

Anti-Immunoglobulin E in the Treatment of Refractory Atopic Dermatitis

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Abstract: Atopic dermatitis (AD) is a common diagnosis seen in both children and adults, and it is often the first manifestation of atopic disease. Research has shown a strong correlation between serum IgE levels, the severity of atopic dermatitis, and co-existing asthma and/or allergic rhinitis.¹⁸ Omalizumab (Xolair®, East Hanover, NJ; Genentech, South San Francisco, CA) is a monoclonal antibody to human IgE and is currently Food and Drug Administration (FDA) approved for the treatment of asthma. We present 3 patients with severe, treatment resistant atopic dermatitis whose cutaneous symptoms significantly improved by treatment with omalizumab.

Key Words: atopic dermatitis, IgE, omalizumab, Xolair®

Atopic dermatitis (AD) is a chronic inflammatory cutaneous disease and is considered to be the most common chronic skin disease of childhood.¹ Recent studies suggest the prevalence of the disease is increasing, approaching 17% in school-age children.² Although many patients may “outgrow” the disease; others may experience disease progression into adulthood. In fact, as many as 58% of infants with AD continue to suffer with persistent inflammation 15–17 years after diagnosis. This pattern of chronic inflammation is characterized by lichenification, thickened skin, hyperpigmentation, and the presence of a debilitating scratch-itch cycle. These processes can impair AD patient’s quality of life, affecting their sleep cycles, work or school performance, and overall emotional well being.^{3,4}

Atopic dermatitis is often the first demonstration of a hereditary phenomenon known as the atopic triad, which includes atopic dermatitis, allergic rhinitis, and asthma.⁶ It has been reported that more than 50% of AD patients eventually

develop asthma and about 75% develop allergic rhinitis.⁴ One of the believed associations with this hereditary predisposition of atopic disease is the production of immunoglobulin E (IgE) antibodies against environmental allergens.⁴ In fact, the skin of AD patients contains increased IgE-bearing Langerhans cells, and upon application of aeroallergens to the skin, the high affinity IgE receptors on this cell type have been found to be critical in provoking the eczematous skin lesions in AD patients. IgE production is influenced by many immunologic mediators involved in inflammation, such as cytokines and interleukins, specifically IL-4, IL-5, and IL-13.⁷ Because the pathogenesis of atopic dermatitis appears to be a complex interaction of genetic predisposition, skin barrier defects, environmental factors, and immunological dysregulation, an optimal therapeutic approach, targeting its etiology, remains to be discovered.⁴

Current therapies for atopic dermatitis include proper skin hydration, topical anti-inflammatory agents, anti-pruritic agents, anti-infectious agents, phototherapy, and systemic therapies including immunomodulators.¹ For milder forms of the disease, topical agents such as topical glucocorticoids and topical calcineurin inhibitors are usually effective, controlling acute exacerbations of skin disease. However, more severe forms of AD often do not respond to monotherapy, requiring combinations of both topical and systemic therapies.⁸ Unfortunately, many of the current systemic therapies, such as cyclosporine, azathioprine, and methotrexate, have adverse side effect profiles, limiting their use in patients.⁹ Ideally, treat-

Key Points

- Atopic dermatitis is often the first demonstration of a hereditary phenomenon known as the atopic triad, which includes atopic dermatitis, allergic rhinitis, and asthma.
- Current therapies for atopic dermatitis include proper skin hydration, topical anti-inflammatory agents, anti-pruritic agents, anti-infectious agents, phototherapy, and systemic therapies including immunomodulators.
- Omalizumab is a DNA-derived, recombinant humanized monoclonal antibody specific for the Fc-binding domain of IgE.

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ment for moderate to severe cases of AD would consist of a safe, effective systemic therapy targeting the pathophysiological processes in this disease.

Omalizumab (Xolair®, Novartis, East Hanover, NJ; Genentech, South San Francisco, CA) is a DNA-derived, recombinant humanized monoclonal antibody specific for the Fc-binding domain of IgE.¹⁰ This binding reduces the serum levels of free IgE and by occupying free IgE's Fc region; this prevents IgE from attaching to circulating inflammatory cells, such as basophils, mast cells, and other immunologic mediators.¹¹ In addition, omalizumab therapy also downregulates FcεRI receptor expression on mast cells, basophils, and antigen presenting cells, such as dendritic cells, and T-cell activation may be decreased.¹¹ The Food and Drug Administration (FDA) has approved omalizumab for the treatment of moderate persistent to severe persistent asthma in patients 12 years and older. The patients must also be symptomatic, using inhaled corticosteroids, as well as have a positive skin test to aeroallergens.⁶ The recommended omalizumab dosing is based on body weight and pre-treatment serum IgE levels, where the upper limit of serum IgE levels studied was 700 IU/mL.¹² Omalizumab is administered subcutaneously every 2 or 4 weeks and doses greater than 150 mg are divided among more than one injection site. Omalizumab is an expensive medication with a current average wholesale price per vial of \$541.25 (annual minimum cost estimated at \$6495.00).¹³ Off-label treatment uses of omalizumab are being explored in other atopic diseases, such as allergic rhinitis, food allergies, and atopic dermatitis. Omalizumab is also being explored in the treatment of chronic autoimmune urticaria since this condition is thought to be related to anti-FcεRIα antibodies, and Fcε receptor cell surface expression is feed-back-regulated by free serum IgE levels.¹⁴

Recent case studies of omalizumab for the treatment of severe atopic dermatitis have reported both failures and successes.^{11,12} In some studies low dose therapy appears effective while in others dose escalation was necessary.^{12,15} One prospective study with twenty one patients showed clinical improvement.¹⁷ We present 3 severe, treatment resistant AD patients (aged 6–38 years) who all improved with varying magnitudes by omalizumab therapy. All patients had a history of asthma, allergic rhinitis, and atopic dermatitis since early childhood (age ≤2). All patients had ImmunoCAP® testing (UniCAP® 100 [ImmunoCAP 100]; Pharmacia Diagnostics AB, Uppsala, Sweden) performed, testing positive to numerous aeroallergens and food allergens, and high IgE titers (1,429–36,732 IU/mL). Physician assessments on initial presentation and on 12 week follow up after initiation of omalizumab therapy were used to generate SCORAD (SCORing Atopic Dermatitis) objective scores. Developed by the European Task Force in 1993, the SCORAD index is the most commonly used scoring system for measuring the severity of atopic dermatitis and is often performed prospectively by clinicians

in their office.^{18,19} An objective SCORAD score can be used to determine the severity grading for atopic dermatitis into 3 categories: mild (objective SCORAD <15), moderate (objective SCORAD 15–40), and severe (objective SCORAD >40).¹⁸ This was done retrospectively in our case review with the physician who performed the initial examination on all 3 patients as well as the follow-up patient evaluations and examinations.

Case Series

Case One

A 12-year-old Caucasian female with severe, refractory atopic dermatitis presented to the clinic with complaints of intractable pruritus. The patient was diagnosed with AD at 15 months of age, and she reported a dramatic worsening of her eczema over the last 5 years. Her past medical history was also significant for moderate persistent asthma and allergic rhinitis. She had a family history significant for a mother with allergic rhinitis. On physical examination, erythematous plaques with areas of lichenification and excoriations were noted covering most of her body, with the most extensive lesions on her upper and lower extremities. Initial SCORAD objective score was 78 (Table 1), graded as severe AD. Prior therapies included topical corticosteroids, topical calcineurin inhibitors, bland emollients, diluted bleach baths, oral doxepin, nonsedating antihistamines, leukotriene inhibitors, and a 2 month course of methotrexate. She also required courses of antibiotic therapy, as well as multiple courses of oral steroid dosing for acute flares in her AD. ImmunoCAP® testing was performed, which was positive for 16 aeroallergens and 11 food allergens. Her serum IgE level was 36,732 IU/mL (normal range 0–393 IU/mL). She was started on omalizumab 375 mg subcutaneously [3 injections] given every 2 weeks. During her treatment with omalizumab, the patient continued her therapy of montelukast, cetirizine, pimecrolimus, fluticasone ointment, and oral doxepin. Mild improvement was noted at the first two week treatment period and by physician assessment; moderate improvement was noted at 12 weeks after initiating therapy. The SCORAD objective score at 12 weeks was 40.7, still graded as severe AD; however, this improvement almost changed her severity grading to moderate AD (Table 2). The patient remains on omalizumab after 18 months of therapy. Over the course of her therapy, she only required one treatment with oral steroids for an eczema flare. Currently, the patient continues to have mild to moderate atopic dermatitis requiring topical steroid ointments; however, she no longer requires oral steroid regimens.

Case Two

A 38-year-old Caucasian male with a past medical history significant for severe persistent asthma, allergic rhinitis, and atopic dermatitis, was referred for severe, recalcitrant

Table 1. Clinical summary for 3 severe atopic dermatitis patients treated with omalizumab^a

Age, race, sex	History of atopy	Prior therapies	Initial skin examination	ImmunoCAP [®] testing	Initial IgE level (IU/mL)
12-yr-old, Caucasian, female	asthma, allergic rhinitis, atopic dermatitis	extensive topical & oral treatment, 2 month course of methotrexate	Diffuse erythematous plaques, lichenification, & excoriation, most severe on arms & legs SCORAD objective score = 78	16 aeroallergens & 11 food allergens	36,732
38-yr-old, Caucasian, male	asthma, allergic rhinitis, atopic dermatitis	extensive topical & oral treatment, etanercept injections biweekly	Diffuse erythematous plaques & post inflammatory hyperpigmentation, most severe on upper arms & hands SCORAD objective score = 70.8	17 aeroallergens & 6 food allergens	1429
6-yr-old, African American, male	asthma, allergic rhinitis, atopic dermatitis	extensive topical & oral regimes only	Diffuse, scaly hyperpigmented plaques, most severe on face & abdomen SCORAD objective score = 73.9	16 aeroallergens & 13 food allergens	4090

^aSCORAD, SCORing Atopic Dermatitis.

eczema. He reports being diagnosed with AD at age 2 and reports having allergen immunotherapy as a child. His family history was significant for a mother diagnosed with Crohn disease; however, there was no family history of atopic diseases. On physical examination, diffuse erythematous plaques and areas of hyperpigmentation were noted, which were worse on the upper arms and hands. Initial SCORAD objective score was 70.8 (Table 1), graded as severe AD. Prior therapies included oral doxepin, nonsedating antihistamines, topical corticosteroids, topical calcineurin inhibitors, and etanercept injections twice weekly (to treat suspected psoriatic component in his dermatitis). ImmunoCAP[®] testing was performed, which was positive for 17 aeroallergens and 6 food allergens. He had serum IgE level of 1429 IU/mL (normal range 0–393 IU/mL). He was started on omalizumab 375 mg subcutaneously [3 injections] given every 2 weeks. During his treatment with omalizumab, the patient continued his therapy of cetirizine, clobetasol cream, doxepin, and pimecrolimus. The

patient stopped taking etanercept approximately 12 weeks after initiation of omalizumab treatment. The patient's cutaneous symptoms showed mild improvement by 4 weeks, and he continued to improve subsequently. The SCORAD objective score at 12 weeks was 49.7, graded as severe AD but improved from his initial presentation (Table 2). In addition, the patient's respiratory symptoms markedly improved with omalizumab therapy. Approximately 2 months after omalizumab initiation, allergen immunotherapy was started, and the patient continued to improve with no side effects reported. Unfortunately, despite initial improvement, the patient decided to discontinue omalizumab therapy after approximately 11 months due to time constraints in his work schedule, as well as economic factors.

Case Three

A 6-year-old African American male with a past medical history significant for severe persistent asthma, allergic rhi-

Table 2. Therapeutic summary for 3 severe atopic dermatitis patients treated with omalizumab^a

Age, race, sex	Omalizumab dosage	Evaluation at 12 wk of omalizumab therapy	Duration of treatment with omalizumab	Change in severity grading of atopic dermatitis
12-yr-old, Caucasian, female	375 mg SC qowk	Moderate improvement by physician assessment, SCORAD objective score = 40.7	18 mo of treatment, with continued therapy	Severe AD→borderline moderate AD SCORAD: 78→40.7
38-yr-old, Caucasian, male	375 mg SC qowk	Mild improvement by physician assessment, SCORAD objective score = 49.7	11 mo	Severe AD→improved, severe AD SCORAD: 70.8→49.7
6-yr-old, African American, male	300 mg SC qowk	Significant improvement by physician assessment, no active lesions, SCORAD objective score = 14.1	3 mo	Severe AD→mild AD SCORAD: 73.9→14.1

^aAD, atopic dermatitis; SCORAD, SCORing Atopic Dermatitis; SC, subcutaneously; qowk, every other week.

nititis, and severe atopic dermatitis was seen for allergy consultation. The patient was diagnosed with AD shortly after his birth. His family history was significant for a father with asthma and allergic rhinitis. On physical examination, scaly, hyperpigmented plaques were present diffusely over his entire body with the most severe lesions present on his face and abdomen. Initial SCORAD objective score was 73.9 (Table 1), graded as severe AD. The patient was of normal weight and stature and appeared healthy. Prior therapies included doxepin, nonsedating antihistamines, leukotriene inhibitors, topical corticosteroids, topical calcineurin inhibitors, and emollients. ImmunoCAP® testing was performed, which was positive for 16 aeroallergens and 13 food allergens. He had a serum IgE level of 4090 IU/mL (normal range 0–393 IU/mL). He was started on omalizumab 300 mg subcutaneously, given every 2 weeks. During his omalizumab therapy, the patient continued his pretreatment therapy of cetirizine, clobetasol cream, montelukast, mometasone furoate ointment, and pimecrolimus. Within 4 weeks of starting omalizumab, the patient's cutaneous symptoms significantly improved, and, at 12 weeks, he had sparse eczematous lesions. The SCORAD objective score at 12 weeks was 14.1, graded as mild AD; this was significant improvement from his initial presentation (Table 2). Doxepin was discontinued at 6 weeks, and allergen immunotherapy was started at 8 weeks. The patient continued to markedly improve thereafter, and omalizumab was discontinued after approximately 3 months of therapy. Since beginning omalizumab therapy, he has experienced only rare, very mild exacerbations in his atopic dermatitis.

Discussion

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to IgE at its high affinity FcεRI receptor binding site.⁶ In addition, treatment with omalizumab leads to downregulation of the FcεRI receptor expression on mast cells, basophils, and antigen presenting cells, such as dendritic cells, and T-cell activation may be decreased.¹¹ The specific pharmacotherapeutic target of omalizumab has led to off-label uses in other atopic diseases, such as atopic dermatitis. We examined the use of omalizumab in 3 patients with severe atopic dermatitis.

Omalizumab has overall been well tolerated, but there are concerns for anaphylaxis and heart disease. The most common adverse event reported is injection site reaction.¹¹ Other adverse effects include headache, dizziness, upper respiratory tract infection, pharyngitis, viral infections, and acute urticaria.^{11,12} In one study, it was reported that patients treated with omalizumab had an overall incidence of adverse effects of 72.2% as compared to 75.5% in the placebo group. In another study, there were also no antibodies found against the high affinity IgE receptor or to omalizumab.¹² In clinical studies, the most adverse reactions were anaphylaxis (0.1%) and malignancies (0.5%). However, there was no statistically significant difference of malignancy comparing patients treated with oma-

lizumab to placebo.⁶ There has been concern over delayed anaphylactic reactions to omalizumab and the FDA has given the drug a boxed warning. In a recent review, “post-marketing, based on estimated exposure of 57,300 patients (June 2003–December 2006), the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of patients.”²⁰ The FDA is currently conducting a study examining a disproportionate increase in cardiovascular problems” in patients receiving Xolair®. In our study, none of the patients experienced any adverse effects from omalizumab.

The three patients in this study all experienced clinical improvement and decreased exacerbations in their AD after being treated with omalizumab. However, the patients continued to have some flaring in their symptoms of AD, and the level of clinical improvement for each patient varied. The differences in their clinical outcomes may reflect the multifactorial etiology of AD, with IgE as one of several potential mediators. Interestingly, the youngest patient had the most clinical improvement, yet this could be contributed to the natural progression of AD, with many children “outgrowing” the disease with age. Although the precise role of IgE in atopic dermatitis is not known, several reports have shown that atopic dermatitis patients have the highest serum IgE levels of allergic diseases.²¹ In patients with very high IgE levels and eczema, hyper-IgE syndrome (Job syndrome) must be considered in the differential diagnosis; however, none of the patients in this case series had the typical recurrent staphylococcal lung infections and skin abscesses as seen in Job syndrome. The serum IgE levels in our patients were much higher than those included in the initial studies of asthma patients treated with omalizumab; however, omalizumab therapy is not contraindicated in serum IgE levels greater than 700 IU/mL. The pretreatment serum IgE levels ranged from 1,429 to 36,732 IU/mL in our patients, and this could account for the therapeutic success seen in these highly atopic patients. In addition, the varying magnitudes of clinical improvement of our patients could reflect insufficient dosing of omalizumab, since their pretreatment IgE levels fell outside the dosing administration table.

Conclusion

Taking into account financial expenses and unknown long term risks of malignancy, omalizumab should be considered for treatment resistant AD patients, in particular those with high IgE levels, whose symptoms are not controlled by routine therapeutic regimens. This medication certainly has proven useful in treating asthma, but the continued exploration of omalizumab in the treatment of other conditions, such as allergic rhinitis, food allergies, chronic urticaria, and atopic dermatitis, may be beneficial as shown in this case series. Omalizumab could potentially be used as a safer alternative in the future, sparing the use of high potency topical corticosteroids, oral steroid dosing, and systemic therapies. The

data from this small, retrospective case series provides further preliminary evidence indicating the advantageous effects of anti-IgE therapy in the treatment of severe, refractory atopic dermatitis. There is one small prospective study documenting improvement with omalizumab and atopic dermatitis, but future, large randomized, double-blind, placebo-controlled, multicenter trials are warranted to adequately assess omalizumab's efficacy in AD patients and to see if certain subsets of patients benefit more than others.

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