Omalizumab (Xolair) in Children Above 12 Years With Chronic Urticaria: A Review of Literature

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1. Context

Generally, 15-25% of general population experience urticaria during their life. The prevalence of chronic urticaria is about 0.1-0.3% in children and most often occurs between ages of 6-11 years. There are several causes for development of chronic urticaria. Known etiologies of chronic urticaria in children vary from 21% to 83%. Chronic urticaria caused by infections is more common in children than adults. Diagnosis of chronic urticaria is based on clinical history and physical examination and routine laboratory testing in the absence of a clinical history is rarely helpful. Similar to adults, antihistamines are the first line of treatment. Omalizumab as a biological engineering molecule is a recombinant humanized monoclonal antibody, which targets the CH3 domain of the ε chain of the free IgE. Omalizumab has been used in patients with H1-antihistamine-refractory chronic idiopathic urticaria (CIU). Here in we made a review about possible mechanisms by which omalizumab may be effective in children above 12 years with chronic urticaria, and also focused on its therapeutic effects, onset criteria and possible side effects.

Keywords: Omalizumab; Chronic Urticaria; Child; Therapeutics
dren older than two years. In cases not responding to antihistamines despite 4-fold increasing the usual dosage of drugs, other therapeutic agents such as anti-leukotrienes and/or H1 blockers are added. Immune suppressive agents such as cyclosporine are also administered in the next step (29, 30). Although antihistamines are cornerstones of pharmacological treatment to relieve urticaria symptoms, there are several studies that recommended other therapeutic options such as immunoglobulin or Omalizumab, which have been missed in the treatment of childhood refractory urticarial (31-33). Omalizumab as a recombinant monoclonal antibody has been used in the treatment of moderate to severe allergic asthma resistant to traditional treatments. Omalizumab inhibits binding of IgE to FcεRI receptors on surface of basophils and mast cells (15, 34). Although, the use of omalizumab has not been garneted for urticaria and not used routinely, it has been administered in patients with autoimmune chronic urticaria resistant to usual treatment. Nausea, headaches, swelling of the inside of nose, throat or sinuses, cough, joint pain and upper respiratory tract infection have been more common side effects of Xolair (35). This paper aimed to review possible mechanisms by which omalizumab may be effective in childhood chronic urticaria, and focused on its therapeutic effects, onset criteria and possible side effects.

2. Evidence Acquisition

International databases including PubMed and Google scholar searched using following keywords: Xolair, Omalizumab, Chronic Urticaria Children, and Pediatric. Then among the selected article, after excluding duplicates, independent titles and abstracts or studies and screening done by two independent reviewers, the articles related to efficacy of omalizumab in children above 12 years with chronic urticaria were included. The qualitative results are presented and discussed here.

3. Results

3.1. Omalizumab in Children With Chronic Urticaria

Omalizumab as a biological engineering molecule is a recombinant humanized monoclonal antibody, which targets the CH3 domain of the ε chain of the free IgE. When Omalizumab binds to free IgE, free IgE cannot attach to high-affinity IgE receptor (FcεRI) on effector cells such as mast cells, basophils and dendritic cells. As a result, the mediator release is balanced from these cells and antigen presentation by dendritic cells is inhibited (36-38). Increased total IgE levels have been observed in several studies, primarily in children. The correlation between severity of chronic urticaria and IgE levels may be described by the effect of IgE on activation and degranulation of mast cell. This phenomenon causes upregulation of FcεRI expression on mast cell surface, prolonged mast cell survival and increased histamine associated with leukotriene release (39-41).

Most investigations about Omalizumab have been performed in moderate to severe asthma in adults and children. However, it has been investigated in the treatment of food allergy, atopic dermatitis and other IgE mediated conditions such as urticaria (36). In a study by Saini et al. Omalizumab has been used in patients with H1-antihistamine-refractory chronic idiopathic urticaria (CIU). The age range of studied population was 12 to 75 years. Patients were divided into three experimental groups and one placebo. In experimental groups, patients received a single subcutaneous dose of 75, 300, or 600 mg of Omalizumab for four weeks. A stable dose of H1-antihistamines was added in placebo group. They found that patients with CIU had lower levels of serum IgE compared to patients with asthma and Omalizumab was effective in patients with low and high baseline IgE. They suggested that flat dosing of Omalizumab might be sufficient in patients with CIU. The best effect of Omalizumab was achieved with a single dose of 300-600 mg in CIU patients who were symptomatic in spite of receiving H1-antihistamines (42).

Boyce described the first case report of a successful treatment of urticaria by Omalizumab in a girl with persistent asthma and cold urticaria and symptoms were controlled completely (43). Based on this case report and considering the potential role of IgE in induced urticaria, Metz et al. and others described a successful treatment for patients with urticaria, cholinergic, solar, cold, heat, and delayed pressure urticaria (35, 44-51).

Bailey and Shaker in a review on update on childhood urticaria and angioedema concluded that long-term corticosteroids therapy and other immunomodulating agents such as omalizumab need an understanding of the adjustments between potential risks and expected benefits of the therapy, evaluating possible side effects of therapy against the natural history of underlying disease and consultation for decision making was recommended in cases of severe refractory CIU in which immunomodulators or monoclonal antibody therapy is considered (52).

Recently, Metz et al. in a review on Omalizumab in CU, revealed a possible novel pathogenic pathway as an additional mechanism in chronic spontaneous urticaria. They concluded that treatment with Omalizumab as a monoclonal anti-IgE antibody was effective in more than 50% of patients with CSU, also called CIU and a great proportion of patients with induced urticaria such as solar or cold urticaria that are resisted to common antihistamine agents (18).

Maurer et al. in a randomized double blind placebo controlled trial evaluated the efficacy and safety of Omalizumab for the treatment of patients with moderate to severe CIU. In this study, adolescent above 12 years were studied. Three subcutaneous injections of Omalizumab in doses of 75 mg, 150 mg and 300 mg were administered
at 4-week intervals and followed up by 16 weeks. The primary efficacy outcome was evaluated based on weekly itch-severity score ranging from 0 to 21 for higher score indicated more severe itching. Suppression of symptoms was significant after week 12 in patients who received higher doses of Omalizumab (150 to 300 mg). They also found that most complications were observed in patients receiving the highest dose of Omalizumab. Finally, the results revealed that Omalizumab reduced clinical manifestations of CIU in patients who remained symptomatic in spite of using usual doses of H<sub>1</sub>-antihistamines (53).

Although, antihistamines remain a cornerstone of therapy in treatment of all kinds of urticaria, anti-immunoglobulin E monoclonal antibodies such as Omalizumab may be novel therapies for particular urticaria subtypes. It has been demonstrated that patients with autoimmune idiopathic urticaria (AIU) showed the lowest response to standard treatment with antihistamines. Therefore, some investigators studied using anti-immunoglobulin E monoclonal antibodies agents such as Omalizumab in the treatment of AIU (51).

Successful treatment of recalcitrant urticaria with Omalizumab has been reported frequently in the literature, and currently, Omalizumab is most commonly prescribed for urticaria based on the guideline for asthma (54-56). Due to little information about the optimal regimen of Omalizumab and to develop an algorithm for defining dose, dose interval and clinical response in different urticaria subtypes, and to improve cost-effectiveness and quality of life in these patients, not responding to treatment with high dose non-sedating H<sub>1</sub> antihistamines (nsAH), Yusal et al. studied 27 patients including six children and 21 adults with recalcitrant urticaria who failed to respond to high dosage of nsAH. The most common type of urticaria was CSU (85%) as a whole, but all of 6 children were included. They found no association between types of urticaria, serum level of IgE, presence of body weight, age of the patients, concomitant disease and response to Omalizumab treatment. Associated with high-dose antihistamine therapy, subcutaneous Omalizumab was also prescribed with a dose of 150 mg regardless of serum IgE level and body weight every second week. In patients with treatment failure after 2 to 3 doses of Omalizumab, the dose was increased to 300 mg with 8 weeks interval. These patients showed different responses to the increasing dose of Omalizumab. The results revealed that Omalizumab was highly effective and a reliable treatment in various types of CU and in contrast to the dosing adjustment of Omalizumab in asthmatic patients, adjustment of Omalizumab dose with body weight and serum IgE level was not necessary for successful treatment of CU. They suggested that patients with recalcitrant urticaria should be treated individually and Omalizumab should be started when systemic treatment with fourth-line drugs was ineffective or not feasible (54). Ghaffari et al. in a review, about etiologies, clinical manifestations, diagnosis and treatment of chronic urticaria in children stated that Omalizumab has been effective in pediatrics above 12 years with CU, especially in autoimmune cases who were resistance to antihistamine therapy, but up to now, it has not been used routinely in a wide range (57).

An immediate and definitive response to single dose of Omalizumab has also been reported in a child with severe cyclosporine-resistant chronic urticaria by Asero et al. (58).

At present, childhood urticaria management in children who are at least 12 years is suggested to be similar as adults and treatment as an essential step of the management aimed to provide a symptom relief (27, 59). In another study, Omalizumab as an immunomodulation was described in severe cases of CU, especially in autoimmune baseline cases (60).

To identify the efficacy of Omalizumab in chronic refractory urticaria, Ishizaka et al. performed a retrospective review between 2009 and 2012. They aimed to identify CU phenotypes responsive to Omalizumab therapy by characterizing patients and their response patterns. Demographic information, laboratory data and dosing/response to Omalizumab in 19 patients including 7 males and 12 females treated with Omalizumab were collected. Of total 19 patients, only one was an 8-year old boy. The age range was 8 to 69 years. Omalizumab was administered for 1 to 16 months and the mean duration was 6.05 months. They reported that response patterns to Omalizumab were not related to demographic patterns. They also found no statistically significant differences among autoimmune positive versus autoimmune negative patients. The results showed no statistically significant differences between CU patients and elevated or normal IgE levels. The response of patients to Omalizumab was 89% including 47% complete response and 42% partial response, 11% had no response. The 8-year old boy in this study with refractory CU associated with angioedema who had no response to cyclosporine and frequent steroid therapy, showed complete response to Omalizumab treatment and was symptom free (37). It has been suggested that Omalizumab might exert some of its effects via direct basophil stabilization or through effects on pathogenic IgE antibodies, which may explain the rapid onset of action of Omalizumab or due to its unknown mechanism of action (37, 41, 52, 61). Recently, it has been proposed that a fixed dose of Omalizumab, independent of the level of IgE or patient’s weight can be effective and sufficient for the management of CU patients (37, 41).

Marrouche and Grattan in a review on childhood urticaria found that although H<sub>1</sub>-antihistamines remain a cornerstone in the treatment of urticaria, treatment remains mainly symptomatic and current therapies are not sufficient to control symptoms in all patients. They noted that Omalizumab is a new promising therapeutic modality, which its efficacy and safety in adults and adolescents older than 12 years with chronic idiopathic urticaria is continuing to establish and its mechanism of action is not clear (62).
4. Conclusions

In conclusion, patients with chronic urticaria should undergo a stepwise therapy to decrease both the cost of treatment and risk of complications. Although the efficacy of Omalizumab has been shown in CU as well as other allergic disorders, despite the benefits mentioned before, more information is needed for optimal use and considering safety of this agent in these conditions (67) and in spite of its few side effects, careful consideration is required when this agent is administered (35). According to the results of this review, we recommend Omalizumab in children above 12 years and in cases that are non-responsive to high dose of H1-antihistamines, besides its high costs and limited availability. There is a need for more studies for use of this drug in children below 12 years.

Authors’ Contributions

Javad Ghaffari and Soheila Shahmohammadi participated as the chief executive designer of the study and in writing of the manuscript; Hossein Ashrafi and Ali Reza Ranjbar participated in drafting the manuscript, and Negar Ghaffari participated in collecting medical records of the study.

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