

Montelukast as an adjuvant to mainstay therapies in patients with seasonal allergic rhinitis

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Summary

Background Drug selection for optimal treatment of allergic rhinitis may be difficult and involve many diverse factors.

Objective To evaluate montelukast, in the treatment of patients with seasonal allergic rhinitis, as an adjuvant to mainstay therapies, i.e., antihistamines and corticosteroids.

Methods The study was a prospective, three-phased (per lasted 2 weeks) clinical trial. In phase I, patients were separated into two groups, based on the predominating symptoms: (1) runners (patients with moderate to severe sneezing/itchy, watery nose/itchy, watery eyes), and (2) blockers (patients with moderate to severe nasal congestion). The runners received antihistamine loratidine 10 mg daily, and the blockers received intranasal corticosteroid mometasone furoate 200 µg. In phase II, if patients were dissatisfied with the initial treatment, they were assigned to receive another study drug additionally. In phase III, for the patients unsatisfied with the treatment of loratidine plus mometasone furoate, montelukast 10 mg once daily was added.

Results Of the 169 patients who entered phase I, 150 could be evaluated for treatment efficacy and safety. There were 108 runners and 42 blockers. Physicians' and patients' assessments indicated that in phase I 58 runners (60.0% of 50 runners) and 36 blockers (33.3% of six blockers) were satisfied with their therapy. In phase II, 30 runners (27.7%) and two blockers (4.7%) were satisfied with the addition of other study drug. Totally 62.6% of patients were satisfied at the end of phase I, and 84.0% at the end of phase II. Sixteen patients (66.6% of 24 patients) were satisfied with the addition of montelukast to the previous two drugs (in total, 10.6% of patients). Fourteen patients (12.2%) treated with loratidine, and three patients (0.3%) treated with mometasone, reported side-effect.

Conclusion The results of this trial indicate that 10% of patients with seasonal allergic rhinitis may be treated with the supplement of montelukast to mainstay therapy.

Keywords efficacy, leukotriene receptor antagonist, loratidine, mometasone furoate, montelukast, rhinoconjunctivitis

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Introduction

Newer H1-receptor antagonists and intranasal corticosteroids are the mainstay of seasonal allergic rhinitis (SAR) therapy [1]. However, some patients may be poor responders to the mainstay therapies. The leukotriene receptor antagonists may be an alternative for the treatment of SAR. However, studies with leukotriene receptor antagonists on symptoms of SAR reported inconsistent results.

In its consensus statement, the European Academy of Allergy and Clinical Immunology advocated a stepwise therapeutic approach that took into account specific diagnosis and patient characteristics [1]. Although oral antihistamine plus nasal corticosteroid is recommended for inadequate control of

symptoms, to our knowledge, no studies have examined the effectiveness of combination therapy in patients not responding to the first antihistamine or intranasal corticosteroids therapy.

In the present study our aim was to investigate whether non-responders to mainstay therapies respond to combinations of these drugs, and to estimate how often a leukotriene receptor antagonist is necessary in the treatment of SAR as a supplement to mainstay therapies.

Materials and methods

Patients

Male and female subjects aged 16 years or older who had a documented history of SAR and were otherwise in good health were considered for enrolment. A positive skin prick test to at least one seasonal allergen prevalent in the geographical area

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was required. Participants had at least one of the following symptoms that need treatment: watery nasal discharge, sneezing, itchy nose, nasal congestion, watery eyes, and itchy eyes. Patients were separated into two groups based on the most dominant symptom: (1) runners (sneezing/itchy nose/watery nose/watery eyes/itchy eyes), and (2) blockers (nasal congestion).

Patients were excluded from the study if they had been treated with study drugs or decongestants within 1 week, with astemizole within 56 days, or with topical corticosteroids within 1 month or a systemic steroid within 3 months before the commencement of the study. Patients were not included in the study if they had asthma grade 4 or higher, severe concurrent disease, nasal polyps or deviated nasal septum, or if they had received immunotherapy within 3 years of the study, were pregnant or lactating women, had experienced adverse reactions to an antihistamine, nasal corticosteroid, or had exhibited multiple drug allergies.

All patients gave informed consent.

Design of the study

The study was a prospective, three-phased, symptom directed clinical trial, conducted during the pollen season.

Each phase lasted 2 weeks. Patients were evaluated at four visits. Visit 1 marked the beginning of phase I; visit 2 marked the end of phase I and the beginning of phase II; visit 3 marked the end of phase II and the beginning of phase III; visit 4 marked the end of phase III.

Patients' and physicians' assessments were performed at each visit. The physician, who assesses the patients, was blind to treatment.

In phase I, the runners received loratidine 10 mg every evening and the blockers received intranasal corticosteroid mometasone furoate nasal spray 200 µg every morning. In phase II, patients and physicians determined either to continue the current study medications or, if patients were dissatisfied with their current treatment, they were assigned to receive another study drug additionally. In phase III, for the patients dissatisfied with the treatment of loratidine plus mometasone furoate, montelukast 10 mg once daily was added. Study drugs were evaluated at the end of each phase for efficacy and safety.

Outcome measures

Patient compliance Patients were instructed to fill out a diary card and bring their medication with them. If there were no regular marks on the diary cards or they had more pills than expected with them, they were noted as non-compliant. The compliance was evaluated at visits 2, 3 and 4.

Efficacy Using a 3-point scale (0 = complete absence of symptom, 1 = there are symptoms but they are bearable without treatment, 2 = symptoms that need treatment), baseline assessments of SAR symptoms were recorded. At visits 2, 3 and 4, patients and physicians completed global assessments of the efficacy of treatment for rhinitis by using a 3-point scale (0 = complete absence of symptoms, 1 = there are symptoms but patient needs no further treatment, 2 = symptoms that need further treatment).

Safety The nature, incidence, and severity of any adverse events were collected through medical history and physical examination.

Statistical methods

A mean symptom severity score was calculated for each symptom, and from these scores a mean total symptom severity score was calculated. Wilcoxon or Cox procedure was used to compare symptom severity between baseline scores (beginning of the phase) and treatment scores (end of the phase). Analyses were done for each phase.

The patients' and physicians' evaluation of overall effectiveness of study medication were presented as the proportion of patients whose treatment was successful for each treatment group.

Results

A total of 169 patients were enrolled in the trial. The mean age was 35.0 years (16–72 years); 63.3% of patients were female. Of the 169 patients who entered the study, 150 could be evaluated for treatment efficacy and safety. Five patients could not be evaluated because of non-compliance, two because of severe drowsiness; 12 patients were lost to follow-up.

Efficacy

Phase 1 Of the 150 patients, 108 were runners and 42 were blockers. Patients treated with loratidine improved significantly, except runny nose and nasal congestion (Fig. 1). Patients treated with mometasone furoate improved significantly, except eye symptoms (Fig. 2).

Physicians' and patients' assessments indicated that in phase I, 58 runners (53.7%) and 36 blockers (85.7%) were satisfied with their therapy.

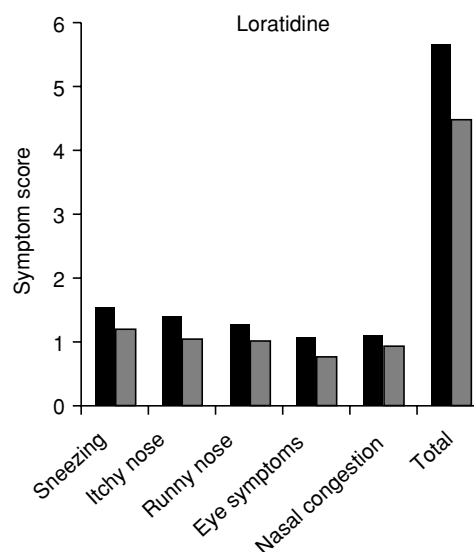


Fig. 1. Symptom scores in patients treated with loratidine. ■, baseline values; ▒, end of first phase.

Phase II After the switching of the 56 non-responders to combination therapy; 30 (60.0% of 50 runners) non-responders to loratadine and two (33.3% of six blockers) non-responders to nasal corticosteroid responded to combination therapy during the second study phase. The combination therapy was significantly effective in the reduction of symptoms except nasal congestion and eye symptoms (Fig. 3).

In total, 62.6% of patients were satisfied at the end of phase I, and 84.0% at the end of phase II. Twenty-four were again classified as non-responders.

Phase III Fourteen patients (70.0% of 20 runners) in the runners group and two patients (50.0% of four blockers) in the blockers group were satisfied with the addition of montelukast

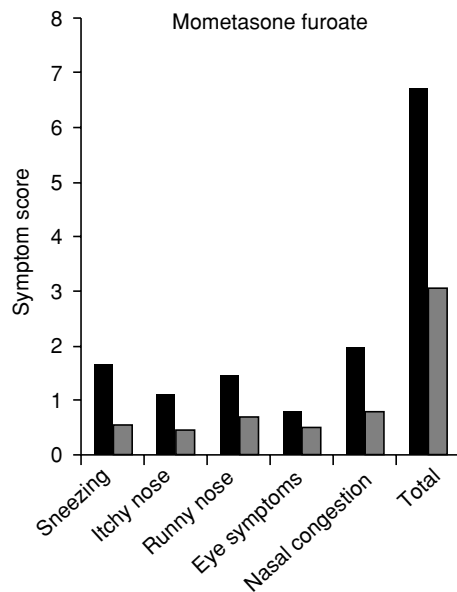


Fig. 2. Symptom scores in patients treated with mometasone furoate. ■, baseline values; ▒, end of first phase.

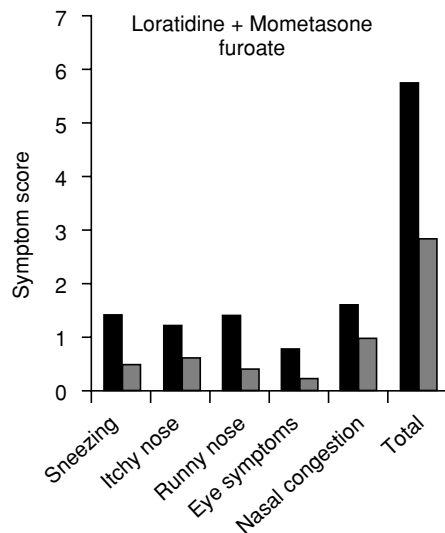


Fig. 3. Symptom scores in second phase. ■, before second phase; ▒, end of second phase.

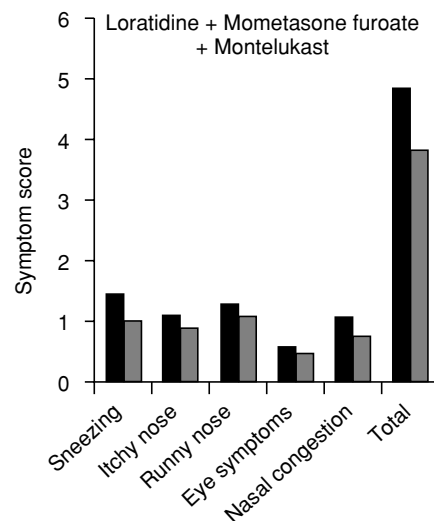


Fig. 4. Symptom scores in third phase. ■, before third phase; ▒, end of third phase.

to the previous two drugs. Sixteen patients (66.6% of 24 patients) were satisfied with the combination of three drugs. Reduction of symptom severity was not significant (Fig. 4).

In total, 10.6% of the whole patients needed the addition of montelukast to their treatment. Six patients in the runners group and two patients in the blockers group (totally 5.3%) remained unsatisfied at the end of study.

Side-effects

Fourteen patients (12.2% of 114 patients) treated with loratadine reported side-effects. In two of them, loratadine was not effective and they were excluded from study, because of severe drowsiness at the end of phase I. Another two patients complained of severe drowsiness but loratadine was evaluated as effective. The reported side-effects were drowsiness (10 patients), headache (four patients), increase of appetite (two patients), xerostomi (two patients), irritability (two patients).

Three patients (0.3% of 92 patients) treated with mometasone furoate reported headache, nasal irritation and bleeding.

Discussion

The efficacy of antihistamines and nasal corticosteroids in SAR are well established. Treatment with the leukotriene receptor antagonists has been reported to be effective in some studies [2, 3], but not effective in others [4–6].

In the present study, loratadine was significantly effective in relieving sneezing, itchy nose, runny nose and eye symptoms, whereas mometasone furoate was significantly effective in relieving sneezing, itchy nose, runny nose and nasal congestion.

The present study was designed to measure the efficacy of step-wise treatment and the satisfaction of the patients, and to evaluate the efficacy of an alternative drug if the patient did not respond to the mainstay therapies. At the end of phase I, 62.6% of the patients, treated with symptom-based treatment modality, were determined to be satisfied with their therapy and were not switched to combination therapy.

A total of 84.0% of the patients were satisfied at the end of phase II. Combination therapy was significantly efficacious on sneezing, itchy nose and runny nose. This result suggests that, non-responders to monotherapy may respond to the combination therapy. Thus, more than one drug may be tried in SAR, if the first step fails.

According to results of present study, 66.6% of patients with SAR, not responding to combination therapy, may be treated with the supplement of leukotriene antagonist. In other words, 10% of patients with SAR may need leukotriene antagonist for their symptom relief. Only 24 non-responders were studied in this manner, and there was no statistical difference in respect to symptom relief.

It was reported that leukotriene receptor antagonists are primarily effective on nasal congestion [2, 3]. Since there were only four blockers in phase III, it was not possible to evaluate the effect on nasal congestion in this study.

Concomitant use of montelukast and loratadine in the treatment of SAR has been found to improve the SAR symptoms and quality of life significantly compared with placebo and each agent alone. Montelukast alone and loratadine alone have been found to cause modest improvements in rhinitis end-points [7].

In studies where patients are not blinded to treatment, it is possible that patient bias may have had some impact on efficacy results [8]. To reduce the impact of patient bias, the decision to change medication was a patient and physician consensus made after reviewing patient symptoms and examination at the beginning of next phase.

The methodology of this study paralleled the clinical treatment of SAR. In clinical practice, patients and physicians may change therapies after an initial period or use a second medication for relief of symptoms. The patients' preference of one drug over another depends on a combination of effects and side-effects [9]. On the other hand, the effectiveness of a drug on symptoms of SAR does not mean that the patients were satisfied [10]. The present study classifies patients as satisfied or unsatisfied, thus achieving an overall estimation of the efficacy of the drugs. This may aid in the selection of the appropriate drug for individual patients.

In the clinical decision making process, the physician must consider factors relating to a patient's quality of life and learn the extent to which symptoms affect the patient [11].

In conclusion, it may be stated that the selection of a drug may be based on the predominating symptoms in patients with SAR, and a leukotriene receptor antagonist may be tried in

patients who do not respond to mainstay therapies. To use antileukotrienes routinely may increase the cost of treatment unnecessarily.

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