The Leukotriene Antagonist Zafirlukast as a Therapeutic Agent for Atopic Dermatitis

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1
A 42-year-old man presented with a 10-year history of atopic dermatitis that was refractory to treatment with UV light, oral antihistamines, and high-potency topical corticosteroids. On presentation, he denied any other medical problems and was taking no medicines. His condition improved with the use of cyclosporine; however, this regimen was discontinued secondary to transaminitis due to hepatitis C infection, which was treated with interferon alfa. His atopic dermatitis flared after discontinuation of cyclosporine therapy. A physical examination showed erythroderma involving more than 70% of his body surface area approximately 2 weeks after cyclosporine therapy was discontinued.

CASE 2
A 61-year-old man presented with a lifelong history of atopic dermatitis. His condition did not improve with the use of high-potency topical corticosteroids and UV-B phototherapy. He had no other medical problems and was taking no medicines. On physical examination he had an erythematous dermatitis with scale involving 25% of his body surface area.

CASE 3
A 41-year-old woman presented with a 10-year history of atopic dermatitis and urticaria. Other medical problems included asthma, for which she was using a β-adrenergic inhaler. On physical examination, she had erythematous patches on her chest and back. Her atopic dermatitis was initially controlled with the use of 0.1% triamcinolone acetonide ointment applied twice daily. The dermatitis recurred despite topical therapy and oral antihistamines, including terfenadine, loratadine, hydroxyzine hydrochloride, and cetirizine hydrochloride, and the patient's respiratory symptoms eventually worsened.

CASE 4
A 47-year-old man presented with a history of atopic dermatitis that had been treated with numerous courses of prednisone during the 7 years prior to his visit to our department. During this period, his prednisone dosage varied between 10 and 40 mg/d. His dermatitis was uncontrolled without prednisone during that time. He had no other medical problems and was taking no other medicines. Topical therapy consisted of 0.1% triamcinolone acetonide ointment and 0.2% zinc pyrithione applied twice daily. On physical examination, he had an eczematous dermatitis involving 25% of his body surface area.

THERAPEUTIC CHALLENGE
Our goal was to alleviate symptoms in patients with atopic dermatitis refractory to other therapeutic modalities or in patients in whom the immunosuppressive effects of prednisone or cyclosporine contraindicated the use of those agents.

SOLUTION
Each patient began treatment with zafirlukast, 20 mg orally twice per day. Within 2 days, the erythroderma of patient 1 subsided and his atopic dermatitis is now limited to scattered erythematous patches involving less than 15% of his body surface area while continuing zafirlukast therapy. In patient 2, the dermatitis subsided within 2 weeks and his skin remains markedly improved 6 weeks after therapy was begun. In patient 3, no eczematous patches remained after 2 weeks of therapy. The patient was able to discontinue treatment with antihistamines and topical corticosteroids. In patient 4, the prednisone dosage was reduced to 5 mg/d and his atopic dermatitis subsided to several patches involving less than 5% of his body surface area within 2 weeks of starting treatment with zafirlukast.
We report 4 cases, the first thus published, in which the cysteinyl leukotriene (LT) inhibitor zafirlukast successfully alleviated symptoms of atopic dermatitis. Zafirlukast is currently available in the United States as Accolate (Zeneca Pharmaceuticals, Wilmington, Del) and is indicated in the treatment of mild to moderate asthma.1

Atopic dermatitis may be defined as a chronically relapsing, eczematous disorder associated with a history of asthma, a family history of atopic disease, or elevated serum levels of IgE.2 While the pathogenesis of atopic dermatitis is not completely understood, increasing evidence supports the potential role of soluble mediators, including LTs.3,4 Leukotriene antagonists have been used successfully in the treatment of asthma and allergic rhinitis.5-7 However, the potential therapeutic benefit of these agents in inflammatory disorders of the skin is yet to be determined.

The LTs are metabolites of the arachidonic acid pathway.8 Arachidonic acid, 1 of the 3 essential fatty acids, is released from membrane phospholipids through the activation of phospholipase A2. Arachidonic acid metabolism proceeds via 2 major pathways. The cyclooxygenase pathway leads to synthesis of prostaglandins and thromboxane while the 5-lipoxygenase pathway leads to synthesis of the LTs. Leukotriene synthesis begins with the translocation of activated 5-lipoxygenase to the cell membrane where it forms a complex with 5-lipoxygenase activating protein. This complex catalyzes the metabolism of arachidonic acid to 5-hydroperoxyeicosaenoic acid and subsequently to LTA4, which may be converted to LTE4, or may be conjugated with glutathione to form LTC4 and subsequently LTD4 and LTE4.

Leukotrienes mediate chemotaxis, airway constriction, smooth muscle contraction, and vascular permeability.9 Zafirlukast has been shown to inhibit LTD4 and histamine-mediated cutaneous vascular permeability.10 This function indicates a potential role for zafirlukast in a number of inflammatory skin disorders.

Zafirlukast appeared to be well tolerated in previous clinical trials for asthma.11 The most commonly occurring adverse effects included pharyngitis and headache. In addition, zafirlukast has been infrequently associated with elevations in alanine aminotransferase values, which resolved with the discontinuation of the drug. It is likely that zafirlukast inhibits the cytochrome P-450 system and has been associated with increased prothrombin time values in patients concomitantly treated with warfarin. No adverse effects were experienced by our patients.

It appears that zafirlukast alleviated the symptoms of atopic dermatitis in the patients described herein. More extensive and controlled studies of zafirlukast in individuals with atopic dermatitis as well as other inflammatory skin disorders will be necessary to evaluate the potential role of LT antagonists as therapeutic agents for cutaneous disease.