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# Montelukast Is Not Effective in Controlling Allergic Symptoms Outside the Airways

## A Randomised Double-Blind Placebo-Controlled Crossover Study

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**Key Words**
Allergic conjunctivitis · Allergic rhinitis · Asthma · Atopic dermatitis · Atopic syndrome · Montelukast

**Abstract**
***Background:*** Subjects with atopic syndrome often perceive symptoms from various organs. A single drug that acts on all the syndrome's manifestations would be the ideal treatment. The role of montelukast, a cysteinyl-leukotriene receptor antagonist, is established in treating allergic rhinitis and asthma, but its ability to alleviate atopic symptoms outside the airways is controversial. Our aim was to assess if montelukast could be used to treat all the various symptoms seen in subjects with atopic syndrome. ***Methods:*** A randomised, double-blind, placebo-controlled crossover study on the effect of montelukast in atopic syndrome was conducted during the 2007 pollen season. Forty-five pollen-sensitised subjects who had allergic symptoms from both the upper and lower airways and allergic symptoms outside the airways (conjunctivitis, oral symptoms, eczema and/or urticaria) were recruited. The primary outcome parameter was the allergic symptoms, which were assessed using a questionnaire. Secondary outcome parameters were lower-airway inflammation (exhaled nitric oxide) and the need for rescue medication (inhaled $\beta_2$-agonists and oral antihistamines). ***Results:*** There were no differences between montelukast and placebo treatments in allergic symptoms, in exhaled NO concentration or in the need for oral antihistamines. The need for inhaled $\beta_2$-agonists was significantly lower during montelukast treatment. ***Conclusions:*** Montelukast was not effective in treating allergic symptoms outside the airways in subjects suffering from different manifestations of the atopic syndrome. Based on the current results, montelukast should not be recommended as a general drug to treat all the symptoms of atopic syndrome, but it should be considered as a drug for asthma and rhinitis.



### Introduction

Atopic allergy affects roughly 25% of the population in western countries. Typical manifestations of the atopic syndrome are asthma, rhinitis, conjunctivitis, atopic eczema, and oral symptoms caused by cross-reactivity between pollen allergens and those in fruits or vegetables. Cysteinyl-leukotrienes (cys-LT) are lipid mediators produced by inflammatory cells like eosinophils, basophils, macrophages and mast cells [1]. Cys-LTs play a crucial

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**Table 1.** Outcome parameters during the final week of montelukast or placebo treatment in 45 patients with atopic syndrome

| | Montelukast | Placebo | p value |
|---|---|---|---|
| Symptoms | | | |
| Cough | 0.47 ± 0.12 | 0.39 ± 0.09 | 0.521 |
| Chest tightness | 0.28 ± 0.09 | 0.24 ± 0.06 | 0.657 |
| Blocking of the nose | 1.14 ± 0.14 | 1.14 ± 0.13 | 0.947 |
| Sneezing | 0.75 ± 0.10 | 0.75 ± 0.12 | 0.974 |
| Itching, tearing and redness of the eyes | 0.70 ± 0.12 | 0.66 ± 0.11 | 0.702 |
| Itching of the skin | 0.56 ± 0.11 | 0.63 ± 0.12 | 0.371 |
| Redness or hives of the skin | 0.35 ± 0.10 | 0.35 ± 0.10 | 0.971 |
| Oral symptoms while eating fresh fruits or vegetables | 0.20 ± 0.06 | 0.17 ± 0.04 | 0.522 |
| Sleepiness | 0.53 ± 0.11 | 0.52 ± 0.12 | 0.905 |
| Sleep disturbances due to allergic symptoms | 0.18 ± 0.06 | 0.17 ± 0.06 | 0.937 |
| Headache | 0.17 ± 0.04 | 0.22 ± 0.07 | 0.511 |
| General feeling of sickness | 0.30 ± 0.08 | 0.35 ± 0.09 | 0.579 |
| Mean of scores above | 0.47 ± 0.06 | 0.47 ± 0.06 | 0.956 |
| Rescue medication | | | |
| Antihistamine use, capsules/week | 11.0 ± 2.0 | 10.0 ± 1.6 | 0.525 |
| Inhaled $\beta_2$-agonist use, puffs/week | 1.1 ± 0.5 | 1.8 ± 0.7 | 0.048 |
| Measurement of inflammation | | | |
| Exhaled NO concentration, ppb | 31.6 ± 6.1 | 30.3 ± 5.5 | 0.658 |

NO = Nitric oxide; ppb = parts per billion.

role in the pathophysiology of atopic inflammation in airways and in other tissues. Montelukast, a cys-LT receptor 1 antagonist, is shown to be beneficial in treating allergic asthma and allergic rhinitis, but the role of montelukast in treating other symptoms of the atopic syndrome is controversial [1]. We conducted a randomised, placebo-controlled, double-blind, crossover study to assess the efficacy of montelukast in controlling allergic symptoms in subjects with various manifestations of atopic syndrome.

## Subjects and Methods

*Subjects*

We recruited 61 atopic subjects from our clinic. The patients included were: 18–40 years of age; had a wheal diameter ≥4 mm on skin-prick test for both birch and timothy pollen, and experienced allergic symptoms during pollen season in both upper airways (allergic rhinitis) and lower airways (asthma-like symptoms or diagnosed asthma). In addition, the patients had at least 1 of the following symptoms outside the airways: allergic conjunctivitis; atopic eczema; oral symptoms provoked by vegetables or fruits, or urticaria in allergen exposure (subjects with physical urticaria were not included). The exclusion criteria were: severe allergic symptoms needing regular glucocorticoid-treatment; smoking; other chronic disease or regular drug treatment, and pregnancy.

*Study Protocol*

The subjects were enrolled in the study and a baseline assessment was performed on each in winter 2007 (before the pollen season). After enrolment, the subjects were instructed to contact the study nurse when they first experienced allergic symptoms at the beginning of the pollen season. Those subjects who perceived allergic symptoms were then randomised into 2 groups. One group was treated with montelukast 10 mg tablets (Singulair, Merck Frosst Canada Ltd, Kirkland, Que., Canada) once a day for 3 weeks, and with matching placebo tablets for the next 3 weeks. The other group was treated in the reverse order. Short-acting antihistamine capsules (Benadryl [acrivastine] 8 mg, 1–3 capsules a day; Gödecke GmbH, Freiburg, Germany) and a short-acting inhaled $\beta_2$-agonist (Buventol Easyhaler [salbutamol] 200 μg, 1–4 times a day; Orion Pharma, Espoo, Finland) were allowed as needed.

The primary outcome parameter was the allergic symptoms experienced during the final week of each 3-week treatment period. Each day the subjects recorded the severity of 12 allergic symptoms on a scale that ran from 0 to 3 (table 1). The secondary outcome parameters were lower-airway inflammation, measured by exhaled nitric oxide (NO) concentration, and need for symptom-relieving medication (antihistamine or inhaled $\beta_2$-agonist). The study was approved by the local ethics committee, and all the subjects gave their written informed consent.

*Statistics*

The pre-calculated sample size was 44, based on a power of 90% to detect a treatment effect of at least half the standard deviation of the symptom score (usually considered as 'moderate clinical significance') with an α-error of 5%. All the parameters were normally distributed, and a paired t test was used to compare the outcome parameters between the treatments. The results are presented as means ± SEM.

## Results

Of the 61 subjects recruited before the pollen season, 7 refused to give their consent and 5 did not suffer from noticeable allergic symptoms that year. The remaining 49 subjects perceived allergic symptoms and were thus eligible for randomisation into the 2 study arms. Four subjects dropped out during the treatment: 2 subjects forgot to take the study medication, 1 suffered from sleepiness caused by the rescue antihistamine and 1 subject needed more potent medication for eye symptoms during montelukast treatment. Altogether 45 subjects (33 females, mean age 28 years) completed both treatments. Of these 45 subjects, 5 had prediagnosed asthma, 39 had conjunctivitis, 33 suffered from oral symptoms, 13 had mild-to-moderate atopic eczema and 14 had mild-to-moderate occasional urticaria in allergen exposure. Twenty-two subjects started with montelukast and continued with placebo, while 23 subjects were treated with the reverse order. There were no significant differences in any of the baseline measures (allergic symptoms or exhaled NO concentration) between the group starting with montelukast and the group starting with placebo ($p > 0.18$ for all variables).

*Montelukast versus Placebo*

Between montelukast and placebo treatments, there were no significant differences in the total symptom score, in any of the 12 individual symptoms, in exhaled NO concentration or in the need for antihistamine capsules. The need for inhaled salbutamol was significantly lower during montelukast than placebo treatment (table 1).

## Discussion

There is substantial evidence showing that montelukast is efficacious for the treatment of asthma and allergic rhinitis in children and adults [1]. We found that there was less need for symptom-relieving asthma medication during montelukast treatment, but no difference in lower-airway symptoms between the groups. This might be due to the small number of subjects with real asthma, as the majority had only a history of occasional lower-airway symptoms during pollen season (cough, mild wheezing). However, as the efficacy of montelukast in treating airway disorders is evident, the primary focus of this study was on its effects outside the airways.

Montelukast has been found to be effective in 2 relatively small randomized placebo-controlled studies on treating atopic dermatitis in children [2, 3], but not in larger studies in adults [4, 5]. In addition, there are some case reports and small studies showing a mild effect of montelukast in treating chronic urticaria, but there are also negative studies [6, 7] and the overall evidence is limited [8, 9]. The present study does not suggest a role for montelukast in treating atopic dermatitis or urticaria in adults, as we found no effect of montelukast on these skin manifestations. To our knowledge, this is the first study assessing the effect of montelukast on allergic oral symptoms, and the current negative result does not support the use of montelukast in treating this disorder either.

The 2007 pollen season was mild in Finland, with the mean birch pollen level in Helsinki being 15% of the long-term average and hay pollen levels of 45%. The mild pollen season could partially explain the negative effect of montelukast in this study, although the subjects eligible for randomisation and treatment did perceive symptoms and also needed antihistamines and/or inhaled $\beta_2$-agonists.

In conclusion, montelukast was not effective in treating allergic symptoms outside the airways in subjects suffering from different manifestations of the atopic syndrome. Based on the current results, montelukast should not be recommended as a general drug to treat all the symptoms of atopic syndrome, but it should be considered as a drug for asthma and rhinitis.

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