Combination therapy of omalizumab with house dust mite immunotherapy in chronic spontaneous urticaria associated with sensitization to dust mites-case series

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a heterogeneous disorder with recurrent pruritic wheals and/or angioedema. The anti-immunoglobulin E (omalizumab) is used in CSU patients resistant to four-fold second-generation anti-histamines. Most clinical trials have experienced relapse after stopping omalizumab treatment. Here, we present a case series of five cases of chronic atopic urticarial concomitant allergic rhinitis and asthma which have shown immunologically significant positivity to Dermatophagoides pteronyssinus and Dermatophagoides farinae. Disease control was achieved (Urticaria Activity Score 7 <6) in four cases by combination therapy of omalizumab with house dust mite (HDM) Allergen Immunotherapy (AIT) and remained sustained for three years on follow-up even after discontinuation of AIT for one year. We hypothesize that this combined therapy may contribute to enhanced clinical efficacy, safety, and faster achievement of disease control in CSU.

Key words: Angioedema, Chronic spontaneous urticarial, House dust mite, Omalizumab, Urticaria activity score
The treatment was initiated with combined HDM AIT along with omalizumab. Disease control was achieved within three months and was maintained for one year (UAS 7 improved to 5). Disease control was sustained during three years follow-up without any adverse events (AEs).

**Case 2**

A 52-years-old male presented with complaints of recurrent wheals associated with intense itching all over the body with on and off sneezing and wheezing on dust exposure for the past 2 years. He was diagnosed as a case of CSU associated with allergic rhinitis/asthma. There was no improvement in his symptoms with increasing doses of anti-histamines and OCS (UAS 7 was 26). His total IgE-711 IU/mL, absolute eosinophil count-220 cells/µL, and SPT was positive for DP-5 mm, DF-5 mm (Table 1). He was given combined HDM AIT with Omalizumab. Disease control was achieved within four months of initiating treatment (UAS 7 improved to 4) and was sustained for three years on follow-up.

**Case 3**

A 51-years-old female presented with complaints of recurrent hives, skin rash after the intake of a drug (nonsteroidal anti-inflammatory drugs), sneezing, and wheezing for the past 10 years. She was diagnosed a case of CSU associated with allergic rhinitis and drug allergy. She had no improvement with oral histamines and immunosuppressants (OCS and HCQs) (UAS 7 was 34). Her total IgE-3604 IU/ml, absolute eosinophil count-185 cells/µL, specific IgE was positive for DP-0.49 kUA/L, DF-0.73 kUA/L and SPT was positive for DP-6 mm, DF-6 mm (Table 1). She was given HDM AIT with omalizumab and she achieved disease control within 5 months (UAS 7 decreased to 4) which was maintained for three years on follow-up.

**Case 4**

An 8-years-old male child presented with complaints of oral itching, lip edema, and hives on various parts of the body after intake of raw fruits (apple and peach) along with sneezing and wheezing on exposure to dust since he was six months old. He was diagnosed as CSU associated with allergic rhinitis, asthma, and food allergy. He had been on regular anti-histamines, nebulization with inhaled corticosteroids/Long-acting beta-agonists, and OCS as per need with no improvement (UAS 7 was 30). His total IgE-139 IU/ml, absolute eosinophil count-1997 cells/µL and SPT was positive (wheal size) for DP-7 mm, DF-6 mm (Table 1). He was given HDM AIT with omalizumab and disease control (UAS 7 decreased to 3) was achieved in three months and was maintained for three years on follow-up without any AEs.

**Case 5**

A 67-years-old female presented with a history of spontaneously occurring recurrent pruritus, wheals occurring on various body parts along with itchy eyes, sneezing, running nose, and dyspnea on exposure to dust for the past 20 years. She was diagnosed as a case of CSU associated with contact urticaria, allergic rhinitis, and asthma. The symptoms were poorly controlled even after
anti-histamines, cyclosporine, and low dose OCS (UAS 7 was 32). Her total IgE-1100 IU/ml, absolute eosinophil count-200 cells/µL, specific IgE was positive for DP-37.8 kU/A/L, DF-65.5 kU/A/L, and SPT was positive (wheat size) for DP-6 mm, DF-6 mm (Table 1). She had an anaphylactic reaction to the first dose of HDM AIT so, only Omalizumab was given for 10 months but she responded poorly (UAS 7 reduced to 28). She was diagnosed as the omalizumab-resistant phenotype of CSU.

DISCUSSION

CSU is an immune-mediated disorder that affects 1% of the general population. This chronic condition is associated with various comorbidities, decreased quality of life, and reduced ability to maintain normal activities. There are two endotypes of CSU, Type I autoimmune CSU-mediated by IgE antibodies to auto-allergens (auto-allergic) and Type IIb autoimmune CSU-mediated by autoantibodies that target activating mast cell receptors. High total IgE levels (associated with Type I autoimmune) were related to omalizumab responsive vs. omalizumab resistant CSU phenotype (18% vs. 41%, respectively) while concomitant autoimmunity (which may support Type II autoimmune) was related to resistant-CSU phenotype (55% vs. 20%, respectively) [5,6].

Dietary elimination, antihistamines, and corticosteroids only provide symptomatic relief. Omalizumab was approved for the treatment of CSU in August 2014. The international guidelines on CSU recommend to “treat CSU until it is gone.” The use of second-generation antihistamine (SgAH) at the licensed dose is recommended as the first-line treatment in CSU and up dosing of this SgAH up to four-fold is recommended in treatment-resistant patients. The humanized anti-IgE mAB-Omalizumab is recommended as the only third-line treatment option and is an effective treatment for patients with CSU with any of the 3 phenotypes (wheals only, angioedema only, and wheals plus angioedema) in an effective dose of 300 mg, every four weeks till remission of CSU is achieved (weekly UAS 7 of 0). A retrospective observational study reported that at the end of 3-month therapy, UAS 7 of 6 or less was achieved in 43 and 16 of the 79 previously partial responders or non-responders (UAS 7 >7) patients with 450 and 600 mg/4 weeks, respectively [7,8]. Twenty patients did not achieve disease control despite high doses. In another study, 50 of 78 patients with CSU with partial response to omalizumab 300 mg/4 weeks became responders after up dosing to 450 mg/4 weeks [9]. Omalizumab is considered as an add-on treatment to SgAHs in CSU. However, it has been shown to be effective without the need for concomitant SgAH treatment in up to 60% of patients included in 16 studies [10]. Recent studies have shown that up to 61% of patients will experience clinical worsening after omalizumab discontinuation, even if the treatment was maintained for one year [11-13].

Our five cases of CAU were associated with allergic rhinitis and asthma were sensitized to HDM (positive SPT to DP and DF). Four of these cases were given HDM AIT with increasing concentration by cluster doses till MTD was achieved during the build-up phase. We could achieve 250 BU of HDM as MTD for one year along with the injection of omalizumab 150 mg every four weeks for 6–10 months. Disease control was achieved in four cases (UAS-7 for assessing disease activity [Disease control (UAS 7 <6), Disease remission (UAS 7=0)] according to the EAACI/GA/LEN/EDF/WAO guidelines). Case 5 got anaphylaxis with the first dose of HDM AIT. AIT could not be continued, and she was given only omalizumab for 10 months, but disease control could not be achieved despite adding cyclosporin at 2 mg/kg and was diagnosed as an omalizumab-resistant phenotype of CSU. It could be because of associated co-morbidities (Hypothalamic-pituitary-adrenal suppression, contact urticarial, and poorly controlled asthma).

Dust mites’ allergies have been hypothesized as important pathogenic factors for CSU. Mites are common allergens, colonizing beds, sofas, carpets, and any other woven material. They sensitize and induce atopic diseases. Our four cases (case 1–4) achieved disease control (UAS 7 <6) with combined treatment of omalizumab and HDM AIT (MTD 250 BU) for one year. We speculate that 30–40% of the patients suffering from HDM induced CAU, a subgroup of CSU with concomitant allergic rhinitis and asthma benefitted with combined AIT with omalizumab. Omalizumab has a synergistic effect with a reduction of allergenicity while AIT induces anti-inflammatory effect, T-cell tolerance by decreased allergen-induced proliferation and production of T-regulatory cells. The combination of AIT and omalizumab resulted in prolonged inhibition of allergen-specific IgE binding which might contribute to enhanced clinical efficacy, safety, and faster achievement of Maximum tolerance dose (MTD 250 BU) during the build-up phase of HDM allergen vaccine. The authors have published case series on clinical efficacy and safety of combined HDM subcutaneous immunotherapy and omalizumab in allergic rhinitis and asthma [14].

CONCLUSION

Current evidence indicated that CAU, a subgroup of CSU is an IgE-mediated disease. Our approach of combining omalizumab with HDM AIT is for patients with a long-standing history of CSU, poorly responding to standard conventional therapy as per urticaria guidelines. Our five cases have a strong association of CSU with HDM sensitization. We could achieve disease control in four cases. Further studies are required to better understand the etiopathogenesis of this disease.

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REFERENCES


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