

Montelukast in the treatment of children with moderate-to-severe atopic dermatitis: A pilot study

Pei AYS, Chan HHL, Leung TF. Montelukast in the treatment of children with moderate-to-severe atopic dermatitis: A pilot study. *Pediatr Allergy Immunol* 2001; 12: 154–158. © Munksgaard 2001

The primary action of leukotrienes includes contraction of human airway muscle, chemotaxis, and increased vascular permeability, with secondary effects of inhibiting allergen-induced early and late responses. Although there is limited available information and research regarding leukotrienes in atopic dermatitis (AD), there is evidence to support their role in the pathogenesis of the disease. We conducted a pilot study to test the efficacy of montelukast, a cysteinyl-leukotriene-1 receptor antagonist, in 15 patients (6–16 years of age) with moderate-to-severe AD, using a randomized double-blind placebo-controlled crossover study. These patients had chronic moderate-to-severe AD, despite being on conventional therapy. They were randomized either to placebo for 4 weeks and then the study drug for 4 weeks, or vice versa. There was a 2-week run-in period for all participants before commencement of the study, and a 2-week washout before crossover. At enrollment and on each follow-up visit, every patient was assessed by a single observer and objectively scored for disease extent and severity. A subjective score was given for the impact of eczema on daily living. There was statistical improvement in patients on active treatment compared with placebo in the severity of AD ($p < 0.05$). Our findings suggest that leukotriene receptor antagonist as an adjunct treatment has an anti-inflammatory effect on moderate-to-severe AD. A larger trial is needed to ascertain its efficacy fully.

**Ann Yuk Sau Pei¹,
Henry Hin Lee Chan² and
Ting Fan Leung¹**

¹Department of Paediatrics and ²Division of Dermatology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

Key words: atopic dermatitis; T-helper-cell imbalance; cysteinyl-leukotriene-1 receptor antagonist; children

Dr Ann Pei, Department of Paediatrics, 6F Clinical Sciences Building, Prince of Wales Hospital, Shatin, N.T., Hong Kong
Tel.: (852) 2632-2982
Fax: (852) 2636-0020
E-mail: annpei@cuhk.edu.hk

Accepted 2 February 2001

Atopic dermatitis (AD) is a common chronic relapsing pruritic skin disorder of childhood. The pathophysiology is recognized as an interplay of immunological and autonomic abnormalities with environmental allergens and genetic factors (1–4).

Leukotriene receptor antagonists are a relatively new and effective treatment for asthma (5–8) as cysteinyl-leukotrienes have been found to be important mediators in its pathogenesis (9,10). The role of these mediators in AD, however, has not been fully defined. Leukotrienes are released from eosinophils, mast cells, and macrophages (11), interacting functionally in allergic reactions against a background of an imbalance between T-

cell clones and resulting in preferential cytokine production following the T-helper 2 profile (1,2). Leukotrienes are also present in eczematous skin, being produced by peripheral leucocytes and eosinophils. Available information of the experience in other atopic diseases (12–14) allows us to make a tentative hypothesis that leukotriene receptor antagonists will have a role in the treatment of AD. We tested our hypothesis in this pilot study, which also provides an assessment of efficacy and an estimate of the sample size needed for further evaluation.

Patients and methods

Target population

Fifteen patients (6–16 years of age) with AD, as defined by the UK working party refinement of Hanifin & Rajka's diagnostic criteria for AD (15),

This project was self-funded and not supported by Merck Sharp & Dohme Ltd, either financially or otherwise.

were recruited from the Paediatric Dermatology out-patient clinic of the Prince of Wales Hospital (Shatin, Hong Kong). At the time of recruitment, written consent was obtained. The ethical committee at the Chinese University of Hong Kong approved the trial.

Patients included had active disease despite being on conventional treatment with a moderately potent topical steroid of at least class II (UK classification, with class I being the weakest), soap substitutes, and emollients.

The severity of their disease was assessed by quantifying six signs of AD: erythema; edema/papulation; oozing/crusting; excoriation; lichenification; and dryness.

Eight areas of the body (the head and neck, front of the trunk, the back, genitalia, and four limbs) were graded on a scale of 0–3, as follows: 0=none, 1=mild, 2=moderate, and 3=severe. The maximum score for any given area was 18 and for any given patient was 144. All patients were required to have a severity score of at least 40 to qualify for enrollment. Those with a score of less than 40 were considered to have mild disease.

An extent of disease score was taken by estimating the percentage of body surface area involved, using 9% each for the head and neck, right upper limb, and left upper limb; 18% each for the dorsal aspect of the trunk, ventral aspect of the trunk, right lower limb, and left lower limb; and 1% for the genitalia.

A questionnaire for subjective assessment of the impact of the AD on daily living, similar in content to the Children's Dermatology Life Quality Index (16), was also completed on each visit, with additional questions about the effect on relationships with family members and impact on social life. This was translated into the Chinese language to enable better communication. Points were given on a scale of 1–4; the maximum score possible for 13 questions was 52. The higher the score, the worse the disease.

Exclusion criteria

Exclusion criteria were as follows: patients on systemic steroids, immunosuppressives or Chinese herbal medicine during the previous 6 weeks; antibiotic therapy during the previous 6 weeks; the presence of skin conditions other than AD; or infections of any kind.

Randomization

Patients were randomized to receive either 5 mg of montelukast once daily (Merck, Sharp & Dohme, Northumberland, UK) or a chewable

ascorbic acid placebo, which was comparable in size and color to the study drug. Randomization involved the use of 16 sealed envelopes with either group A or group B written inside. Only the pharmacist preparing the study drug and placebo was aware of the coding.

Run-in period

At enrollment, patients and their carers were given a talk about proper skin care and correct application of topical emollient and treatment. Standardized topical treatment was started 2 weeks before the trial and cream-based preparations were used in view of the hot and humid weather during the study period. This included 70% light liquid paraffin as soap substitute, aqueous cream as emollient, and 0.05% Clobetasone Butyrate cream twice daily.

Follow-up

The same physician saw all patients at 2-weekly intervals. After 4 weeks of drug or placebo, there was a washout period of 2 weeks before they crossed-over to the second phase.

Statistical analysis

Baseline characteristics between groups were compared using the Student's *t*-test (Table 1). Scores for both patient groups were compared using the Mann–Whitney *U*-test, and the change of the scores from baseline in drug and placebo were compared using the Wilcoxon signed-ranks test. A *p*-value of <0.05 was considered as statistically significant.

Results

A total of 15 patients were recruited, 11 of whom completed the study (six in group A and five in group B). Of the four patients who dropped out of the study, one patient in group A deteriorated during the placebo phase and attended a herbalist, one patient in group B received antibiotics for a sore throat, another improved in the drug phase but deteriorated after crossover, and the fourth had severe eczema and dropped out after 4 days. The demographic data for the patients are listed in Table 1.

Disease severity score

Despite randomization, the median disease severity scores were different in groups A and B at the start of the study (Table 1). Patients in group B (drug before placebo) had more severe atopic

Table 1. Characteristics of the patient population

	Group A	Group B	p-Value
Number of patients	6	5	
Mean age $\pm$ SD	9.67 $\pm$ 1.63	12.40 $\pm$ 1.52	0.019*
Mean age at onset (months)	46	20	0.033*
Gender (M:F)	2:4	2:3	0.819
Other atopic disorders	4	5	0.455
Disease severity score (mean)	52	78	0.018*

*A p-value of <0.05 was considered statistically significant.
F, female; M, male.

eczema. After the drug phase, there was a significant decrease in the severity score (median score at the start, 78; at the end, 45; $p<0.05$). The median score increased during the placebo phase but remained lower than the starting score (start of study, 78; end of study, 55). The net change in the median severity scores during the drug and placebo phases were compared (Table 2) and a statistically significant difference was identified ($p=0.043$).

Group A patients (placebo before drug) showed some improvement in the disease severity score during both the placebo phase (median score at the start, 52; at the end, 35; $p=0.075$) and the drug phase (start, 41.50; end, 33; $p=0.29$). The degree of improvement in the two phases were compared using the change of median score from baseline (Table 2). This did not reach significant levels.

Extent of disease score

The change in the median extent-of-disease score was not statistically significant for either group (Table 2).

Patient index score

The subjective patient score for the effect of AD on daily living remained similar throughout the study, both within and between different groups.

All patients tolerated the drug and placebo well during the period of this study. None of those who dropped out did so as a result of untoward side-effects.

Discussion

Leukotriene B4 (LTB4) and the cysteinyl-leukotrienes LTC4, LTD4, and LTE4, arise from the oxidative metabolism of cell membrane arachidonic acid and belong to a larger group known as the eicosanoids. The name leukotriene is derived from the term 'leucocyte' (leucocytes are one of the major sources of leukotrienes and the conjugated triene that is their structure; ref. 17). These potent mediators of inflammation and modulators of T-lymphocyte activity are found to be elevated in individuals with AD, where there is up-regulation of the leukotriene pathway (18) with spontaneous and enhanced generation of LTB4 and LTC4 from peripheral blood leucocytes (19,20). Monocytes in these individuals show enhanced chemotaxis (21). Although both atopic and non-atopic skin epidermal cells are capable of producing LTB4 and LTC4 (22), these are present in elevated and biologically active concentrations in the lesional skin of atopics (23,24), and dermatitides rich in eosinophils have high concentrations of LTC4 and LTD4 (25) and increased chemotaxis and chemokinesis (26). The integrated effects of locally produced prostaglandin E2 and LTB4 in tissue inflammation results in greater T-suppressor-cell activity and relatively increased concentrations of interleukin (IL)-4 and IL-5. This tilts the balance towards the immediate-type hypersensitivity reaction rather than T-helper-1-dominant macrophage and T-cell-mediated delayed-type responses. Only very limited studies have been completed on the effects of LTD4 antagonists in human allergic skin diseases, which have been shown to increase skin threshold responses to intra-dermal histamines

Table 2. The net change in clinical score at different phases of the study

Stage of study	Severity score		Extent score		Index score	
	Group B	Group A	Group B	Group A	Group B	
Drug phase	-7.0 (-14.0, 4.0)	-20.00 (-55.5, -13.5)	-12.2 (-33.8, 3.1)	-3.3 (-21.9, 10.2)	1.0 (-1.0, 3.3)	2.0 (-0.5, 5.0)
Placebo phase	-22.5 (-25.0, 3.0)	-5.0 (-14.5, 2.5)	-22.9 (-35.6, -18.7)	0.7 (0.2, -21.0)	-1.5 (-3.3, 2.8)	-1.00 (-4.0, 1.0)
Drug phase vs. placebo phase	$p=0.463$	* $p=0.043$	$p=0.249$	$p=0.345$	$p=0.223$	$p=0.078$

Data represent the change of median score from baseline with inter-quartile range (in parentheses).

*A p-value of <0.05 was considered statistically significant.

(27). Some inhibitors may also act at more than one level and antagonists similarly could modify the expression of more than one class of arachidonic-derived mediators (25). Therefore, although the cysteinyl-leukotriene-1 receptor has not been defined in AD, the available information raises the possibility that leukotrienes play an important role in its pathogenesis.

In this randomized, double-blind placebo-controlled crossover study, group A and group B patients had differences despite randomization (Table 1). Patients in group B (drug before placebo) had more severe AD, were older (mean age of 12.4 years), and had an earlier onset of disease. It is interesting that this group of patients with more severe disease, who took the drug in the first phase before placebo, showed significant improvement, whereas the group with relatively less severe eczema, who took placebo first, did not. This could be because clinical improvement was most easily detected, within the limited time of this study, in patients with the most severe disease.

Patients who started with the placebo first, and who did not show any marked improvement, in fact had a more prolonged run-in period. If the duration of drug treatment was longer, the effect of montelukast becomes more marked.

Group B (drug before placebo) finished the study with a diminished severity score (median score at the start, 78; end, 55). Although there was a rebound of the score when drug treatment was stopped, it did not reach pretreatment levels. This could be explained by a possible carry-over effect of the drug or the extended effects of altered inflammatory mediators. Indeed, it would be interesting to investigate the modulatory effect that montelukast may have on the T-helper-cell imbalance.

The extent of eczema in our patients remained unchanged, probably because the severity of the dermatitis needs to improve sufficiently before any significant change in the extent of the disease can be detected. An improvement in the extent of eczema may have become evident if the treatment period had been longer because, unlike atopic asthma, where the reversal of bronchoconstriction is immediate, AD is a chronic disease and time is needed for skin changes to disappear. Therefore, the extent of the disease may not be a sensitive marker of improvement for patients with extensive moderate-to-severe AD.

It is interesting that the subjective index score did not necessarily equate with clinical improvement or deterioration. The same finding has been reported previously (28). It has been postulated that parents' interpretation of their child's morbidity is inaccurate, being dependent on expecta-

tion and tolerance. The attitude of people surrounding a child's life may also have an impact on the subjective score. Despite significant eczema, one child who has a supportive family and understanding peers, may be happy. On the other hand, a less-fortunate child may be the subject of bullying and social isolation. Despite the same amount of improvement with treatment, the subjective scores may differ.

Our understanding and knowledge of leukotriene receptors are limited but it is clear that some leukotriene receptors exist in multiple states of affinity and specificity that transduce different cellular functional responses and are distributed in more than one cellular compartment (25). Therefore, although montelukast is a selective cysteinyl-leukotriene receptor antagonist and does not theoretically antagonize LTB₄, blocking the cysteinyl-leukotriene receptor appears to be sufficient to cause the beneficial effect observed in our patients.

There are as yet no publications on the effect of leukotriene antagonists on AD, perhaps because its pathogenesis is more complex and leukotrienes are only a piece of the puzzle. However, the results of this pilot study justify a larger trial to test the benefits of leukotriene receptor antagonists. Montelukast, as a rescue measure is an apparently safe and enticing option in the management of difficult AD.

A sample size of 55 was calculated based on the results of this study and we propose a longer washout period between treatment phases and a longer treatment phase.

In conclusion, our results showed that montelukast could be useful in decreasing the disease severity in a group of patients with severe and extensive atopic eczema. A large-scale study is required to investigate its efficacy fully.

References

1. BOS JD, KAPSENBURG ML, SILLEVIS SMITT JH. Pathogenesis of atopic eczema. *Lancet* 1994; 343: 1338-41.
2. BOS JD, WIERENGA EA, SILLEVIS SMITT JH, et al. Immune dysregulation in atopic eczema. *Arch Dermatol* 1992; 128: 1509-12.
3. MAURER D, STINGL G. Immunoglobulin E binding structures on antigen-presenting cells present in skin and blood. *J Invest Dermatol* 1995; 104: 707-10.
4. COX HE, MOFFATT MF, FAUX JA, WALLEY AJ. Association of atopic dermatitis to the beta subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 1998; 138: 182-7.
5. KNORR B, MATZ J, BERNSTEIN JA, NGUYEN H. Montelukast for chronic asthma in 6-14 year old children: a randomized, double-blind trial. Paediatric Montelukast Study Group. *JAMA* 1998; 279: 1181-6.
6. WEISBERG SC. Pharmacotherapy of asthma in children,

- with special reference to leukotriene receptor antagonists. *Paediatr Pulmonol* 2000; 29: 46–61.
7. DRAZEN JM. Asthma therapy with agents preventing leukotriene synthesis or action. *Proc Assoc Am Physicians* 1999; 111: 547–59.
8. KRAWIEC ME, WENZEL SE. Use of leukotriene antagonists in childhood asthma. *Curr Opin Pediatr* 1999; 11: 540–7.
9. VOLOVITZ B, TABACHNIK E, NUSSINOVITCH M, SHATAIF B. Monteleukast, a leukotriene receptor antagonist decreasing the concentration of leukotrienes in the respiratory tract of children with persistent asthma. *J Allergy Clin Immunol* 1999; 104: 1162–7.
10. O'BYRNE PM. Asthma treatment: antileukotriene drugs. *Can Respir J* 1998; 5 (Suppl. A): 64A–70A.
11. DRAZEN JM, ISRAEL E, O'BYRNE PM. Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med* 2000; 340: 197–206.
12. ELLIS MH. Successful treatment of chronic urticaria with leukotriene antagonists. *J Allergy Clin Immunol* 1998; 102: 876–7.
13. SPECTOR S, TAN RA. Antileukotrienes in chronic urticaria. *J Allergy Clin Immunol* 1998; 101: 572.
14. MARKAM A, FAULDS D. Monteleukast. *Drugs* 1998; 56: 251–6 [Discussion 257].
15. HANIFIN JM, RAJKA G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venerol (Stockh)* 1980; 92 (Suppl.): 44–7.
16. LEWIS-JONES MS, FINLAY AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol* 1995; 132: 942–9.
17. SALA A, ZARINI S, BOLLA M. Leukotrienes: lipid bioeffectors of inflammatory reactions. *Biochemistry (Mosc)* 1998; 63: 84–92.
18. NEUBER K, HILGER RA, KONIG W. Interleukin-3, interleukin-8, FMLP and C5a enhance the release of leukotrienes from neutrophils of patients with atopic dermatitis. *Immunology* 1991; 73: 83–7.
19. RUZICKA T, RING J. Enhanced releasability of prostaglandin E2 and leukotrienes B4 and C4 from leukocytes of patients with atopic eczema. *Acta Dermatol Venerol* 1987; 67: 469–75.
20. SAMPSON AP, THOMAS RU, COSTELLO JF, PIPER PJ. Enhanced leukotriene synthesis in leukocytes of atopic and asthmatic subjects. *Br J Clin Pharmacol* 1992; 33: 423–30.
21. CZARNETZKI B. Increased monocyte chemotaxis towards leukotriene B4 and platelet activating factor in patients with inflammatory dermatosis. *Clin Exp Immunol* 1983; 54: 486–92.
22. ROSENBAACH T, GRABBE J, MOLLER A, SCHWANITZ HJ, CZARNETZKI BM. Generation of leukotrienes from normal epidermis and their demonstration in cutaneous disease. *Br J Dermatol* 1985; 113 (Suppl. 28): 157–67.
23. FOGH K, HERLIN T, KRAGBALLE K. Eicosanoids in skin of patients with atopic dermatitis: prostaglandin E2 and leukotriene B4 are present in biologically active concentrations. *J Allergy Clin Immunol* 1989; 83: 450–5.
24. RUZICKA T. Leukotrienes in atopic eczema. *Acta Dermatol Venerol (Suppl.) (Stockh)* 1989; 144: 48–9.
25. AN S, GOETZL EJ. Lipid mediators of hypersensitivity and inflammation. In: MIDDLETON E JR, REED CE, ELLIOT FE, eds. *Allergy: Principles and Practice*, 5th edn, Vol. I (14). St Louis, MO: Mosby 1998, pp. 168–82.
26. SHIMIZU T, KRISTJANSSON S, WENNERGREN G, STRANNEGARD IL, STRANDVIK B. Leukotriene B4 and C4 generation by blood leukocytes after *ex vivo* stimulation by Ca-ionophore and opsonized zymosan in children with atopic dermatitis. *Pediatr Allergy Immunol* 1994; 5: 95–9.
27. BERNSTEIN JA, GREENBERGER PA, PATTERSON R, GLASS M, KRELL R, THYRUM PT. The effect of the oral leukotriene antagonist, ICI 204,219, on leukotriene D4 and histamine-induced cutaneous vascular reactions in man. *J Allergy Clin Immunol* 1991; 87: 93–8.
28. EMERSON RM, CHARMAN CR, WILLIAMS HC. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. *Br J Dermatol* 2000; 142: 288–97.