Treatment of recalcitrant atopic dermatitis with omalizumab

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Atopic dermatitis is a common diagnosis that presents a therapeutic challenge. Although multiple therapeutic modalities exist, there is no single monotherapy that has proven exceptional in ameliorating the symptoms of this disease. Current topical and systemic therapeutic options offer benefit but carry varying degrees of adverse effects that often limit their application. We present 3 patients with severe, recalcitrant atopic dermatitis successfully treated with omalizumab. (J Am Acad Dermatol 2006;54:68-72.)

Atopic dermatitis is a chronic cutaneous inflammatory disease that begins in childhood and often persists into adulthood.[1,2] It is characterized by pruritic skin lesions and frequently associated with respiratory allergy, an atopic diathesis, or both.[2] The syndrome of atopy may include allergic rhinoconjunctivitis, allergic asthma, and atopic dermatitis.[3] This is often associated with an elevated serum immunoglobulin E (IgE) level. A multitude of factors contribute to atopic dermatitis, including secondary infection, environmental allergens, temperature and environmental changes, psychologic stress, and exogenous irritants.[1] For unclear reasons, the prevalence of atopic dermatitis is increasing—estimates postulate involvement of greater than 20% of the general population.[4,5]

The clinical manifestations of atopic dermatitis are characteristic. Severe pruritus with resultant scratching and cutaneous lesions is typically diagnostic. Pruritus is often worse at night, leading to disturbances in sleep.[2]

Most cases of moderate to severe atopic dermatitis do not respond satisfactorily to any single therapeutic modality and many management strategies are limited by their systemic toxicities. Currently we do not have effective monotherapies with acceptable safety profiles to control the symptoms of this disease.

Omalizumab (Xolair, Novartis, East Hanover, NJ) is a recombinant DNA-derived humanized IgG16-kappa monoclonal antibody to human IgE. Omalizumab is currently approved for the treatment of asthma in patients 12 years and older with serum IgE levels not exceeding 700 IU/mL. We have evaluated the efficacy of omalizumab in 3 patients aged 10 to 13 years with refractory atopic dermatitis and IgE levels far exceeding those of patients with asthma, with the goal of evaluating the efficacy and safety of this agent in the management of this disease.

CASE SERIES

Case 1

A 10-year-old African American girl with recalcitrant atopic dermatitis presented for treatment. The patient was thin, short statured, and otherwise healthy, with a family history of atopy. Laboratory analysis revealed a serum IgE level of 1990 IU/mL (normal range 0-393 IU/mL). Prior therapies included topical corticosteroids (triamcinolone, halobetasol), topical tacrolimus, bland emollients, repeated courses of oral antibiotics (trimethoprim-sulfamethoxazole), systemic corticosteroids, sedating and nonsedating H1-blocking antihistamines (diphenhydramine, hydroxyzine, cetirizine), leukotriene inhibitors (montelukast), and cyclosporine. Bacterial cultures from skin swabs were positive for methicillin-resistant *Staphylococcus aureus*. The patient was positive for 7 aeroallergens by radioallergosorbent testing. After extensive topical and systemic therapies with minimal response, the patient was treated with omalizumab (300 mg subcutaneously [two injections]), repeated at 2-week

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Table I. Therapeutic outline of 3 patients treated with omalizumab for recalcitrant atopic dermatitis

	Patient 1	Patient 2	Patient 3
Discontinued before omalizumab therapy	Prednisone, cyclosporine	Prednisone, cyclosporine, UV therapy	Prednisone
Visit*	Omalizumab†	Omalizumab†	Omalizumab†
1	Start 300 mg	Start 150 mg	Start 150 mg
2	Continue 300 mg	Continue 150 mg	Continue 150 mg
3	Increase to 450 mg	Increase to 300 mg	Continue 150 mg
4	Continue 450 mg	Increase to 450 mg	Continue 150 mg
5	Continue 450 mg	Continue 450 mg	Increase to 300 mg
6	Continue 450 mg	Continue 450 mg	Continue 150 or 300 mg
7	Continue 450 mg	Continue 450 mg	Continue 150 or 300 mg
8	Continue 450 mg	Continue 450 mg	Continue 150 or 300 mg
9	Continue 450 mg	Continue 450 mg	Continue 150 or 300 mg
10	Continue 450 mg	Continue 450 mg	Continue 150 or 300 mg
11	Continue 450 mg	Continue 450 mg	Continue 150 or 300 mg
12	Continue 450 mg	Continue 450 mg	Continue 150 or 300 mg
Concurrent medications	TMP-SMX, tacrolimus ointment, triamcinolone ointment, montelukast, hydroxyzine	TMP-SMX, tacrolimus ointment, triamcinolone ointment, montelukast, hydroxyzine, cetirizine	Tacrolimus ointment, montelukast, hydroxyzine

TMP-SMX, Trimethoprim-sulfamethoxazole.
*Patient visit intervals were approximately 2 weeks.
†Omalizumab injected as subcutaneous injection.

intervals (Table I). During her therapy, she continued using trimethoprim-sulfamethoxazole, topical tacrolimus and triamcinolone ointment, montelukast, and hydroxyzine. The dose was subsequently increased to 450 mg (3 injections). The patient noted a significant improvement during the first 2-week treatment period and continued to improve thereafter. All laboratory examinations (comprehensive chemistry panel, complete blood cell count with differential, urinalysis) continued to produce normal results with monthly monitoring throughout her therapeutic course.

Case 2

A thin, short-statured, 13-year-old Caucasian boy with an 11-year history of atopic dermatitis presented with intractable itching. At the time of presentation, the patient had involvement of approximately 80% total body surface area. The patient was positive for 12 aeroallergens by radioallergosorbent testing. Previous therapeutic regimens included bland emollients, topical corticosteroids (hydrocortisone butyrate, trimacinolone), antihistamines (hydroxyzine, fexofenadine), montelukast, topical tacrolimus, trimethoprim-sulfamethoxazole, oral prednisone, and cyclosporine. The patient was refractory to all therapies and combinations. Laboratory analysis revealed a serum IgE level of 6120 IU/mL (normal range 2-170 IU/mL). Omalizumab was started in the patient (150 mg subcutaneously [one injection]) in 2-week intervals (Table I). After initial failure to show improvement, the dose was increased to 300 mg (two injections) on the third dose and 450 mg (3 injections) on the fourth dose. After the fourth treatment, the patient had an approximate 50% improvement by patient and physician global assessment. The patient continued to improve with continued treatments at 450-mg dosing in addition to continuation of trimethoprim-sulfamethoxazole, topical triamcinolone and tacrolimus, leukotriene receptor blockers, and histamine blockade (Fig 1). Monthly laboratory examination findings (comprehensive chemistry panel, complete blood cell count with differential, urinalysis) remained normal during therapy.

Case 3

A short, thin, 12-year-old Caucasian boy with chronic atopic dermatitis presented with intractable pruritus. The patient had approximately 80% body surface area involvement and medical history of asthma. The patient was positive for 15 aeroallergens by radioallergosorbent testing. He had been treated with multiple doses of oral prednisone and corticosteroid inhalers. His parents requested that oral prednisone not be used because of prior chronicity of use. Laboratory examination revealed a baseline serum IgE level of 2890 IU/mL (normal range 2-170 IU/mL). Pulmonary function tests were also performed, demonstrating changes consistent with asthma. Topical tacrolimus, montelukast, and

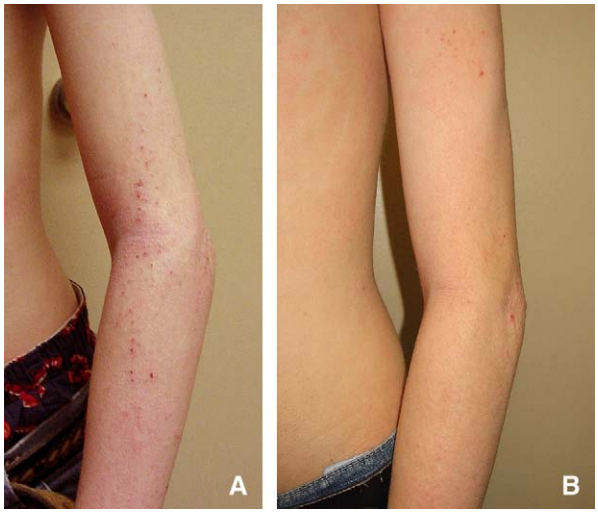

Fig 1. Comparison of pretreatment (**A**) and 4 months of therapy with omalizumab (**B**) of patient 2.

hydroxyzine were initially started in the patient with only mild improvement. Omalizumab was started at 150 mg (subcutaneously) at 2-week intervals (Table I). He continued using topical tacrolimus, montelukast, and hydroxyzine after initiation of omalizumab. The dose was increased to 300 mg and subsequent doses of either 150 mg (one injection) or 300 mg (two injections) were administered at 2-week intervals based on clinical severity. The patient's cutaneous examination markedly improved and he was tapered from his corticosteroid inhaler and nebulizer after previous daily use for several years. All laboratory examination results (comprehensive chemistry panel, complete blood cell count with differential, urinalysis) remained normal with monthly monitoring.

DISCUSSION

Atopic dermatitis is a multifactorial disease—its pathophysiology has been linked to immunologic mechanisms demonstrated by cytokine patterns and immunoglobulin profiles. Acute atopic dermatitis is characterized by a Th_2 immune response (IL-4, IL-5) whereas chronic atopic dermatitis is more encompassed by a Th_1 immune profile (IL-2, TNF-alpha).[2] Multiple factors are involved in the differentiation of these immune responses and are reviewed in detail by Leung and Soter.[2]

Although diagnosis is often straightforward, management remains a therapeutic challenge. A multitude of therapeutic options exist, ranging from bland emollients to potent topical and systemic medications. The presence of elevated serum IgE levels and high-affinity FcεRI receptors on mast cells and mononuclear antigen-presenting cells in patients with atopic dermatitis identifies a potential pharmacotherapeutic target. We examined the use of omalizumab, a recombinant DNA-derived humanized IgG16-kappa antibody against human IgE, to treat refractory atopic dermatitis.

The Th_2 immune response in atopic dermatitis is marked by eczematous cutaneous lesions, eosinophilia, and elevated serum IgE levels. The role of eosinophils and IgE in atopic dermatitis has been extensively reviewed.[3,6] High-affinity IgE receptors (FcεRI) are prominent in atopic dermatitis.[3] These FcεRI receptors are present on mast cells and mononuclear antigen-presenting cells.[4] Such mononuclear antigen-presenting cells include macrophages, Langerhans cells, dermal dendritic cells, and inflammatory dendritic epidermal cells, which lack Birbeck granules, have weaker anti-CD1a reactivity (compared with Langerhans cells), but possess more affinity to anti-FcεRIα receptors.[5] The significance of this high-affinity receptor for IgE has been demonstrated by studies in which blockade of the FcεRI receptor site by anti-FcεRI antibodies results in a paucity of allergen binding.[7,8] FcεRI-bound allergen-specific IgE have been unequivocally detected in patients who are allergic.[8] In addition, Valenta et al[9] demonstrated that patients with atopy have circulating IgE antibodies against various human proteins, suggesting that IgE-defined allergens need not be derived from exogenous sources.[3,10,11] Hide et al[12] postulated that patients with atopic dermatitis exhibit IgE-mediated hypersensitivity to human sweat antigen. Multiple studies have indicated the role of IgE-reactive autoantigens in atopic dermatitis.

Our patients are unique as their IgE levels far exceeded the typical range previously considered acceptable for treatment with omalizumab (>700 IU/mL). Patients with severe atopic dermatitis are often marked by a profound Th_2 profile, as exemplified by extreme levels of IgE. This association is clearly demonstrated by our patients with serum IgE levels ranging from 1990 to 6120 IU/mL. As these patients failed to improve with conventional therapies, a trial of a potentially more effective alternative (omalizumab) was indicated. A recent report by Krathen and Hsu[13] found no benefit in treating severe adult atopic dermatitis with omalizumab; however, omalizumab in combination therapy was useful in our 3 patients.

Patients were monitored closely for clinical changes and potential adverse effects. No patients developed injection-site reactions nor were any other adverse effects reported. Further, routine monthly comprehensive laboratory analysis, including comprehensive metabolic panel, complete blood

cell count with differential, and urinalysis were performed based on the theoretic concern of immune complex formation, serum sickness, or both; however, no abnormalities were identified.

The most commonly reported adverse effects of omalizumab in one study included headache (15%), dizziness (9%), and acute urticaria (9%).[14] The authors noted no other serious adverse events, no antibodies detected to either omalizumab or high-affinity IgE receptors, and no clinically significant laboratory changes.[14] A larger study of 419 patients reported the most common side effects to be lower respiratory tract infections and nasopharyngitis along with a slight increase of injection-site reactions (5.3% vs 1.3% with placebo).[15] However, the overall incidence of adverse effects in patients treated with omalizumab compared with those treated with placebo was 72.2% and 75.5%, respectively.[15] The US labeling for omalizumab noted similar findings, with 45% of patients treated experiencing injection-site reactions versus 43% of patients treated with placebo.[16]

Omalizumab has warnings for both malignancy and anaphylaxis; however, their incidence appears to be remote. A database of 4127 patients treated with omalizumab revealed 20 cases of malignancy with an incidence of 0.5% compared with 0.2% in control patients.[16,17] Of these, several were recurrences of pre-existing disease and the majority occurred in less than 1 year.[16,17] Further analysis of the incidence of malignancy with omalizumab demonstrated a similar incidence with the general population.[17] Only 3 patients in a database of 4127 patients (<0.1%) had anaphylaxis-like reactions.[16] Omalizumab only binds free IgE without cross-linking IgE that is already bound to FcϵRI receptors, thus, minimizing the risk of anaphylaxis.[17,18]

The US labeling for omalizumab notes 1 in 1723 (<0.1%) of patients to have low titers of antibodies to omalizumab.[16] In a study of 282 patients retreated with omalizumab, there were no detectable antibodies to omalizumab.[19] No clinical cases of serum sickness syndrome potentially related to immune complex deposition have been reported.[17]

Current dosing is intended for patients with asthma. Dosing is based on weight and serum IgE level with a maximum dose. As most patients with severe atopic dermatitis have profoundly elevated serum IgE levels, the current dosing guide is arbitrarily prohibitive and must be re-examined. IgE levels were not reassessed after the treatment course as it is known that total serum IgE levels are elevated during treatment as a result of formation of omalizumab:IgE complexes and that elevated serum IgE may persist for up to 1 year posttreatment. Per recommendations from asthma trials, IgE levels during this period should not be used to monitor therapeutic response or to determine future dosing.[16]

This report is novel for several reasons. First, we present a novel therapeutic indication for omalizumab as adjunctive therapy in children with severe atopic dermatitis. Second, this study deviates from the approved standard dosing regimen guidelines for asthma, as the IgE levels in our patients far exceed the current therapeutic cut-off IgE level of 700 IU/mL. Third, omalizumab was administered in different subcutaneous sites at each treatment session to cause less pain. In addition, use of lidocaine before omalizumab injection made for easier administration. Administration of omalizumab is simple; however, its viscosity may preclude home administration. In addition, the need for proper mixing before dispensing makes this difficult to administer outside of the clinical setting.

Optimal candidates with atopic dermatitis are likely those with severe, refractory cases in which systemic therapies were not successful. Combination therapy such as with psoriasis appears most useful. Care must be taken to taper patients with asthma concurrently using inhaled corticosteroids to avoid exacerbation before onset of action of omalizumab. Omalizumab may represent a safer alternative to traditional therapies when treating individuals with severe atopy who remain unresponsive to other therapeutic measures.

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