sum of the MSC score and individual scores for itchy eyes and ears, itchy throat, cough, and postnasal drip and ranged from 0 to 56. The NC score (ranging from 0 to 4) and the TSC plus NC score (ranging from 0 to 60) were also calculated for each patient.

Global Satisfaction

All patients evaluated global satisfaction with treatment on a 0- to 10-cm visual analog scale that ranged from 0 (very dissatisfied) to 10 (very satisfied) at the end of treatment. The patient's willingness to take the same medication during the next pollen season was evaluated by answering the question, "Do you want to take the same treatment during the next pollen season? (yes or no)."

Evaluation of Safety

Safety was evaluated according to the frequency, severity, nature, and duration of any AEs reported by the patients during the entire study. Any abnormalities noted during the physical examinations and evaluation of vital signs and abnormal laboratory findings were also evaluated.

Statistical Analysis

The sample size was calculated on the basis of a previous study,¹⁶ which compared the efficacy and onset of action of 5 mg of levocetirizine vs 5 mg of desloratadine in ragweed sensitive patients exposed to pollen challenge in the EEC. Assuming a true difference of 1.8 between the mean MSC scores of the 2 active treatment groups (levocetirizine and montelukast) and a common SD of 4.8, it was estimated that a sample size of 151 patients in each active group would provide 90% power to show a statistically significant difference between the 2 active treatments, at a .05 significance level. Because randomization was to be performed in a 3:3:2 ratio, a total of 403 patients (151 levocetirizine, 151 montelukast, and 101 placebo) were considered for entry into the study.

All efficacy analyses were performed on the intent-to-treat population, which consisted of all randomized patients who took at least 1 dose of study medication. The reduction from baseline in MSC score during the first treatment period, the primary efficacy measure, and the secondary efficacy measures estimating change from baseline in symptom scores by periods 2 and 3 were analyzed using an analysis of covariance (ANCOVA), including treatment as factor with 3 levels (levocetirizine, montelukast, and placebo) and baseline as a covariate. The pairwise between-group differences were estimated by the difference in least square means together with 95% confidence intervals (CIs). The onset of action was analyzed using a repeated-measures ANCOVA. The time to

the first feeling of improvement during the first treatment period was summarized using the Kaplan-Meier method, and treatment comparisons were performed with the log-rank test. Global satisfaction with treatment was analyzed using an analysis of variance model with treatment as factor, whereas the patient's willingness to take the same medication during the next pollen season was analyzed by comparing the frequency distributions with a Fisher exact test.

RESULTS

Disposition and Demographic Characteristics of the Study Patients

A total of 611 patients were screened between July and October 2006, of whom 403 were randomized to receive treatment (Fig 2) (102 placebo, 152 levocetirizine, and 149 montelukast). A total of 396 patients (98.3%) completed the study. Of the 7 patients who discontinued study participation, 4 (1.0%) withdrew because of an AE (cold and diarrhea in 1 placebo patient and rash and dyspnea in 1 and 2 montelukast patients, respectively). Two patients (0.5%) withdrew for other reasons, and 1 patient withdrew consent. All treatment groups were similar at the beginning of the study (Table 1) with respect to demographic characteristics and symptom severity.

Efficacy Assessments

Evaluation of the mean change from baseline in the MSC score during period 1, the primary efficacy measure, showed that this was progressively decreased to a greater extent in the levocetirizine group compared with the montelukast and placebo groups (Fig 3 and Table 2). The reduction from baseline

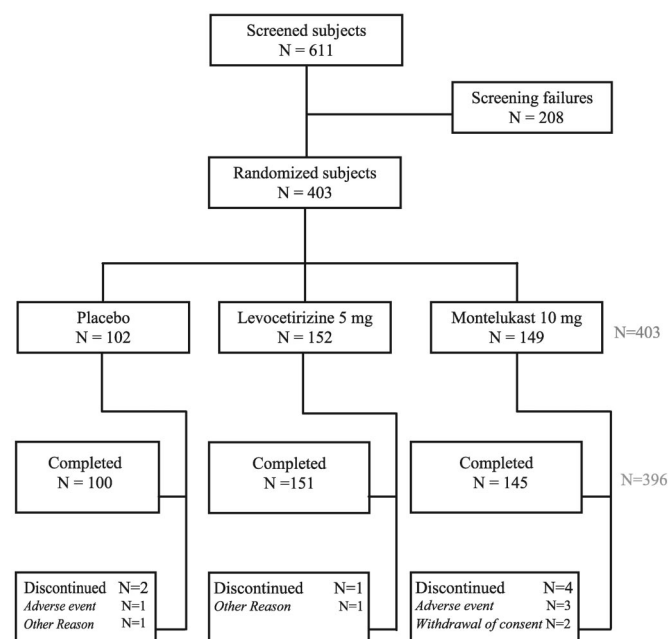


Figure 2. Disposition of the study patients.

Table 1. Demographic Characteristics and Baseline Clinical Characteristics

Characteristics	Placebo (n = 102)	Levocetirizine (n = 152)	Montelukast (n = 149)	Overall (N = 403)
Age, mean (SD) [range], y	38.24 (14.00) [18.6–71.3]	38.58 (12.70) [18.5–68.9]	34.63 (11.71) [18.0–77.2]	37.03 (12.80) [18.0–77.2]
Sex				
Female	62 (60.8)	87 (57.2)	86 (57.7)	235 (58.3)
Male	40 (39.2)	65 (42.8)	63 (42.3)	168 (41.7)
Race				
White	48 (47.1)	83 (54.6)	78 (52.3)	209 (51.9)
African American	26 (25.5)	38 (25.0)	45 (30.2)	109 (27.0)
Asian/Pacific islander	18 (17.6)	19 (12.5)	19 (12.8)	56 (13.9)
Other ^a	10 (9.8)	10 (6.6)	7 (4.7)	27 (6.7)
American Indian/Alaskan Native	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.5)
Weight, mean (SD) [range], kg	77.94 (17.45) [48.0–137.0]	76.77 (18.76) [42.0–144.0]	78.35 (20.06) [45.0–150.0]	77.65 (18.90) [42.0–150.0]
Height, mean (SD) [range], cm	165.34 (8.53) [143.0–186.0]	166.80 (8.80) [145.0–188.0]	167.30 (9.89) [131.0–189.0]	166.61 (9.17) [131.0–189.0]
Symptoms scores, mean (SD)				
MSC	17.87 (7.54)	17.59 (6.64)	17.33 (7.11)	
TSC	27.13 (11.01)	26.50 (9.98)	26.12 (10.24)	
TSC plus NC	29.31 (11.57)	28.76 (10.45)	28.35 (10.78)	

Abbreviations: MSC, major symptoms complex (sum of scores for runny nose, itchy nose, sniffles, nose blows, sneezes, and watery eyes); NC, nasal congestion; TSC, total symptoms complex (sum of scores for MSC, itchy eyes and ears, itchy throat, cough, and postnasal drip).

^a Mixed race.

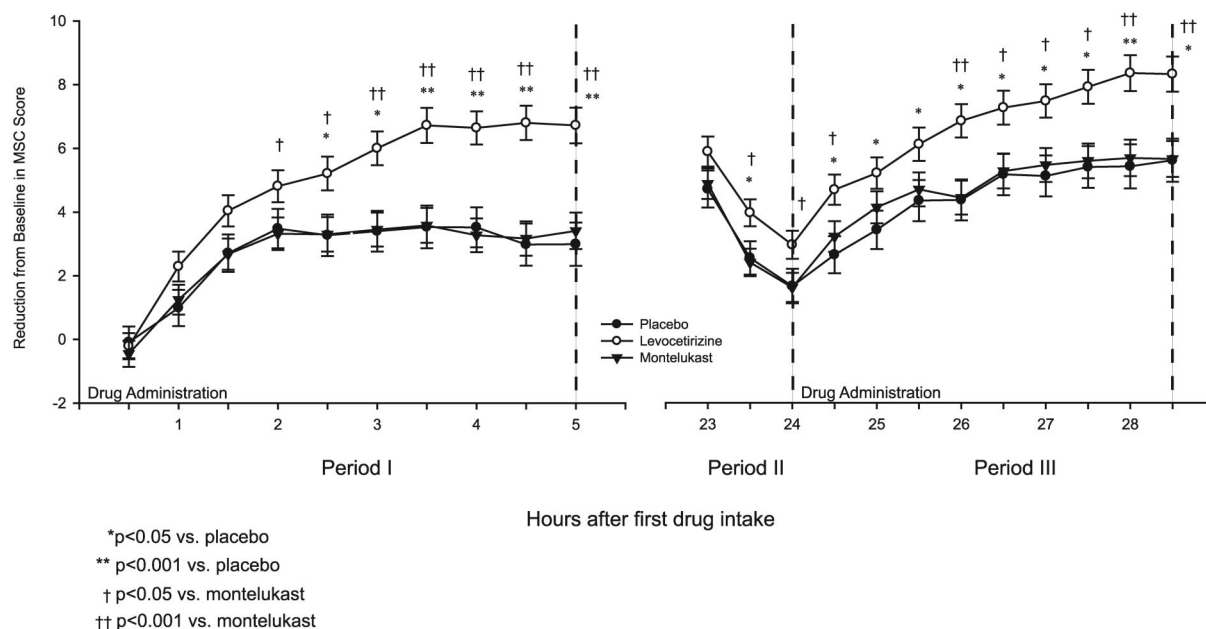


Figure 3. Effect of treatment with placebo, 5 mg of levocetirizine, or 10 mg of montelukast on the mean change from baseline in the major symptom complex (MSC) score after treatment with first dose of study medication and a second intake after 24 hours.

in the MSC score was significantly greater in the levocetirizine group compared with the montelukast and placebo groups. Administration of levocetirizine also led to greater decreases in the mean MSC scores during study periods 2 and 3 and during the entire study period compared with montelukast and placebo (Fig 3 and Table 2).

Similarly, the TSC scores were also decreased to greater levels in the levocetirizine group over each of the study periods; the effects of levocetirizine were significantly superior compared with placebo during each of the study periods and significantly superior compared with montelukast during study periods 1 and 3 (Table 3). Evaluation of the change in

Table 2. Comparison of the Change From Baseline in the MSC Score for the Treatment Groups During Study Periods 1, 2, and 3 and the Entire Study

Treatment	No. of patients	Baseline MSC score, mean (SD)	Change from baseline, adjusted mean (SE)	Difference vs placebo, adjusted mean (95% CI)	Difference vs montelukast, adjusted mean (95% CI)
Period 1 (0–5 h after first dose)					
Placebo	102	17.87 (7.54)	–2.69 (0.51)		
Levocetirizine	152	17.59 (6.64)	–4.91 (0.42)	–2.22 (–3.51 to –0.92) (<i>P</i> < .001 ^a)	–2.18 (–3.35 to –1.01) (<i>P</i> < .001 ^a)
Montelukast	149	17.33 (7.11)	–2.73 (0.42)	–0.03 (–1.34 to 1.27) (<i>P</i> = .96)	
Period 2 (22.5–24 h after first dose)					
Placebo	100	17.75 (7.52)	–2.93 (0.48)		
Levocetirizine	151	17.59 (6.66)	–4.22 (0.39)	–1.29 (–2.51 to –0.06) (<i>P</i> = .04 ^a)	–1.29 (–2.39 to –0.18) (<i>P</i> = .02 ^a)
Montelukast	146	17.17 (7.01)	–2.93 (0.40)	0.00 (–1.23 to 1.23) (<i>P</i> = .10)	
Period 3 (0–4.5 h after second dose)					
Placebo	100	17.75 (7.52)	–4.58 (0.56)		
Levocetirizine	151	17.59 (6.66)	–6.86 (0.45)	–2.27 (–3.69 to –0.86) (<i>P</i> = .002 ^a)	–2.00 (–3.27 to –0.72) (<i>P</i> = .002 ^a)
Montelukast	145	17.23 (7.00)	–4.86 (0.46)	–0.28 (–1.70 to 1.15) (<i>P</i> = .70)	
Total treatment					
Placebo	102	17.87 (7.54)	–3.47 (0.46)		
Levocetirizine	152	17.59 (6.64)	–5.62 (0.38)	–2.14 (–3.32 to –0.96) (<i>P</i> < .001 ^a)	–1.97 (–3.03 to –0.91) (<i>P</i> < .001 ^a)
Montelukast	149	17.33 (7.11)	–3.65 (0.38)	–0.17 (–1.35 to 1.01) (<i>P</i> = .78)	

Abbreviations: CI, confidence interval; MSC, major symptoms complex (sum of scores for runny nose, itchy nose, sniffles, nose blows, sneezes, and watery eyes).

^a Significant difference at the .05 level (2-sided test).

the TSC plus NC scores demonstrated similar profiles to changes in the TSC score with levocetirizine compared with montelukast or placebo. Evaluation of the NC scores individually, however, demonstrated that neither active treatment was significantly superior to placebo during any study period, although the reduction from baseline in the NC score was significantly higher in the montelukast group compared with the levocetirizine group during period 2 (adjusted mean difference, 0.16; 95% CI, 0.00–0.31; *P* = .047).

Time of Onset of Action

Levocetirizine achieved an onset of action within 2.5 hours of administration, as indicated by significant difference in reduction from baseline in the MSC scores from this time point onward until the end of pollen exposure compared with placebo (Fig 3). In contrast, time of onset of action for montelukast could not be determined, because this agent did not lead to any significant difference from baseline in the MSC scores during the study compared with placebo.

Time to First Feeling of Improvement by the Patient

Kaplan-Meier estimates showed the median time to first feeling of improvement was 85 minutes (95% CI, 73.0–115.0

minutes) in the levocetirizine group, 92 minutes (95% CI, 73.0–148.0 minutes) in the montelukast group, and 101 minutes (95% CI, 72.0–143.0 minutes) in the placebo group. Levocetirizine was statistically significantly superior to montelukast (*P* = .02), although no statistically significant difference was reported between the 2 active treatment groups and the placebo group.

Global Satisfaction

Global satisfaction according to the patients' visual analog scale scores at the end of study period 3 was slightly higher in the levocetirizine group (mean [SD], 54.85 [30.22] mm) compared with the montelukast group (mean [SD], 51.66 [30.34] mm) and the placebo group (mean [SD], 50.25 [33.14] mm). However, any differences in adjusted means were not statistically significant among the treatment groups. At the end of study period 3, 90 patients (60.0%) in the levocetirizine group, 75 patients (52.4%) in the montelukast group, and 57 patients (57.0%) in the placebo group indicated willingness to take the same medication during the next pollen season, without significant differences among any of the treatment groups.

Table 3. Comparison of the Change From Baseline in the TSC Score for the Treatment Groups During Study Periods 1, 2, and 3 and the Entire Study

Treatment	N	Baseline TSC score, mean (SD)	Change from baseline, adjusted mean (SE)	Difference vs placebo, adjusted mean (95% CI)	Difference vs montelukast, adjusted mean (95% CI)
Period 1 (0–5 h after first dose)					
Placebo	102	27.13 (11.01)	–4.28 (0.76)		
Levocetirizine	152	26.50 (9.98)	–7.58 (0.63)	–3.30 (–5.24 to –1.36) (<i>P</i> < .001 ^a)	–2.94 (–4.69 to –1.19) (<i>P</i> = .001 ^a)
Montelukast	149	26.12 (10.24)	–4.64 (0.63)	–0.36 (–2.31 to 1.59) (<i>P</i> = .72)	
Period 2 (22.5–24 h after first dose)					
Placebo	100	26.95 (11.00)	–4.00 (0.69)		
Levocetirizine	151	26.46 (10.00)	–5.99 (0.56)	–1.99 (–3.74 to –0.23) (<i>P</i> = .03 ^a)	–1.44 (–3.02 to 0.15) (<i>P</i> = .08)
Montelukast	146	25.97 (10.15)	–4.55 (0.57)	–0.55 (–2.32 to 1.22) (<i>P</i> = .54)	
Period 3 (0–4.5 h after second dose)					
Placebo	100	26.95 (11.00)	–6.99 (0.84)		
Levocetirizine	151	26.46 (10.00)	–10.11 (0.68)	–3.12 (–5.24 to –1.00) (<i>P</i> = .004 ^a)	–2.41 (–4.32 to –0.50) (<i>P</i> = .01 ^a)
Montelukast	145	26.04 (10.15)	–7.70 (0.69)	–0.71 (–2.84 to 1.42) (<i>P</i> = .51)	
Total treatment					
Placebo	102	27.13 (11.01)	–5.33 (0.69)		
Levocetirizine	152	26.50 (9.98)	–8.40 (0.57)	–3.08 (–4.84 to –1.31) (<i>P</i> < .001 ^a)	–2.50 (–4.09 to –0.91) (<i>P</i> = .002 ^a)
Montelukast	149	26.12 (10.24)	–5.90 (0.57)	–0.58 (–2.35 to 1.19) (<i>P</i> = .52)	

Abbreviations: CI, confidence interval; TSC, total symptoms complex (sum of major symptoms complex score plus scores for itchy eyes and ears, itchy throat, cough, and postnasal drip).

^a Significant difference at .05 level (2-sided test).

Safety Evaluation

Overall, 63 patients (15.6%) reported treatment-emergent AEs, with a slightly higher incidence in the placebo group (19.6%) than in the levocetirizine group (15.8%) and the montelukast group (12.8%). All AEs were described as mild or moderate in severity by the investigator. No treatment-emergent serious AEs were reported. Overall, 10.8% of AEs in the placebo group, 9.2% in the levocetirizine group, and 8.1% in the montelukast group were classified by the inves-

tigator as drug related. The most common AEs are summarized in Table 4.

DISCUSSION

The findings from the present study are in accordance with the findings of other studies investigating the effect of levocetirizine on the development of SAR symptoms, following both natural^{6,7} and controlled pollen exposure,^{16,17} thus confirming the therapeutic efficacy of 5 mg of levocetirizine.

Table 4. Most Frequent Adverse Events in Each Treatment Group

Adverse event	Placebo (n = 102), No. (%)	Levocetirizine (n = 152), No. (%)	Montelukast (n = 149), No. (%)
Abdominal pain	2 (2.0)	4 (2.6)	2 (1.3)
Diarrhea	2 (2.0)	1 (0.7)	1 (0.7)
Fatigue	3 (2.9)	3 (2.0)	0 (0.0)
Flushing	2 (2.0)	0 (0.0)	0 (0.0)
Headache	5 (4.9)	4 (2.6)	4 (2.7)
Nausea	3 (2.9)	1 (0.7)	0 (0.0)
Rash	0 (0.0)	1 (0.7)	3 (2.0)
Sedation	2 (2.0)	3 (2.0)	0 (0.0)

Day and colleagues¹⁶ investigated the comparative clinical efficacy of levocetirizine and desloratadine, using a study design similar to the one in the present study. A total of 373 ragweed sensitized patients were exposed to ragweed pollen in an environmental exposure unit (EEU). Although both active treatments were significantly more effective than placebo in reducing baseline MSC and TSC scores during each of the 3 study periods, levocetirizine was also significantly more effective than desloratadine, providing significantly greater symptom relief in all periods. Furthermore, levocetirizine demonstrated a faster onset of action (1 hour) compared with desloratadine (3 hours).¹⁶

Similarly, a randomized, double-blind, crossover study that investigated the effect of single doses of 5 mg of levocetirizine, 10 mg of loratadine, and placebo in 73 SAR patients exposed to grass pollen in the Vienna Challenge Chamber demonstrated that both active treatments were significantly more effective than placebo in decreasing the baseline MSC score (for rhinorrhea, sneezing, nasal and ocular pruritus, and watery eyes).¹⁷ Levocetirizine was significantly superior and faster in its action than loratadine (45 minutes for levocetirizine vs 75 minutes for loratadine). In another 3-way crossover Vienna Challenge Chamber study that compared 5 mg of levocetirizine, 120 mg of fexofenadine, and placebo in 94 patients with SAR, 5 mg of levocetirizine was also found to be significantly more effective and longer acting than 120 mg of fexofenadine in reducing mean MSC scores (for rhinorrhea, sneezing, itchy nose, and itchy eyes) from baseline.¹⁸

In the present study, levocetirizine's efficacy in improving symptoms of SAR was superior to montelukast's, both in the first 5 hours after drug intake and at the end of the dosing interval. This finding supports previous findings of 3 recent clinical studies that compared the efficacy of levocetirizine to montelukast in allergic rhinitis.^{19–21} The first study involved 418 patients with SAR who were administered 5 mg of levocetirizine, 10 mg of montelukast, or placebo once daily more than 2 days in the EEU. The adjusted mean MSC scores between levocetirizine and montelukast were significantly different in period 2 (22.5 to 24 hours after first dose; $P < .001$), period 3 (0 to 4.5 hours after second dose; $P < .001$), and the total treatment period ($P < .001$).¹⁹ In the second study, 20 patients with persistent allergic rhinitis received 5 mg of levocetirizine, 10 mg of montelukast, both, or placebo for more than 6 weeks in a crossover fashion. The study showed that levocetirizine was significantly superior to montelukast in improving mean total nasal symptom score from baseline ($P < .05$), with the combination of montelukast and levocetirizine being significantly superior to montelukast alone ($P < .001$) but not to levocetirizine alone.²⁰ The third study involved 338 patients with SAR and randomized to parallel groups receiving 5 mg of levocetirizine, 10 mg of montelukast, both treatments, or placebo for more than 4 weeks. The improvement from baseline for the daytime symptom score was 0.43 (95% CI, 0.47–0.28) for the levocetirizine group, 0.34 (95% CI, 0.39–0.18) for the montelukast group, and 0.70 (95% CI, 0.73–0.52) for the combi-

nation group.²¹ The combination was significantly superior to any of the 2 monotherapies ($P < .01$); the numerical difference between the 2 monotherapies was not statistically tested.

The efficacy of montelukast in allergic rhinitis compared with oral antihistamines in general was evaluated in 2 recently published meta-analyses.^{22,23} Both analyses showed that montelukast was more effective than placebo in improving rhinitis symptoms and quality of life as measured by the Rhinoconjunctivitis Quality of Life Questionnaire. In 1 meta-analysis,²³ montelukast showed no statistical difference to oral antihistamines, even though the antihistamines were numerically superior; in the other,²² montelukast was statistically significantly inferior to oral antihistamines.

The EEC studies provide additional pharmacodynamic data that are not available in clinical multicenter trials designed to provide information about long-term efficacy and safety. The most important advantage is that several conditions of an outdoor pollen allergy study environment can be reproduced without variables (such as unpredictable pollen levels, variable antigenicity of pollen, weather during the study period, different pollen exposures in the study population, and reliability of participants reporting) that normally confound other study methods. Larger exposure chambers such as the EEC and EEU provide the potential to conduct clinical trials with large numbers of individuals investigated under well-defined and exactly the same exposure conditions at 1 sitting. The Food and Drug Administration authorities in the United States have endorsed the EEC and EEU as valid models for investigating the time to onset and duration of action, short-term effects of antiallergic drugs.²⁴

In conclusion, this study confirms the therapeutic efficacy and safety of 5 mg of levocetirizine in the treatment of symptoms of SAR and additionally demonstrates superiority of 5 mg of levocetirizine over 10 mg of montelukast in terms of onset of effect immediately after exposure to pollen and sustained efficacy at the end of the dosing interval.

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