

Do the leukotriene receptor antagonists work in children with grass pollen-induced allergic rhinitis?

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Although cysteinyl-leukotriene receptor antagonists were recently approved for use in allergic rhinitis (AR), there has been no study to date investigating their application in children. The aim was to evaluate whether montelukast provides any benefit in nasal allergen challenge-induced symptoms in children, and whether it could improve the control provided by an antihistamine during pollen season. Two randomized studies, one a double-blind, placebo-controlled, nasal allergen challenge study and one an open-label, cross-over, parallel-group clinical study, were performed in 18 (11.7 ± 0.7 years) and 32 children (10.5 ± 0.5 years), respectively, with grass pollen allergy. In the first study, the effect of a single dose of montelukast and its combination with loratadine were compared with placebo on nasal responses induced by allergen challenge. In the second study, the additive effect of montelukast to loratadine was tested in an open-label cross-over clinical study. In the challenge study, early-phase and late-phase nasal reactions peaked at 15 min and 4 h after the challenge respectively. During the early phase, combination improved total nasal symptoms ($p = 0.004$) during the first hour and sneezing ($p = 0.012$) at 15 min compared with placebo group. During the late phase, montelukast ($p = 0.017$) and combination ($p = 0.011$) caused less nasal obstruction at 4 h and combination caused less sneezing at 6 h ($p = 0.015$). In the clinical trial, montelukast provided protection on seasonal increase in pulmonary symptoms [0 (0, 14) vs. 6.5 (0, 27.7); $p = 0.016$] and on the decrease in FEF_{25–75} [–0.09 (–0.34, 0.17) vs. –0.28 (–0.66, 0.02); $p = 0.002$]. However, there was no improvement in nasal symptoms and flows. Although we showed protection against nasal challenge-induced congestion with montelukast, we were not able to show the same in the clinical study possibly because of low pollen counts and mildness of the symptoms of the patients with AR. However, montelukast provided better control of pulmonary symptoms and protection from seasonal decrease in lung function, indicating its potential therapeutic benefit in children with AR.

Ozlem Keskin¹, Evrim Alyamac¹, Ayfer Tuncer¹, Cahit Dogan², Gonul Adalioglu¹ and Bulent Enis Sekerel¹

¹Hacettepe University Faculty of Medicine, Pediatric Allergy and Asthma Unit, ²Hacettepe University Faculty of Science, Biology Part, Ankara, Turkey

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Bulent E. Sekerel, Hacettepe University School of Medicine, Ihsan Dogramaci Children's Hospital, Pediatric Allergy and Asthma Unit, Hacettepe, 06100 Ankara, Turkey
Tel.: +90 312 305 1700
Fax: +90 312 311 2357
E-mail: b_sekerel@yahoo.com

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Allergen challenge in susceptible asthmatic individuals invokes an early allergic response induced by the release of mediators such as histamine and leukotrienes. Many patients also experience a late-phase response associated with

tissue edema, infiltration and recruitment of inflammatory leukocytes. Studies with leukotriene modifiers show that both early- and late-phase bronchoconstrictive responses to allergen are noticeably leukotriene dependent (1).

Cysteinyl-leukotrienes have long been implicated in the pathogenesis of allergic inflammation. This group of chemical mediators has diverse functions, including smooth muscle constriction, mucus secretion, mucosal edema, and eosinophil chemotaxis (2).

Experimental data from the previous studies strongly support the view that the pathophysiology of allergic rhinitis (AR) and asthma are very similar, and share common underlying inflammatory mechanisms. The immunopathology of these disorders is characterized by IgE-dependent mast cell activation, the release of inflammatory mediators such as histamine and leukotrienes, the subsequent recruitment and activation of leukocyte populations and the presence of a predominant Th2-type cytokine profile to drive events (3). Further similarities come from responsiveness to corticosteroid therapy. Despite the similarities in the inflammatory process between these two disorders, there are notable differences in the pathology of the diseases and in clinical disease expression. It is widely believed that these mostly result from the differences in the effector organs.

Montelukast, a cysteinyl-leukotriene receptor antagonist (LTRA) and an antiasthmatic drug, was recently approved for clinical use in the treatment of AR through clinical studies performed in adults (4–11). To our knowledge, no previous studies have investigated the efficacy of antileukotrienes in the treatment of AR in children.

We hypothesized that a leukotriene receptor antagonist, montelukast, would also inhibit allergen-induced early- and late-phase nasal allergic reactions and improve the control of rhinitis in children with grass pollen-induced AR. For these reasons, we performed two randomized studies, one a double-blind, placebo-controlled, *in vivo* nasal allergen challenge study and one an open-label, cross-over, parallel-group clinical study. Our observations form the basis of this report.

Material and methods

Study designs and ethical considerations

The investigation included two studies. The first study (Study I) was conducted to investigate the protective effect of montelukast and montelukast/loratadine combination vs. placebo on nasal challenge-induced symptoms and nasal flows, and it had a double-blind, cross-over design. The second study (Study II) was an open-label, cross-over, parallel-group clinical study and aimed to investigate the additive effect of mont-

elukast to loratadine during grass pollen season. Both studies were conducted according to good clinical practices for trials on medical products in the European Community (EC-GCP guidelines). All parents and patients gave written informed consent to participate in the studies, which were approved by the Hacettepe University Ethics Committee. Both study protocol and informed consent were in agreement with the declaration of Helsinki. None of the pharmaceutical companies funded the study or contributed to study design, outcome evaluation, or writing of the manuscript.

Patients

Eighteen (nine girls, nine boys) and 32 (11 girls, 21 boys) children with grass pollen-induced AR were consecutively recruited from our Pediatric Allergy and Asthma Outpatient Clinic for Study I and Study II respectively. Inclusion criteria for patients were as follows: (i) a history of AR (rhinorrhea, nasal itch, sneezing, nasal obstruction) in at least two consecutive grass pollen seasons; (ii) a positive skin prick test with a biologically standardized grass pollen extract (50,000 SBU/ml) (Allergopharma, Reinbek, Germany) (area of the wheal response at least as big as that of the positive control, histamine 10 mg/ml); and (iii) baseline forced expiratory volume in 1 s (FEV1) greater than 80% of predicted value. Exclusion criteria were as follows: (i) upper and lower respiratory tract infection in the previous 8 weeks; (ii) current individual and/or parental smoking habit; (iii) sensitization to perennial allergens (i.e. house dust mites, cat, dog, molds, foods, cockroach); (iv) rhinitis of other origins; (v) use of allergen-specific immunotherapy; and (vi) presence of any other chronic and/or systemic disease. Radiographs were used to exclude the presence of sinusitis, nasal polyps, or deviated nasal septum. Excluded medications were systemic corticosteroids within 1 month; cromolyn, nedocromil, or nasal or ophthalmic corticosteroids within 2 weeks; any antihistamines, oral or inhaled beta-adrenergic agonists or inhaled anticholinergic agents within 1 week; and any systemic and topical decongestants within 24 h.

Study I (nasal challenge study)

Eighteen children (11.7 ± 0.7 years) were allocated for Study I, which consisted of three visits with at least a 7-day washout period between each visit. The effects of a single dose of montelukast (5 mg) and montelukast/loratadine

combination (5/10 mg respectively) were evaluated and compared with placebo on nasal responses induced by nasal allergen challenge. In each visit, patients attended the clinic early in the morning (07.00–09.00 AM) and were given the study drug in a predetermined randomized order. Two hours after the administration of the study drug, nasal challenge with grass pollen extract was performed. Symptom scores of rhinoconjunctivitis, number of sneezes and nasal flow volumes determined by an anterior rhinomanometry were evaluated just before drug administration, just before nasal challenge and after 15, 30, 45, and 60 min (early phase), and 2, 4, 5, and 6 h (late phase) of the challenge. The symptoms in the early (0–1 h) and late phases (2–6 h) were calculated with the summation of the symptoms at 15, 30, 45, 60 min and 2, 4, 5, 6 h respectively. Study drugs were put in opaque gelatin capsules and taken with a half glass of water. For safety reasons, FEV1 was measured before and after each challenge (15 and 30 min), and a short interval history was taken with regard to their allergic diseases and potential adverse effects of medications.

Specific nasal challenge test was performed as detailed previously (12). One puff (0.05–0.06 ml) of a mixture of grass pollen allergen solution (*Poa pretenses* 10,000 BAU/ml + *Phleum Pratense* 10,000 BAU/ml + *Festuca elatior* 10,000 BAU/ml) was applied directly to the head of the inferior turbinate using a metered pump spray on both sides of the nose.

Study II (clinical study)

Thirty-two children (10.5 ± 0.5 years) were included in Study II, which had an open-label parallel-group, cross-over design. In the first week of May, patients were assigned to either open-label loratadine (10 mg/day) or montelukast/loratadine (5/10 mg/day) treatments. After 3 weeks, children who received montelukast/loratadine were treated with loratadine, and vice versa, for another 3 weeks. Patients were instructed to use cetirizine (10 mg/day) and ocular cromolyn (one drop/dose up to four daily doses) on demand basis. When the patients considered the nasal symptoms as bothersome for three consecutive days or more, in spite of using study and rescue medications, they were put on nasal corticosteroid for 10 days. There were no wash-out periods between the two treatment arms and the study was performed during the 6 weeks of the high pollen season according to records of the previous year (from the first week of May to the third week of June). All patients were instructed

to keep a diary throughout the study to record symptom intensity and use of study and rescue medications. Recorded symptoms were nasal (discharge, sneezing, congestion, itching), eye (itching, lacrimation, redness) and lower airway symptoms (cough, dyspnea, wheezing) and were assessed for both daytime (completed in the evening) and nighttime (completed in the morning).

Each patient attended the clinics on four different occasions. On visit 1 (initial visit), children were evaluated for exclusion and inclusion criteria and informed consent was obtained. On visit 2 (randomization visit), children were randomized according to allocation number to one of the two treatment arms to receive either loratadine or montelukast/loratadine once daily at bedtime for 3 weeks and were evaluated for nasal flow volumes and spirometry. Rhinomanometric and spirometric evaluations were conducted during visit 3, and cross-over of the study groups was done. Visit 4 was the final visit of the study and served for collection of diary cards and evaluation of nasal flow volumes and airflows to evaluate the second phase of the study.

The technicians of the lung function and nasal laboratories were blinded to the treatment arms and all tests were done at the same time of the day (07.00–09.00 PM).

Symptom scoring

Symptom scores included nasal (discharge, sneezing, congestion, itching), eye (itching, lacrimation, redness) and lower airway symptoms (cough, dyspnea, wheezing) and were assessed on a scale with minimum and maximum scores of 0 and 3 respectively (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe) (13). The number of sneezing following nasal provocation also reported. Although diaries were collected after each challenge in Study I, they were collected only at the end of Study II (visit 4).

Rhinomanometry

Nasal flow volumes were evaluated by anterior rhinomanometry using Rhinomanometry 2000 (Allergopharma Joachim Ganzer KG, Hamburg, Germany). Total nasal flow was measured with patients breathing tidal volumes through a face-mask with their mouth closed. All measurements were made while in the sitting position with a good seal around a purpose-built soft facemask. Flow rates were calculated at nasal pressures of 75, 150 and 300 Pa.

Quality of life questionnaire for allergic rhinitis (RQLQ)

Questionnaire for AR was used in Study II and completed during the randomization visit and after each treatment period. This RQLQ evaluates seven domains: sleep, non-nose and non-eye symptoms, practical problems, nasal symptoms, eye symptoms, activities, and emotions, using a 0 (best) to 6 (worst) scale.

Pulmonary function tests

Pulmonary function tests (FEV₁, FVC, FEV₁/FVC, FEF_{25–75}) were evaluated with a computerized spirometer (V max 22, Sensor Medics, Yorba Linda, CA, USA).

Pollen counts

Study I was performed outside the pollen season (November to December 2003) and Study II was performed during the 2004 grass pollen season. Airborne pollen grains were sampled daily by a Burkard volumetric pollen trap (Rickmansworth, Hertfordshire, UK) at Hacettepe University Faculty of Biological Sciences, Ankara, Turkey. Grass pollen counts were expressed as the total weekly count of grains per m³ of air. All of the study patients were living within 30 km of the spore trap.

Statistics

Primary outcome measure of first study was the control of nasal symptoms used to power the study at 80% to detect a 25% difference between active treatments vs. placebo, supposing a mean total nasal symptoms of 7 ± 2 in the placebo group with a sample size of 18 completed patients per protocol in a cross-over design. Secondary outcome measure included the area under the 60 min and 2- to 6-h time–response curve (AUC) for individual and total nasal symptoms.

Primary outcome measure of second study was the control of nasal symptoms used to power the study at 80% to detect a 15% difference between combination treatment vs. loratadine treatment, supposing a mean daily total nasal symptoms of 8 ± 2 in the loratadine treatment period with a sample size of 32 completed patients per protocol and control of lower airway symptoms; preserving pulmonary function measures served as secondary outcome measures.

Comparison of three treatment groups of the cross-over challenge study were done by using Friedman test because of skewed data and if a significance exists, two treatment group compar-

isons were made with Wilcoxon Matched-Pairs Signed Rank test. Bonferroni correction set at 95% confidence intervals (CI) was performed for challenge study, setting α -error at 0.017 (two-tailed). Mann–Whitney U-tests was used to compare two unrelated groups. A 5% significance level was used. All analyses were performed using SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Study I (nasal challenge study)

All of the 18 patients recruited for the study completed the study protocol; their characteristics are summarized in Table 1. As expected, early phase and late-phase nasal reactions peaked at 15 min and 4 h after the challenge respectively. In all groups, nasal challenge did not cause any pulmonary symptoms during early (0–1 h) or late (2–6 h) phases.

During the early phase (0–1 h), comparison of three study groups (placebo, montelukast, and montelukast/loratadine) only revealed significant differences in favor of combination treatment at 15 min for sneezing ($p = 0.012$) (Fig. 1a). The remaining individual symptoms during the early phase were not different between the three study groups. However, comparison of total nasal symptoms at 15 min was in favor of combination treatment vs. montelukast and placebo groups ($p = 0.011$ and 0.004 respectively).

During the late phase (2–6 h), comparison of the three study groups (placebo, montelukast and montelukast/loratadine) only revealed significant differences in favor of montelukast and combination treatment at 4 h for nasal obstruction ($p = 0.017$ and 0.011 respectively) (Fig. 1b). Comparison of nasal obstruction between 2 and 6 h was in favor of montelukast and combination groups vs. the placebo group ($p = 0.02$ for both). Comparison of sneezing at 6 h was in favor of combination group vs. the placebo group ($p = 0.015$).

Table 1. Patients' characteristics

	Nasal challenge study	Clinical study
Number, n	18	32
Mean age [year (range)]	11.7 (7–18)	10 (8.3–11.9)
Sex (male/female)	9/9	22/10
Mean duration of rhinitis [year (range)]	3.6 (2–8)	3 (2–4.2)
Presence of asthma, n (%)	4 (22)	12 (38)
Use of inhaled corticosteroid, n (%)	3 (16)	9 (28)

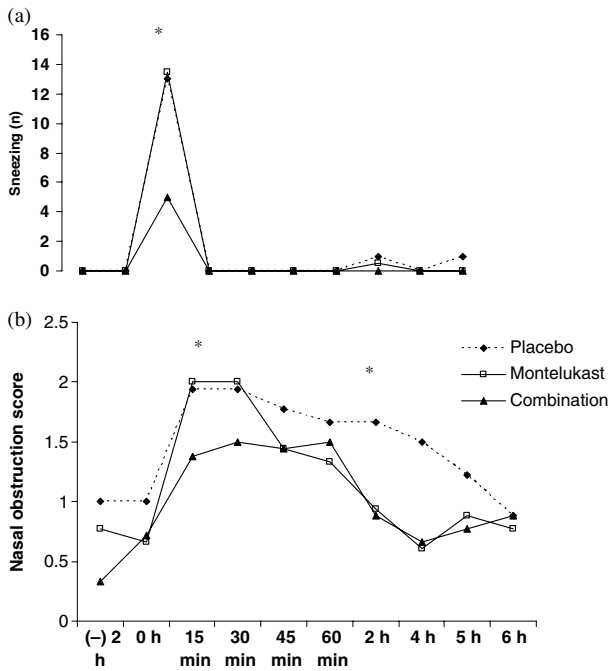


Fig. 1. Nasal challenge study. (a) Median number of sneezes before (–2 and 0 h) and after (15, 30, 45, 60 min and 2, 4, 5, 6 h) nasal provocation test. (b) Mean scores of nasal obstruction before (–2 and 0 h) and after (15, 30, 45, 60 min and 2, 4, 5, 6 h) nasal provocation test. * $p < 0.05$.

Nasal flow rates

Although it did not reach statistical significance, while nasal flow rate was decreased at 15 min of the challenge in the placebo group compared with basal flow rate [–49.5 (–109.3, 2) cm^3/s] [median (interquartile range)], it was increased [13 (–69, 185.5) cm^3/s] in the combination group compared with the baseline flows.

Area under curve analysis (AUC)

During early phase (0–1 h), comparison of the three study groups [placebo (292.5 (211.9–354.4), montelukast 288.8 (208.1–391.9) and montelukast/loratadine 187.5 (148.1–241.9)] for AUC of total nasal symptoms revealed significant difference ($p = 0.04$, Friedman) but the differences between two groups were not significant.

Comparison of AUC for sneezing during early phase (0–1 h) was in favor of montelukast/loratadine 26.3 (0–30) vs. the placebo 30 (30–30) ($p = 0.02$).

Comparison of the three study groups [placebo 120.0 (90–123.8), montelukast 112 (71.2–121.9), and montelukast/loratadine 97.5 (52.5–120.0)] for AUC of nasal obstruction scores during early phase (0–1 h) revealed significant difference ($p = 0.005$, Friedman) but the differences between two groups were not significant.

Comparison of AUC for nasal obstruction scores during 2–6 h was in favor of montelukast 2 (0–5) and combination 2 (0–8) groups vs. the placebo 6 (2–8) group ($p = 0.014$ and 0.016 respectively (Fig. 2).

Study II (clinical study)

All of the 32 patients recruited for the study completed the study protocol and their characteristics are summarized in Table 1. However, compliance with the diary recording was not perfect; five patients were considered falsified because their parents reported their children completing their diaries just before the visit. Thus, only 27 diaries were included into the analysis. Compliance to treatment regimens was 100% according to the diary card recordings/reports. According to the returned study drugs, in two patients (one in loratadine and one in loratadine/montelukast group) three more tablets (either loratadine or montelukast) were used which were accounted as lost. Pollen counts were significantly higher during the first phase of the study (Fig. 3). Pollen season caused nasal symptoms in all patients during both of the study phases (Fig. 3). Although we have calculated the power of the clinical study with a mean daily total nasal symptoms of 8 ± 2 in the loratadine treatment period to detect the additive effect of montelukast to loratadine with a 15% difference, we have seen that mean daily total nasal symptom score was only 2.4 ± 0.5

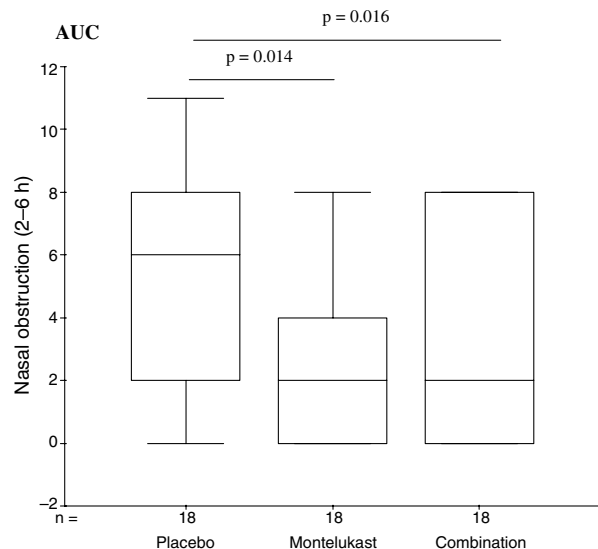


Fig. 2. Nasal challenge study. Area under curve (AUC) analysis for nasal obstruction scores during late phase (between 2 and 6 h after nasal provocation test). Data are median and interquartile range.

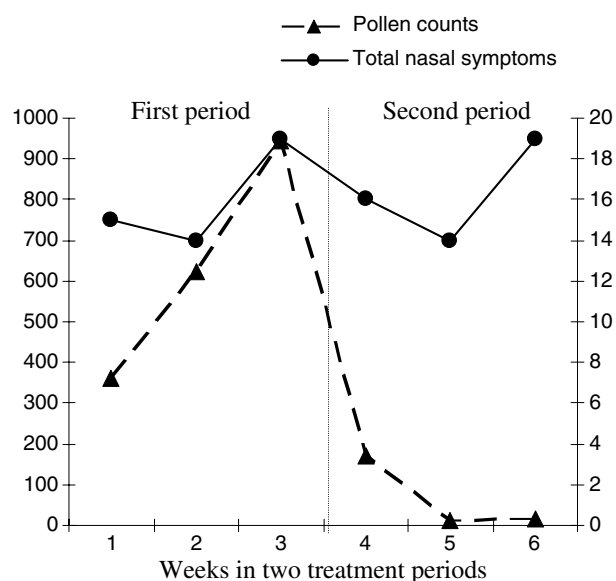


Fig. 3. Clinical study. Pollen counts and weekly total nasal symptoms (TNS) of the whole study group during two treatment periods in the clinical study.

when children were on loratadine treatment. Moreover, in the first phase, 10 of 12 (83%) from the loratadine and eight of 15 (53%) from the loratadine/montelukast group reported pulmonary symptoms, whereas during the second phase, these numbers were eight of 14 (57%) and five of 12 (41%) respectively. Pollen season caused eye symptoms in 12 of 12 (100%) from the loratadine and in 15 of 15 (100%) from the loratadine/montelukast group during the first phase of the study, vs. in 13 of 14 (92%) and in 10 of 13 (76%) for loratadine and loratadine/montelukast groups, respectively, during the second phase of the study.

Combination loratadine/montelukast treatment did not differ from the loratadine treatment in terms of nasal flow rates, nasal symptom scores (morning and evening), quality of life scores (RQLQ) and eye symptoms ($p > 0.05$, Wilcoxon). Although one patient from the loratadine group required nasal corticosteroid, none of the combination group required the addition of nasal corticosteroid ($p = 0.32$).

Baseline FEV₁ (% predicted) values of all groups were 98% (89–105), and there was no significant difference between the two groups. The combination group reported a lower pulmonary symptom score [0 (0, 14)] compared with the loratadine group [6.5 (0, 27.7)] ($p = 0.016$) (Fig. 4a), and the decrease in FEF_{25–75} was significantly less with loratadine/montelukast treatment [−0.09 (−0.34, −0.17)] compared with the decrease with loratadine treatment [−0.28

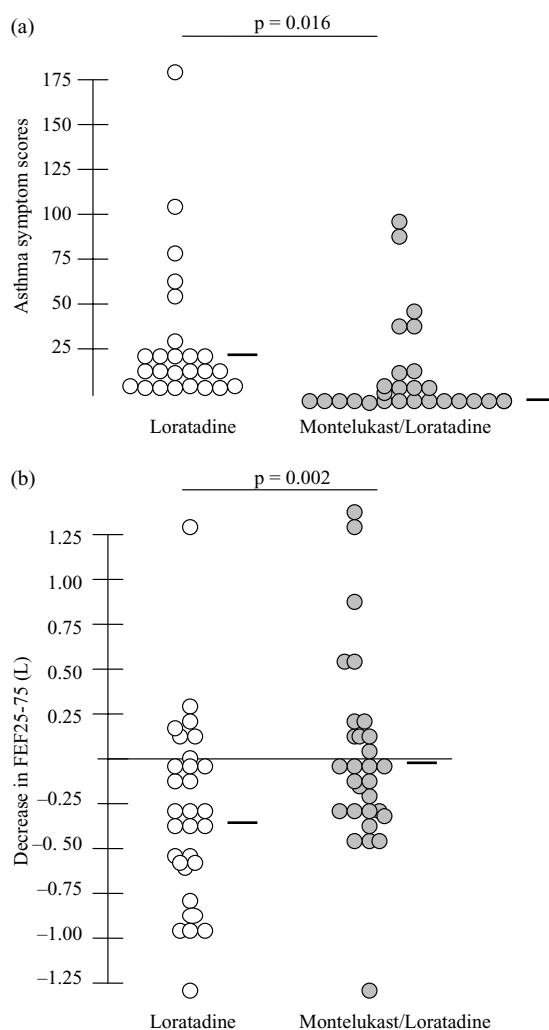


Fig. 4. Clinical study. (a) Individual and median asthma symptom scores in loratadine/montelukast (combination) and loratadine periods. (b) Individual and median decrease in FEF_{25–75} measures during the grass pollen season compared with pre-season. —: median values.

(−0.66, 0.02)] ($p = 0.002$) (Fig. 4b). FVC, FEV₁, and FEV₁/FVC were not different between the two study groups.

Discussion

Allergic rhinitis is characterized by the symptoms of nasal itch, sneezing, rhinorrhea, and nasal stuffiness. These symptoms are a consequence of the local release of mediators from activated cells within the nasal mucosa, through interactions with end-organ receptors. The inflammatory cells in AR have the capability of generating leukotriene mediators in addition to their ability to release other mediators that are also of potential relevance to symptom generation in rhinitis, such as

histamine, prostoglandins, and kinins (14). Several studies have identified clear increments in LTC₄, LTD₄, and LTE₄ levels in nasal lavage fluid in association with the immediate nasal response accompanied by lavage changes in histamine, tryptase, and prostaglandin D₂ (15–17). Repeated nasal lavage sampling after allergen challenge has revealed a peak in LTC₄ 5 min post-challenge, which remains elevated 30 min post-challenge but returns to baseline levels by 60 min (18). Repeated nasal lavage 4–12 h post-challenge reveals a second increment in LTB₄, LTC₄, and histamine without an increase in tryptase or PGD₂ (19–21). Nasal insufflation studies show that both LTC₄ and LTD₄ induce an increase in nasal airway resistance, as measured by rhinomanometry (18, 22, 23). The nasal challenge studies with LTC₄ and LTD₄ have consistently identified no effect on nasal pruritis or sneezing, in contrast to the effects of nasal histamine insufflation. The effects of LTRAs have been investigated in a limited number of studies in both the allergen challenge setting and clinical rhinitis in adult patients (5–11, 24). In nasal allergen challenge studies it was demonstrated that 5-lipoxygenase inhibitors modified allergen-induced nasal obstruction, with no significant influence on induced sneezes or nasal itch, suggesting that leukotrienes are predominantly involved in allergen-induced vascular changes (25, 26). In our challenge study, it was shown that montelukast and montelukast/loratadine compared with placebo were effective in preventing nasal obstruction in the late phase (2–6 h) of the nasal allergen challenge. Because histamine is not a significant mediator of the late-phase allergic response, antihistamines are not typically effective at relieving late-phase nasal obstruction. But, cysteinyl leukotrienes, which are increased in nasal secretions after antigen challenge, may be among the most significant mediators underlying nasal obstruction during the late-phase response, and it is expected that antileukotrienes can block nasal obstruction in the late phase. Although there are some accumulating contradictory data about the efficacy of montelukast and its combination with antihistamines on nasal obstruction in adults, studies are needed in children. This is the first nasal allergen challenge study with montelukast and its combination with antihistamines showing the efficacy of a single dose of montelukast on nasal obstruction in children with AR. Our results tell us that children will feel better in case of late-phase nasal obstruction if they take a single

dose of montelukast 2 h before going to a picnic in the grass pollen season.

In the clinical study, we have demonstrated that loratadine/montelukast combination was not significantly superior to loratadine treatment in nasal symptom scores, AR quality of life questionnaire scores and nasal flow rates. But we have investigated the efficacy of the loratadine/montelukast treatment in asthma symptom scores and pulmonary function testing in children with AR, with or without asthma, during grass pollen season. The links between AR and asthma are well established. Our results support the use of a single agent such as montelukast for the treatment of the comorbid diseases of asthma and AR. Cysteinyl leukotrienes are important mediators in the pathophysiology of both asthma and AR and they are found in bronchial and nasal airway lining fluid obtained from patients with asthma and AR, respectively, both in natural disease and after mucosal challenge with allergens (27–30). Inhaled leukotrienes causes bronchoconstriction and eosinophil influx in asthma patients (31, 32). In a proportion of AR individuals, bronchial challenge with histamine or methacholine may reveal bronchial hyperresponsiveness even in the absence of any asthmatic symptoms, and this may reflect subclinical inflammatory changes in the lower airways. Leukotriene receptor antagonists, which inhibit the actions of leukotrienes, have proved to be effective therapies in the treatment of asthma. It is logical that antileukotriene treatment may also affect the lower airway symptoms in children with AR with or without asthma because of the presence of subclinical inflammatory changes in the lower airways of these children. Perry et al. showed that montelukast has a protective effect against lower and upper airway responses to short-term allergen exposure using a well-characterized cat challenge model as a means of simultaneously exposing both the lower and upper airways to an indoor allergen (33).

Nasal obstruction is an important feature of AR. It can be measured in the laboratory by acoustic rhinomanometry which measures function in terms of nasal resistance. But measuring the nasal flow rates only one time was not enough to demonstrate the differences in our study group in the clinical study. It would be better to follow up the nasal flow rate measures daily. We thus recommend daily follow-up for nasal flow rates in those studies which intend to show improvement in nasal flow rates.

The duration that children stay outside is a very important factor affecting the severity of the symptoms during grass pollen season. Thus, following the patient's nasal symptoms with diaries may give only limited knowledge about the efficacy of the treatment drugs. The time spent outside is highly variable – while one child may prefer to stay at home and read a book or watch television, another prefers to play games in the garden or wander around in the park. Furthermore, perception of the symptoms may differ from one patient to another. In addition, the variability of the pollen counts in different treatment periods may affect the response to treatment in parallel-group studies.

The mean of daily total nasal symptoms were supposed to be 8 ± 2 in the power analysis of the clinical study. However, although our patients had pollen-induced AR, their overall symptoms were relatively mild (mean daily total nasal symptoms was 2.4 ± 0.5 in the loratadine treatment period), suggesting that further studies are required to evaluate putative additivity of response with combined histamine H1-receptor and leukotriene receptor antagonists in more severe patients in children's age group. It is, however, conceivable that if we had selected, for example, patients with more severe symptoms, this might have identified a greater potential for additivity of response. The power of our clinic study decreased because of the mild symptoms of our patients. Furthermore, although we included 32 patients in the clinical study, only 27 diaries were available for evaluation. The low number of subjects indicates a possibility of type II error where it might have failed to show a small benefit of montelukast. Much more stronger effect of montelukast on asthma symptoms and pulmonary function test might have given a chance to observe a significant difference with this number of patients. Perhaps the putative benefits of such combination therapy may become evident only when looking at concomitant effects on asthma control in patients who have concomitant AR.

We have shown that montelukast treatment prevented a decrease in FEF_{25-75} . FEF_{25-75} may have the potentiation to reflect the small airway pathology. It has been shown that the presence of mast cells in the small airway may cause small airway disease in patients with asthma (34). It is also well known that mast cells are a very important source of leukotrienes (35), and that inhaled drugs generally fail to reach small airways. Oral drugs like LTRA are more capable

of reaching the small airways via the blood-stream. Prevention of the decrease in FEF_{25-75} by LTRA may be related to the presence of a high number of mast cells in the small airways and blockage of leukotrienes released from these mast cells.

While we have compared the effectiveness of the placebo, montelukast and montelukast/loratadine in the treatment of AR in the first step (nasal allergen provocation study), we compared loratadine with loratadine/montelukast in the second step (clinical study). In the clinical study, we did not apply placebo or montelukast alone for ethical reasons. In our opinion, children would feel quite ill and have a diminished quality of life if administered placebo or montelukast alone. We tested the efficacy of placebo and montelukast in the nasal allergen provocation study.

To conclude, although we showed that a single dose of montelukast provides protection against allergen challenge-induced nasal obstruction, we were not able to show the same in the clinical trial, possibly because of low pollen counts and mildness of the symptoms. However, clinical trial also showed that the addition of montelukast over antihistamine provides benefits in controlling lower airway symptoms and the prevention of seasonal decrease in lung functions, indicating its potential therapeutic value in children with AR.

List of contributors

Dr O Keskin participated in the development of the protocol and analytic framework for the study, and had primary responsibility for patient screening, enrollment, and for manuscript preparation.

Dr E Alyamac participated in the analytic framework for the study and contributed to patient screening and writing of the manuscript.

Dr A Tuncer and Dr G Adalioglu supervised the design and execution of the study, and contributed to the final data analyses and writing of the manuscript.

Cahit Dogan had primary responsibility for sampling and analysis of airborne pollen grains.

Dr BE Sekerel had primary responsibility for protocol development and contributed to outcome assessment, preliminary data analysis, and writing of the manuscript.

Disclosure of potential conflict of interest

None disclosed.

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