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Comparison of the characteristics of patients with chronic urticaria receiving standard- or high-dose omalizumab

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Key words

Urticaria; omalizumab updosing; D-dimer; anti-TPO positivity; low IgE.

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Impact statement

D-dimer level seems to be a predictor for omalizumab updosing. IgG-anti-TPO positivity and low IgE do not predict the need for dose escalation.

Summary

Background. *In patients whose chronic urticaria (CU) cannot be controlled with omalizumab 300 mg and antihistamines, the dose can be increased up to 600 mg. The study aimed to compare the clinical characteristics of patients receiving 300 mg versus higher doses of omalizumab, and to evaluate baseline predictors for updosing.* ***Methods.*** *A total of 159 patients who have been followed up at a tertiary care allergy center and received omalizumab for at least 12 months were included. The clinical characteristics of those who received the standard-dose omalizumab (Group 1) were compared to the ones who received therapy over the standard dose (Group 2).* ***Results.*** *A total of 139 (87%) were in Group 1, and 20 (13%) were in Group 2. CU duration at baseline was shorter in Group 2. Chronic inducible urticaria was present in 2%, and 40% of the patients in Group 1 and 2, respectively. Elevated D-dimer level was associated with high-dose omalizumab use ($p < 0.001$). Area under the curve in the ROC analysis was 0.812 and the cutoff value of D-dimer level was 0.46 mg/dl ($p = 0.001$, sensitivity and specificity 67%, and 84%, respectively). The anti-TPO positivity was higher in patients with low IgE (31% vs 8%, $p = 0.008$).* ***Conclusions.*** *Nearly one in every ten patients required higher doses of omalizumab therapy. D-dimer level seems to be a predictor for omalizumab updosing and unresponsiveness to standard dose. IgG-anti-TPO positivity and low IgE do not predict the need for dose escalation; however, this result should be strengthened with a larger number of patients.*

Introduction

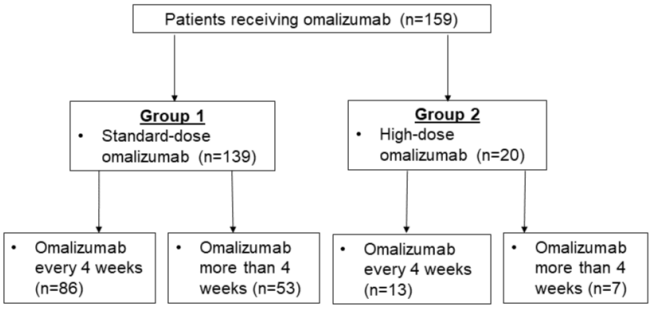
Chronic urticaria (CU) is a disease that persists for more than six weeks, with itchy and edematous papules/plaques, and may be associated with angioedema due to deep dermis or subcutis involvement, or with the development of both (1). The prevalence of CU varies between 0.5-1% in the general population (2). Identifiable triggering factors are stress, trauma, medications, food additives, temperature changes, pressure, surgery, hormones, physical exercise, autoimmunity, and infections (3, 4). While it is primarily recommended to move away from detectable triggers, some patients need to take regular treatment. While modern second-generation antihistamines (sgAHs) constitute the main drugs in the first step of the treatment algorithm, it is recommended to initiate omalizumab as a second-line treatment in patients who do not respond to high-dose sgAHs (5, 6). Undoubtedly, the use of omalizumab in different doses is effective in remission and the maintenance of this remission (7). However, with the standard dose of 300 mg, adequate control may not be achieved in approximately 30% of patients treated for six months. Several studies have found that a significant number of patients with chronic spontaneous urticaria (CSU) can be effectively treated with higher doses of omalizumab who tend to have higher body mass index (BMI), older age, and low immunoglobulin E (IgE) levels (8, 9). Predictable risk factors to clinically distinguish patients requiring high-dose omalizumab from those receiving standard-dose omalizumab have still not been clearly identified. The study aimed to compare the clinical characteristics of patients receiving standard- or high-dose omalizumab and to disclose the likely predictors to be in the high-dose group.

Materials and methods

Study design and participants

The study was conducted as a prospective, single-center, cross-sectional survey. This observational real-life study included a total of 159 CU patients receiving omalizumab from September 1, 2014, to July 31, 2023 at a tertiary care allergy clinic. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, revised in 2013, and was approved by Hacettepe University Ethics Committee (2023/11-04). In accordance with the recommendations of Zuberbier *et al.*, patients with compatible clinical histories were diagnosed with chronic spontaneous urticaria and chronic inducible urticaria (10). As of August 30, 2014, omalizumab was approved for use in antihistamine-resistant urticaria in Turkey and started to be used in our clinic. Inclusion criteria were provision of written informed consent, age ≥ 18 years, and use of omalizumab for at least 12 months. One (0.6%) patient diagnosed with urticarial vasculitis and treated with 600 mg of omalizumab was excluded from analysis. Study groups are shown in **figure 1**. Individuals receiving standard- or high-dose omalizumab were defined as Groups 1 and 2, respectively.

Figure 1 - *The flow chart of the study population.*



Data collection and laboratory measurements

The patients' pre-omalizumab or baseline laboratory values were recorded from the hospital database retrospectively. During regular hospital visits or omalizumab prescriptions and/or injections, informed consent was obtained through face-to-face interviews, and a questionnaire was subsequently used to prospectively document their current treatments, treatment durations, times of treatment changes, attacks, disease control, and medication adherence. In addition to the demographic characteristics of the patients, the survey form included the questions about the disease duration, the presence of angioedema, allergic diseases, urticaria exacerbations requiring systemic corticosteroids in the last year, admissions to the emergency room due to urticaria attacks, omalizumab doses and intervals, comorbidities, medications, urticaria control, baseline blood eosinophil and basophil counts, antinuclear antibody (ANA), IgG-anti-thyroid autoantibody (IgG-anti-TPO), specific immunoglobulin E (IgE) level (for the phadiatop, food mix, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat, dog, *Aspergillus fumigatus*, alternaria) or skin prick test (including *Phleum pratense*, *Artemisia vulgaris*, *Parietaria officinalis*, *Corylus avellena*, *Betula verrucosa*, *Olea europaea*, *D. pteronyssinus*, cat, dog, *Alternaria alternata*, *Claudosporium herbarum*, *Aspergillus fumigatus*, latex, blatella, acarus siro, positive control, negative control, corn, hazelnuts, peanuts, walnuts, almonds, chicken, egg white, egg yolk, orange, lemon, banana, peach, strawberry, cherry, tomato, bean, carrot, pea, crab, shrimp, mussel) results, pre-treatment C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), D-dimer level, total IgE level, urticaria control test (UCT), and medication adherence report scale were applied to all patients during their visits. Serum total IgE was measured by a chemiluminescent immunoassay (ImmunoCAP; Thermo Fisher Scientific, Sweden), and the cutoff value of low IgE level was < 43 IU/mL (11). A cut-off of less than 50 $\times 10^6/mm^3$ was accepted as eosinopenia which was the most frequently used cutoff in the literature (12-14). Basopenia was accepted as less than $10 \times 10^6/mm^3$, as previously described (14, 15). The cutoff value for elevated ESR was calculated with (age/2) for men, and with [(age+10)/2)] mm/h for women (16, 17). D-dimer level was measured by enzyme-linked immunosorbent assay, and the reference range was 0-0.55 mg/L.

Assessments of the treatment responses and compliances

Disease control within the last month was determined by the UCT. The UCT is an easy-to-administer, self-reported questionnaire assessing disease control in patients with CU, and it provides a final score between 0 and 16. Those with scores < 12 points and an increase of < 3 compared to baseline are accepted as uncontrolled or non-responder, and those ≥ 12 points and an increase of ≥ 3 compared to baseline are accepted as controlled or responder (18). Medication adherence report scale (MARS) was also performed. The total score of the scale is 25 points. As the total score increases, the compliance stands for better. MARS is validated in Turkish version by Sen *et al.* (19).

Follow-up during omalizumab treatment

As second-line therapy standard-dose omalizumab was initiated to patients who were non-responders to high-dose sgAHs, considering the EAACI/GA²LEN/EuroGuiDerm/APAACI guidelines (20). If the urticaria was still uncontrolled after at least four months of 300 mg of omalizumab, the dose was increased to 450 mg. In patients whose urticaria was still uncontrolled for at least additional three months of 450 mg of omalizumab, the dose was increased to 600 mg as recommended by Kocaturk *et al.* (21). If urticaria was under control for at least six months, the patient was considered for either decreasing the dose or extension of the injec-

tion interval by one week after every injection. However, during the enrollment process, it was observed that some patients were not taking regular antihistamines, which resulted in inadequate urticaria control. It was decided to follow up with standard-dose omalizumab therapy while adding regular antihistamines to the treatment regimen. Also, individuals whose urticaria could not be controlled with high-dose omalizumab were investigated for immunodeficiency, vasculitis, and other systemic diseases, which could have been among the differential diagnoses (1). One of our patients was diagnosed with common variable immunodeficiency (CVID) and initiated on intravenous immunoglobulin (IVIG) therapy. Eight months after starting IVIG, the patient's urticaria was completely controlled, and the omalizumab dose was reduced to 450 mg, administered once every four weeks.

Statistical analysis

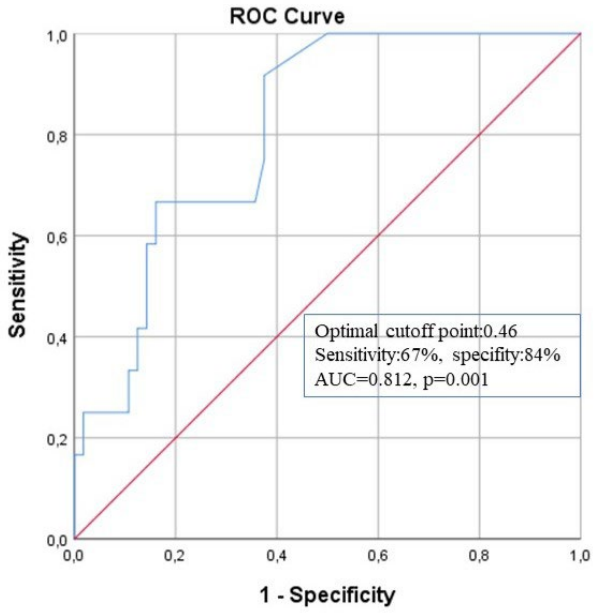
Data were analyzed using SPSS vn. 23.0 software. Descriptive data were presented as numbers (n) and percentages (%). Numerical variables showing normal distribution were stated as mean± standard deviation values, and otherwise as median and interquartile range (IQR) values. The Chi-Square or Fisher Exact test for categorical variables and the Mann-Whitney U or the Kruskal Wallis test for continuous variables were used. The independent samples t-test was applied to comparisons of parametric variables between two groups. Spearman correlation coefficient was used for non-normally distributed parameters. The possible factors identified with univariate analyses were further entered into the cox regression analysis, with backward selection according to the $p \leq 0.20$, to determine independent predictors of high-dose omalizumab use. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-I error level was used to infer statistical significance. Receiver operating characteristic (ROC) curve analysis was done to assess baseline D-dimer level, baseline blood eosinophil count, duration of CU, CU duration at baseline, and regular antihistamine use during omalizumab treatment as potential predictors of uncontrolled urticaria.

Results

There was a total of 159 patients in the study. The median age of the patients was 43 years (IQR: 34-53); nine (6%) of the patients were over 65 years old, and 100 (63%) were female. Individuals receiving standard- or high-dose omalizumab were defined as Groups 1 and 2, respectively. Forty-one (26%) patients were obese, and the rate of obesity was similar in both groups. Asthma was the most common comorbidity, occurring in 25% of the patients, and the rate of asthma was similar in both groups. All patients received omalizumab treatment for at least 12 months. Of these, 139 (87%) were in Group 1, and 20 (13%) were in Group 2. Overall, urticaria was under control in 142 (89%) patients. The median baseline IgE level was similar in the two groups (**table I**). In Group 2, the median D-dimer level was significantly higher, regular antihistamine use during omalizumab treatment was more likely, and CU duration at baseline was shorter. Female gender, presence of angioedema, eosinopenia, basopenia, low IgE, IgG-anti-TPO positivity, duration of CU, duration of omalizumab treatment, serum CRP level, and ESR were similar in both groups (**table I**). The anti-TPO positivity was higher in patients with low IgE (31% *vs* 8%, p = 0.008). Simultaneous IgG-anti-TPO positivity and low IgE were similar in Group 1 and 2 (3% and 5%, p = 0.61). The median CU duration at baseline was shorter in Group 2 (12 *vs* 24 months, p = 0.009). Omalizumab updosing was administered at a median of 19 weeks into the treatment. The urticaria was controlled in 16 (80%) individuals in Group 2. Among controlled patients, omalizumab dose intervals were increased up to ten weeks in six (35%).

Urticaria was not controlled in a total of 17 patients, with 4 patients (20%) in Group 2 and 13 patients (10%) in Group 1. The rate of uncontrolled urticaria were similar in Groups 1 and 2 (p = 0.15). Uncontrolled patients in Group 1 were actually candidates for dose escalation. Also, 50% of uncontrolled patients in Group 2 had accompanied chronic inducible urticaria (CIndU) to CSU. In our study, cold urticaria was present in two patients, delayed pressure urticaria in two, cholinergic urticaria in four,

Figure 2 *- The association between the baseline D-dimer level and high-dose omalizumab use.*



ROC analysis revealed D-dimer level is related to high-dose omalizumab use (AUC: 0.812, p = 0.001, 95%CI [0.701-0.924]). When the cut-off is selected as 0.46 mg/dl, estimated sensitivity and specificity are 67% and 84%, respectively. AUC: area under the curve; ROC: receiver operating characteristic.

Table I *- Demographic and clinical characteristics of the study groups at baseline.*

	All patients (n = 159)	Group 1 (n = 139)	Group 2 (n = 20)	P-value
Age, median years[a]	44 (34-53)	43 (33-52)	48 (38-53)	0.33
Female, n (%)	100 (63)	88 (63)	12 (60)	0.77
BMI, mean, kg/m²	26.2 (5.1)	26.1 (5)	27.4 (5.5)	0.21
Obesity, n (%)	41 (26)	34 (24)	7 (35)	0.31
Types of chronic urticaria*, n (%)	147 (92)	135 (97)	12 (60)	NA
CSU	4 (3)	2 (1)	2 (10)	
CındU	8 (5)	2 (1)	6 (30)	
CSU+CındU				
Duration of chronic urticaria, median months	78 (42-145)	84 (44-156)	54 (34-100)	0.08
Duration of omalizumab treatment, median months	36 (18-66)	36 (17-65)	39 (23-78)	0.27
Chronic urticaria duration at baseline, median months	24 (11-81)	24 (12-88)	12 (6-24)	**0.009**
Presence of angioedema, n (%)	105 (66)	94 (68)	11(55)	0.26
MARS[2], median score	21 (19-25)	22 (20-25)	20 (18-24)	0.42
Blood eosinophil count[b], median /mm³	100 (98-258)	100 (96-265)	100 (95-189)	0.23
Eosinopenia**, n (%)	3 (2)	3 (2)	0 (0)	NA
Blood basophil count[b], median /mm³	10 (9-88)	10 (9-89)	20 (10-55)	0.41
Basopenia**, n (%)	1 (0.6)	1 (0.7)	0 (0)	NA
D-dimer level[c], median mg/L	0.19 (0.03-0.5)	0.1 (0.01-0.3)	0.75 (0.2-3)	**< 0.001**
C-reactive protein level, median mg/dl	0.6 (0.3-1)	0.5 (0.3-0.9)	0.6 (0.4-1.3)	0.45
Erythrocyte sedimentation rate, median mm/h	12.5 (4-23)	13 (4-22)	6 (3-30)	0.75
Elevated ESR, n (%)	21 (13)	17 (12)	4 (20)	0.28
ANA positivity, n (%)	4 (3)	3 (2)	1 (5)	0.45
IgG-anti-TPO positivity, n (%)	21 (13)	17 (12)	4 (20)	0.34
Baseline total IgE[d], median UI/mL	165 (65-347)	158 (61-325)	230 (70-634)	0.53
Low IgE***, n (%)	16 (10)	14 (10)	2 (10)	0.79
Both IgG-anti-TPO positivity and low IgE, n (%)	5 (3)	4 (3)	1 (5)	0.61

[a]Data is presented as mean ± SD if normally distributed, and median (interquartile range) if not normally distributed. Categorical variables are presented as number (percentages). [b]Measured in 127 patients. [c]Measured in 68 (56 [40%] in Group 1, 12 [60%] in Group 2) patients. [d]Measured in 123 patients (110 [79%] in Group 1, 13 [65%] in Group 2). *Types of urticaria are described CSU: chronic spontaneous urticaria, CındU; chronic inducible urticaria. **The cutoff value of eosinopenia and basopenia were 50×10^6 /mm³, and 10×10^6 /mm³, respectively. ***The cutoff value of low IgE level was < 43 UI/mL. [1]UCT, urticaria control test. [2]MARS, medication adherence report scale.

Table II *- Variables associated with high-dose omalizumab use, multivariable analysis.*

	RR (95%CI) *	P-value
Chronic urticaria duration at baseline, months	0.94 (0.88-1.01)	0.08
Duration of chronic urticaria, months	1.01 (0.98-1.04)	0.50
Regular antihistamine use during omalizumab treatment	3.56 (0.25-50.11)	0.35
Blood eosinophil count, median /mm³	0.99 (0.97-1.09)	0.23
D-dimer level, mg/L	4.82 (1.06-21.96)	**0.04**

*RR: Estimated relative risk and 95% confidence interval shown by odds ratio.

and symptomatic dermographism in four patients. The use of systemic corticosteroid burst in the last year was similar in the both groups after omalizumab (24% *vs* 25%, p = 0.90).

There were 16 patients with IgE levels below 43 IU/mL and only eight with IgE levels below 20 IU/mL. Of these, six patients (75%) were in Group 1, while two (25%) were in Group 2.

A positive and moderate correlation was detected between D-dimer level and high-dose omalizumab use (r = 0.43, p < 0.001). In multivariable regression analysis model, independent risk factor was D-dimer level after adjustment for blood eosinophil count, CU duration at baseline, duration of CU, and regular antihistamine use during omalizumab treatment (Nagelkerke R^2 = 0.535, **table II**). D-dimer level was significantly higher in Group 2 (**table I**). ROC analysis revealed that D-dimer level was related to high-dose omalizumab use (AUC: 0.812, p = 0.001, 95%CI 0.701-0.924). When the cutoff was selected as 0.46 mg/dl, estimated sensitivity and specificity were 67% and 84%, respectively (**figure 2**).

No adverse event related to omalizumab use was observed during 156 patient-year experience. Notably, there was a patient with uncontrolled urticaria with 600 mg of omalizumab. She was 25 years old and diagnosed with (CVID) during the follow-up, and IVIG was initiated after the diagnosis. After that, the urticaria was under control, and the omalizumab dose was decreased to 450 mg.

Discussion and conclusions

To identify factors that could predict the necessity for omalizumab dose escalation in patients with CU, a comparative analysis was conducted between 20 patients (12%) requiring high-dose omalizumab and 139 patients on standard dosing. The findings indicated that elevated D-dimer levels were independently associated with the use of high-dose omalizumab. In contrast, baseline total IgE levels, presence of low IgE, eosinopenia, basopenia, IgG-anti-TPO positivity, and obesity did not demonstrate a significant association with the need for increased dosage. Notably, the duration of CU at baseline was shorter among patients in the high-dose omalizumab group, who were also more likely to regularly use antihistamines during omalizumab treatment. Furthermore, 40% of patients in this high-dose group who remained uncontrolled also exhibited CIndU.

Asero *et al*. identified elevated D-dimer levels as a predictor of uncontrolled urticaria following omalizumab treatment, a finding that is consistent with the results of our study (22). In our cohort, an elevated D-dimer level was associated with a 4.8-fold increase in the likelihood of omalizumab updosing. Within the coagulation cascade, fibrin is degraded by plasmin, resulting in the production of fibrin degradation products and the exposure of the D-dimer antigen (23, 24). Therefore, the D-dimer level reflects both the formation (coagulation pathway) and digestion (fibrinolysis) of fibrin. This finding indicates that the coagulation cascade is activated in patients requiring high-dose treatment, and D-dimer, as the final degradation product of this pathway, can serve as an indicator for the need for high-dose omalizumab. Previous reports indicated that a higher BMI (≥ 30 kg/m²) and older age were more prevalent in the high-dose omalizumab group (21, 25). In contrast to the study by Kocatürk *et al*., our study had a larger number of patients in the standard-dose omalizumab group, while the high-dose omalizumab group comprised fewer patients (21). In the study by Curto-Barredo *et al*., the number of patients in both groups was at least twice as high as in our study. This discrepancy may account for the observed differences (25). Additionally, the study by Curto-Barredo *et al*. could not provide a clear explanation for the older age of patients in the high-dose omalizumab group.

The frequencies of comorbidities varied among the study populations (26-28). While hypertension, hypothyroidism, and allergic rhinitis have been reported as the most frequent comorbidities in various studies, asthma was the most prevalent comorbidity accompanying CU in the present study. In these three studies, the patient populations included not only those using omalizumab but also individuals treated with other medications for urticaria, such as antihistamines and cyclosporine, resulting in a heterogeneous group. Additionally, since older patients are more likely to have comorbidities, the number of elderly patients in previous studies was not clearly specified. In contrast, our study included 9 elderly patients (6%) over 65 years of age. Although hypertension and hypothyroidism are generally more common than asthma in general Turkish population, the higher prevalence of asthma compared to hypertension and thyroid diseases in our study may be attributed to the specific cohort of patients receiving omalizumab that we evaluated (29, 30). This result may also indicate that CU and asthma may have a common pathogenesis.

Omalizumab has been used off-label for CIndU. Previous studies have demonstrated its efficacy in the treatment of CIndU (6, 8). In individuals with CIndU, the rate of unresponsiveness to omalizumab was approximately one-third, and this rate was similar in both the standard-dose and high-dose omalizumab groups (31). In our study, the omalizumab dose needed to be increased in 40% of individuals with CIndU in Group 2. The response to omalizumab varies according to the subtypes of CIndU. While the response rate is higher in delayed pressure urticaria and dermographism, it can be as low as 50% in cholinergic and cold urticaria. The high rate of unresponsiveness in our study may be attributed to the higher prevalence of cholinergic and cold urticaria among the subtypes of CIndU. Additionally, CIndU is recognized as a subtype of CU that tends to be more resistant to sgAHs and omalizumab (32). Inhibitors of other molecules, such as Siglec-8, Bruton's tyrosine kinase, C5a receptor, and thymic stromal lymphopoietin, may potentially offer greater benefits than omalizumab in managing CIndU (33, 34).

Type IIb autoimmune CSU (aiCSU) is characterized by higher disease severity, concomitant autoimmune diseases, low levels

of total IgE, elevated levels of IgG-anti-TPO, basopenia, eosinopenia, poor response to antihistamines and omalizumab, and a good response to cyclosporine. In aiCSU, IgG antibodies are primarily directed against a subunit of the high-affinity IgE receptor (FcεRI), causing cross-linking of two adjacent IgE molecules and subsequent mast cell degranulation (35). Less frequently, the IgG is directed against the Fc portion of the IgE molecule itself. However, in a large, recent series of CSU patients, this autoimmune reaction was detected in less than 10% of all patients (4). A recent report by Asero *et al*. investigated the co-occurrence of IgE and IgG autoantibodies to high- and low-affinity IgE receptors (FcεRI and FcεRII), tissue factor, and thyroglobulin. The study found that more than 50% of patients had IgE and IgG antibodies to one or more of these autoantigens (36). Several, but not all, studies have reported a significantly higher prevalence of IgE-anti-TPO in patients with CSU compared to patients with autoimmune thyroid disease (0-70%) and/or healthy controls (0-8%) (37). IgE-anti-TPO and IgG-anti-TPO have been reported to be co-expressed by patients with CSU in several studies (38-42). Kolkhir *et al*. stated that the detection of IgG-anti-TPO antibodies alone is not sufficiently specific for diagnosing patients with aiCSU. However, a useful diagnostic marker for aiCSU in clinical practice is the combination of a high IgG-anti-TPO level and low IgE (37). In our study, IgG-anti-TPO positivity was comparable between both groups. Based on low levels of total IgE and IgG-anti-TPO positivity, the prevalence of aiCSU was determined to be 3%. Kohlkir *et al*. reported that 50% of individuals with aiCSU responded to omalizumab, whereas in our study, 80% of individuals with aiCSU responded to standard-dose omalizumab, and 20% required high-dose omalizumab (4).

In this study, we adopted a cutoff value of 43 IU/mL for low IgE, as defined by Ertas *et al*. among Turkish population (11). As mentioned above, low IgE can be considered a predictor of a slow or partial response to omalizumab in relation to aiCSU, and individuals with low IgE may indirectly require dose escalation of omalizumab (11, 37, 43). However, in this study, the rate of low IgE was similar in both groups. Additionally, the prevalence of individuals with simultaneous IgG-anti-TPO positivity and low IgE was also comparable between the two groups. IgE in different CSU cohorts may possess different physicochemical properties, which could explain the variations in treatment responses to omalizumab (44). Asero examined 86 patients with CSU and baseline IgE levels < 40 IU/mL, further subdividing low IgE groups (45). The highest nonresponse rate, at 85%, was observed in the group with IgE levels below 20 IU/mL. However, in our study, there were 16 patients with IgE levels below 43 IU/mL and only eight with IgE levels below 20 IU/mL. Of these, six patients (75%) were in the standard-dose omalizumab group, while two were in the high-dose group. Therefore, 25% of the eight patients with IgE levels below 20 IU/mL were nonresponsive to the standard dose. When adopting a 20 IU/mL cutoff as per the study by Asero, we found that not only was the number of patients too low for a meaningful comparison, but also that 25% of these patients were nonresponsive. These findings may not support the data reported by Asero possibly due to the smaller sample size when using the same cutoff value for low IgE.

In a study conducted by Kolkhir *et al*. eosinopenia was associated with high disease activity in patients with CSU. High CSU activity was observed in one-third of patients with eosinopenia and/or basopenia, compared to 15% of patients with normal or elevated eosinophil levels (14). Unlike this study, eosinopenia and basopenia were not observed in Group 2. Eosinopenia and basopenia predicted non-response to omalizumab in CSU patients with high specificity and moderate to low sensitivity (14). However, further studies are needed to achieve higher sensitivity. In our study, eosinopenia and/or basopenia were not predictive factors for the response to standard-dose omalizumab.

Although some publications suggest that elevated ESR may be associated with high disease activity, aiCSU, and unresponsiveness to standard-dose omalizumab, data on the relationship between omalizumab dose escalation and elevated ESR are limited (46, 47). Our results indicated that baseline ESR and elevated ESR were similar in both groups, and neither appeared to predict the need for omalizumab dose escalation.

CU duration at baseline was not a predictor for omalizumab dose escalation, although it was shorter at baseline in Group 2, which is consistent with the current literature (9, 21).

The EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines recommend evaluating the effectiveness of standard-dose omalizumab at 16 or 24 weeks (20). In our study, dose escalation was administered at a median of 19 weeks, indicating a relatively long dose escalation period. As this was a real-life study, the timing of dose escalation may have changed due to differences in patient perceptions of control, trigger factors, accompanying comorbidities, adherence to control visits, challenges within the healthcare system (25). Our cohort includes a heterogeneous group of patients in Group 1 who had minimal, partial, or no response to standard-dose omalizumab. Consequently, a significant number of patients might have continued on the standard dose for an extended period with a partial response. Additionally, a personalized treatment approach to dose escalation may have further prolonged the duration.

The present study has several limitations. Compared to the standard-dose omalizumab group, the number of patients in the high-dose omalizumab group was relatively smaller. Since this was an observational real-life study, the omalizumab dose may have been increased for patients with partial or poor responses in the standard-dose group. Consequently, not all patients in the high-dose group were entirely unresponsive.

In conclusion, D-dimer level seems to be a predictor for omalizumab updosing. IgG-anti-TPO positivity and low IgE do not predict the need for dose escalation; however, these results should be strengthened with a larger number of patients.

Previous presentations

GT presented as a poster presentation at the XXIX National Allergy and Clinical Immunology Congress between 29 November-3 December 2023, and presented as a poster in UCARE Conference between 7-9 December 2023, São Paulo, Brazil.

Fundings

None.

Contributions

GT: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, writing – original draft, writing – review & editing. ED: formal analysis, project administration, supervision, visualization, writing – original draft, writing – review & editing; GK, AFK: supervision, visualization, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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