Case Report

Successful Treatment by Combination Therapy of Omalizumab (Anti-IgE) and House Dust Mite Allergen Immunotherapy for Severe Refractory Steroid-Dependent Atopic Dermatitis with Rhinitis and Asthma - A Case Report-Follow Up for 5 Years

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Abstract

Chronic Atopic Dermatitis (AD) is characterized by genetic predisposition, skin barrier disruption and aberrant immune response to environmental allergens as well as innate immunity dysregulation. The complex interplay among barrier deficiency and immunological mechanism contributes to the development of progression and chronicity of this disease. Most of the patients with moderate to severe AD are unable to receive systemic therapy because of adverse events with currently available immunosuppressants. Systemic corticosteroids are frequently used for severe refractory atopic dermatitis and during exacerbations but many patients also develop adverse side effects.

We report a case of severe refractory steroid-dependent Atopic Dermatitis with Rhinitis and Asthma, early onset difficult to treat, symptoms only responded to oral corticosteroids (OCS). Our patient improved in response to combined therapy by House Dust Mite Subcutaneous Allergen Immunotherapy (HDM SCIT) and Anti-IgE (Omalizumab) for three years and further maintained disease control during follow-up for two years after cessation of therapy. The combined synergistic approach with (HDM SCIT and Omalizumab) resulted in improved Quality of Life and marked decrease in severity of the disease with reasonable safety profile.

ABBREVIATIONS

AD: Atopic Dermatitis; SCORAD: Scoring Atopic Dermatitis; Dp: Dermatophagoides pteronyssinus; Df: Dermatophagoides farinae; HDM: House Dust Mite; SCIT: Subcutaneous Allergen Immunotherapy; RCAT: Rhinitis Control Assessment Test; ACT: Asthma Control Test; DLQI: Dermatology Life Quality Index; OCS: Oral Corticosteroids; PEFR: Peak Expiratory Flow Rate

INTRODUCTION

Atopic Dermatitis (AD) is a common inflammatory skin disease that affects 20%-30% of children and 7% to 10% of adults [1,2]. Skin barrier impairment and abnormal immune response are both critical in the pathogenesis of the disease. The defective epidermal barrier is caused by altered expression of keratinocyte differentiation genes and abnormal content of extracellular lipids, which results in increased permeation to allergens, irritants and microbes [3]. Approximately 20% of patients with AD have moderate to severe forms of the disease and is associated with important immunological markers are elevated serum immunoglobulins E (IgE) levels, Thymic stromal lympho-proteins (TSLP), Thymus and activation regulated chemokine (TARC) and OX40 ligand (OX40L) [4]. The European Academy of Dermatology and Venereology Taskforce on AD defined severe disease as a SCORAD severity score of greater than 40 or BSA involvement is more than 10% and associated with impairment of the patient’s quality of life, such as with regard to sleep quality, emotional, mental health disturbance and interference with daily activities [5].

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House dust mites (HDMs) belong to the most potent indoor allergen sources worldwide and are associated with allergic manifestations in the respiratory tract and the skin. House dust mite allergens display protease activity and are able to disrupt intercellular junction and activate several innate immunity receptors. Few allergens from HDMs have been extensively characterized regarding their IgE binding frequencies, allergic reactions, clinical relevance in diagnosis of HDM allergy. Der p 11 is a major allergen for patients suffering from atopic dermatitis (AD), whereas it is only a minor allergen for patients suffering from respiratory forms of HDM allergy. Allergen-specific immunotherapy containing Der p 11 has shown to be effective for the treatment of AD [Novak et al., 2012] [6,7].

Atopic dermatitis is frequently associated with food allergen sensitization and food challenge proven IgE-mediated food allergy is present in up to one-third of patients with moderate-to-severe atopic dermatitis. Food allergens such as milk, egg and peanut have been related to AD exacerbations especially during childhood [8,9].

Staphylococcus aureus colonizes frequently AD skin. [18] polyclonal enterotoxins activate T-cells have the ability to release huge amount of IgE and other Immunoglobulin isotypes. The staphylococcal enterotoxin B strongly promotes the secretion of Th17/Th22 cytokines and switch toward Th1 and Th 17 profile also could contribute to autoimmune disorders [7].

Omalizumab is a recombinant DNA-derived humanized IgG monoclonal antibody that specifically binds to free human immunoglobulin E in the blood and interstitial fluid. A number of case series describe a beneficial effect of omalizumab in patients with moderate to severe AD [10-12]. This molecule binds specially to the third constant domain of the heavy chain of the human IgE in the Fc region, thus competing with IgE specific receptors (FcεRI and low affinity IgE receptor CD 23), that also binds to IgE by Fc region. The use of monoclonal anti-bodies, like conventional Immunotherapy has not been associated with persistent disease modifying effects. Novel monoclonal antibodies have potential in combination with allergen to augment the effect of conventional Allergen Immunotherapy. When combined with immunotherapy it lessens immunotherapy-associated side-effects, increasing tolerability. This allows patients to receive higher doses faster Immunotherapy is given to higher risk patients with asthma [13].

There is conflicting evidence on the use of AIT for patients with AD. The European Academy of Dermatology’s recent guideline agree with the Joint Task Force that although AIT should not be first-line treatment for all AD patients, there is a subset of highly sensitized patients with house dust mite, birch or grass pollen sensitization with symptom exacerbation that may benefit [14]. The most recent guidelines from the American Academy of Dermatology suggests that there is insufficient data to recommend AIT use, whereas the joint Task Force suggests that clinicians can consider AIT use in select patients with aeroallergens sensitivities [15]. Recommendations posed by Ridolo et al., revolve around three considerations: a) sensitization to aeroallergens must be proven with skin prick test and/or IgE assay, b) exposure to aeroallergens induces AD flare-ups, c) physician must choose a standardized product for AIT [16].

In our experience with this case of severe refractory steroid-dependent Atopic Dermatitis with Rhinitis and Asthma with allergen sensitization to house dust mites and high level of total IgE, has a significant improvement in SCORAD score (Scoring Atopic Dermatitis)- 75/103 to 10/103, DLQI (Dermatology Life Quality Index)-20/30 to 28/30, RCAT (Rhinis Control Assessment Test)-10/25 to 22/25, ACT (Asthma Control Test)-11/25 to 23/25, PEFR (Peak Expiratory Flow Rate)-350 L/mth to 500 L/mths after combining HDM SCIT and anti-IgE (Omalizumab) for 3 years and maintained disease control during follow-up for two years even after cessation of combined therapy by House Dust Mite Subcutaneous Allergen Immunotherapy (HDM SCIT) from Greer Laboratories, Inc and Anti-IgE (Omalizumab) from Novartis Ltd.

**CASE DISCUSSION**

We report the case of a 20 years old male who has been suffering from severe refractory steroid-dependent Atopic Dermatitis with Rhinitis and Asthma, onset at the age of 4 years, poorly responding to conventional treatment (topical corticosteroids, leukotriene inhibitors, anti-histamines, courses of cyclosporin oral and OCS). He has had history of irregular intake of OCS, suspected steroid-dependency, 4-8mg methylprednisolone alternate days (64 mg methylprednisolone per month). Symptoms exacerbate on exposure to dust, ingestion of alcohol, peanuts and eggs. On physical examination we used SCORAD score (Scoring Atopic Dermatitis)- 75/103, DLQI (Dermatology Life Quality Index)-20/30, RCAT (Rhinis Control Assessment Test)-10/25, ACT (Asthma Control Test)-11/25, PEFR (Peak Expiratory Flow Rate)-350 L/mt to assess severity of the disease and Quality of Life to measure subjective and objective parameters.

**In-vivo and In-vitro test:** Table 1: Total IgE->15000 IU/ml, Absolute Eosinophil Count-400 cells/μl, Skin Prick Test (SPT) were positive for D. pteronyssinus- 6mm, D. farinae -6mm, Cockroach-4mm, Egg- 6mm, peanut-4mm.

**Specific IgE:** were positive for D. pteronyssinus- 62.2 Kua/l, D. farinae- 58.0 Kua/l, Cockroach-1.76 Kua/l IU/ml.

**Recommendation**

He was given combined therapy by House Dust Mite Subcutaneous Allergen Immunotherapy (HDM SCIT Greer Laboratories, Inc) and Anti-IgE (Omalizumab 150mg every 3-4 weeks) (Table 2) with effective dose [gradual up-dosing protocol of build-up phase to achieve Maintenance dose (MD) - 500 AU per 4 weeks] with supportive therapy for 3 years. He achieved gradual improvement, SCORAD score-10/103, DLQI-28/30, RCAT-22/25, ACT-23/25, PEFR-500L/mths along with occasional use of OCS (8 mg methylprednisolone per month).

**DISCUSSION**

Our case represents an extreme spectrum of severe refractory steroid-dependent Atopic Dermatitis with Rhinitis and Asthma. Our patient had history of taking cyclosporins 5mg/kg/day but found no significant benefit even after 3 months of therapy and only responded to OCS (4 to 8 mg methylprednisolone) on alternate days.
Table 1: Clinical characteristics of the patient.

<table>
<thead>
<tr>
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<th>2019</th>
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<tbody>
<tr>
<td>SCORAD</td>
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</tr>
<tr>
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<td>28/30</td>
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<tr>
<td>PEFR</td>
<td>350 L/mt</td>
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<td>22/23</td>
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<td>Eosinophil % / AEC</td>
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<td>6.2% / 440 cells/ul</td>
</tr>
<tr>
<td>Serum cortisol</td>
<td>10.1 mcg/dl with 64 mg/month OCS</td>
<td>13.63 mcg/dl with 8 mg/month OCS</td>
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</tbody>
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Table 2: Combined House dust mite extract (Dp-50%, Df-50% 500 AU per MD) for Subcutaneous Cluster doses X 7 visits X 4 months till MD achieved for 3 years as per schedule along with Inj Omalizumab (150 mg) X 15 days before AIT followed by 300 mg every 2-3 weeks till MD-500AU achieved, then 150 mg once a month for 3 years.

| Doses of HDM (Dp-50%, DF-50%) SCIT-500 AU | 0.05 ml (1 dose) 0.05/0.1 ml (2 doses) 0.1/0.15 ml (2 doses) 0.15/0.2 ml (2 doses) 0.2/0.25 ml (2 doses) 0.5 ml (1 dose) 0.5 ml as MD for 3 years 0.5 ml as MD for 3 years 0.5 ml as MD for 3 years |
|-------------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Inj Omalizumab                             | 300 mg 300 mg 300 mg 300 mg 300 mg 300 mg 150 mg 150 mg 150 mg 150 mg 150 mg |
| Cluster Dose frequency                     | First day 50 AU 15 days 15 days 15 days 15 days 20 days 450 AU 20 days 500 AU 20 days 500 AU 20 days 500 AU 20 days 500 AU 20 days 500 AU 4-6 weeks 500 AU |

We used different scales both for the severity of the disease and the compromised Quality of Life before and after treatment with HDM SCIT and Anti-IgE (Omalizumab- Novartis Ltd). The combination to immunotherapy with Omalizumab has been & shown to decrease symptoms score upto 48% Vs SCIT alone with a decrease in rescue medication use during seasonal exposure.

We started combined therapy by House Dust Mite Subcutaneous Allergen Immunotherapy (HDM SCIT Greer Laboratories, Inc) and Anti-IgE (Omalizumab- Novartis Ltd) along with concomitant therapy (moisturizing agent, topical steroids, antihistamines along with tapering dose of OCS-oral methylprednisolone). His skin inflammation settled (SCORAD-10/103, DLQI-28/30, RCAT-22/25, ACT-23/25, PEFR-500L/mts) after 6 months and he continued his therapy along with supportive therapy for 3 years. Patient had an improvement in Quality of Life and severity of disease as well as less side-effect to OCS. We emphasize that in a patient of severe refractory steroid-dependent Atopic Dermatitis with Rhinitis and Asthma; recommend combined therapy is effective therapeutic regime by House Dust Mite Subcutaneous Allergen Immunotherapy (HDM SCIT) and Anti-IgE (Omalizumab- Novartis Ltd).

Though there are multiple articles suggesting the efficacy of AIT in AD. The majority of the clinical trials investigating Allergen Immunotherapy (AIT) as a potential treatment for severe AD with allergen sensitization only concentrate on HDM AIT [17].

Patients with severe refractory Atopic Dermatitis with Rhinitis and Asthma are often polysensitized towards a large number of different allergen molecules and thus exhibit extremely complex IgE sensitization profile as found in our patient and diagnosis was confirmed by Skin Prick Test-9mm wheal size and Specific IgE: D. pteronyssinus-62.2 Kua/L and D. farinae-58.0 Kua/l along with consistent history of exacerbation of symptoms after exposure to dust. Polysensitization contributes to difficult interpretation of clinically relevant allergen for AIT. Our patient has a long history of aggravation of AD and worsening of symptoms of sneezing, wheezing, cough and shortness of breath on dust exposure. Though the exact mechanism by which exposure to the dust in
worsening AD is still unclear nevertheless in patient with AD are patch tested with HDM CD4 T-cells specific to HDM are found in the patch of skin that is suggestive of eczematous characteristics.

It is worthy to note in Figure 1, that a good response was observed in our patient after 6 months of combined therapy by House Dust Mite Subcutaneous Allergen Immunotherapy (HDM SCIT Greer Laboratories, Inc) and Anti-IgE (Omalizumab-Novartis Ltd).

Our findings concur with a similar study made by Ramirez del Pazo et al., in age group of 12-52 years old patients, treated with Omalizumab as an adjuvant therapy and found significant decrease in Dermatological Life Quality Index (DLQI), a questionnaire for adults similar to CDLQI [18]. Carabello et al., showed that in the AIT-treated group with AD there was a statistically significant improvement over control group in SCORAD as well as reduction in overall OCS [19]. Research in AIT efficacy in HDM-sensitized patients showed similar results with a dose-dependent decline in SCORAD after 1 year of AIT therapy and a decrease in OCS use [20]. A similar meta-analysis conducted by Bae at al., included 8 randomized control trials and found that patients with improvements in their AD symptoms had an odds-ratio (OR) of 5.35 of being treated with AIT when compared to placebo [21].

Dupilumab, a monoclonal antibody (mAb) that targets the shared a subunit of the IL-4 and IL-13 receptors and effectively blocks TH2 immune response, was recently approved for the treatment of moderate to severe AD in adults 18 years or older whose disease is not adequately controlled with topical treatments but long term safety profile of dupilumab monotherapy is unknown [22]. Currently there are no published studies combining dupilumab with AIT.

We attribute that combined therapy by House Dust Mite Subcutaneous Allergen Immunotherapy (HDM SCIT Greer Laboratories, Inc) and Anti-IgE (Omalizumab- Novartis Ltd) is potentially effective, safe, and steroid-sparing and improves Quality of Life.

**CONCLUSION**

Severe refractory steroid-dependent Atopic Dermatitis with Rhinitis and Asthma is an extremely complex disease and poses a challenge for clinicians and patients alike. Clinicians should stratify the patients according to their clinical and inflammatory profile. The combined therapy by House Dust Mite Subcutaneous Allergen Immunotherapy (HDM SCIT Greer Laboratories, Inc) and Anti-IgE (Omalizumab- Novartis Ltd) was found to be more durable, showed long term tolerance, efficacious and safe. Further prospective controlled larger trials are required to verify this approach.

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