

MONTELUKAST TREATMENT IN CHILDREN WITH MODERATELY SEVERE ATOPIC DERMATITIS

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Running Title: Montelukast. Children. Moderate Severe. Atopic Dermatitis

Key Word: Montelukast. Children. Moderate Severe. Atopic Dermatitis.

Abbreviations: AD: Atopic Dermatitis, ADSS: Atopic dermatitis severity score, LT: Leukotriene, LTR: Leukotriene receptors, LTRA: Leukotriene receptors antagonists.

Background: Moderately severe atopic dermatitis makes up nearly one-fifth of children with atopic dermatitis.

Objective: To determine the clinical and laboratory effects of montelukast in moderately severe atopic dermatitis.

Methods: Randomized, double-blind, placebo-controlled, crossover trial with washout period, conducted from May 2002 to February 2006. The study involved 25 patients, 2-16 years old with dermatitis. Patients received oral montelukast (9 patients, Group B) or placebo (16 patients, Group A) in phase 1, and were crossed over to placebo or montelukast, respectively, for phase 2. Patients included if >10% of skin was involved and failed response to 2 week conventional treatment. Itching, sleep disturbance, frequency of use of oral antihistamines & topical steroids, severity scores were serially assessed. In addition, eosinophil and serum IgE were serially collected.

Results: Most of patients were 6-10 years of age. Both groups had comparable gender distribution. The patients in Group B were more likely to have a history of bronchial asthma (55.6%) or allergic rhinitis (33.3%) than patients in Group A, but were less likely to have a positive history of atopy. While on montelukast, there was a reduction of mean score for itching in phase 2, for sleep disturbance in phase 2, for antihistamines in phase 1, for extent-of-disease in phase 1 and 2, and for severity score in phase 2 and blood eosinophil & IgE in phase 2.

Conclusion: Montelukast reduces itching, sleep disturbance, disease extent and severity, blood eosinophil count and serum IgE.

INTRODUCTION

Atopic dermatitis [AD] is a chronic, relapsing, inflammatory disorder of skin that occurs in all age groups, but more common in children (1). Its occurrence is associated with other atopic disorders and usually occurs in persons with positive personal (2), or family history of atopy (3). While about 80% of these cases are mild in severity (4), at least 20% of cases are moderate-to-severe (5). Severe atopic dermatitis prolongs duration of disease (6), negatively affects quality of life (7), increases medical cost (8), and even affects child's growth (9). The refractoriness to treatment of moderate-to-severe AD poses a challenge to the treating physician and exerts a psychological burden to the patient or his/her family. This has prompted a continuous search for more effective and novel types

of treatment of moderate to severe AD in the last few years (10, 11.) The objectives of the present study were to determine in children with moderately severe AD if daily oral montelukast is 1) clinically effective in relieving itching and sleep disturbance 2) reduces daily use of oral antihistamines and topical steroids; and 3) if it decreases serum IgE and absolute eosinophil count.

METHODS

Subjects

The present study included 25 patients (9 males and 16 females), 2 to 16 years of age, with moderate-to-severe AD, with or without allergic rhinitis and or asthma who failed to respond to conventional therapy. Patients were consecutively recruited from the allergy-immunology clinics at the Hamad Medical Corporation. The study was approved by the Research Committee of the Hamad Medical Corporation. All patients fulfilled the criteria of Hanifin and Rajka for the diagnosis of AD (12).

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Study Design

The study was a 12-week randomized double blind, placebo-controlled trial with a crossover, and 2-week washout period periods from May 2002 to February 2006. Patients were randomized to either arm of the study: 16 patients were assigned to receive placebo for 4 weeks, then montelukast for 4 weeks (Group A), and 9 to receive montelukast for 4 weeks then crossed to placebo (Group B), as in Fig. 1. Each patient acted as their own control. The study comprised 6 clinic visits spaced 2 weeks apart: the baseline visit was for screening and run-in, the first for allocation randomization, and the second and the third to collect efficacy and safety data. During the fourth visit each patient was crossed-over to the other arm of the study. The fifth and sixth visits were for collection of efficacy and safety data.

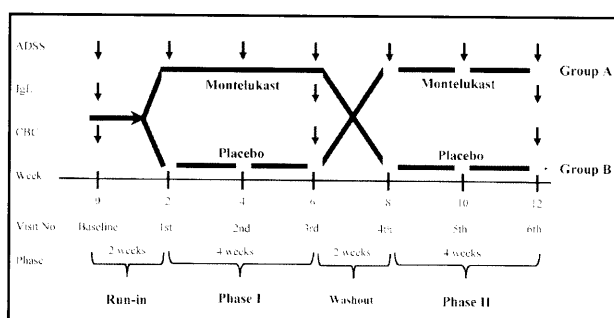


Figure 1: Study scheme showing clinic visits. The study was 12 weeks, randomized, double blind, placebo controlled trial with crossover design and 2 week washout after 6th visit. Clinical examination & ADSS were conducted each visit. Blood was sampled for CBC (including eosinophil) and total serum IgE in all subjects on weeks numbered 0, 6, and 12 as indicated.

The diagnosis eczema was set, using the Hanifin and Rajka criteria as described Previously (12). At each clinical visit the eczema was evaluated with the SCORAD (Severity Scoring of Atopic Dermatitis) (13), a standard index for assessing eczema. The children were classified to have mild (SCORAD <25); moderate (SCORAD 25-50); or severe (SCORAD >50) eczema. During the study, each child was evaluated by the same investigator during to reduce the inter-observer variability.

The studied subjects were patients with SCORAD >25, and who failed to respond to conventional treatment (i.e. when indicated, moisturizers, oral cetirizine, topical mometasone 0.1% cream, and oral clarithromycin allergen avoidance when necessary).

All patients or their legal guardians gave an informed written consent after the purpose, risks, and potential benefits of the study were explained to them.

The patients who had current pyoderma, or who were on any one of the following medications such as oral

corticosteroids, ketotifen, montelukast, zafirlukast, calcineurin inhibitors, or zileuton within 2 weeks of enrollment or had a history of allergic reactions to one of LTRA were excluded from the study. Nasal medications for allergic rhinitis and inhaled asthma medications were permitted provided that the dosage was unchanged during the trial.

Randomization was done by pulling one of 2 sealed envelopes with either group A or group B inside. The hospital pharmacist did coding both drugs. Montelukast 5 mg tablets and placebo of identical appearance were supplied by Merck Inc. & Laboratory. Each patient received montelukast 5mg (one 5 mg tablet for children <12 years, and two tablets for older children) and matching placebo for 28 days.

During the screening period, each patient provided a complete history and a comprehensive examination was performed. Blood was collected for eosinophil count, total serum IgE, and specific IgE levels (by UniCAP, Pharmacia CAP System) for a panel of common allergens including *D. pteronyssinus*, *D. farinae*, milk, soy, wheat, fish, eggs, and peanut. Each patient was educated on AD and its skin care, and remained on conventional treatment for 2 weeks. Efficacy assessment was done through Daily Symptoms and Medication Cards completed by each patients throughout the study.

Comparisons of AD clinical and severity scores, and laboratory data were performed with the non-parametric Wilcoxon's rank sum test for the non-paired samples. Chi-square and Fisher exact tests analysis was performed to test for differences in proportions of categorical variables between two or more groups. The level $p < 0.05$ was taken as the cutoff value for significance.

RESULTS

Table 1 shows the socio-demographic characteristics of the studied subjects by the group A with placebo and group B with montelukast. Increasing scores of itching sleep disturbance, and ADSS indicate clinically worsening AD, while decreasing score indicate AD improvement. Likewise, higher scores of oral antihistamines and topical steroids indicate deteriorating AD, while lower indicate less need for medications to control AD. Montelukast was well tolerated by all patients.

Table 2 presents the clinical history of allergy by group A with placebo and group B with montelukast. The patients in group B were more likely to have a history of bronchial asthma (55.6%) than the patients in group A (37.5%). Family history of allergy was comparable in both groups. Each subject acted as their own control.

	Group A*	Group B*	P-value
Number of patients	16	9	
Sex			
Male	8(50%)	5(55.6%)	0.790
Female	8(50%)	4(44.4%)	
Ages(years)			
2-5	7(43.8%)	3(33.3%)	0.847
6-10	7(43.8%)	5(55.6%)	
11-16	2(12.5%)	1(11.1%)	

Table 1: Socio-Demographic Characteristics Of The Studied Subjects By Groups.

* Group A began with placebo then crossed over to montelukast.

* Group B began with montelukast then crossed over to placebo.

Score	Group A*	Group B*	P-Value
Itching Score			
Phase 1	26.94±6.06(P†)	27.89±7.13(M)	0.887
Phase 2	16.63±4.06(M†)	29.11±5.22(P)	0.066
Sleeping Disturbance			
Phase 1	16.81±4.54(P)	21.67±7.60(M)	0.569
Phase 2	9.88±3.61(M)	18.44±6.40(P)	0.279
Antihistamine Use (Avg. Times/Day)			
Phase 1	0.68±0.14(P)	0.69±0.17(M)	0.887
Phase 2	0.60±0.13(M)	0.80±0.10(P)	0.329
Topical Steroids Use (Avg. Times/Day)			
Phase 1	0.72±0.14(P)	0.78±0.25(M)	0.865
Phase 2	0.72±0.15(M)	0.99±0.30(P)	0.581
AD Extent of involvement Score			
Phase 1	24.35 ±2.38(P)	15.93±4.36(M)	0.079
Phase 2	15.00±2.34(M)	26.43±5.05(P)	0.070
AD Severity Score			
Phase 1	52.81±5.50(P)	53.59±18.00(M)	0.365
Phase 2	45.77±7.38(M)	69.11±12.(P)	0.126

Table 3: Clinical and Drug use of Group A and Group B.

*Group A began with Placebo then crossed over to Montelukast.

* Group B began with Montelukast then crossed over to Placebo.

† M – Montelukast.

P - Placebo.

All patients completely finished the various phases of the study.

Table 3 shows the clinical drug use Montelukast of the group A versus placebo group B. No statistical significant difference was found between the groups for each outcome variable.

Table 4 shows the laboratory data of peripheral eosinophil count and serum IgE concentration. While on montelukast, there was a decrease in mean scores for absolute eosinophil count for serum IgE .

Variable	Group A	Group B	P-Value
Number of patients	16	9	
Bronchial asthma	6 (37.5%)	5(55.6)	0.383
Allergic Rhinitis	5 (31.3%)	3(33.3)	0.92
Food Allergy	1(6.2%)	0(0.0)	

Table 2: Clinical History Of Allergy By Group.

* Group A began with placebo then crossed over to montelukast.

* Group B began with montelukast then crossed over to placebo.

	Group A* Geometric Mean	Group B* Geometric Mean	P-Value
Absolute Eosinophil Count(cells/μl)			
Phase I	437.5	602.2(M)	0.306
Phase II	306.8(M†)	564.6(P)	0.225
Serum IgE(IU/dl)			
Phase I	268.7(P)	513.8(M)	0.612
Phase II	389.9(M)	514.3(P)	1.00

Table 4: Laboratory Data Of Group A And Group B.

* Group A began with placebo then crossed over to montelukast.

* Group B began with montelukast then crossed over to placebo.

† M – Montelukast.

P – Placebo.

DISCUSSION

Inflammation is an integral feature of atopic dermatitis. LT play some role in this inflammation but their involvement in the inflammatory process is not well defined even in recent literature (14). In spite of this, there is compelling evidence that LT play some role in pathogenesis of atopic dermatitis (15). This has provided a pathophysiological rationale for trials of LTRA in treating atopic dermatitis (16). Most of these trials enrolled adult patients with atopic dermatitis and results seem to be inconsistent, possibly due to several factors.

Yanasei *et al.* (17) studied 8 adults of moderate to severe AD treated with 10mg montelukast in a randomized, double-blind, placebo-controlled crossover trial for 8 weeks. A statistically significant improvement was seen after 4 weeks of treatment. Capella *et al.* (18) compared 10 mg/day, montelukast in 32 adults with moderate to severe AD vs. combined conventional regimen (oral clarithromycin and cetirizine, topical corticosteroids, and hydrating preparation). Reductions of SCORAD were similar in both groups of treatment. Eustachio *et al.* (19) treated 20 adults with 10 mg montelukast in a randomized, double-blind, placebo-controlled study for 6 weeks. In the montelukast group, SCORAD was reduced by 20%, but daytime pruritis and sleep loss combined score was not different from placebo. Angelova-Fischer (20) *et al.*

reported success with montelukast in 2 cases of severe AD, with patients reporting reducing itching, sleep disturbance and clinical signs.

The current randomized, double-blind, placebo-controlled, crossover study is one of few studies to examine the effect of montelukast on a variety of subject and objective and outcome variables in children with moderately severe AD. Compared to placebo, montelukast therapy showed a modest, numerical but not statistically significant decrease, in daytime itching and sleep disturbances without any decrease in the frequency of use of oral antihistamines or topical steroids. This is also supported by Pei *et al.* (21) who studied 15 children with moderate to severe AD in a randomized, double-blind, placebo-controlled, crossover trial using 6 mg daily montelukast for 4 weeks. Montelukast significantly reduced severity score of AD but not the extent of the disease. However, patient subjective score in that study was not different between or within the groups. In contrast, there is still some evidence that montelukast is effective in treating patients with moderate to severe AD (22).

Collectively from these trials and from the current study, it seems that montelukast has some efficacy in reducing "histaminic effects" (itching and sleep loss secondary to nighttime itching) of LT in AD and that this efficacy is additive to, but not alternative to antihistamines.

In this study, there was also modest, but non-significantly decreased severity and extent of atopic dermatitis. This is also reported by Concha del Rio (23) who treated 18 children with 5mg montelukast for a period of 24 weeks. The decrease of disease severity and extent was significant with montelukast in 13 of 18 patients. Other studies did not confirm this decrease in severity or extent of disease (21).

Our study revealed that montelukast has modest effect peripheral blood eosinophil count and serum IgE levels. These are known to be elevated in most patients with atopic AD (24), and that the degree of elevation tends to parallel the extent and severity of the disease in most instances (25). This could be explained by the facts that blood eosinophils are influenced by the presence of AD (26) and that eosinophil count and serum IgE correlate well with some LT generation (27), and montelukast LTRA is a competitive inhibitor of LTR

In spite of its apparent limitation, the relatively small sample size, some strengths of this study include its design and inclusion of antihistamine and steroid usage, and laboratory parameters.

In conclusion, montelukast therapy has modest efficacy in reducing daytime itching, sleep disturbance, severity scores, eosinophil counts and serum IgE levels. It seems that montelukast could be used as an adjunctive therapeutic agent in these cases.

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New reports in the May issue of **Annals of Allergy, Asthma & Immunology** include studies on:

■ **Role of cigarette use in the epidemic of asthma in children. See NEWS RELEASE below. Original article:** "Environmental Tobacco Smoke and the Epidemic of Asthma in Children: the Role of Cigarette Use" – Renee D. Goodwin, Ph.D, MPH, Columbia University, New York, N.Y. Parallel increases in childhood asthma and cigarette use among adults during the past century in the United States identified by an investigator at Mailman School of Public Health suggests that the increase in cigarette use may be a contributing factor to the rise in asthma among children. *This work was supported by National Institutes of Health grant from NIMH and grant from NIDA.*

■ **Maternal smoking and obesity greater risk factors for wheezing in boys than girls. Original article:** "Risk Factors for Wheezing in Early Adolescence: a Prospective Birth Cohort Study in Brazil" – Ana M. B. Menezes, Ph.D., Universidade Federal de Pelotas, Pelotas, Brazil; and others. In this study tracking 4,452 adolescents from age 4 to 11, maternal smoking and obesity were associated with an increased risk of wheezing in boys but not in girls. *This analysis was supported by the Wellcome Trust's initiative entitled Major Awards for Latin America on Health Consequences of Population Change.*

■ **Acute pediatric asthma screening for poor short-term outcome. Original article:** "Screening for Poor Short-term Outcome in Acute Pediatric Asthma" – Martha W. Stevens, M.D., MSCE; and others. Between 20 percent and 30 percent of 1.6 million emergency department (ED) visits annually among children younger than 18 years result in hospital admission. Investigators developed and validated a simple risk score that identifies patients at high risk for poor outcome, which would allow interventions to be targeted to a subgroup most likely to benefit. *This work was funded by a grant from the Maternal and Child Health Bureau Research Program.*

■ **Childhood exposure to rodents has protective effect on adult sensitivity. Original article:** "Inverse Association Between Rural Environment in Infancy and Sensitization to Rodents in Adulthood" – Samuel Dorevitch, M.D., MPH, University of Illinois at Chicago, School of Public Health, Chicago. It is not known whether early childhood exposure to hygiene hypothesis factors modifies the risk of sensitization to aeroallergens among adults. This study demonstrates that living in a rural setting during the first year of life is associated with protection from sensitization to rodent allergens in the workplace decades later.

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