

Efficacy of Montelukast and Loratadine as Treatment for Allergic Rhinitis in Children

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SUMMARY The objective of this study was to compare the effectiveness of montelukast combined with loratadine once daily to loratadine alone for a 2-week treatment course of allergic rhinitis in a randomized, double-blind placebo controlled trial which enrolled 115 children, 6-15 years old. The patients were randomly assigned to receive montelukast and loratadine (treatment group) or placebo and loratadine (control group). The primary outcome was the mean percent change of the total daytime nasal symptom scores (PDS) and secondary outcomes were the mean percent changes of the nighttime nasal, daytime eye and composite symptom scores (PNTS, PES, PCS), as well as the nasal secretion, turbinate swelling and nasal congestion scores (PNSS, PTSS, PNCS). There were no significant differences in the PDS of the 2 groups. The change in the night time nasal congestion score (PNTS-congestion) was higher in the treatment group, but not statistically significant ($p = 0.077$). Only the mean percent change in decreased turbinate swelling was significantly greater in the montelukast and loratadine group than the loratadine alone group (-22 ± 7 vs. -1 ± 5 , $p < 0.05$).

The management of allergic rhinitis (AR) includes environmental control measures and pharmacotherapy. Specific therapies consist of oral and intranasal corticosteroids (INCS), cromolyn, anticholinergics and immunotherapy. INCS are the most potent medications and are now considered to be the first line therapy for moderate to severe cases of AR.¹

A persistent nasal blockage in AR after antihistamine treatment may be attributable to nasal mucosal engorgement induced by cysteinyl leukotrienes (Cyst-LTS).² Leukotriene levels are increased in the early as well as the late phase of the allergic reaction. Nasal insufflation studies show that both, leukotriene

C₄ (LTC₄) and leukotriene D₄ (LTD₄) induce an increase in nasal mucosal blood flow and nasal airway resistance.³⁻⁵ Evidence of using leukotriene receptor antagonists (LTRAS) in AR suggests that LTRAS can alleviate daytime and nighttime nasal symptoms but most studies were done on seasonal allergic rhinitis (SAR) and adult patients.⁶⁻⁹

There are few data on perennial AR in children. LTRAS and H₁ antihistamines have different

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mechanisms of action which may give possible additive effects or different patterns of response to individual symptoms. Theoretically a combination therapy could provide enhancing and complementary effects. The link between asthma and AR is well established. Evidence suggests that inhaled beclomethasone significantly reduces growth in asthmatic children after one year of use.^{10,7,11} To avoid this side effect of corticosteroid (CS), LTRAS which are effective for both asthma and AR may play an important role in the treatment of children.

MATERIALS AND METHODS

Study design

This randomized, placebo-controlled trial (with a 1-week, single-blind run-in period and a 2-week, double-blind treatment period) was conducted between July 2002 to October 2003 at the outpatient clinics of Thammasat Chalerm Prakiat Hospital, Thammasat University and Siriraj Hospital, Mahidol University. Clinic visits were scheduled at screening (visit 1), after a 7-day single-blind run-in period (visit 2), and after 2 weeks of treatment according to randomization (visit 3). During the run-in period patients received only Tripolidine HCl and pseudoephedrine HCl as needed to relieve symptoms. During the randomization period patients were randomly allocated using block randomization to receive loratadine 5 mg if the patient's weight was < 30 kg, 10 mg if the patient's weight was \geq 30 kg and montelukast 5 mg (Singulair, Merck)^{8,12,13} in the treatment group or loratadine and placebo in the control group once daily at bedtime for 2 weeks. The Montelukast and placebo tablets were identical in odor, taste and aroma. The medical compliance was determined from the returned tablet count. A physical examination for nasal secretion and turbinate swelling was also done at each visit.

The study protocol and informed consent were reviewed and approved by the Ethics Committee of Thammasat University before study initiation, and written informed consent was obtained from a parent or guardian of each patient.

Patients

Children 6 to 15 years old with a clinical history of perennial AR for at least 1 year and a positive

skin test to at least 1 of 8 allergens (Bermuda, Johnson, Cat Pelt, Dog Epithelium, *Dermatophagoides pteronyssinus*, *D. farinae*, American cockroach and German cockroach) and/or a typical nasal cytology for AR were eligible for the study. Study exclusions included acute asthmatic attacks, upper respiratory tract infections and sinusitis diagnosed by physical examination and/or nasal cytology without using paranasal sinus X-rays.

Medications that were prohibited prior to the study included: nasal or inhaled corticosteroids within 2 weeks, oral corticosteroids within 1 month, cetirizine, ketotifen, oral or inhaled long acting beta agonists or inhaled anticholinergics within 1 week and loratadine or fexofenadine within 72 hours.

Daily rhinitis diary card

Recorded on the daily diary card, the allergic rhinitis and conjunctivitis symptoms were assessed on a 4-point scale (0 to 3) for both daytime (diary card completed in the evening) and nighttime (diary card completed on awakening). The daytime and nighttime questions pertaining to the nasal (rhinorrhea, itching, sneezing and congestion) and eye (tearing, itching, redness and puffiness) symptoms and their rating were described to every patient by the same technician. The ratings of the symptoms were: 0 = not noticeable; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms. The rating had to be performed by the same person every day, either the patients themselves or the same caregiver to increase credibility of the subjective scale. Each dose of Tripolidine HCl and pseudoephedrine HCl was scored as scale 2 and was included in the total daytime nasal symptom scores of the run-in and randomization periods. Patients had to record a level of total daytime nasal symptoms of at least 42 out of a maximum 84 score during the 7-day single-blind run-in period to be eligible for randomization.

Safety evaluation included physical examinations and monitoring for adverse experiences and complications, using non-leading questions throughout the study.

Outcome measurements

The primary outcome was the mean percent change of the total daytime nasal symptom scores

(PDTS), defined as the total score of four daytime nasal symptoms.

The secondary outcomes were the mean percent changes of the nighttime nasal symptom scores (PNTS), daytime eye symptom scores (PES), composite symptom scores (PCS) (total score of day and nighttime nasal symptom score), nasal secretion (PNSS) turbinate swelling (PTSS), and nasal congestion scores (PNCS). The criteria for the physical examination scores were: scale 0 represented not noticeable; scale 1 represented minimal or mild; scale 2 represented moderate; scale 3 represented numerous or severe secretion and swelling, with subsequent congestion.

The credibility of the nasal examinations of the subjects in each center was markedly enhanced by the single-observer design of this trial for every patient, which eliminated the inter-observer reliability issue.

Sample size and statistical analyses

The study was designed to have 80% power of detection (two sided test and α -level of 0.05) of a difference between the two groups of a 25% change from the baseline daytime nasal symptom scores. This required 43 patients in each treatment group to complete the study. Efficacy analysis included all randomized patients who had at least one post-treatment assessment and a medication compliance \geq 80%.

Nominal variables were compared with Chi-square analysis or the Fisher exact test. The Student-unpaired- t test was used for comparison of group means for normally distributed data and the Mann-Whitney u test was used for non-normally distributed data.

RESULTS

Patients

Of 268 screened patients, 178 (66.4%) patients were enrolled in the run-in period. Absence of reactivity to 1 or more allergens and infection were the most common reasons for excluding patients from the run-in period. One hundred and fifteen (42.9%) patients had a score \geq 42 and were randomized into two groups; 13 patients were withdrawn from the study due to protocol deviations, loss to fol-

low up or infection. The rates and reasons for withdrawal were similar among the two groups. The patient baseline characteristics (Table 1) were also similar in the two groups.

Efficacy

Concomitant montelukast and loratadine use in the treatment group significantly ($p < 0.05$) improved turbinate swelling (PTSS) compared to placebo and loratadine (Fig. 1).

The treatment group also had greater improvements in the nighttime nasal symptom scores particularly in the nasal congestion symptom score but there was no statistically significant difference ($p = 0.077$) (Fig. 2). PDTS, PNTS, PES, and PCS ex-

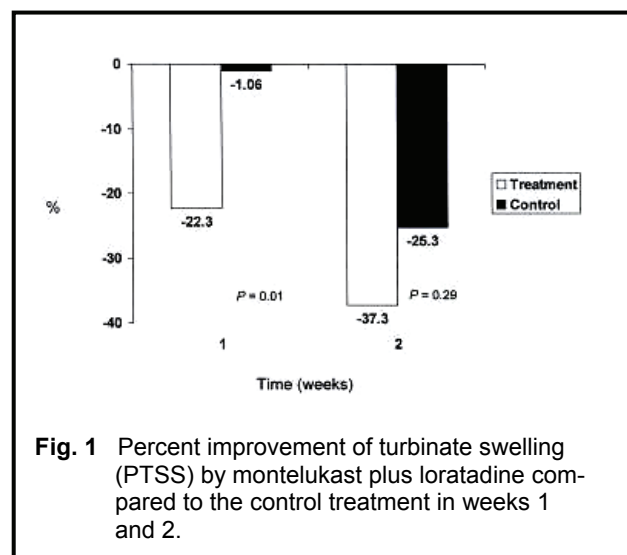


Fig. 1 Percent improvement of turbinate swelling (PTSS) by montelukast plus loratadine compared to the control treatment in weeks 1 and 2.

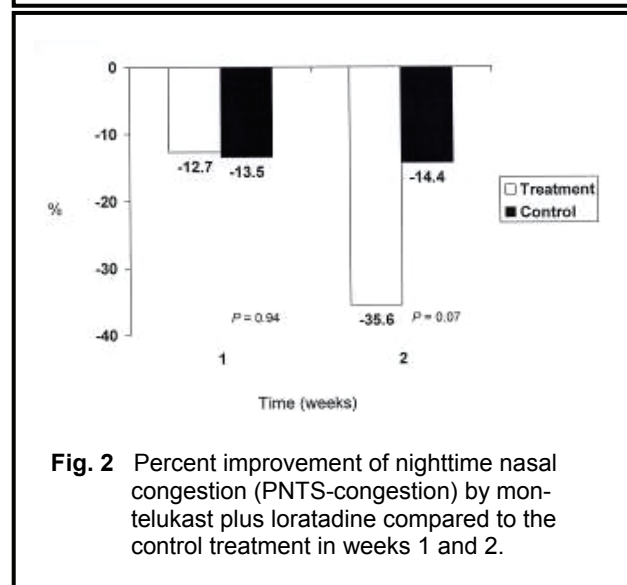


Fig. 2 Percent improvement of nighttime nasal congestion (PNTS-congestion) by montelukast plus loratadine compared to the control treatment in weeks 1 and 2.

perienced greater changes in the treatment group after the 2-week therapy period but the results were not significantly different.

DISCUSSION

A study of 1,620 adult patients with SAR performed in the year 2000 revealed that montelukast was significantly better than placebo in daytime nasal symptoms score (DTS) and nighttime symptom scores (NTS).⁹ The spring 2000 and 2003 study demonstrated that montelukast improved DTS and

NTS in SAR patients compared to placebo.^{7,14} Philip *et al.*¹⁵ and van Adelsberg *et al.*¹⁶ studied the effectiveness of either montelukast or loratadine alone compared to placebo for seasonal allergic rhinitis in adult patients. They reported a significant improvement of daytime and nighttime nasal symptoms for either agent compared to placebo. Meltzer *et al.*⁸ enrolled 460 adult seasonal allergic rhinitis patients and randomly gave montelukast 10 or 20 mg, loratadine 10 mg, montelukast 10 mg with loratadine 10 mg or placebo once daily in the evening for 2 weeks. They found a significantly greater improvement in daytime

Table 1 Baseline characteristics of the study groups

Characteristics	Control group	Treatment group	p-value
No. patients			
Male	35	39	
Female	24	17	0.19 †
Age, years (mean ± SD)	7.4 ± 3.3	6.6 ± 2.8	0.25 †
Total daytime nasal symptom scores (mean ± SD)	58.9 ± 13.8	61.2 ± 12.7	0.60 *
Nighttime nasal symptom scores (mean ± SD)	40.4 ± 13.2	36.8 ± 14.2	0.29 *
Daytime eye symptom scores (mean ± SD)	10.8 ± 9.9	11.8 ± 11.3	0.46 **
Composite symptom scores (mean ± SD)	79.4 ± 21.4	75.7 ± 24.4	0.70 *
Nasal symptoms, No. (%)			
Rhinorrhea	58 (98.3)	53 (94.6)	0.47 †
Sneezing	53 (89.8)	53 (94.6)	0.27 †
Itching	51 (86.4)	47 (83.9)	0.88 †
Nasal blockage	58 (98.3)	54 (96.4)	0.73 †
Nasal examination, No. (%)			
Boggy blue nasal mucosa	57 (92.2)	50 (89.2)	0.36 †
Nasal secretion	56 (94.9)	51 (91)	0.14 †
Allergic shiner	47 (79.7)	44 (78.5)	0.86 †
Eye symptoms, No. (%)			
Eye swelling	12 (20.3)	12 (21.4)	0.56 †
Tearing	27 (45.8)	17 (30.3)	0.17 †
Itching	42 (71.2)	32 (57.1)	0.24 †
Eye examination, No. (%)			
Hyperemic conjunctiva	21 (35.6)	19 (33.9)	0.58 †
Edema of conjunctiva	8 (13.6)	7 (12.5)	0.89 †
Tearing	21 (35.6)	24 (42.8)	0.38 †
Side effects (run-in), No. (%)	10 (20.3)	11 (19.6)	0.40 †
Side effects (randomized), No. %	2 (5.1)	5 (8.9)	0.50 †
Complications (run-in), No. (%)	0	2 (3.5)	0.19 †
Complications (randomized), No. (%)	1 (1.7)	2 (3.5)	0.58 †
Complications (final), No. (%)	2 (3.4)	2 (3.5)	0.66 †

†Chi-square test

*Student-unpaired- t test

**Mann-Whitney u test

nasal symptoms scores in the concomitant montelukast and loratadine group compared to the placebo or single agent groups but other end points, including individual daytime nasal symptoms (congestion, rhinorrhea, itching, and sneezing), nighttime symptoms, and the composite score were significantly improved only when the combined group was compared to the placebo group. Pullerits *et al.*¹⁷ studied 62 patients in three groups, including nasal glucocorticoid, montelukast, a combination of montelukast and loratadine or placebo. Their results also demonstrated that the combined treatment was significantly more effective than montelukast alone for daytime nasal symptom prevention but for nighttime symptom, neither combined treatment nor montelukast alone provided any significant symptom prevention compared to placebo.

Our study differed from previous trials in the following ways: (1) we enrolled perennial allergic rhinitis patients, (2) the target age group was children, (3) we measured nasal secretion, turbinate swelling and nasal congestion scores. In our study, even though PDTS, PNTS, PES, PCS and PNCS were improved in the loratadine and montelukast group compared to loratadine alone, the improvement was not statistically significant. Only the turbinate swelling improved significantly in the treatment group.

The immediate allergic response in the early phase of an allergic reaction causes symptoms such as sneezing, pruritus and rhinorrhea. Fifty percent of AR patients also exhibit a late phase response which includes nasal congestion.¹⁸ Cyst-LTS have an important role in the late phase reaction by increasing vascular permeability, tissue edema, and mucus secretion, and are involved in inflammatory cell recruitment.^{2,4,19} LTC₄ and LTD₄ are released and measurable in nasal secretions when the mucosa is exposed to allergens. After a nasal challenge with LTD₄ of nonatopic subjects, nasal mucosal blood flow significantly increases. Severe nasal blockage is associated with the increased excretion of urinary leukotriene E₄ (LTE₄). The concentration of LTC₄ in nasal washes is reduced in children with persistent asthma who are receiving montelukast.²⁰ A reduction of the peripheral blood eosinophil count is found consistently during montelukast therapy across studies of AR^{15,21} suggesting that montelukast may have

a systemic benefit on the parameters of allergic inflammation. Although loratadine improved nasal symptoms, it failed to reduce eosinophils.⁷ Newer H₁ receptor antagonists are effective in controlling sneezing, rhinorrhea and pruritus but less so with nasal congestion. Since leukotrienes have the potential to increase nasal congestion by binding to leukotriene receptors on target cells, LTRAS may block the effects of leukotrienes on congestion.¹⁹ This supports our results of greater improvements in nasal congestion and turbinate swelling in the treatment group.

The lipophilicity of first generation antihistamines enabled them to cross the blood brain barrier easily and induce actions in the central nervous system such as somnolence, drowsiness, restlessness and nervousness.²² Newer generation oral H₁-antihistamines are preferred for their favorable efficacy and safety without the sedation, anti-cholinergic effect and cardio toxicity compared to the first generation.¹ Oral decongestants have many side effects such as hypertension, palpitations, restlessness, agitation, tremor, insomnia, headache and dry mucous membranes.¹ No clinically meaningful differences in the incidence of clinical adverse events were apparent among the two groups.

In fact, the frequent co-existence of rhinitis and asthma emphasizes the link between AR and asthma.²³ Patients with AR without bronchial hyper-reactivity exhibit an increased eosinophil activity in both upper and lower airways after nasal²⁴⁻²⁶ or segmental bronchial provocation²⁷ and nasal allergen challenge can induce increased bronchial hyper-responsiveness.²⁸ The same pro-inflammatory mediators such as Cyst-LTS, cytokines, histamine, etc. are involved in both nasal and bronchial inflammations in patients with rhinitis and asthma.²⁹⁻³¹ Simultaneous treatments of AR with nasal steroids and antihistamines significantly decreased emergency room visits and hospitalizations for asthma.¹⁸ INCS have a greater efficacy in keeping with their mechanism of action and their broad anti-inflammatory effects compared to leukotriene receptor antagonist (LTRA) monotherapy or in combination with antihistamines for the control of nasal symptoms.^{17,32,33} No growth studies have evaluated the concomitant use of nasal and orally inhaled CS.¹⁸

In asthma, LTRA have been shown to hold an important role in the treatment of mild to moderate persistent asthma for relieving symptoms, improving lung function, decreasing beta-agonist usage and having a steroid sparing effect.^{2,12,34-38} Considering both efficacy and safety, and taking into account common pathophysiological mechanisms of co-existing asthma and AR, LTRAs represent a rational treatment approach.

The small number of patients was a limitation of our study. More than five percent missing data for turbinate swelling during the 2nd week of treatment was enough to render the results of PTSS for that period insignificant. Further investigation of nasal congestion as an outcome measurement may be useful.

In conclusion, there appears to be a significant complementary benefit for nasal decongestion but not for other symptoms when montelukast and loratadine are co-administered in AR.

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