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Factors associated with the efficacy of omalizumab treatment in chronic spontaneous urticaria

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Abstract
Background: Omalizumab is a preferred treatment in antihistamine-refractory chronic spontaneous urticaria (CSU) patients. However, factors that may impact treatment response remain to be explored.
Objective: This study aimed to examine the factors affecting treatment response in CSU patients receiving omalizumab.
Methods: This was a retrospective study that included 123 patients who received omalizumab treatment for CSU between January 2015 and April 2024. After administering omalizumab, we evaluated therapeutic efficacy with the urticaria control test (UCT). According to UCT, patients were classified as complete responders, partial responders, and nonresponders.
Results: The median age of the patients was 42 (31-50) years, and there were 77 (62.9%) female patients. Sixty-four (52%) patients exhibited complete response, and 43 (35%) patients exhibited partial response to omalizumab treatment, whereas 16 (13%) patients were nonresponders. Autoimmune disease (AID) was present in 31 (25.2%) patients. The most common AID was thyroid autoimmunity, seen in 24 (77.4%) patients. AID was significantly higher in omalizumab treatment nonresponders than in partial and complete responders. The presence of an autoimmune thyroid disease was an independent risk factor for failure to respond to omalizumab treatment. Baseline IgE levels were significantly higher in omalizumab treatment responders with a complete response compared to those with a partial response and nonresponders.
Conclusion: Response to omalizumab treatment was influenced by the presence of an AID and baseline serum total IgE level. A concurrent autoimmune thyroid disease was found to be an independent risk factor affecting failed treatment response. Factors that can predict response to omalizumab treatment can help guide patients to more effective treatment.

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Introduction

Urticaria is a disease, characterized by hives, angioedema, or both. Daily or intermittent symptoms are usually accompanied by itching. When the disease lasts more than 6 weeks, it is called chronic urticaria (CU). The prevalence of CU in the general population is 1–3%.[1] While symptoms usually occur spontaneously (chronic spontaneous urticaria, CSU) in the majority of the patients, some have defined triggers (chronic inducible urticaria).[2] CSU is estimated to account for two-thirds of patients with CU. Stress, infections, foods, and medications can trigger exacerbations.[3]

CSU occurs when activated cutaneous mast cells release their mediators. There are different types of autoantibodies associated with mast cell activation. Immunoglobulin E (IgE) autoantibodies directed to self-antigens are produced in type I autoimmune endotype (type I aiCSU). Type IIb endotype (Type IIb aiCSU), however, involves IgG autoantibodies.[1] CSU patients may have type I aiCSU, type IIb aiCSU, or both. Type I aiCSU (or autoallergy) is more common. Omalizumab treatment results in rapid and complete response at a rate of 70%.[4] Response to omalizumab treatment is weak and slow in type IIb aiCSU. These patients usually have a personal or family history of autoimmune diseases (AID).[5]

Management of CSU aims to control signs and symptoms. First-line treatment prevents the triggers known to cause disease exacerbation. In addition, second-generation H1-antihistamines are initiated, whose standard dose can be quadrupled. Steroids are used in CSU exacerbations only for a short period. Omalizumab treatment is recommended for severe cases which cannot be well controlled with high-dose antihistamines.[6] Omalizumab is a humanized, recombinant, monoclonal anti-IgE antibody. It inhibits binding of IgE to high-affinity receptors (Fc¤R) localized on surfaces of mast cells and basophils. It downregulates the IgE receptors existing on these cells. The initial recommended dose for CSU is 300 mg every 4 weeks. The dosage is independent of serum total IgE.[1] The first treatment option as a further treatment in patients refractory to omalizumab is cyclosporine. Cyclosporine is an immunosuppressant that inhibits activation of mast cells, T-cells, and basophils. Low serum total IgE level is associated with poor response to omalizumab but favorable response to cyclosporine. Cyclosporine treatment is more efficacious in patients exhibiting characteristics of type IIb aiCSU, including low total IgE, positive ASST, and the presence of anti-thyroid antibodies.[7,8]

Omalizumab treatment is ineffective in approximately one-third of CSU patients.[9] Moreover, given that the treatment response can take up to 6 months, observing the benefits may become costly.[10] Treatment response varies between defined CSU subgroups. Optimal duration of the treatment and posttreatment management still remains unclear. Urticaria recurs in some patients responding to omalizumab after cessation of the treatment. Determining clinical and laboratory parameters associated with treatment response and recurrence benefits the management of the disease. If treatment is individualized based on these factors, treatments likely to be less effective are avoided. This also provides savings with regard to time and savings. This study evaluated factors affecting response to omalizumab treatment in antihistamine-refractory CSU.

Material and Method

Study Design

This retrospective study was approved by the Ethics Committee of Necmettin Erbakan University (Approval no: 2024/5063). A total of 139 patients receiving omalizumab (Xolair®, Novartis, Switzerland) for antihistamine-refractory CSU between January 2015 and April 2024 in the Department of Adult Immunology and Allergy were evaluated. Of the patients, three were excluded from the study due to missing data, nine were lost to follow-up, and one developed adverse drug effects. Of the remaining patients, 123 patients uninterruptedly treated with omalizumab for at least 12 weeks were included in the study.

Omalizumab treatment protocol

Omalizumab was administered at a dose of 300 mg/4 weeks in the outpatient clinic under medical supervision. Antihistamine was discontinued in patients with complete urticaria regression after starting omalizumab therapy. Omalizumab treatment was discontinued after 24 weeks in patients who showed a complete response. When new symptoms of urticaria developed after cessation of treatment, it was considered a recurrence. We reinitiated omalizumab treatment for these patients.

Clinic and Laboratory values

Patients' demographic characteristics, clinical backgrounds, and laboratory results were obtained from patient files and electronic medical records. Data on possible triggers and comorbidities related to CSU were collected. Laboratory analyses including total IgE, thyroid-stimulating hormone (TSH), anti-thyroid peroxidase (anti-TPO), anti-nuclear antibodies (ANA), autologous serum skin test (ASST), and hemogram results were collected. A skin prick test (SPT) or specific IgE (sIgE) confirmed patients with suspected atopy. The plasma sIgE, IgG-anti-TPO autoantibodies, and total IgE titers were measured using the Phadia Unicap 100 instrument (Thermo Fisher Scientific, Waltham, MA) and the Immuno-CAP system by fluoroenzyme immunoassay (FEIA). Serum total IgE levels of 100 IU/mL or greater were defined as increased. Normal reference range was 0–34 IU/mL and 0.27–4.2 mU/L for anti-TPO and TSH, respectively.

Treatment response

Urticaria control test (UCT) was used to monitor the disease and evaluate its control. UCT evaluates the disease control for last 4 weeks. The patient answers four questions regarding physical symptoms, quality of life, effectiveness of treatment, and general control. Each question is scored on a scale of five (0–4 points). The total score varies from 0 to 16.[11] In our clinic, UCT was recorded monthly before each omalizumab administration. For this study, we addressed UCT results obtained 12 weeks after initiation

of the treatment. A UCT <12 was classified as no response, 12 ≤ UCT <16 as partial response, and UCT = 16 as complete response.. Those with partial and complete responses were generalized and defined as responders.[12] The characteristics of the patients classified according to UCT results were compared. The potential effects of these variables on the omalizumab response were evaluated.

When the time to a UCT ≥12 after the first dose of omalizumab treatment was 2–4 weeks, it was defined as an early response, whereas when it was 12–16 weeks, it was defined as a delayed response.[13] We performed our clinical evaluation in the 12th week, as Turkey recommends discontinuing omalizumab in the 12th week in case of no response. An assessment period of 12 weeks also allows for timely therapeutic intervention.[14]

Statistical analysis

Data entry and statistical analysis were performed by using SPSS for Windows version 18.0 (SPSS Inc. Chicago, IL, USA) package program. Conformity to the normal distribution of the data was examined using visual (histograms and probability graphs) and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk tests). Median values (first quartile–third quartile) were used for the evaluation of numerical data, whereas frequencies and percentiles were used for the expression of categorical data. For comparison of nonnormally distributed three and more groups with numerical data, the Kruskal–Wallis test was used. For paired comparisons between the groups with significant Kruskal–Wallis test results, posthoc Mann–Whitney U test and Bonferroni correction were performed. For comparison of two dependent groups, the signed-rank test was used. Chi-squared test was used for comparison of categorical data. Using possible variables, independent predictors of failure to respond to omalizumab treatment were examined via univariate and multivariate logistic regression analyses. For model fitness, the Hosmer–Lemeshow test was used. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Of 123 patients included in the study, the median age was 42 (31–50) years, and 77 (62.9%) were females. The median disease duration before initiation of omalizumab treatment was 36 (12–60) months. Of the patients, 41 (33.3%) patients had hives with concomitant angioedema. There were 12 (9.8%) patients with concomitant dermographism, 43 (35%) patients with concomitant atopy, and 31 (25.2%) patients with concomitant AID. Among AID, the most common one was thyroid autoimmunity seen in 24 (77.4%) patients. Of those with thyroid autoimmunity, 23 (95.8%) had Hashimoto disease. Other AIDs found included ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, vitiligo, Sjogren's syndrome, and celiac disease (Table 1).

In the patients, median baseline total IgE value was 146.00 (64.60–353.00), which was above normal. Total IgE value was above 100 kUA/L in 55.2% of the patients.

Table 1 Patients' demographic and clinical characteristics.

Patients (n=123)	
Age in years, Median (IQR)	42.00 (31.00–50.00)
Sex, n (%)	
Female	77 (62.9)
Male	46 (37.4)
Age at onset of disease in years, median (IQR)	34.00 (25.00–44.00)
Age at admission in years, median (IQR)	38.00 (28.50–47.00)
Duration of disease in months, median (IQR)	36.00 (12.00–60.00)
Duration of disease in years, n (%)	
< 1 year	20 (16.3)
1–5 years	71 (57.7)
5–10 years	16 (13.0)
> 10 years	16 (13.0)
Concomitant, n (%)	
Angioedema	41 (33.3)
Dermographism	12 (9.8)
Atopy	43 (35.0)
Autoimmune disease	31 (25.2)
Autoimmune disease (n=31), n (%)	
Rheumatoid arthritis	1 (3.2)
Systemic lupus erythematous	1 (3.2)
Autoimmune thyroiditis	24 (77.4)
Crohn's disease	1 (3.2)
Ankylosing spondylitis	2 (6.5)
Vitiligo	1 (3.2)
Sjogren's syndrome	1 (3.2)
Celiac disease	1 (3.2)
Autoimmune thyroid disease (n=24), n (%)	
Hashimoto's thyroiditis	23 (95.8)
Graves' disease	1 (4.2)

ANA was analyzed in 81 patients and ASST in 14 patients. The laboratory results of the patients are summarized in Table 2.

The median number of doses of omalizumab received was 12.00 (6.00–23.00). Of the patients, 64 (52%) patients exhibited complete response and 43 (35%) patients exhibited partial response to omalizumab treatment, whereas 16 (13%) patients were nonresponders. Of the responders, 80 (74.7%) patients were early responders, and 27 (25.3%) patients were late responders. The mean baseline UCT value was 4 (3–4) before treatment and increased to 16 (14–16) after treatment (p<0.001). Of those who completed omalizumab treatment, 90 (73.2%) patients had recurrence. The results of omalizumab treatment are shown in Table 3.

Comparison of clinical parameters by type of response to omalizumab treatment

The presence of AID was significantly higher in nonresponders to omalizumab, compared with partial and complete responders (p=0.010). Baseline IgE serum levels were

Table 2 Patients' laboratory characteristics.

Patients (n=123)	
TSH, mU/L, median (IQR)	1.78 (1.24-2.60)
Anti-TPO, IU/mL, median (IQR)	11.20 (9.0-20.60)
Total IgE, IU/mL, median (IQR)	146.00 (64.60-353.00)
Eosinophils, 10^3u/L, median (IQR)	120.00 (73.00-200.00)
Basophils, 10^3u/L, median (IQR)	30.00 (10.00-50.00)
ANA (n=81), n (%)	
Negative	46 (56.8)
Positive	35 (43.2)
ASST (n=14), n (%)	
Negative	6 (42.9)
Positive	8 (57.1)

TSH: Thyroid-stimulating hormone, Anti-TPO: Anti-thyroid peroxidase autoantibodies, IgE: Immunoglobulin E, ANA: Anti-nuclear antibodies, ASST: Autologous serum skin test

Table 3 Results of omalizumab treatment.

Patients (n=123)	
Number of Omalizumab doses, Median (IQR)	12.00 (6.00-23.00)
Type of response, n (%)	
Nonresponders	16 (13.0)
Partial responders	43 (35.0)
Complete responders	64 (52.0)
Time of response (n=107), n (%)	
Early response	80 (74.7)
Delayed response	27 (25.3)
Recurrence, n (%)	
Yes	90 (73.2)
No	33 (26.8)
Baseline UCT, Median (IQR)	4 (3-4)
Final UCT, Median (IQR)	16 (14-16)
p*	<0.001

*Wilcoxon signed-rank test, UCT: Urticaria control test

significantly higher in the complete responder group (266.0, 135.0-548.5 IU/mL) compared with the partial responder (84.5, 43.0-248.5 IU/mL, p<0.001) and nonresponder groups (90.8, 46.5-205.2 IU/mL, p<0.001). The final UCT value of nonresponders to omalizumab was significantly lower than the other groups (p<0.001) (Table 4).

Factors affecting failure to respond to omalizumab treatment

A regression model including defined variables was formed to predict failure to respond to omalizumab treatment. Variables with a p-value lower than 0.1 in univariate analysis were examined using the backward LR method in multivariate analysis. The logistic regression model was found to be significant, and it predicted failure to respond to omalizumab treatment at a rate of 22.5% (Nagelkerke R^2 = 0.225). The rate of failure to respond to omalizumab in those with autoimmune thyroid disease increased by 3.558 times (Table 5).

Discussion

In the current study, response to omalizumab treatment was observed in 107 (87%) patients. The presence of AID was significantly higher in nonresponders. Among AIDs, the most common was thyroid AID. The presence of thyroid autoimmunity, 95.8% of which was Hashimoto's thyroiditis, was an independent risk factor for failure to respond to omalizumab. Baseline serum IgE value of complete responders to omalizumab was significantly higher than the other groups. The final UCT value of nonresponders to omalizumab was significantly lower than the other groups.

CSU is most common among women over 30 years of age.[15] In this study, median age of disease onset was 34.00 (25.00-44.00) years, and the number of female patients was 77 (62.9%). The disease duration varies from 1 to 5 years on average, although symptoms may persist for more than 5 years in 11-14% of the cases. [16] In the study, the disease duration of 71 (57.7%) patients was 1-5 years. Approximately, 50% of the patients report exacerbations of concomitant angioedema, which results in a more severe and prolonged disease.[1] In our study, however, 41 (33.3%) patients had hives with concomitant angioedema. Some forms of inducible CU like dermographism may accompany CSU. This may lead to a longer disease duration and treatment failure.[7] Atopy is also common among CU patients.[17] However, it is less common in patients who are nonresponders to omalizumab treatment.[18] In this study, 12 (9.8%) patients had concomitant dermographism, and 43 (35%) patients had atopy. Both blood basopenia and eosinopenia are observed in 10-15% of CSU patients. This is associated with CSU activity, presence of autoantibodies, and poor response to omalizumab.[15] The current study showed no significant difference in demographic features, disease duration, basopenia, eosinopenia, concomitant angioedema, dermographism, and atopy between nonresponders, partial responders, and complete responders.

ANA and ASST positivity are expected mainly in type IIb aiCSU. ASST reveals the formation of swelling at the site of intracutaneous injection of autologous serum.[5] Previous studies have reported the effect of a positive ASST on delayed and inadequate response to omalizumab.[7,19] In our study, 8 of 14 patients who underwent ASST were positive, and 6 were negative. One study reported ANA positivity in >5% of CSU patients.[20] In this study, of 81 patients for whom ANA was requested, 35 (43.2%) patients tested positive for ANA. ANA and ASST are not routinely performed in most CSU patients, so we could not assess their impact on treatment response to omalizumab.

In this study, the median number of omalizumab received by the patients was 12.00 (6.00-23.00 A previous study reported that 67.9% were complete responders, 21.6% were partial responders to omalizumab, whereas 10.5% were nonresponders.[21] In our study, however, 64 (52%) patients were complete responders and 43 (35%)

Table 4 Characteristics of complete responders, partial responders, and nonresponders to omalizumab treatment.

Parameter	Complete responders (n =64)	Partial responders (n=43)	Nonresponders (n =16)	P-value
Age in years, median (IQR)	37.0 (29.2-48.0)	44.0 (31.0-52.0)	48.0 (34.2-51.5)	0.270[b]
Female, n (%)	34 (53.1)	30 (69.8)	13 (81.3)	0.056[a]
Duration of disease in months, median (IQR)	36.0 (12.0-60.0)	36.0 (12.0-60.0)	24.0 (12.0-54.0)	0.636[b]
Age at onset of disease in years, median (IQR)	31.0 (22.0-40.0)	39.0 (26.0-47.0)	37.0 (29.5-45.7)	0.096[b]
Age at admission in years, median (IQR)	34.0 (28.0-45.0)	41.0 (28.0-50.0)	44.0 (31.2-47.7)	0.274[b]
Duration of disease in years, n (%)				
<1 year	10 (15.6)	8 (18.6)	2 (12.5)	-
1-5 years	32 (50.0)	28 (65.1)	11 (68.8)	
5-10 years	12 (18.8)	4 (9.3)	-	
>10 years	10 (15.6)	3 (7.0)	3 (18.8)	
Concomitant				
Angioedema, n (%)	25 (39.1)	14 (32.6)	2 (12.5)	0.130[a]
Dermographism, n (%)	7 (10.9)	2 (4.7)	3 (18.8)	-
Atopy, n (%)	19 (29.7)	16 (37.2)	8 (50.0)	0.291[a]
Autoimmune disease	9 (14.1)	15 (34.9)	7 (43.8)	**0.010**[a]
TSH, mU/L, Median (IQR)	1.8 (1.5-2.6)	1.5 (1.0-2.5)	1.3 (0.9-2.4)	0.147[b]
Anti-TPO, IU/mL, Median (IQR)	11.2 (9.0-19.2)	11.2 (9.0-13.9)	13.6 (9.0-135.5)	0.578[b]
Total IgE, IU/mL, Median (IQR)	266.0 (135.0-548.5)	84.5 (43.0-248.5)	90.8 (46.5-205.2)	**<0.001**[b]
Eosinophils, 103u/L, Median (IQR)	130.0 (90.7-245.0)	140.0 (73.0-200.0)	90.0 (52.5-123.0)	0.076[b]
Basophils, 103u/L, Median (IQR)	30.0 (20.0-51.0)	30.0 (20.0-60.0)	0.5 (0-40.0)	0.050[b]
Baseline UCT, Median (IQR)	4 (3-4)	4 (3-5)	3.5 (2.2-5)	0.228[b]
Final UCT, Median (IQR)	16 (16-16)	14 (12-15)	8.5 (5.7-10)	**<0.001**[b]

[a]Chi-squared test, [b]Kruskal-Wallis H test, TSH: Thyroid-stimulating hormone, Anti-TPO: Anti-thyroid peroxidase autoantibodies, UCT: Urticaria control test

Table 5 Factors affecting nonresponse to omalizumab treatment.

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age in years	−0.981 (0.946-1.017)	0.296		
Sex; male (Ref: female)	2.911 (0.783-10.828)	0.111		
Disease duration, months	1.014 (0.988-1.042)	0.284		
Age of onset	−0.983 (0.947-1.020)	0.359		
Age at admission	−0.984 (0.949-1.021)	0.402		
Angioedema (Ref: No)	4.015 (0.867-18.596)	0.076	4.062 (0.842-19.598)	0.081
Dermographism (Ref: Yes)	2.513 (0.602-10.490)	0.206		
Atopy (Ref: Yes)	2.454 (0.823-7.320)	0.107		
Autoimmune disease (Ref: Yes)	2.690 (0.907-7.978)	0.074		
Autoimmune thyroid disease (Ref: Yes)	4.118 (1.350-12.563)	**0.013**	3.558 (1.079-11.730)	**0.037**
TSH	1.210 (0.789-1.854)	0.383		
Anti-TPO	−0.999 (0.997-1.002)	0.576		
Eosinophils	1.007 (1.000-1.013)	0.058		
Basophils	1.030 (1.004-1.056)	0.212		
Total IgE	1.003 (0.999-1.007)	0.108		

Hosmer-Lemeshow: 0,550, Nagelkerke R Square: 0.225, TSH: Thyroid-stimulating hormone, Anti-TPO: Anti-thyroid peroxidase autoantibodies, IgE: Immunoglobulin E

patients were partial responders to omalizumab, whereas 16 (13%) patients were nonresponders. These findings suggest that further studies are needed to enhance the complete response to omalizumab. Of 107 responders, 80 (74.7%) were early responders. Among the patients whose omalizumab treatment was discontinued after 6 doses, treatment was re-initiated due to recurrence in 90 (73.2%). Patients' median baseline UCT value was 4 (3-4) before treatment, whereas posttreatment UCT value was 16 (14-16) (p <0.001). UCT is a reliable and short tool for

the evaluation of CSU.[9] Previous studies reported 113.5% increased UCT scores with omalizumab treatment.[21] In this study, the final UCT value of nonresponders to omalizumab was significantly lower than the other groups (p<0.001).

In this study, the median IgE value was 146.00 (64.60-353.00), which is above the normal range. Previous studies have reported a positive effect on omalizumab treatment response in patients with higher baseline total IgE levels.[8,19,22] Likewise, in this study, initial serum IgE values were higher in complete responders to omalizumab than in other groups (p<0.001). Elevated total IgE levels were common in complete responders and rarely detectable in nonresponders to omalizumab. However, low total IgE levels were prevalent in nonresponders and were rarely detectable in complete responders.

CSU patients have a greater risk of comorbid AID.[20] One study reported the presence of at least one AID in 28% of CSU patients.[23] In the current study, 31 (25.2%) patients had AID. Autoimmune thyroid disease is the most common autoimmune comorbidity in CSU, the most common being Hashimoto's thyroiditis. Anti-thyroid and ANA are the most common autoantibodies in CSU. Previous studies have reported that ≥ 10% of CSU patients have anti-thyroid antibodies.[24] In this study, 24 (19.5%) patients had autoimmune thyroid disease with anti-thyroid antibodies. Of these, 23 (95.8%) patients had Hashimoto's thyroiditis and 1 (4.2%) had Grave's disease. Thyroid dysfunction is more common in women with CSU. Similarly, thyroid autoimmunity was more common in female patients in our study. The presence of AID was significantly higher in nonresponders to omalizumab (p=0.010). Although insignificant, the failure rate to respond was higher in women (p=0.056). We attribute it to the higher rate of AIDs in women. In the regression analysis performed to predict failure to respond to omalizumab, the rate of failure to respond increased by 3.558 in those with thyroid autoimmunity (odds ratio [OR], 3.558; 95% confidence interval [CI], 1.079–11.730, p=0.037). In those with autoimmune thyroid diseases, anti-thyroid antibodies do not directly involve mast cell degranulation. Nevertheless, they may increase the sensitivity of these cells to other activating signals, leading to development of urticaria. Furthermore, the products of chronic inflammatory response caused by these antibodies cause mast cell degranulation.[24] Based on this study, common autoimmune factors may simultaneously exist in thyroid autoimmunity and CSU. CSU patients should be, therefore, evaluated for thyroid AIDs that may coexist. When necessary, treatments would also contribute to treating urticaria.[24]

A limitation of this study is the small study population. Data routinely collected in our clinic were included in the analysis. However, the lack of data reduced the size of the study group. Also, since it is a single-center study, it is difficult to generalize to the general population. Nevertheless, our results will contribute to the factors affecting the response to omalizumab treatment. That is because the baseline serum IgE level and the presence of thyroid autoimmunity tend to predict the response to omalizumab treatment. Further studies are needed to confirm and reproduce these results. It would thus aid in switching to more effective treatments for potential nonresponders.

Conclusion

CSU is a disease that has variable disease course and is characterized by spontaneous remissions and recurrences. Omalizumab is a treatment preferred in antihistamine-refractory CSU. Patient-specific predictors for response to omalizumab treatment remain to be defined. This study revealed the effectiveness of omalizumab in CSU. Furthermore, it also demonstrated that serum total IgE level and the presence of autoimmune thyroid disease may aid in predicting response to omalizumab treatment. It may also guide switching to more effective treatments in potential nonresponders. More studies are warranted to clarify predictors affecting response to omalizumab treatment and to make it come into routine use.

Ethics Committee Approval

Ethics committee approval was received for this study from the Ethics Committee of Necmettin Erbakan University, who approved this study protocol (approval no: 2024/5063). The study followed the guidelines and principles of the Declaration of Helsinki.

Authors Contributions

FAA was concerned with conceptualization, data curation, methodology, investigation, resources, validation, review & editing, writing of the original draft, visualization, and project administration. FÇ was responsible for conceptualization, formal analysis, methodology, validation, review & editing, writing of original draft, and visualization. TÖ was interested in conceptualization, formal analysis, methodology, validation, review & editing, writing of original draft, and visualization. RE was in charge of conceptualization, formal analysis, methodology, validation, visualization, and review & editing. FSA was responsible for data curation, formal analysis, investigation, project administration, resources, writing of original draft, and review & editing. MK was concerned with conceptualization, formal analysis, methodology, validation, visualization, and review & editing. MEG was involved in formal analysis, data curation, investigation, project administration, resources, writing of original draft, and review & editing. ŞA was responsible for formal analysis, methodology, validation, project administration, supervision, and review & editing.

Conflicts of Interest

The authors have no conflict of interests to declare.

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References

1. Casale TB, Gimenez-Arnau AM, Bernstein JA, Holden M, Zuberbier T, Maurer M. Omalizumab for patients with

chronic spontaneous urticaria: A narrative review of current status. Dermatol. Ther. 2023;13(11):2573–88. https://doi.org/10.1007/s13555-023-01040-9
2. Maurer M, Zuberbier T, Metz M. The classification, pathogenesis, diagnostic workup, and management of urticaria: An Update. Handb. Exp. Pharmacol. 2022;268:117–33. https://doi.org/10.1007/164_2021_506
3. He L, Yi W, Huang X, Long H, Lu Q. Chronic urticaria: Advances in understanding of the disease and clinical management. Clin. Rev. Allergy Immunol. 2021;61(3):424–48. https://doi.org/10.1007/s12016-021-08886-x
4. Larenas-Linnemann D. Biomarkers of autoimmune chronic spontaneous urticaria. Curr. Allergy Asthma Rep. 2023;23(12):655–64. https://doi.org/10.1007/s11882-023-01117-7
5. Kolkhir P, Muñoz M, Asero R, Ferrer M, Kocatürk E, Metz M, et al. Autoimmune chronic spontaneous urticaria. JACI. 2022;149(6):1819–31. https://doi.org/10.1016/j.jaci.2022.04.010
6. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734–66. https://doi.org/10.1111/all.15090
7. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. Allergy. 2021;76(10):2965–81. https://doi.org/10.1111/all.14757
8. Marzano AV, Genovese G, Casazza G, Fierro MT, Dapavo P, Crimi N, et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: A study of 470 patients. JEADV. 2019;33(5):918–24. https://doi.org/10.1111/jdv.15350
9. Bérard F, Ferrier Le Bouedec MC, Bouillet L, Reguiai Z, Barbaud A, Cambazard F, et al. Omalizumab in patients with chronic spontaneous urticaria nonresponsive to H1-antihistamine treatment: Results of the phase IV open-label SUNRISE study. BJD. 2019;180(1):56–66. https://doi.org/10.1111/bjd.16904
10. Straesser MD, Oliver E, Palacios T, Kyin T, Patrie J, Borish L, et al. Serum IgE as an immunological marker to predict response to omalizumab treatment in symptomatic chronic urticaria. J Allergy Clin Immunol Pract. 2018;6(4):1386–8.e1. https://doi.org/10.1016/j.jaip.2017.10.030
11. Salameh P, Gutsche A, Aulenbacher F, Buttgereit T, Weller K, Siebenhaar F, et al. Urticaria control test real-world performance: A post-hoc analysis. Allergy. 2024;79(1):229–32. https://doi.org/10.1111/all.15813
12. Yu R, Qian W, Zheng Q, Xiong J, Chen S, Chen A, et al. Analysis of the efficacy and recurrence of omalizumab use in the treatment of chronic spontaneous urticaria and chronic inducible urticaria. Int. Arch. Allergy Immunol. 2023;184(7):643–55. https://doi.org/10.1159/000529250
13. Ghazanfar MN, Holm JG, Thomsen SF. Effectiveness of omalizumab in chronic spontaneous urticaria assessed with patient-reported outcomes: A prospective study. JEADV. 2018;32(10):1761–7. https://doi.org/10.1111/jdv.15045
14. Ferrer M, Boccon-Gibod I, Gonçalo M, İnalöz HS, Knulst A, Lapeere H, et al. Expert opinion: Defining response to omalizumab in patients with chronic spontaneous urticaria. EJD. 2017;27(5):455–63. https://doi.org/10.1684/ejd.2017.3085
15. Kolkhir P, Giménez-Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. Nat. Rev. Dis. Primers. 2022;8(1):61. https://doi.org/10.1038/s41572-022-00389-z
16. Foti C, Romita P, Ambrogio F, Fanelli M, Panebianco R, Vena GA, et al. Analysis of clinical factors as possible predictors of response to omalizumab and relapse after treatment discontinuation in chronic spontaneous urticaria. Dermatol. Ther. 2022;35(2):e15248. https://doi.org/10.1111/dth.15248
17. Chen Q, Yang X, Ni B, Song Z. Atopy in chronic urticaria: An important yet overlooked issue. Fron. Immunol. 2024;15:1279976. https://doi.org/10.3389/fimmu.2024.1279976
18. Asero R. Omalizumab in severe chronic urticaria: Are slow and non-responders different? Eur. Ann. Allergy Clin. Immunol. 2021;53(6):263–6. https://doi.org/10.23822/EurAnnACI.1764-1489.167
19. Deza G, Bertolín-Colilla M, Pujol RM, Curto-Barredo L, Soto D, García M, et al. Basophil FcεRI expression in chronic spontaneous urticaria: A potential immunological predictor of response to omalizumab therapy. ActaDV. 2017;97(6):698–704. https://doi.org/10.2340/00015555-2654
20. Kolkhir P, Borzova E, Grattan C, Asero R, Pogorelov D, Maurer M. Autoimmune comorbidity in chronic spontaneous urticaria: A systematic review. Autoimmun. Rev. 2017;16(12):1196–208. https://doi.org/10.1016/j.autrev.2017.10.003
21. Bernstein JA, Kavati A, Tharp MD, Ortiz B, MacDonald K, Denhaerynck K, et al. Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: A systematic review of 'real-world' evidence. Expert Opin. Biol. Ther. 2018;18(4):425–48. https://doi.org/10.1080/14712598.2018.1438406
22. Weller K, Ohanyan T, Hawro T, Ellrich A, Sussman G, Koplowitz J, et al. Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. Allergy. 2018;73(12):2406–8. https://doi.org/10.1111/all.13586
23. Kolkhir P, Altrichter S, Asero R, Daschner A, Ferrer M, Giménez-Arnau A, et al. Autoimmune diseases are linked to type IIb autoimmune chronic spontaneous urticaria. AAIR. 2021;13(4):545–59. https://doi.org/10.4168/aair.2021.13.4.545
24. Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review. Allergy. 2017;72(10):1440–60. https://doi.org/10.1111/all.13182