Successful treatment of severe atopic dermatitis with cysteinyl leukotriene receptor antagonist montelukast*

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SUMMARY

Leukotrienes are potent proinflammatory mediators derived from of arachidonic acid through the 5-lipoxygenase pathway. Experimental data suggest a role for cysteinyl leukotrienes in the pathogenesis of atopic dermatitis and there is a rationale for the use of pharmacological agents to antagonize their effects in the treatment of atopic dermatitis.
We report 2 cases of severe atopic dermatitis successfully treated with montelukast as a single therapeutic agent in a daily dose of 10 mg for 8 weeks when corticosteroid treatment was contraindicated or failed to control the disease. Our observations suggest that montelukast may be used as an alternative steroid sparing medication for severe atopic dermatitis, especially in patients with associated asthma and rhinitis.

KEY WORDS

atopic dermatitis, steroid sparing treatment, cysteinyl leukotriene receptor antagonists, montelukast

Introduction

Cysteinyl leukotrienes (CysLTs) are potent proinflammatory mediators derived from arachidonic acid through the 5-lipoxygenase pathway. They exert pharmacological effects by interaction with at least two different receptors, the CysLT1 and CysLT 2. There is evidence that the pathobiologic phenomena underlying the manifestations of atopy-related asthma and rhinitis are mediated by the cysteinyl leukotriene 1 receptor subtype. By competitive binding to the CysLT1 receptor, leukotriene receptor antagonists (LTRAs) block the effects of cysteinyl leukotrienes and alleviate the symptoms of asthma and allergic rhinitis. Because of the common association of atopic dermatitis (AD) with allergic asthma and rhinitis, improvement of atopic eczema was anecdotally reported in patients receiving LTRAs to control the manifestations of airway disease. These observations have been confirmed in studies in small groups of pediatric and adult patients with atopic dermatitis.

We report 2 cases of severe atopic dermatitis successfully treated with montelukast as a single therapeutic agent in a daily dose of 10 mg for 8 weeks after corticosteroid treatment had contraindicated or failed to control the disease.

*montelukast - Singulair tablets,, MSD

Materials and methods

The *Severity Scoring Atopic Dermatatis (SCORAD) index*, introduced by the European Task Force on AD (1), was used to measure the severity of the disease and to evaluate the effect of treatment. *Montelukast sodium* (Singulair tablets, MSD), the LTRA antagonist, was administered in a single oral daily dose of 10 mg every evening for 8 weeks. Topically applied preparations included only emollients which the patients had used on a long-term basis before the administration of montelukast.

The effect of the treatment was evaluated at weekly intervals for the first 8 weeks and then on a monthly basis up to six months.

Case report 1

A 32-year old woman with severe exacerbation of atopic dermatitis was admitted to the Department of Dermatology, University of Medicine-Sofia in December 2002. The onset of the disease was in the 4th month of life with the appearance of symmetric erythematous oozing plaques on the cheeks and the extensor parts of the limbs. In infancy and childhood the disease relapsed frequently and tended to affect severely the flexures of the upper and lower extremities. Bronchial asthma was diagnosed at the age of 4 and allergic rhinitis at 6. The patient had a positive family history for atopy.

Throughout the years the clinical manifestations of atopic dermatitis were controlled by the use of topical or systemic corticosteroids depending on the severity of the flare-ups. A psychoaffective disorder diagnosed in 1999 limited systemic steroid use and since 2000 the disease had been extremely difficult to control, with remissions usually lasting 3-4 weeks.

On admission the patient's general condition was rather poor. Widespread erythema was present with marked exudation on the face, neck, trunk (Figure 1) and extremities (Figure 2). Numerous excoriations were seen. Cheilitis sicca and eyelid dermatitis were present, generalized lymphadenopathy was also expressed. Subjective symptoms included chills and a sever pruritus resulting in loss of sleep.

The SCORAD index was 85 and 80% of the body surface area was affected. Laboratory tests were within a normal range, except the level of total serum IgE which was 660 IU/ml (normal values < 100 IU/ml).

The patient presented a therapeutic rather than a diagnostic problem since the flare-up could not be controlled by topical preparations, and the use of systemic corticosteroids or phototherapy had been ruled out. As an alternative we used an oral dose of LTRA montelukast, 10 mg/ 24h every evening for 8 weeks. The patient did not receive any other systemic medication and emollients (white petrolatum for the body and the Avene thermal spring water preparation for the face) were the only topical agents used during the period of treatment.

10 days after the initial administration of montelukast the exudation was no longer present, the erythema was less pronounced (Figures 3 and 4) and the pruritus had subsided. The SCORAD score had decreased to 38.5. No relapse was observed in the period up to the end of treatment nor at the monthly check-up examinations (up to a total of 6 months).

Case report 2

A 19-year old woman with severe flare-up of atopic dermatitis came for consultation to our department in March 2003. The patient had had a history of atopic eczema since early infancy. The manifestation of the disease in childhood and adolescence were relatively mild and managed by topical steroid preparations. In the previous 3 years relapses had been frequent and difficult to manage with topical treatment alone.

The exacerbation on admission to the hospital was triggered to weeks earlier by a depot corticosteroid injection administered by a general practitioner. The injection had been administered following the failure of treatment with a potent topical corticosteroid preparation. Allergic asthma had been diagnosed at the age of 5 years, and rhinitis at the age of 9 years. She also had a positive family history for AD.

On admission 78% (estimated by the rule of the 9s) of the body surface area was affected and the SCORAD index was 70.6. Erythema and symmetrically distributed oozing was most severely pronounced on the cheeks, the neck, the supra and infraclavicular area, the cubital and popliteal folds as well as the volar surfaces of the forearms. Numerous excoriations on the trunk and extremities were seen. The patient complained of severe pruritus and fatigue. The remaining examinations and laboratory tests were within a normal range, except the elevated total serum IgE 2470 IU/ml.

As an alternative to treatment with systemic corticosteroids, based on the good results observed in the above described case, we administered montelukast sodium tablets in a single daily oral dose of 10 mg for 8 weeks. A significant improvement of the patient's condition was observed at the end of the first week, and was most pronounced for the erythema, exudation and pruritus. The SCORAD index was reduced to 34.6 by day 10. The remission was stable and the patient did not present any exacerbation in the course of the follow-up examinations (up to a total of 6 months).

Discussion

We report significant improvement of skin findings in 2 two patients with severe atopic dermatitis following treatment with montelukast as a single therapeutic agent. The patients had at least a one year history of

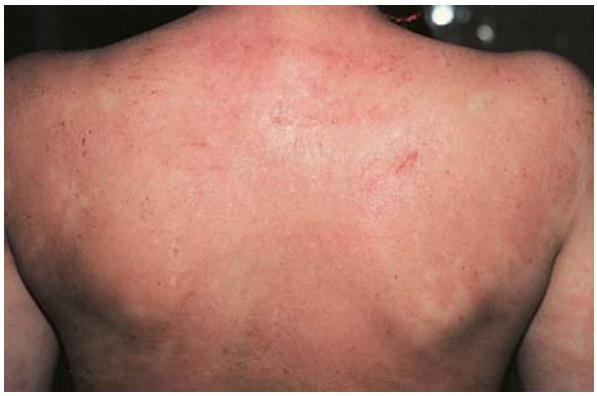

Figure 1. Erythema and excoriations on the back, before treatment.

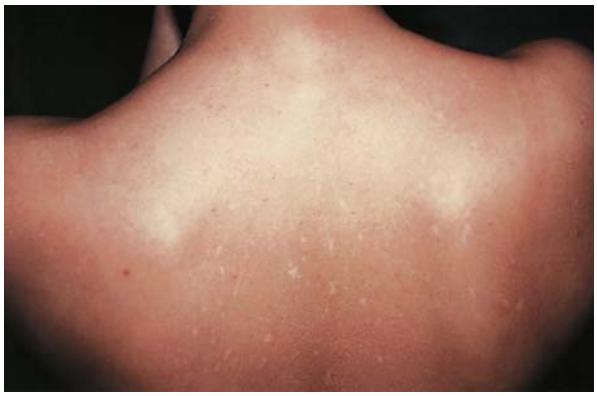

Figure 2. Same area showing substantial improvement after 10 days of treatment with montelukast.

active disease, intermittent or persistent in course, that could not be managed further with topical or systemic corticosteroids, phototherapy or immunosuppressive agents.

A significant improvement in the skin findings, and in particular for the erythema and exudation was observed after 10 days of treatment. Significant alleviation of pruritus was reported by the patients within the first week, which is in line with previously published reports (2). Undesirable side effects were not recorded during the period of treatment.

Montelukast belongs to the group of cysteinyl LTRAs successfully applied for alleviation of the symptoms of bronchial asthma. Based on clinical observations and supported by trials, their therapeutic implications have extended beyond the scope of asthma (3) to the management of chronic urticaria (4,5) and atopic dermatitis (6,7).

LTRAs exert their pharmacological activities by antagonizing the effects of CysLT. Eosinophils, basophils and mast cells (8) are the most important sources of CysLT (LTC4, LTD4, LTE4). CysLTs induce bronchoconstriction, increase vascular permeability and mucus secretion and facilitate the recruitment of eosinophils in the airways (9). Moreover, they are the most potent bronchoconstrictors known to date (10).

LTC4, LTD4 and LTE4 are produced by LTC4 synthase from a precursor leukotriene LTA4 which in turn is a component of the lypoxygenase pathway of the arachidonic acid metabolism. LTC4 synthase is an enzyme produced by inflammatory cells and particularly by eosinophils (11). It is interesting to mention that the gene for LTC4 synthase is in the same locus as genes encoding important proinflammatory cytokines such as IL-4, IL-5 and IL-13 on chromosome 5q13 (12).

CysLTs exert their influence by interaction with at

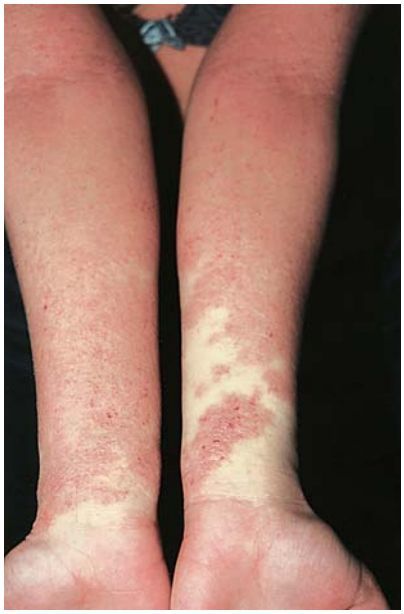

Figure 3. Severe involvement of the forearms, before treatment.

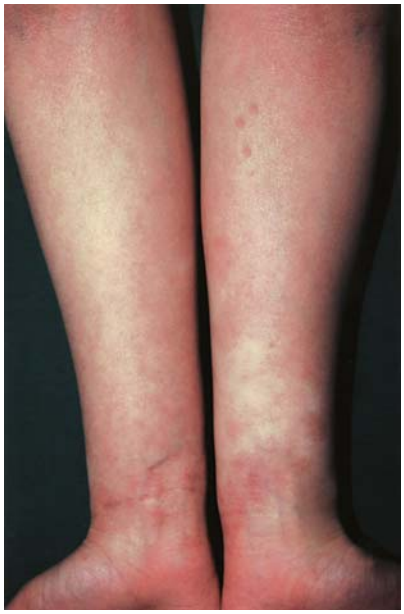

Figure 4. The forearms showing substantial improvement after 10 days of treatment.

least two different receptors: CysLT1 and CysLT2 (13). The pathobiologic phenomena attributed to CysLTs in the pathogenesis of asthma, urticaria and possibly of atopic dermatitis are mediated by the CysLT1 receptor subtype (14).

In 1999 Lynch et al. (15) cloned and sequenced the human CysLT1 receptor and mapped the receptor gene to the long arm of the X chromosome at bands 13-21 (Xq13-q21). CysLT1 receptor expression was demonstrated on cells with particular importance in asthma and atopy such as eosinophils, monocytes/macrophages, CD19+ B lymphocytes and CD34+ granulocyte precursor cells, by Figueroa et al. (16). The same group of investigators hypothesized that 1) CysLTs prime the maturation of CD34+ precursor cells to eosinophils, macrophages and lymphocyte subsets in the peripheral blood and, 2) CysLTs amplify the recruitment of inflammatory cells in the lungs. The extent of damage depends on the activation in an autocrine and paracrine manner of the CysLT1 receptors on interstitial granulocyte precursor cells, eosinophils and macrophages ('positive feedback' mechanism).

All marketed LTRAs couteract these pathobiologic phenomena by binding competitively to the CysLT1 receptor. Their beneficial effects in asthma are attributed not only to reduction of airway hyperreactivity but also to interference with inflammation pathways. However, while the effects of CysLTs on the airways have been extensively investigated, their role in the pathogenesis of atopic dermatitis is still incompletely understood.

Improvement of atopic dermatitis was anecdotally reported in patients receiving LTRAs to control the symptoms of associated bronchial asthma or other atopy related conditions such as allergic rhinitis (17). The efficacy, safety and cost-effectiveness of CysLTRAs in adult patients with moderate to severe atopic dermatitis was communicated by Capella et al. (18) in a single blind study, comparing montelukast (10mg/ 24h for 6 weeks) to a combined regimen of cetirizine, clarythromycin, topical corticosteroids and emollients. These observations were further supported by the first double-blind placebo controlled crossover study on montelukast efficacy in 8 adult AD patients by Yanase and David-Bajar (19). The results of the first double-blind placebo controlled crossover study of montelukast efficacy in pediatric patients (aged 6-16) with AD were reported several months later by Pei et al. (20).

Successful management of severe atopic dermatitis (erythroderma) with montelukast has already been reported in medical literature (21), with the difference that in that case report the improvement could not be attributed exclusively to montelukast as the patient received a combined treatment regimen.

Conclusion

Montelukast was administered as an alternative therapeutic regimen in cases where the use of mainstay corticosteroid therapy had been contraindicated or failed to control the manifestations of the disease. Our report suggests that montelukast may be helpful as a single alternative corticosteroid sparing medication in cases of severe AD, especially in patients with associated asthma and rhinitis.

List of abbreviations

CysL	*cysteinyl leukotrienes*
CysLT1	*cysteinyl leukotriene receptor 1*
CysLT2	*cysteinyl leukotriene receptor 2*
LTRAs	*leukotriene receptor antagonists*
CysLTRAs	*cysteinyl leukotriene receptor antagonists*
LTC4	*leukotriene C4*
LTD4	*leukotriene D4*
LTE4	*leukotriene E4*
LTA4	*leukotriene A4*

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A U T H O R S ' A D D R E S S E S

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