

Leukotriene receptor antagonism may not be effective in atopic dermatitis treatment after all

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Summary

What is known and Objective: Literature evidence suggests leukotriene involvement in the pathogenesis of atopic dermatitis. This article aimed to discuss whether the off-label use of montelukast, a leukotriene receptor antagonist, is justifiable for the treatment of atopic dermatitis.

Comment: Most non-randomized studies supported the use of montelukast for atopic dermatitis treatment. However, evidence from these studies should be interpreted with caution as it is relatively weak due to the absence of randomization, control groups and blinding processes, subjecting the results to high risk of selection and reporting biases. The inconsistent findings across RCTs may be related to the limited number of patients, nuances in study designs, varying severity of disease and the concomitant use of steroids in some of the studies.

What is new and Conclusion: Current literature evidence is limited to rationally support the use of montelukast in atopic dermatitis treatment. For now, the conventional treatments should be preferred in the clinical setting.

KEYWORDS

atopic dermatitis, leukotriene, leukotriene receptor antagonist, montelukast, off-label use

1 | WHAT IS KNOWN AND OBJECTIVE

Atopic dermatitis (AD) is a chronically relapsing eczematous skin disorder characterized by inflammation and pruritus, with concurrent cutaneous physiological dysfunctions, including xerosis.^{1–3} The present standard therapies for mild AD include the use of topical corticosteroids for inflammation and the regular application of emollients. For moderate-to-severe cases, short-term use of systemic oral glucocorticoids or other steroid-sparing immunosuppressive agents, such as cyclosporine A, azathioprine and methotrexate is warranted in addition to the treatments mentioned above.⁴

Leukotrienes (LTs) are potent biological pro-inflammatory mediators derived from arachidonic acid through the 5-lipoxygenase pathway.⁵ Basophils, mast cells and eosinophils play a major role in the production of biological LTs.⁵ Leukotrienes are classified into two groups, those with the presence of a sulphur bond linkage (cysteinyl LTs: LTC₄, LTD₄, LTE₄) and those that do not (LTB₄).⁵ Comparing to

healthy subjects, it is reported that patients with AD exhibit increased spontaneous releasability of LTs from their leucocytes.⁶ In support of that, by employing the suction blister technique, LTC₄ has been found in the skin of patients with AD.⁷ Also, absolute eosinophil count, an important source of LTs, has been shown to be positively correlated with the severity of the skin disorder.⁸ In addition, it is reported that patients with AD of higher severity have increased activated circulating basophils in vivo and enhanced basophil releasability of LTs, as compared to healthy volunteers.⁹ Furthermore, increased urinary concentrations of LTE₄, a stable metabolite of LTC₄ and LTD₄, and being an essential indicator of whole-body cysteinyl LT production in vivo, have also been noted in patients with AD.¹⁰ All these results collectively support the association of the leukotriene pathway with pathogenesis of AD.

Montelukast is an orally administered, cysteinyl-leukotriene-1 receptor antagonist (LTRA) that is approved by the FDA for the prophylaxis and chronic treatment of bronchial asthma and allergic

rhinitis.¹¹⁻¹³ Due to the common association of atopic dermatitis with asthma and allergic rhinitis, or what is collectively known as the “atopic triad,” the improvement of atopic eczema was anecdotally reported in patients receiving montelukast to control the manifestations of airway diseases.¹ In fact, the review paper by Nettis et al² concluded that clinicians should try montelukast in all cases of AD unresponsive to conventional treatments. This article aimed to discuss whether the off-label use of montelukast is justifiable for the treatment of atopic dermatitis.

2 | COMMENT

2.1 | Evidence from non-randomized studies

In 2001, Biswas et al¹⁴ conducted a non-interventional observational cohort study and found that of the 16 patients who used montelukast for asthma or allergic rhinitis treatment, five patients experienced montelukast-associated AD symptom relief based on the causality assessment by their general practitioners. This observation was supported by several case series with sample size ranging from two to seven patients. Kagi et al¹⁵ reported that in all his 4 patients with AD of the face refractory to topical steroids, dermatitis was resolved 2 weeks after starting treatment with montelukast 10 mg daily, with alleviation of pruritus symptoms being the most prominent. Angelova-Fisher and Tsankov¹⁶ demonstrated that montelukast 10 mg daily, used as monotherapy, was able to significantly improve the clinical manifestations of two patients with severe AD when corticosteroid treatment was contraindicated or failed to control the disease. In particular, an improvement of pruritus was observed within the first week of treatment. Based on the observations, they advocated the potential use of montelukast as a steroid-sparing agent in AD treatment.

Hon et al,¹⁷ who studied the benefits of montelukast in seven paediatric patients with ages ranging from 3 to 16 years, also reported a positive response based on the reduction in SCORAD index. This is a severity score for AD based on three assessed components: intensity, extent (ie body surface area affected by AD) and subjective symptoms (ie itch and sleeplessness) of the skin disorder.¹⁸ The total SCORAD score decreased in five patients, ranging from a 30% to 84% reduction, whereas no differences were observed in the other two patients. It is worth noted that only the intensity score was reduced, while the disease extent and subjective symptoms remained the same. This result showed inconsistency with the previous two case series which reported the antipruritic effect of montelukast. Silverberg et al¹⁹ could not replicate the same therapeutic effects in 7 studied patients and demonstrated no sustained benefit of montelukast for patients with extensive AD that was refractory to oral antihistamines and mid-to-high potency topical steroids.

The results from these non-randomized studies supported the use of montelukast for AD treatment with the exception of one study by Silverberg et al.¹⁹ However, evidence from these studies should be interpreted with caution as it is relatively weak due to the absence of randomization, control groups and blinding processes, subjecting the

results to high risk of selection and reporting biases. Furthermore, the sample sizes of the studies were very small.

2.2 | Evidence from randomized clinical trials (RCTs)

Most of the published RCTs investigated patients with moderate-to-severe AD. By employing a cross-over pilot study, Pei et al²⁰ investigated fifteen AD paediatric patients, ranging in age from 6 to 16 years, and demonstrated a reduction in disease severity, with no significant effects on disease extent and health-related quality of life (QoL). This result concurred with the outcome of a case series by Hon et al,¹⁷ confirming that montelukast could only alleviate the intensity of AD clinical manifestations with no efficacy in the reduction in AD-affected body surface area and subjective symptoms, including pruritus. On the contrary, Melamed et al²¹ showed that montelukast was only effective in reducing pruritus, with modest effects on the other clinical AD manifestations. Only Yanase et al²² (n = 8 subjects) and Eustachio et al²³ (n = 32 subjects) demonstrated the superiority of montelukast with respect to placebo in the alleviation of the overall clinical AD manifestations when 10 mg daily of the drug was administered to the adult subjects.

Capella et al²⁴ reported a randomized, single-blind study consisting of 32 adult AD patients. The authors investigated the therapeutic effects of montelukast in patients with AD as compared to an active quadruple-combined regimen comprising topical steroid, oral antibiotic (clarithromycin), antihistamine and hydrating creams for 6 weeks. They reported marked SCORAD improvement in both groups but no statistical difference between groups. Similarly, via an open-label trial of 31 patients, Rahman et al²⁵ showed that montelukast was superior to the active dual-regimen comparator group comprising topical steroid and oral antihistamine. These results, however, have to be evaluated with thorough consideration, taking into account the small sample size and the absence of double-blinding.

Interestingly, the larger size RCTs could not reproduce the positive findings. Jeon et al²⁶ conducted a paediatric study comprising 54 patients and could not show any significant differences between the montelukast and placebo groups in terms of SCORAD score and urinary LTE4. This is consistent with another trial outcome by Veien et al²⁷ (n = 59 subjects), in which concomitant active topical or systemic treatment was strictly not permitted during the interventional period. Friedmann et al²⁸ confirmed this outcome in a parallel-group trial with 54 evaluable subjects. In fact, he found that the improvement in the montelukast group was slightly inferior to that in the placebo group, demonstrating how prominent the placebo effect can be in atopic dermatitis trials. This result also concurred with the findings obtained by Lehtimäki et al,²⁹ who recruited 49 pollen-sensitized subjects experiencing allergic symptoms from both the upper and lower airways, and allergic symptoms outside the airways (conjunctivitis, eczema and/or urticaria). The authors found no significant improvement with montelukast in allergic symptoms outside the airways in patients suffering different manifestations of the atopic syndrome.

In addition, four published RCTs, including a cross-over study by Ehlayel et al,³⁰ compared the amounts of rescue medications (oral



antihistamines, topical steroids and oral antibiotics) required by patients from treatment (montelukast) and control groups. No significant differences were observed, demonstrating the limited potential of montelukast as an adjunct therapy for atopic dermatitis as well.

The inconsistent findings across the RCTs may be related to the limited number of patients, nuances in study design, the varying severity of disease and the concomitant use of steroids in some of the studies. Interestingly, all the studies with positive findings had relatively small sample sizes, suggesting the possibility of type II errors due to the limited sample size and power.

3 | WHAT IS NEW AND CONCLUSION

The current clinical data suggest that montelukast has very limited efficacy in the overall amelioration of clinical manifestations of AD.⁴ In most of the RCTs that exhibited a positive response, montelukast was only shown to be a good antipruritic agent, with minor to no significant differences observed in the other measured primary outcomes, in particular the body surface area affected by AD. Therefore, the off-label use of montelukast in treating AD should not be recommended in the clinical setting at this time. This is to avoid the delay in the provision of more effective conventional treatments (ie optimal skin hydration, use of corticosteroid creams and, for moderate-to-severe conditions, the use of steroid-sparing immune suppressants).

Furthermore, despite numerous in vitro and in vivo studies identifying leukotriene to be an important mediator in the pathogenesis of AD, most clinical studies could not support the theory of leukotriene receptor antagonism as an effective treatment for this atopic skin disorder. This may be due to the high selectivity of montelukast in blocking the action of only one type of leukotriene, which is the LTD₄. Nevertheless, montelukast remains a useful treatment for mild-to-moderate bronchial asthma and allergic rhinitis. Its limited efficacy in AD highlights the fact that, although these diseases are related, the underlying pathophysiology clearly differs. Future research priorities may shift from receptor antagonism investigation to the study of leukotriene synthesis inhibition at the upstream of the leukotriene pathway.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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