# Efficacy of Omalizumab in Patients with Chronic Spontaneous Urticaria and Its Association with Serum IgE Levels and Eosinophil Count

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**ABSTRACT** Chronic spontaneous urticaria can be treated with several drugs such as antihistamines, leukotriene antagonists, cyclosporine, doxepin, hydroxychloroquine, colchicine, and corticosteroids. However, treatment-resistant urticaria significantly reduces quality of life. In recent years, omalizumab has been considered to be an effective treatment option in treatment-resistant cases. We aimed to investigate the clinical efficacy of omalizumab in urticaria and its possible association with serum IgE levels, total eosinophil counts, and basophil percentages. Medical records of 11 patients with chronic spontaneous urticaria treated with omalizumab were reviewed retrospectively. Treatment response, urticaria activity score, serum basophil percentages, eosinophil, and IgE levels evaluated before and at the end of the therapy. Ten patients healed completely with omalizumab. One patient did not respond to therapy. No correlation was observed between serum IgE levels and treatment outcome. However, serum eosinophil levels decreased and basophil percentages increased with omalizumab treatment. Omalizumab is a safe and effective treatment choice in patients with chronic spontaneous urticaria. We suggest that omalizumab may have an effect in the treatment of urticaria through eosinophils.

**KEY WORDS:** eosinophil, immunoglobulin E, omalizumab, urticaria

## INTRODUCTION

Omalizumab is a monoclonal antibody which binds to high-affinity IgE receptors. A decrease in serum free IgE levels of up to 90% can be observed at the end of the 16-24 weeks of omalizumab therapy in patients with asthma (1). It has been suggested that decreased IgE levels lead to down-regulation of expression of high-affinity IgE receptors on basophils and mast cells (1). Furthermore, omalizumab has an effect of disintegration of IgE from basophil and mast cells (1). Chronic urticaria presents with pruritic wheals that last more than six weeks (2).

Chronic urticaria can be divided into chronic spontaneous urticaria and chronic inducible urticaria. Chronic spontaneous urticaria describes chronic urticaria without any external stimulus (3). It is not always easy to treat patients with chronic urticaria. The disease decreases quality of life at least as much as ischemic heart disease does (2). Omalizumab is widely used in Europe and the United States for the treatment of patients with chronic spontaneous urticaria who do not response to high doses of antihistamines (4).

In this study, we aimed to investigate the effect of omalizumab in the treatment of patients with treatment resistant chronic spontaneous urticaria and to look for a possible association with serum IgE levels and total eosinophil or basophil levels.

## PATIENTS AND METHODS

The study was approved by the local ethic committee. Medical records of the patients with chronic spontaneous urticaria were reviewed retrospectively. Eleven patients (2 male, 9 female) with chronic spontaneous urticaria treated with omalizumab between January 2014 and March 2017 were included in the study. The age range was between 19 and 59. The average duration of disease was 44.7 months (4-146 months). All the patients were previously treated with high-dose oral antihistamines. The median duration of antihistamine therapy was six months (range 2-12 months). Moreover, four patients had received systemic steroids for two months and one patient received doxepin for two months and montelukast for one month without benefit.

Serum total IgE levels, serum total eosinophil counts, serum eosinophil and basophil percentages, and urticaria activity scores were evaluated before and at the end of the administration of the last dose of omalizumab therapy. Omalizumab in a dose of 300 mg was administered by subcutaneous injection every 4 weeks. The treatment was stopped when no response was observed despite four sessions of omalizumab therapy.

Clinical response and disease severity were evaluated using the urticaria activity score (UAS) which was assessed as the sum of itch severity and hive count occurring over 24 hours as described below (5). Pruritus which was not reported as annoying was regarded as mild; pruritus which did not interfere with normal daily activity was regarded as moderate; pruritus which interfered with normal daily activity or sleep was regarded as severe pruritus. Urticaria activity scores 0 and 1 (mild pruritus without any hives) were classified as a complete response to omalizumab therapy.

**Table 1.** Laboratory results and UAS of the patients before and after omalizumab therapy

| Patients | Urticaria activity score | | Serum total IgE levels (IU/mL) | | Serum total eosinophil levels (eosinophil/mm³) | | Serum basophil percentages (%) | | Omalizumab Dose |
|---|---|---|---|---|---|---|---|---|---|
| | Before therapy | After therapy | Before therapy | After therapy | Before therapy | After therapy | Before therapy | After therapy | |
| 1* | 6 | 1 | 171.9 | 125.5 | 68 | 40 | 0.58 | 0.44 | 5 |
| 2* | 6 | 0 | 129.1 | 613 | 109 | 97 | 0.72 | 0.73 | 6 |
| 3* | 6 | 1 | 107.8 | 494.8 | 206 | 193 | 1.13 | 1.24 | 7 |
| 4* | 6 | 1 | 339.6 | 165.1 | 60 | 48 | 0.47 | 0.61 | 8 |
| 5* | 4 | 1 | 549 | 250 | 230 | 149 | 1.03 | 0.78 | 8 |
| 6* | 6 | 1 | 443.2 | 464.7 | 90 | 144 | 0.92 | 1.2 | 8 |
| 7* | 5 | 0 | 169.8 | 443 | 193 | 109 | 0.84 | 0.92 | 8 |
| 8† | 5 | 0 | 2068 | 2131 | 300 | 302 | 1.65 | 1.84 | 13 |
| 9† | 5 | 0 | 97 | 396.7 | 80 | 55 | 0.93 | 1.65 | 22 |
| 10† | 6 | 1 | 25 | 98 | 131 | 180 | 1.42 | 1.53 | 20 |
| 11‡ | 5 | 5 | 25 | 136 | 190 | 166 | 1.22 | 0.98 | 4 |

\* Well responders to omalizumab therapy

† Recurrent cases after cessation of treatment

‡ The patient who did not respond to therapy

0: No pruritus/hives

1: Mild pruritus/hive count <20

2: Moderate pruritus/hive count: 20-50

3: Severe pruritus/hive count> 50 (5).

We used SPSS 22 for data analysis. The Wilcoxon two-sample test was used to compare results before and after treatment.

## RESULTS

Three (27.7%) of 11 patients were still to receiving omalizumab therapy at the time of the study. The treatment course for these patients was 13, 20, and 22 months. After eight months of therapy, having achieved complete remission, omalizumab was discontinued. However, urticarial lesions reoccurred. These three patients were returned to omalizumab within two months. Serum total IgE levels increased in two patients and stayed similar in one patient after omalizumab therapy. Serum total eosinophil levels increased in one, decreased in one, and stayed similar in the third patient. However, serum basophil percentage increased in all three patients (Table 1).

Four (36.6%) of 11 patients received a total of eight sessions of omalizumab 300 mg every four weeks. Therapy was stopped at the end of the eighth month and no recurrence was observed during six-month follow up. Serum total IgE levels increased in one patient, decreased in two of these patients, and stayed similar in one patient after omalizumab therapy. Serum eosinophil levels decreased in three patients and increased in one patient. However, basophil percentage increased in three patients and decreased in one patient.

Three (27.2%) of 11 patients received a total of five, six, and seven sessions of omalizumab, respectively. Therapy achieved complete remission in these patients without recurrence. Serum total IgE levels increased in two of these patients and decreased in one patient. Serum eosinophil levels decreased in all three patients. Serum basophil percentage increased in one patient, decreased in one, and stayed similar in the third patient.

Serum total IgE levels decreased in three (27.7%) patients, increased in six (54.5%) patients, and stayed similar in two (18.1%) patients (Table 2).

Serum total eosinophil levels decreased in eight (72.7%) patients, increased in two (18.1%) patients, and stayed similar in one (9%) patient (Table 3).

Serum basophil percentages decreased in three (27.7%) patients, increased in seven (63.6%) patients, and stayed similar in one (9%) patient (Table 1).

All patients except one showed complete response to omalizumab therapy. Additionally, three patients were still on omalizumab therapy. The complete clinical response of omalizumab therapy was achieved in eight (72.7%) of 11 patients at four weeks and two (18.1%) of patients at eight weeks. One patient did not respond to the treatment despite a total of four sessions of omalizumab therapy. The urticaria activity score of the patient who failed treatment was 5 both before and at the end of the omalizumab therapy (Table 4). The serum total IgE level of this patient increased, while total serum eosinophil count and serum basophil percentage were decreased at the end of the second dose of omalizumab. In addition to urticaria, the patient was diagnosed with atopic dermatitis in childhood. Furthermore, she was allergic to bee venom.

The mean follow-up time was ten months (range: 4-22 months) during therapy. No adverse reaction were observed in patients during the omalizumab therapy or follow-up.

## DISCUSSION

Basophils seem to play an important role in the pathogenesis of chronic spontaneous urticaria. It

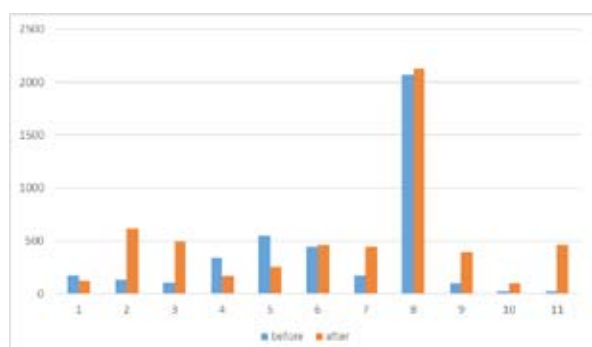**Table 2.** The effect of omalizumab on serum IgE levels (IU/mL)



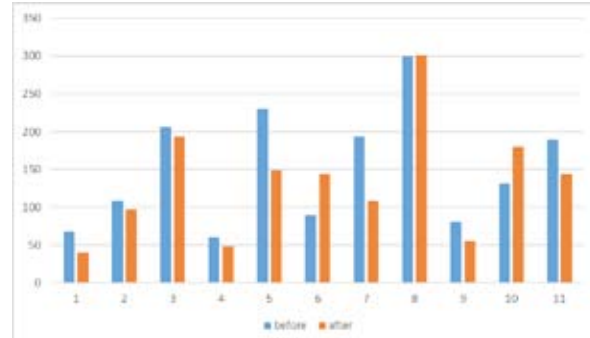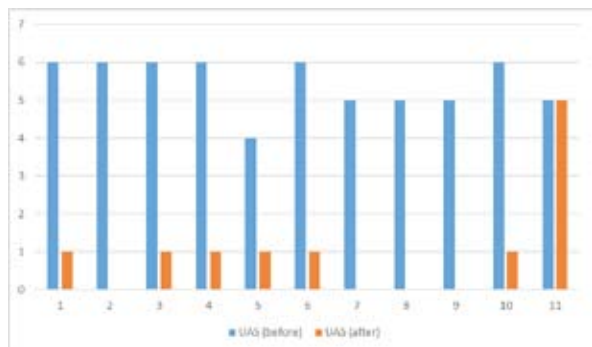**Table 3.** The effect of omalizumab on serum eosinophil levels

**Table 4.** The effect of omalizumab on urticaria activity score.

The urticaria activity scores of the patients numbered 2, 7, 8, and 9 were 0 after therapy.



has been suggested that patients with urticaria taking omalizumab treatment have gradually decreased serum basophil levels as a result of migration of basophils into the tissues. Therefore, basopenia may be correlated with treatment response. Saini *et al.* investigated the effect of omalizumab on serum basophil levels in patients with chronic urticaria. Patients taking omalizumab 75 mg, 150 mg, 300 mg, or placebo were included in the study. Serum basophil levels were measured at baseline and every 12 weeks after the first dose and compared between these four groups. Baseline basophil blood percentages were similar in all groups. However, basophil percentages were higher in patients treated with omalizumab when compared with the placebo group at weeks 12 and 24. Increase in serum basophil percentage was significant in patients taking omalizumab 300 mg monthly. Omalizumab was effective in all treatment groups, most notably in patients taking 300 mg omalizumab per month. Increase in circulating basophils was proposed as a marker of clinical response to omalizumab in patients with urticaria. Omalizumab probably inhibits the migration of basophils from circulation into the tissues. Therefore, it increases serum levels of basophils (6).

Although the main step in all types of urticaria is activation and degranulation of basophils and mast cells, it has been suggested that eosinophils also play an important role in the etiopathogenesis of chronic urticaria (7). In patients with chronic urticaria, vascular endothelial growth factor (VEGF) is mainly produced by eosinophils. Vascular endothelial growth factor increases vascular permeability, induces angiogenesis, and has a vasodilatory effect on endothelial cells. It thus causes wheals, flare reaction, and angioedema (7). Besides producing tissue-damaging molecules, eosinophils lead urticaria by releasing pro-inflammatory and immunoregulatory proteins (8). Eosinophil

cationic protein, eosinophil-derived neurotoxin, and major basic protein are cationic proteins released by eosinophils. They lead to epithelial damage in tissues. Skin samples of patients with chronic urticaria showed deposition of major basic protein and eosinophil cationic protein outside the eosinophils. These proteins have been reported to increase histamine release from basophils and mast cells (8).

Omalizumab is a recombinant humanized monoclonal antibody which has an anti-IgE effect. It prevents free IgE antibodies from binding to the receptors on B cells, dendritic cells, eosinophils, and monocytes (9,10). It also reduces IgE receptor expression on basophils, mast cells, and dendritic cells (11). Moreover, it leads to B cell anergia and reduces IgE synthesis. It has been suggested that omalizumab induces eosinophil apoptosis (12,13). However, the mechanism remains controversial. It may be due to the direct effect of the drug. On the other hand, eosinophil apoptosis may occur as a result of reduction of IgE and T-cell-derived cytokines (14).

High-affinity IgE receptors in dendritic cells present antigens and activate T lymphocytes. However, it is controversial whether high-affinity IgE receptor signaling stimulates cytokine and chemokine synthesis and enhances inflammation. Furthermore, some studies suggest an immune suppressive effect of the signaling by inducing anti-inflammatory cytokines like IL-10. Omalizumab may inhibit the allergic/inflammatory pathway by suppressing antigen presentation and IgE-IgE receptor binding in dendritic cells (15).

Metz *et al.* retrospectively investigated the effect of omalizumab in 51 patients with chronic urticaria. They defined complete response as a >90% reduction of lesions. Total serum IgE levels, autologous serum skin test results, and skin prick tests were examined. 83% of the patients showed complete remission. Mild cutaneous angioedema was observed in one patient after omalizumab injection. They reported no correlation between total serum IgE levels, autologous serum skin test results, skin prick test results, and treatment response. Serum tryptase level was measured as a marker of mast cell activation. No significant difference was observed between baseline serum tryptase levels and levels at 2-4 weeks after treatment (16). However, Ertas *et al.* reported that total serum IgE levels can predict the response to omalizumab in patients with chronic spontaneous urticaria. The patients with chronic spontaneous urticaria who did not response to omalizumab therapy had significantly lower serum IgE levels compared with partial and complete responders (17).

Skiepko *et al*. analysed the changes of serum eosinophilia after 4-month of omalizumab therapy in patients with severe allergic asthma. They found that patients with higher decrease in blood eosinophilia had lower asthma exacerbations during omalizumab therapy (18). Clinical efficacy of omalizumab in asthma is proportional to increased level of peripheral eosinophilia. Therefore, anti-eosinophilic effect of omalizumab may be as important as the anti-IgE efficacy of omalizumab, especially in the treatment of patients with non-allergic asthma (19). Nevertheless, it should be kept in mind that the role of eosinophils may differ in urticaria which is not an allergic disease and in severe asthma which is mostly connected with allergy.

In our study, all patients except one showed excellent clinical improvement with omalizumab treatment. Sustained clinical remission was obtained in 72.7% patients within four weeks. However, serum IgE levels did not correlate with clinical outcome. Approximately half of the patients showed elevated serum IgE levels at the end of the therapy when compared with baseline IgE levels, while others showed decreased serum IgE levels. However, serum total eosinophil count showed a steady decrease and serum basophil percentage showed an increase in most of the patients. Decrease in total eosinophil count can be explained by eosinophil apoptosis induced by omalizumab, which may be parallel to clinical response. On the other hand, increase in serum basophil percentage may occur as a result of inhibition of basophil migration from circulation to the skin by omalizumab.

## CONCLUSION

Omalizumab has high efficacy in the treatment of chronic spontaneous urticaria irresponsive to classical treatment options. We suggest that eosinophils and basophils might play a much more important role than serum IgE levels in the pathogenesis and treatment of chronic spontaneous urticaria with omalizumab. Therefore, serum eosinophil count may be a marker in the follow-up of patients receiving omalizumab treatment, facilitating decisions regarding dosage or cessation of treatment.

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