

The effect of montelukast on allergen-induced cutaneous responses in house dust mite allergic children

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The benefits of a leukotriene modifier on allergen-induced cutaneous responses have not been studied in children. We hypothesized that a leukotriene-receptor antagonist would provide protection against allergen-induced early and/or late phase cutaneous responses in susceptible children. In a randomized, double-blind, placebo-controlled, cross-over study in 6- to 15-year-old house dust mite allergic children, we compared the benefit of either montelukast or a matching placebo for 2 days on cutaneous responses induced by intradermal injection of house dust mite extract. Responses were measured as the mean of the longest diameter and its longest perpendicular of the induration response after 10, 20 min, 4 h and 6 h of the challenge. A total of 30 children were randomized to placebo or montelukast. The mean decline from baseline was significantly greater ($p = 0.04$) in the montelukast-treated children [-5.20 mm (-12.03 – 1.63)] [median (95% CI)] than in the placebo-treated children [0.13 mm (-6.46 – 6.73)] at 6th hour of the challenge, as was the mean diameter ($p = 0.04$), but did not differ in the remaining time points. We concluded that in house dust mite allergic children, montelukast 5 mg provided significant improvement in allergen-induced cutaneous late-phase responses, suggesting its contribution to allergic skin responses and its potential therapeutic value.

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Allergen challenge in susceptible asthmatic individuals invokes an early allergic response induced by the release of preformed 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 approximately 60–80% of early phase and 50–60% of late phase bronchoconstrictive responses to allergen are 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). Montelukast, a cysteinyl-leukotriene receptor antagonist (LTRA), was recently

approved for clinical use in the treatment of chronic asthma and clinical studies demonstrated its effectiveness in a broad range of asthmatic children (3–7).

We hypothesized that compared with placebo, montelukast 5 mg would inhibit allergen-induced early and late phase cutaneous allergic reactions in children and this was tested in a randomized, double-blind, placebo-controlled, cross-over study. Our observations form the basis of this report.

Methods

The Hacettepe University Ethical Review Committee approved the protocol for this study and written informed consent was obtained from each parent or guardian.

Study design

In a randomized, double-blind, placebo-controlled, cross-over study, we examined the effect of montelukast 5 mg/day for 2 days on cutaneous responses induced by intradermal injection of house dust mite extract in 30 susceptible 6- to 15-year-old children. The study consisted of three visits with at least 7-day washout periods between each of them. During visit 1, children were evaluated for exclusion and inclusion criteria, for the estimation of the lowest concentration of the allergen, which caused a strong early cutaneous allergic response (ECAR), and late cutaneous allergic responses (LCAR); informed consent was also obtained. During visit 2, eligible children who were randomized to receive either montelukast or a matching placebo once daily at bedtime for 2 days were evaluated with skin tests approximately 12 h after the last dose. After a 7-day washout period, children who received montelukast were treated with placebo, and visa versa and evaluated again with skin tests during visit 3. For safety reasons, FEV_1 was measured before each test and a short interval history was taken with regard to their allergic diseases and potential adverse effects of medications. Compliances were checked through counting the tablets in containers during visits 2 and 3.

Inclusion and exclusion criteria

Children aged 6–15 years who were in good health except for asthma and/or allergic rhinitis were included in the study. In order to be eligible, they needed to have ECARs and LCARs to *Dermatophagoides pteronyssinus*, a greater value of pre-bronchodilator FEV_1 than 70% of the predicted value and give informed consent. They were excluded if they had any acute or chronic illness in addition to their allergic disorders, used any antihistamines or oral corticosteroids within the past month, had a history of previous immunotherapy, had any systemic symptoms after skin tests or had a history of adverse reactions to any antihistamines or leukotriene-receptor antagonists.

Skin test procedures

During the first visit, participants were tested with four different concentrations (25, 50, 100, 200 AU/ml) of *D. pteronyssinus*, to find the lowest concentration of the allergen, which caused strong (>10 mm) early and late allergic responses, measured as the mean of the longest diameter and its longest perpendicular of the induration.

This concentration was used for further tests and all tests were applied intradermally on the volar surfaces of left forearms with a negative and a positive control on right forearms using saline and histamine phosphate, respectively. On each of the three different 6-h test days, at pretreatment baseline and approximately 12 h after the last dose in each 2-day course of montelukast or placebo, at 08.00 hours, each participant had an identical set of intradermal tests. Responses were evaluated by tracing the circumferences with a ballpoint pen at 10 min, 20 min, 4 h, and 6 h, and transferred to paper using transparent tapes. The study endpoint was the absolute change in mean diameter from baseline.

Statistical methods

Analyses of treatment effects were done using two-tailed paired *t*-tests with 0.05 as the level of significance. Central tendency was expressed by the mean and 95% confidence interval (95% CI). Additionally, the presence of the differences between the three groups (baseline, montelukast and placebo) at different time points of observation were investigated using repeated measures analysis of variance (RM-ANOVA).

Results

Patient demographics

A total of 31 house dust mite allergic children with asthma and/or allergic rhinitis were included in the study. One child was withdrawn before randomization because of noncompliance. The remaining 30 children completed the study and were included in the primary efficacy analyses. Patient characteristics are summarized in Table 1.

Table 1. Characteristics of the study group

	Study group
Number	30
Age* (years) (range)	10.2 ± 2.0 (6–15)
Sex (girl/boy)	10/20
FEV_1 * (% predicted) (range)	93.7 ± 8.8 (73–109)
Concentration of <i>D. pteronyssinus</i> † (number)	
25 AU/ml	2
50 AU/ml	17
100 AU/ml	4
200 AU/ml	7

*Mean ± standard error of the mean.

†Concentration of the antigen that causes strong (>10 mm) early and late cutaneous allergic responses.

Efficacy

In two of the 30 randomized children, more tablets were used than required for the treatment period. These were accounted for by the patients as being lost. The absolute changes in mean diameter from baseline between the placebo and the montelukast groups were not significant at 10 and 20 min and 4 h ($p = 0.677$, $p = 0.312$ and $p = 0.332$, respectively) (Fig. 1). At 6 h, montelukast caused significant decreases of -5.20 mm (-12.03 – 1.63 , 95% CI) compared with 0.13 mm caused by placebo (-6.46 – 6.73) ($p = 0.04$). Group comparisons showed that there were no significant differences between the three groups (baseline, placebo and montelukast) at 10 and 20 min and 4 h (Fig. 2). There was a trend in difference between the three groups at 6 h ($p = 0.144$). At this time point, paired comparisons showed a significantly lower value with montelukast [18.30 (13.41 – 23.19)] compared with placebo [23.63 (17.92 – 29.35)] ($p = 0.04$) and a trend of a lower value compared with baseline measurements [23.50 (18.0 – 29.0)] ($p = 0.13$).

The histamine response was not different with regard to the mean diameter and the absolute change from baseline. There were no significant

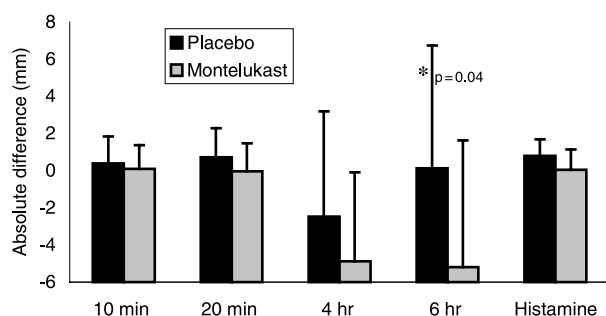


Fig. 1. Absolute difference in mean diameters compared with baseline. Bars and upper end of error lines denote mean values and 95% upper confidence limits, respectively.

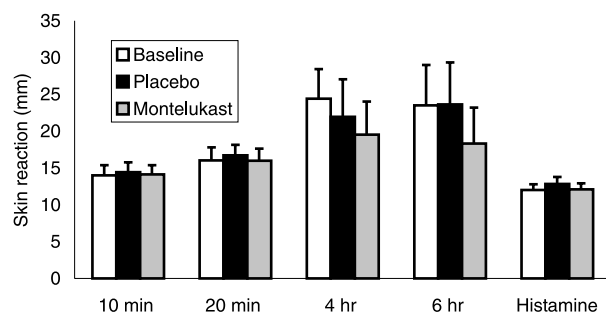


Fig. 2. Mean diameters of induration responses to allergen. Bars and upper end of error lines denote mean values and 95% upper confidence limits, respectively.

differences between the montelukast- and placebo-treated children with regard to the numbers of adverse events observed.

Discussion

This controlled study provides the first *in vivo* clue that a 2-day treatment with a cysteinyl-leukotriene-receptor antagonist, montelukast, may ameliorate the allergen-specific late phase allergic skin response. Although this effect was slight, it supports indirectly the previous *in vivo* and *in vitro* findings that leukotrienes contribute to the cutaneous allergic reactions (1, 2, 8–12).

Experimental data from the previous studies strongly support the view that the pathophysiology of allergic diseases 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. Further similarities come from responsiveness to corticosteroid therapy. Despite the similarities in the inflammatory process between allergic disorders, there are notable differences in the pathology of the diseases and in clinical disease expression. It is widely believed that these mostly come from the differences in the effector organs.

Leukotrienes are produced and released from inflammatory cells, including eosinophils and mast cells. Studies using compounds that block the effects of leukotrienes have demonstrated reduction of early and late phase asthmatic responses to allergen (1, 2). Although it is widely believed that the same mechanism takes place in allergen-induced cutaneous responses, a previous adult study reported that montelukast failed to inhibit early and late phase cutaneous allergic responses (13). We have conducted our study in children using a similar model and observed a reduced response during the late phase with regard to absolute change in mean diameter and a trend of decreased mean diameter, which indicates a slight but significant contribution of leukotrienes in allergic skin responses. Compared with that previous adult study, in our study skin responses to allergen were more reproducible as there were no significant decreases with the placebo treatment. Although this may partly be suggested as the possible reason for the differences between the two study results, we think that the different study populations, as appeared repeatedly in asthma studies, may be another

possible explanation. Furthermore, another possibility that requires further attention is the different degrees of contribution of leukotrienes in allergic cutaneous responses in children compared with adults.

The inhibitory effect of montelukast was only marked at the 6th hour but not at the 4th hour of the challenge. We think that may be partly explained by the presence of varying kinetics of leukotriene release during late phase responses in different time points or by an accelerative effect of leukotriene modifiers on the recovery of the late phase response. Unfortunately our study design does not allow for a definitive conclusion.

Like the previous adult study (13), we did not detect any inhibitory effect of montelukast on cutaneous early responses and this supports the view that there is no need to withhold LTRAs before allergen skin testing. However, our results and of course the previous findings do not exclude the contribution of leukotrienes in early phase responses as has been repeatedly shown in *in vivo* studies previously.

We studied a group of patients with strong early and late cutaneous responses in order to achieve more reproducible results. However, excluding patients with milder responses might have caused a bias. Furthermore, inflammatory cells such as mast cells and eosinophils are believed to be the main sources of leukotriene biosynthesis that might indicate augmented leukotriene release in the presence of tissue inflammation. Therefore one can speculate for a more obvious inhibitory effect of leukotriene modifiers in patients with inflammatory skin diseases. Recently, the effect of adjunct montelukast treatment was tested in 15 children with moderate to severe atopic dermatitis and a statistically significant improvement in the severity of the eczema was reported (14). However, further investigations with a larger sample size are required to clarify this issue.

In conclusion, the results of our study support the contribution of cysteinyl-leukotrienes in allergic skin reactions and additional studies are required to characterize further optimal conditions for the use of leukotriene modifiers in allergic skin diseases.

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