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Case Report

Effective treatment of different H1-antihistamine-refractory chronic urticaria phenotypes with omalizumab

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Abstract

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody. Until now, the efficiency of omalizumab in chronic spontaneous urticaria has been demonstrated in several studies. However in the literature, data showing the efficiency of omalizumab in different phenotypes of H1-antihistamine-refractory chronic urticaria are limited. In this report, the success of treatment with omalizumab from the first dose is presented in three patients with chronic spontaneous urticaria, chronic autoimmune urticaria, and idiopathic angioedema, who were unresponsive to high-dose H1-antihistamine. The symptoms of all patients resolved with the first dose of omalizumab and no symptom recurrence developed during the follow-up period. In this case presentation, the effective treatment of different phenotypes of H1-antihistamine-refractory chronic urticaria is discussed with a review of the literature.

Keywords: Angioedema, antihistamine, child, chronic urticaria, omalizumab, treatment

Introduction

Urticaria is an erythematous and pruritic skin disease that commonly occurs in childhood. Urticaria that persists for six weeks and longer is defined as chronic urticaria. The frequency of chronic urticaria in the childhood age group ranges between 0.1% and 0.3% (1). Chronic spontaneous urticaria, which constitutes a great portion of chronic urticaria, is defined as urticaria occurring without any known trigger factor. Chronic autoimmune urticaria is observed in 40-45% of children who have chronic spontaneous urticaria. In chronic autoimmune urticaria, autoantibodies against high-affinity immunoglobulin (Ig) E receptors, and IgG antibodies interacting with IgE antibody are found. The diagnosis of chronic autoimmune urticaria is made with the basophil histamine release test or basophil activation test (2). Idiopathic angioedema (IA) is defined as painful swelling that occurs suddenly in the subcutaneous tissue and mucosa. Idiopathic angioedema is observed in 10% of children with chronic spontaneous urticaria. Recurrent idiopathic angioedema is substantially rare in childhood (3).

In the treatment of chronic urticaria, the main treatment option is second generation H1-antihistamines. It is recommended that the dose of H1-antihistamine should be increased up to four-fold in treatment-refractory cases (4). In H1-antihistamine-refractory cases, omalizumab, cyclosporine A, and montelukast are the third-line treatment options (4). Omalizumab is a recombinant humanized anti-IgE monoclonal antibody. It was proven that omalizumab was considerably efficient and safe in the treatment of chronic spontaneous

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urticaria in many studies (4, 5). In our country, omalizumab is used in children aged above 12 years who have chronic spontaneous urticaria that does not respond well to H1-antihistamine treatment. In the literature, there are considerably limited data showing the efficacy of omalizumab in various treatment-refractory chronic urticaria phenotypes in childhood (5).

In this article, we present treatment success obtained with omalizumab starting from the first dose in three patients who were followed up in our division with diagnoses of chronic spontaneous urticaria, chronic autoimmune urticaria, and idiopathic angioedema, which did not respond to H1-antihistamine treatment.

Case 1

A seventeen-year-old male patient presented to our outpatient clinic with signs of angioedema that had been recurring for two years. The patient's symptoms began primarily in the fingers and subsequently in the eyes, lips, arms, and feet. It was reported that angioedema occurred every day for approximately 18 months and disappeared spontaneously in at least two hours and at most two days. The angioedema was not found to be related with food additives, drug intake, and other physical factors. There was no personal or familial history of allergy-related disease, chronic disease, infection or congenital angioedema.

In patients who present to our outpatient clinic with a diagnosis of chronic urticaria, complete blood count, biochemical tests, C-reactive protein (CRP), erythrocyte sedimentation rate, stool and urine microscopic examination and cultures, allergen-specific IgE, complement C3, complement C4, antinuclear antibody (ANA), rheumatoid factor (RF), thyroid hormones and antibodies and abdominal ultrasonography are performed for differential diagnosis and to specify other diseases that may be associated with urticaria. All tests were found to be normal in our patient. In addition, the C1 esterase inhibitor level, which was measured to exclude congenital angioedema, and the functional level of the enzyme was found to be within the normal range. The serum triptase level was measured and the basophil histamine release test was performed to exclude systemic mastocytosis and idiopathic anaphylaxis. All test results were found to be normal.

A diagnosis of recurrent idiopathic angioedema was made and H1-antihistamine treatment was initiated at a dose in the normal range. The treatment dose was increased to four-fold because a response to treatment could not be obtained. Montelukast was added to the treatment because, once again, the desired response could not be obtained. However, a reduction in the severity and frequency of our patient's symptoms was not observed. Short-term corticosteroid treatment was added to the treatment in the periods when the attacks were intensive. The frequency of the symptoms decreased with corticosteroid treatment, but they could not be controlled fully. A diagnosis of histamine-refractory idiopathic angioedema was made and tranexamic acid treatment was initiated. However, the drug was discontinued after one month because no reduction was observed in the frequency and severity of the symptoms and subcutaneous omalizumab (300 mg) treatment with an interval of four months was initiated. The serum total IgE level was found as 107.3 IU/mL immediately before initiation of treatment. Surprisingly, the patient's symptoms improved fully with administration of the first dose of omalizumab and all drugs he used were tapered. Our patient has been receiving omalizumab alone for about six months and is being followed up without any symptoms since the first dose.

Case 2

A sixteen-year-old female patient presented to our outpatient clinic with symptoms of urticaria, which had been occurring every day for at least three years. It was reported that her symptoms increased with non-steroidal antiinflammatory drugs (NSAID), exercise, and foods that contained additives. Oral H1-antihistamine treatment and a pseudoallergen-free diet were recommended in another healthcare center, but there was no reduction in the patient's symptoms. Although there was no additional pathology in the patient's personal history, it was learned that her sibling had symptomatic dermographism and her aunt and uncle had congenital angioedema in the familial history. In physical examinations performed at each visit, the 7-day urticaria activity score (UAS7) was 42. All tests that are routinely performed in all patients presenting to our clinic with symptoms of chronic urticaria were found to be normal. The C1 esterase inhibitor level and the functional activity of the enzyme measured in two different healthcare centers and the serum triptase levels were found to be normal. The basophil histamine release test was found to be positive (22%) and the patient was diagnosed as having chronic autoimmune urticaria.

It was learned that the patient received various H1-antihistamines with doses in the normal range, montelukast and albendazole (blindly) treatment before she presented to our clinic. In the follow-up, the symptoms could not be controlled, although high-dose H1-antihistamine treatment was initiated. Three doses of omalizumab were administered with an interval of 4-6-8 weeks each (a total of 12 doses in 13 months). All symptoms recovered in two days with administration of the first dose of omalizumab. In the first week, high-dose oral H1-antihistamine treatment was tapered. Follow-up continued for one year after treatment and the patient's symptoms did not recur.

Case 3

A seven-year old male patient presented to our outpatient clinic with urticaria symptoms, which began at about age three years and occurred almost every day. The patient's symptoms increased especially with stress, food additives, and sweating. In his personal history, it was learned that he had seasonal allergic rhinitis, and urticaria symptoms increased especially in the spring months. In his familial history, it was learned that his mother had contact dermatitis due to nickel allergy. In a physical examination, the 7-day urticaria activity score (UAS7) was 42. The tests performed in all patients who present to our clinic with symptoms of chronic urticaria were found to be normal. Grass pollen sensitivity was found in the allergen-specific IgE test. The serum triptase level and basophil histamine release test were found to be normal. A diagnosis of chronic spontaneous urticaria was made.

It was learned that the patient received various H1-antihistamne medications at normal doses and montelukast treatment before he presented to our clinic and did not respond sufficiently to these treatments. Although high-dose second generation H1-antihistamine treatment was initiated, the patient's symptoms did not improve. It was specified that the patient's compliance with oral treatment was not good and treatment with subcutaneous omalizumab (300 mg) with an interval of four weeks was initiated. All symptoms recovered in three days after administration of the first dose of omalizumab and all oral medications were discontinued in two weeks. The treatment period was completed at one year and recurrence of symptoms did not occur in the 6-month follow-up period. Written and verbal informed consents were obtained from the patients and their parents.

Discussion

In this case presentation, it was mentioned that three adolescents who had treatment-refractory chronic urticaria and idiopathic angioedema benefited from the first dose of omalizumab treatment.

In children with chronic urticaria, symptoms can be controlled to a great extent with second- generation H1-antihistaminic treatment at a dose in the normal range. Guidelines recommend that drug doses may be increased up to four-fold or montelukast or immunosuppressant drugs may be added to treatment in H1-antihistamine-refractory cases. However, success rates in treatment remain at a level of 30-35% (5). In all three of our patients, oral steroids were used only during periods of severe exacerbation because of adverse effects, and cyclosporine A and other immunosuppressant drugs were not preferred because of the potential adverse effects, high treatment cost, and lack of sufficient studies related to this issue in children.

In our country, omalizumab is used in children aged over 12 years who have chronic spontaneous urticaria that does not respond well to H1-antihistamine treatment. There are numerous randomized controlled studies with large series showing the efficacy of omalizumab in chronic urticaria (4, 5). Although some of these studies include pediatric patients, the numbers of children are low (6). Therefore, our knowledge about the efficiency of omalizumab in childhood is limited.

In various studies, complete recovery in symptoms was provided with omalizumab in 70-80% of patients with chronic urticaria (7). In the literature, there are case presentations showing that chronic urticaria symptoms recovered completely with a single dose of omalizumab and a few studies showing the efficacy of omalizumab in idiopathic angioedema (7). We also provided complete recovery in the symptoms in a few days with a single dose of omalizumab in three different treatment-refractory chronic urticaria phenotypes.

In the literature, there is no consensus report related to the dose of administration, dose intervals, and treatment period for omalizumab in children. In numerous randomized controlled studies, administration of omalizumab with four-week intervals was found to be sufficient for complete recovery of urticaria symptoms

(5, 6). In a previous study we conducted, we aimed to reduce treatment costs and the risk of adverse effects and increase the quality of life by establishing the steps of an individualized treatment approach by gradually prolonging dose intervals (8). In our daily practice, the severity of the disease (tested with UAS7) and treatment cost are considered together with the time period of the patient's symptoms, the patient's compliance with treatment and accessibility to our clinic, and individualized treatment approaches are established. We think that we obtained successful outcomes with an individualized treatment approach in all three patients.

In the literature, there is no clear consensus related to the time of discontinuation of omalizumab treatment. Metz et al. (7) reported that omalizumab treatment could be continued for 6-12 months. However, the general approach is in favor of specifying the treatment period according to the patient's clinical response (5). In the literature, it has been reported that symptoms recur in 4-8 weeks in patients with recurrence (7). It has also been reported that symptoms may rarely recur months later (7). Therefore, we completed the treatment period to one year in our patients with chronic urticaria. We observed no recurrence in symptoms in the 6-12 month period after the treatment was ended in all three patients. In addition, there are numerous studies suggesting that omalizumab is a safe treatment option (5, 7, 8). We observed no adverse effects during a total of 30 omalizumab administrations in our three patients, in accordance with previous reports.

Currently, obscurities are present in many issues including chronic urticaria phenotypes in which omalizumab is efficient in children, selection criteria for appropriate patients, drug dose, treatment period, follow-up period, and recurrence rates. No correlation of treatment success with urticaria activity score, symptom period, serum total IgE level and presence of autoimmunity could be shown up to the present time (9). As far as we observed, the efficacy of omalizumab was not correlated with serum total IgE levels, autoimmunity, and accompanying allergic diseases in our patients. It was previously reported that the efficacy of omalizumab was independent of the serum total IgE level (10). This suggests that the rapid action of the drug occurs by way of non-IgE–mediated interactions or systems.

Our results suggest that omalizumab may be a rapidly acting, efficient, and safe treatment option starting from the first dose in children with treatment-refractory chronic urticaria and idiopathic angioedema. On the other hand, variable dose ranges with individualized treatment approaches may increase patient compliance and treatment success and reduce treatment cost. The role of omalizumab in the treatment of various chronic urticaria phenotypes in childhood will be elucidated with further studies with larger series, which will help establish individualized treatment approaches.

Informed Consents: Written informed consent was obtained from the parents of the patients who participated in this study.

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References

1. Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. Pediatr Allergy Immunol 2008; 19: 363-6. [CrossRef]
2. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol 2008; 122: 569-73. [CrossRef]
3. Carr TF, Saltoun CA. Chapter 21: Urticaria and angioedema. Allergy Asthma Proc 2012; 3: 70-2. [CrossRef]
4. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014; 69: 868-87. [CrossRef]
5. Kaplan AP. Treatment of chronic spontaneous urticaria. Allergy Asthma Immunol Res 2012; 4: 326-31. [CrossRef]
6. Church MK, Weller K, Stock P, Maurer M. Chronic spontaneous urticaria in children: itching for insight. Pediatr Allergy Immunol 2011; 22: 1-8. [CrossRef]
7. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. J Dermatol Sci 2014; 73: 57-62. [CrossRef]
8. Uysal P, Eller E, Mortz CG, Bindslev-Jensen C. An algorithm for treating chronic urticaria with omalizumab: dose interval should be individualized. J Allergy Clin Immunol 2014; 133: 914-5. [CrossRef]

9. Asero R, Pinter E, Marra AM, Tedeschi A, Cugno M, Marzano AV. Current challenges and controversies in the management of chronic spontaneous urticaria. Expert Rev Clin Immunol 2015; 11: 1073-82. [CrossRef]

10. Chang TW, Chen C, Lin CJ, Metz M, Church MK, Maurer M. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. J Allergy Clin Immunol 2015; 135: 337-42.[CrossRef]