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A double-blind, placebo-controlled trial of montelukast in adult atopic eczema

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Summary

Background Montelukast is an antagonist of cys-leukotriene receptors used mainly in the treatment of asthma- and seasonal-allergic rhinitis. Initial reports concerning the use of montelukast in atopic dermatitis (AD) have been encouraging, although not consistent.

Objectives We have undertaken a randomized, double-blind, parallel-group, placebo-controlled trial to investigate further the efficacy of montelukast in the treatment of atopic eczema.

Methods Following a screening visit, subjects received placebo treatment for 2 weeks in a single-blind phase, followed after visit 2 by an 8-week, double-blind period of treatment with montelukast 10 mg daily or placebo. Subjects were patients aged 16–60 years under our care for treatment of AD of moderate severity, defined by a six-area, six-sign atopic dermatitis (SASSAD) score in the range 12–50. Response to treatment was assessed by investigators and by subjects using a seven-point scale, with response defined as marked improvement or better. In addition, the SASSAD score was used to monitor the severity of clinical signs. The proportion of skin involved was estimated and visual analogue scales were used to record the severity of pruritus and sleep disturbance. Topical corticosteroid usage was recorded using a five-point scale. Adverse events were recorded.

Results Sixty subjects were recruited and 54 completed the study. The treatment groups were well matched for disease severity at baseline (SASSAD scores were 25 and 29 in the montelukast and placebo groups, respectively). There were no significant differences between the treatment groups in any of the parameters used to assess treatment response. The improvement in mean SASSAD score from baseline (visit 2) to the end of treatment was marginally superior in the placebo group, 1.41 points on montelukast vs. 1.76 on placebo, a difference of 0.35 (95% confidence interval –6.1 to 6.8). Adverse events were generally of a mild nature except for a brief septicaemic illness in one subject receiving montelukast.

Conclusions The data do not support previous reports of efficacy of montelukast in treatment of AD.

Keywords atopic dermatitis, eczema, montelukast, randomized double-blind placebo-controlled trial, SASSAD

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Montelukast is a specific and potent antagonist of cys-leukotriene (cys-LT) receptors licensed for use in the treatment of asthma- and seasonal-allergic rhinitis [1]. The cys-LTs are biologically active mediators derived from arachidonic acid, which include LTC₄, LTD₄ and LTE₄, and collectively account for the biological activity known as slow-reacting substance of anaphylaxis. Several different cell types produce leukotrienes following immunological challenge, including mast cells

and eosinophils. These leukotrienes mediate many responses associated with inflammation, including changes in vascular permeability, inflammatory cell influx, smooth muscle contraction and increased mucus production in the airways.

Atopic eczema is known to involve a range of inflammatory cells and mediators, which are very similar to those seen in the airways in asthma [2]. There is some evidence for the involvement of leukotrienes in atopic

eczema. Schauer *et al.* [3] have demonstrated that eosinophils from patients with atopic eczema produce increased levels of LTE_4 . Two recent studies have investigated urinary LTE_4 levels in patients with atopic eczema. Fauler *et al.* [4] identified raised levels in patients with atopic eczema, whereas Sansom *et al.* [5] failed to identify an increase in urinary LTE_4 . There are therefore good theoretical reasons as to why blockade of cys-LT effects might be of therapeutic benefit in atopic eczema.

Initial clinical observations on the effects of this approach have been encouraging [6–9]. There are also encouraging reports on the use of other anti-leukotriene agents such as zafirlukast [10] and zileuton [11]. Other investigators have failed to confirm this response [12, 13].

Montelukast is a drug widely used in the treatment of atopic asthma and has demonstrated a remarkably benign safety profile. It would therefore be extremely useful if it this drug was effective in atopic eczema, since, in many patients, two diseases could be treated safely with the same agent.

We have therefore undertaken a trial to investigate further the efficacy of montelukast in the treatment of atopic eczema.

Method

Trial design

This was a randomized, double-blind, parallel-group, placebo-controlled trial conducted in two centres. Following a screening visit, subjects received placebo treatment for 2 weeks in a single-blind phase, followed by an 8-week period of treatment with montelukast or placebo. Clinic visits for assessments took place at the end of the placebo phase (visit 2), and after 4 and 8 weeks of randomized treatment (visits 3 and 4).

Subjects

Subjects were male and female patients aged 16–60 years, under the care of our departments for treatment of atopic eczema and who had suffered from the disease for at least 1 year. Atopic eczema was defined according to the criteria of Hanifin and Rajka [14]. Disease severity was required to be moderate, defined as a six-area, six-sign atopic dermatitis (SASSAD) score between 12 and 50 at visits 1 and 2.

Exclusion criteria included pregnancy and lactation, known sensitivity or contraindication to montelukast and any co-existing skin disease, illness or other condition likely to require admission to hospital or impair assessments or influence treatment response.

Treatments

Subjects received placebo treatment for 2 weeks in a single-blind phase, followed by an 8-week period of treatment with montelukast 10 mg daily or matching placebo. Treatment was supplied by the sponsor in containers labelled with sequential subject numbers containing medication in computer-generated randomized sequence. Treatment was allocated to subjects in strict numerical sequence. Investigators and subjects were blinded to the treatment allocation throughout the study.

Concomitant treatment: patients were allowed to use emollients, antihistamines and mild, moderately potent or potent topical corticosteroids provided that the use of these had been stable over the preceding month. Subjects were instructed that topical steroids should be applied only when required. No other treatments for eczema were permitted. No changes to the concomitant medication were permitted other than adjustment of the quantity and frequency of application of topical steroid as required.

Assessments

Response to treatment was assessed by investigators and by subjects using a seven-point scale: very much better, markedly improved, a little better, the same, a little worse, markedly worse, very much worse. Response was defined as marked improvement or better.

In addition, the SASSAD score was used to monitor the severity of clinical signs [15].

The proportion of skin involved in the disease was estimated at each visit using the rule of nines.

Visual analogue scales, 10 cm long and marked “worst ever” at one end and “none” at the other, were used at each visit to record the severity of pruritus and sleep disturbance over the previous week.

Topical corticosteroid usage was recorded using a five-point scale: none, occasional, alternate days, once daily, twice daily. Subjects were asked which category most accurately reflected their treatment activity at screening or since the previous visit.

Adverse events were elicited using non-leading questions at each visit and were recorded.

Statistics

The primary end-point was the proportion of the subjects in each treatment group demonstrating at least a marked improvement as assessed by the investigator. Differences between the two groups in the proportion of patients responding to the treatment were assessed using the χ^2 test.

Changes in sign score, area involved, pruritus and sleep disturbance were assessed using two-tailed *t*-tests for

independent samples and the results confirmed using non-parametric methods (Wilcoxon's rank sum test).

Analysis was performed on the InStat statistical package (GraphPad software Inc.).

The sample size estimate was based on the responder/non-responder dichotomy representing the primary response criterion. It was estimated that 29 evaluable subjects would be required in each limb to provide 80% power to detect a difference in the response rate of 30% between treatment limbs, at α 0.05.

Ethical considerations

The protocol was approved by the Southampton and Southwest Hampshire Research Ethics Committee and the Warwickshire Research Ethics Committee. All subjects were required to provide written consent.

Results

Demographics

Sixty subjects were recruited, 20 males and 40 females. Demographic data and disease severity at baseline are given in Table 1.

One patient in each treatment group was lost to follow-up after baseline. An evaluable "intention to treat population" of 29 subjects therefore remained in each group. Between 4 and 8 weeks two further subjects in each group were lost to follow-up. In addition, one patient receiving montelukast was withdrawn due to dizzy spells, and one subject in the placebo group was withdrawn due to worsening of eczema.

Treatment response

Response to treatment is summarized in Table 2. Changes in SASSAD score over the course of the study are shown in Fig. 1.

There were no significant differences between the treatment groups in any of the parameters used to assess

Table 2. Response to treatment

	Active (N = 29)	Placebo (N = 29)
Investigator global assessment 'markedly improved' or better	8	12
Patient global assessment 'markedly improved' or better	6	10
Mean improvement in SASSAD (SD)*	1.41 (12.2)	1.76 (12.2)
Mean improvement in area involved*	6%	4%
Mean improvement in pruritus score* (VAS, range 0–10)	0.1	0.8
Mean improvement in sleep disturbance* (VAS, range 0–10)	1.0	1.6

*Changes from baseline to end of treatment.

SASSAD, six area, six sign atopic dermatitis; VAS, visual analogue scale.

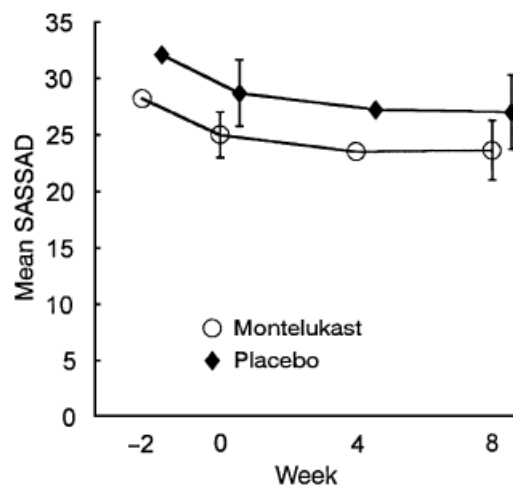


Fig. 1. Mean six area, six sign atopic dermatitis (SASSAD) scores (error bars show standard errors of the mean, missing data imputed by last observation carried forward).

treatment response. The improvement in mean SASSAD score from baseline (visit 2) to the end of treatment was marginally superior in the placebo group, 1.41 points on montelukast vs. 1.76 on placebo, with a difference of 0.35 [95% confidence interval (CI) -6.1 to 6.8].

Patterns of topical steroid usage are demonstrated in Fig. 2.

Virtually identical results were obtained at each of the two centres.

Adverse events

There was only a single serious adverse event, an episode of septicaemia occurring at the end of the treatment period in a patient on montelukast. This patient made a rapid recovery. Only one subject was withdrawn due to an adverse event. This was a patient receiving montelukast

Table 1. Baseline demographics

	Active (N = 30)	Placebo (N = 30)
Mean age	31	35
Mean % skin affected	37	34
Mean SASSAD (week 0)	25	29
Mean pruritus score	5.8	5.7
Mean sleep disturbance score	4.6	4.0
No using a potent* topical steroid as required	23	24

*As classified by the British National Formulary.

SASSAD, six area, six sign atopic dermatitis.

who suffered from dizzy spells. Adverse events were otherwise of a fairly mild nature, e.g. respiratory tract infections, headaches, flares of eczema, mild gastrointestinal disturbances, and were fairly evenly distributed between the treatment groups.

Discussion

This randomized, double-blind, placebo-controlled study has not confirmed a benefit of montelukast over placebo in treatment of moderately severe atopic dermatitis (AD). The primary end-point in this study, a 7-point scale assessing response, was a subjective one. However, the results are made more conclusive by the additional objective assessments constituting the secondary end-points. Although the 95% CIs for the change in SASSAD are still compatible with a clinically useful treatment effect, the improvement in the montelukast group was slightly inferior to that in the placebo group, and this pattern was reflected in the other parameters assessed. There was therefore no overall trend towards improvement, relative to placebo, that would suggest a beneficial effect of montelukast. An important point demonstrated

by this study is just how large the placebo effect can be in trials on treatments for atopic eczema.

Our findings are consistent with the observations of Silverberg and Paller, who observed no benefit in the majority of the seven patients they treated with montelukast or zafirlukast. Our results appear to conflict with a number of previous reports of AD benefiting from treatment with montelukast or other leukotriene antagonists; however, the majority of these previous reports have been uncontrolled and/or were not double blinded (see Table 3). Data from uncontrolled and unblinded studies have to be interpreted with caution because of the spontaneous fluctuation that occurs in AD, the possibility of placebo effect and the potential for bias to influence the assessment of response.

Three previous studies have been double blinded and placebo controlled. Eustachio *et al.* reported a response in parallel-group study with 20 adult subjects, and Pei *et al.* reported response to montelukast in a trial of crossover design with 15 children (aged 6–16). However, Veien *et al.* did not confirm this response in a parallel-group trial with 53 evaluable subjects. The current study, which is the largest performed so far, has again failed to demonstrate efficacy of montelukast in treatment of AD.

A notable difference in design between this study and that of Veien *et al.* is the continuation of standard treatments for eczema in the current study, including topical steroids. We adopted this design largely because this reflects the population in which montelukast would be employed, if it were beneficial. Because patients were using topical steroids only as required, the current study allowed us to monitor steroid usage and measure any possible steroid-sparing effect. This is a useful end-point to monitor. Unfortunately, no such effect was demonstrated.

Our results argue strongly against a central role for cys-LTs in the pathogenesis of AD generally or in the pruritus that characterizes this disease. This is surprising for a number of reasons. Firstly, increased quantities of cys-LTs

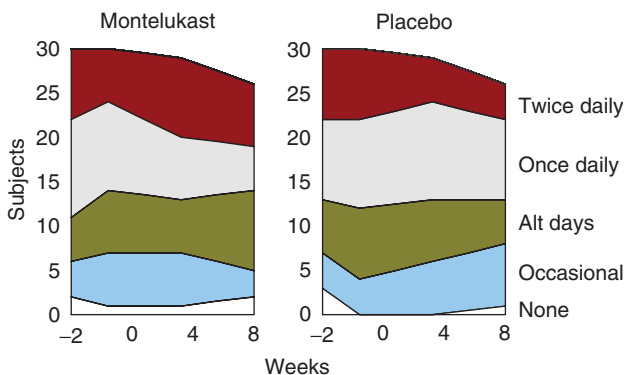


Fig. 2. Topical steroid usage monitored using a five-point scale.

Table 3. Previous publications on the use leukotriene antagonists in AD

Author and reference number	Evaluable subjects	Age group	Active medication	Design	Concomitant therapy
Eustachio [6]	20	18–28	Montelukast 10 mg o.d.	DB, PC, R, PG	Emollients
Yanase [7]	8	≥ 18	Montelukast 10 mg o.d.	DB, PC, R, XO	White petrolatum
Pei [8]	11	6–16	Montelukast 5 mg o.d.	DB, PC, R, XO	Topical steroids
Hon [9]	7	2–18	Montelukast 5–10 mg o.d.	Open	Topical steroids, antihistamines
Carucci [10]	4	41–61	Zafirlukast 20 mg b.d.	Open	Topical steroids
Woodmansee [11]	6	≥ 12	Zileuton 600 mg q.d.s.	Open	Emollients
Silverberg [12]	7	4–65	Montelukast 10 mg o.d. or Zafirlukast 20 mg b.d.	Open	Topical steroids
Veien [13]	53	16–70	Montelukast 10 mg o.d.	DB, PC, R, PG	Emollients

DB, double-blind; AD, atopic dermatitis; PC, placebo-controlled; R, randomized; XO, crossover; PG, parallel-group; o.d., once daily; b.d., twice daily; q.d.s.,

are generated in patients with atopic eczema as reflected by the augmented excretion in the urine [4]. Secondly, there are data suggesting involvement of cys-LTs in immediate-type allergic reactions that are commonly found in patients with atopic eczema. Fauler et al. [4] found elevated levels of cys-LTs in the urine of patients with atopic eczema, although Sansom et al. [5] could not confirm this. Also, skin chamber samples from skin challenges with allergens contain elevated levels of cys-LTs [16–18]. Although there has been a main focus on cys-LTs because of their involvement in immediate-type allergic reactions and asthma, the lack of effect of montelukast in eczema does support the idea that the eczematous inflammation is more a lymphocyte-mediated one than a mast cell-mediated one. The fact that some studies have observed good clinical effects of cys-LT receptor antagonists leaves open the possibility that there is mechanistic heterogeneity within the population of eczema patients. Whether other leukotrienes such as LTB₄ are involved in the pathogenesis, as suggested by the findings of high levels of LTB₄ in skin samples [19, 20], may become clear when effective antagonists for this mediator become available. In the meantime, the occasional patients who show a reproducible clinical response to treatment with cys-LT receptor antagonists clearly form a minority sub-group with a different pathogenetic process from the majority.

Acknowledgements

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