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Original Research

A 10-Year Real-World Analysis of Omalizumab Use in Chronic Spontaneous Urticaria Patients at a Dermatology Clinic

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Abstract

Objectives: Chronic spontaneous urticaria (CSU) is characterized by recurrent wheals and/or angioedema lasting more than 6 weeks. The disease is marked by unpredictable, severe itching attacks, significantly impacting patients' quality of life and often prompting them to seek medical treatment. This study aimed to evaluate the efficacy of omalizumab in patients with CSU and identify the factors that determine its effectiveness.

Methods: This retrospective descriptive study analyzed registered data of 159 patients with CSU who received omalizumab at a tertiary dermatology clinic. The study recorded patient demographics, allergic conditions, omalizumab dosage, treatment response time, efficacy, duration of use, and additional medications. It also included assessments of total IgE levels.

Results: Of 159 patients with CSU, 112 (70.4%) were females, and 42 (29.6%) were males with a median age of 43 years (IQR = 20). Among the patients, 156 (98.1%) received a 300 mg dose of omalizumab, while 3 (1.9%) received 450 mg. Additionally, 41 (25.8%) required antihistamines and corticosteroids in addition to omalizumab, while 118 (74.2%) were treated with omalizumab alone. The median response time was 3 months, with 116 (73%) showing complete responses and 39 (24.5%) showing partial responses. Four patients (2.5%) showed no response. When patients were categorized into two groups—those receiving only omalizumab and those on combination therapy, the median response time to omalizumab was statistically significantly longer in the combination therapy group (mean=2.53±0.76, median=3, IQR=1 vs. mean=3.49±1.63, median=3, IQR=0). When patients were categorized into two groups based on a total IgE cut-off value of 20 IU/ml, the group with IgE levels greater than 20 had a significantly higher proportion of full responders.

Conclusion: The majority of patients with CSU in this study responded well to omalizumab, with a significant proportion achieving complete responses. Additionally, higher IgE levels (>20 IU/ml) were associated with a greater likelihood of full response to treatment. These findings suggest that omalizumab is an effective agent for CSU, with the possibility of enhanced response in patients with elevated IgE levels.

Keywords: IgE, omalizumab, urticaria

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Chronic spontaneous urticaria (CSU) is characterized by recurrent wheals and/or angioedema lasting more than 6 weeks.[1] The disease is marked by unpredictable, severe itching attacks that interfere with daily activities and are often associated with sleep disturbances, significantly impacting patients' quality of life and often prompting them to seek medical treatment.[2,3] The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline recommends initiating treatment for chronic urticaria with second-generation H1 antihistamines, with the option to increase the dose up to four times if needed. If symptoms remain uncontrolled after 2-4 weeks, omalizumab should be considered as a second-line treatment.[4] Studies assessing the overall efficacy of omalizumab therapy in CSU patients have yielded varying results. However, a meta-analysis reported a 72.2% of complete response rate in 45 studies and a 17.8% partial response rate across 37 studies.[5]

Omalizumab is effective in treating patients with CSU, but the factors predicting the response remain largely unknown. In the literature, there are numerous studies to predict the responsiveness of patients with chronic urticaria (CU) to omalizumab. These studies investigated whether factors such as total IgE, D-dimer, baseline ANA, anti-TPO levels, and disease duration influenced patients' response to omalizumab.[6-16] However, these studies have yielded varying results, which have been attributed to factors such as the proportion of patients with chronic inducible urticaria in the study population, the duration of patient follow-up, prior medications, and differing test cut-off values. In this study, we assessed disease control in patients receiving omalizumab and examined the relationship between total IgE levels, the additional medications they were using, and their treatment outcomes. Thus, this study aimed to appraise the efficacy of omalizumab in patients with CSU and clarify the factors that determine its effectiveness.

Methods

This retrospective descriptive study analyzed registered data of patients with CSU who received omalizumab at a tertiary dermatology clinic from June 2015 to June 2024. The Ankara Training and Research Hospital Scientific Research Ethics Committee granted approval for the study (date: 25.09.2024, no: 214/2024). Participants were provided with complete information and written consent was attained. The study was conducted in compliance with the most recent version of the 'Helsinki Declaration' and the 'Guidelines for Good Clinical Practice'.

The patient cohort consisted of 159 patients over 18 years with diagnosis of CSU. The diagnosis of CSU was made clinically with history and dermatological examination based on the criteria defined in the international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline by the dermatologists conducting the study. The demographic details of the patients, along with any associated allergic conditions, were documented. The dose of omalizumab, treatment response time, efficacy, duration of use, and any additional medications used alongside omalizumab were recorded. The efficacy of omalizumab was categorized into three groups: A complete response was specified as the full resolution of symptoms associated with CSU, a partial response as a decrease in symptoms with occasional persistence of complaints, and no response as no change in the frequency or severity of symptoms. Lastly, the patients' total IgE levels were assessed. The laboratory reference range for total IgE was 0-100 IU/ml. Participants were categorized and assessed based on standard reference values and the 20 IU/ml cut-off value established in Asero's study.[13]

Statistical Analysis

All analyses for the study were performed using IBM SPSS Statistics for Windows, Version 20.00 (Armonk, New York, USA: IBM Corp.), and a p-value of under 0.05 was interpreted as indicating statistical significance. The Shapiro-Wilk test was employed to test the normality of data. Continuous variables with a non-parametric distribution were presented as the median and interquartile range (IQR). Categorical variables were reported as counts and percentages. The Mann-Whitney U test was utilized for comparing independent continuous samples, while Pearson's chi-square test was utilized for categorical variables. Fisher's exact test was preferred when the expected count of one cell or more cells was below five.

Results

A total of 159 patients with CSU were included in this study. There were 112 (70.4%) females and 42 (29.6%) males in the patient group. The patients' ages were between 18 and 79 years, with a median age of 43 years (IQR=20). Eighteen (11.2%) patients had a history of accompanying allergic diseases. The demographic and clinical traits of patients with CSU receiving omalizumab are given in Table 1.

Out of 159 patients, 156 (98.1%) were receiving the standard 300 mg dose of omalizumab, and 3 (1.9%) were receiving 450 mg of omalizumab. While 41 (25.8%) patients needed antihistamines and systemic corticosteroids alongside omalizumab, 118 (74.2%) patients were treated with omalizumab alone. The median response time to omali-

Table 1. The demographic and clinical characteristics of patients with CSU receiving omalizumab

	Patient group (n=159)
Sex (n/%)	
Female	112 (70.4)
Male	47 (29.6)
Age [Median, (IQR), years]	43 (20)
Accompanying allergic diseases (n/%)	
Allergic asthma	11 (6.8)
Allergic rhinitis	3 (1.9)
Allergic conjunctivitis	1 (0.6)
Atopic dermatitis	3 (1.9)
Total Ig E [Median, (IQR), IU/ml]	120 (286)
Total Ig E Classification (n/%)	
Normal	71 (44.7)
High	88 (55.3)

IQR: Interquartile range. Data were expressed as median and IQR in continuous variables and n (%) in categorical variables.

zumab was 3 months (IQR=1), with 39 (24.5%) patients showing a partial response and 116 (73%) patients experiencing a complete response. No response to treatment was noted in 4 (2.5%) patients (Table 2).

When patients were categorized into two groups—those receiving only omalizumab and those on combination therapy, the mean response time was 2.53±0.76 months (median=3, IQR=1) in the omalizumab group and 3.49±1.63 (median=3, IQR=0) in the combination therapy group, respectively. The median response time to omalizumab was statistically significantly longer in the combination therapy group ($p<0.001$). Additionally, the number of patients achieving a complete response was statistically significantly higher in the group of patients receiving omalizumab alone than those on combination therapy. In contrast, the number of patients with partial or no response was statistically significantly higher in the combination therapy group ($p<0.001$).

When patients were divided into two groups based on normal and high total IgE levels, no statistically significant difference was found in the response (no, partial, complete) to omalizumab treatment ($p=0.447$). There was no statistically significant difference in the median response time to omalizumab between the groups with normal and high IgE values ($p=0.992$). No statistically significant difference was found in the number of patients receiving omalizumab alone versus combination therapy between the groups with normal and high IgE values ($p=1$). When patients were categorized into two groups based on a total IgE cut-off value of 20 IU/ml, the group with IgE levels greater than 20 had a significantly higher proportion of full responders ($p=0.045$) (Table 3).

Discussion

CSU impacts around 0.5-1% of the population, making it a relatively common condition and highlighting the importance of effective treatment to alleviate symptoms and signs of the disease.[17,18] Antihistamines and omalizumab

Table 2. Treatment details of patients with CSU receiving omalizumab

	Patient group (n=159)
Omalizumab Dose (n/%)	
Omalizumab 300 mg	156 (98.1)
Omalizumab 450 mg	3 (1.9)
Other treatments used in addition to omalizumab (n/%)	
Only omalizumab	118 (74.2)
H1-antihistamines (the standard dose or up to 4 times the standard dose)	37 (23.3)
H1-antihistamines (the standard dose or up to 4 times the standard dose) and systemic corticosteroids	4 (2.5)
Response time to omalizumab [Median, (IQR), months]	3 (1)
Efficacy of omalizumab (n/%)	
No response	4 (2.5)
Partial response	39 (24.5)
Complete response	116 (73)
Duration of omalizumab use [Median, (IQR), months]	11 (15)

IQR: Interquartile range. Data were expressed as median and IQR in continuous variables and n (%) in categorical variables.

Table 3. Omalizumab treatment responses based on a total IgE cut-off value of 20 IU/ml

	Total Ig E≤20 IU/ml	Total Ig E>20 IU/ml	p
Efficacy of omalizumab (n/%)			
No response	1 (14.3)	3 (2)	0.045*
Partial response	3 (42.9)	36 (23.7)	
Complete response	3 (42.9)	113 (74.3)	

Data were expressed as n (%) in categorical variables. Fisher's Exact test was used. *p>0.05

are commonly employed to manage the condition. However, a deeper understanding of the disease's pathogenesis may help to explain why these treatments are less effective in certain patients. The mechanisms of CSU have been recognized as type I auto-allergic, which involves IgE autoantibodies against autoantigens and type IIb autoimmune, caused by IgG autoantibodies that target FcεRIα and/or IgE.[19,20] Omalizumab, a humanized monoclonal antibody targeting human IgE, effectively treats around 80% of CSU patients.[21] However, individuals with type IIb autoimmunity may show resistance to omalizumab.[22] These mechanisms, however, have yet to be fully explored.

This study presents a 10-year analysis of patients who received omalizumab for CSU at a dermatology clinic. In summary, over 10 years of data from a dermatology clinic, 73% of CSU patients achieved a complete response with omalizumab. Patients with a total IgE level above 20 IU/ml had a higher complete response rate. Additionally, even when extra treatments such as antihistamines and systemic steroids were added for those who did not have a full response to omalizumab, their complete response rate remained lower than that of patients who responded exclusively to omalizumab.

CU is primarily seen in adults, with the peak onset occurring between the ages of 20-40, and it occurs more frequently in females than in males.[23,24] In line with the literature, middle-aged women comprised 70.4% of our patient group. In our study group, the complete response rate to omalizumab was 73%, partial response was 24.5%, and non-response was 2.5%. While our complete response rate aligns with the meta-analysis of 45 studies, the low rate of non-responders can be attributed to the absence of chronic inducible urticaria in our patient population.[5]

A number of studies in the literature investigated the link between total IgE levels and the treatment outcomes of omalizumab. Some of these studies found no association between treatment success and baseline total IgE levels.[6,11] Ghazanfar et al.[11] assessed 117 patients with CSU and found no relationship between initial IgE levels and urticaria control at the third month of omalizumab treatment. Similarly, in a study involving 159 CU patients, Tuncay et al.[6] found no difference in total IgE levels between patients with controlled and uncontrolled symptoms with the standard dose of omalizumab for 6 months. On the other hand, several studies have identified a prognostic correlation between initial total IgE levels and the clinical response to omalizumab. Asero assessed the total IgE levels of 86 patients with severe CSU, categorizing them into four groups: 0-9, 10-19, 20-29, and 30-39 IU/ml. He found that the group with total IgE levels between 0-9 IU/ml had the fewest numbers of early responders and the highest number of nonresponders. Additionally, patients with total IgE levels below 20 constituted approximately 85% of the nonresponders.[13] Based on these findings, Asero drew two conclusions. First, IgG-mediated type IIb inflammation may be implicated in patients with low total IgE levels, although this is not true for all such patients, as some with low IgE levels have type I autoimmunity and thus respond to omalizumab. Second, IgE levels cannot be considered an absolute predictor of treatment response, as there are patients with low IgE levels who respond to omalizumab and others with IgE levels higher than 20 IU/ml who do not.[13] Ertas et al.[9] took a different approach to the topic, reporting that 44 (47%) out of 93 patients with CSU achieved a complete response, and 29 experienced a relapse after discontinuing the medication. They also found that the duration until relapse was shorter in patients with higher baseline IgE levels.[9] Again, from a different point of view, Yang et al.[15] found that a higher baseline IgE level was linked to a quicker response to omalizumab. Niwa et al.[22] took the measurement of total IgE levels one step further and assessed the serum levels of IgG anti-IgE autoantibodies, IgG anti-FcεRIα autoantibodies, total IgE, and free IgE in a cohort of 61 patients with CSU. They reported that the levels of IgG anti-IgE and IgG anti-FcεRIα autoantibodies were significantly elevated in early nonresponders. However, there was no significant difference in the levels of these autoantibodies between late responders and late nonresponders. In contrast, late responders had significantly elevated levels of total and free IgE. It should be noted that the group of late responders included patients who either responded early or showed a more gradual response over time, rather than only those with slow or delayed responses. They concluded that since omalizumab reduces the binding of IgE to mast cells and basophils, it may also indirectly reduce FcεRI expression on the cell surface and thus have some effect on IgG anti-FcεRIα induced type IIb autoinflammation. On the other hand, IgG anti-IgE autoantibodies reduce the binding of omalizumab to IgE, reducing the effectiveness of the treatment.[22,25] In our study, when patients were divided into two groups based

on normal and high total IgE levels, no significant difference was found in response to omalizumab treatment. However, when patients were grouped based on a total IgE cut-off of 20 IU/ml, the group with IgE levels above 20 IU/ml showed a significantly higher proportion of full responders. Based on the synthesis of all studies, it can be suggested that in the group with lower total IgE levels (<20 IU/ml), baseline total IgE, while not a definitive indicator, may be useful in predicting treatment response.

Another notable finding of this study was that even when additional antihistamines were given to patients who did not fully respond to omalizumab, their complete response rate remained lower compared to those who responded solely to omalizumab. Additionally, the median response time to omalizumab was significantly longer in the combination therapy group. Similar to our study, Tuncay et al.[6] reported that, as expected, the rate of regular antihistamine use during omalizumab treatment was higher in patients with uncontrolled symptoms in their study of 159 CU patients. Although the EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines recommend daily use of second-generation H1 antihistamines with omalizumab to prevent wheals and angioedema, not all patients on omalizumab therapy require daily antihistamines.[4] On the other hand, it should be kept in mind that the complete response rate did not increase in patients receiving the combination (omalizumab and antihistamines) treatment based on the findings of both our study and the study by Tuncay et al.[6]

The limitations of this study include its retrospective nature and incomplete data regarding the duration of the disease. Additionally, objective scoring systems such as the Urticaria Control Test or Urticaria Activity Score 7 (UAS7) score were not used; instead, treatment success was evaluated and classified based on the frequency of symptoms in the patients.

Conclusion

In conclusion, the majority of patients with CSU in this study responded well to omalizumab, with a significant proportion achieving complete responses. Additionally, higher IgE levels (>20 IU/ml) were associated with a greater likelihood of full response to treatment. These findings suggest that omalizumab is an effective agent for CSU, with the possibility of enhanced response in patients with elevated IgE levels.

Disclosures

Ethics Committee Approval: The study was approved by the Ankara Training and Research Hospital Scientific Research Ethics Committee (date: 25.09.2024, no: 214/2024).

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