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Eosinophilic cationic protein and D-Dimer are potential biomarkers to predict response to antihistamines but not to omalizumab in chronic spontaneous urticaria

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ABSTRACT

Introduction: Biomarkers that could reliably anticipate the effectiveness of antihistamines and omalizumab in treating chronic spontaneous urticaria (CSU) have not been conclusively identified. Our objective was to examine how eosinophilic cationic protein (ECP), tryptase, D-dimer, and total Immunoglobulin E (IgE) impact the response to antihistamine and omalizumab treatments in individuals with CSU. Methods: In this cross-sectional retrospective study, CSU patients that had undergone treatment with either antihistamines or omalizumab for a minimum of 12 weeks between 2015 and 2021 at an Allergy and Immunology Department were analyzed. Several demographic and laboratory parameters including eosinophil counts, mean platelet volüme (MPV), sedimentation, C-reactive protein (CRP), antinuclear antibodies (ANA) and Anti-thyroperoxidase (Anti-TPO) and total IgE, tryptase, ECP and D-dimer were retrived from patient files. The association of these biomarkers with Urticaria Control Test (UCT) and the effect of these biomarkers on treatment response were evaluated. Treatment response was assessed using the UCT, with a score of UCT ≥ 12 indicating a responder and UCT < 12 indicating a non responder. Results: The patients in the omalizumab group were older, had a longer disease duration and had worse urticaria control (lower baseline UCT scores). 421 patients were treated with antihistamines and 88 patients were treated with omalizumab. ECP was found to be inversely correlated with baseline UCT ($p < 0.001$ r=−0.268). ECP and D-dimer levels of non-responder patients in the antihistamine group were significantly higher than in responder patients (ECP: 49 ng/mL vs 28.1 ng/mL, $p < 0.001$) (D-dimer: 0.60 mg/L vs 0.30 mg/L, $p < 0.001$), while there were no significant difference in terms of tryptase and total IgE. These four biomarkers were similar, in omalizumab responders and non responders. Conclusion: In this study with CSU, we looked at predictors of responses to treatments. ECP can serve as a marker of poor urticaria control and may predict antihistamine refractoriness along with D-dimer.

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Tryptase; treatment; omalizumab; antihistamines; eosinophilic cationic protein; D-dimer

1. Introduction

Chronic spontaneous urticaria (CSU) is defined by the appearance of wheals and angioedema or both for more than 6 weeks [1]. As per international guidelines, if standard doses of second-generation H1-antihistamines (sgAHs) fail to elicit a response in the management of CSU, it is advised to escalate the dose of antihistamines up to four-folds and subsequently consider omalizumab treatment [2]. Nonetheless, it is important to note that each patient might have distinct immunopathological pathways contributing to CSU that may lead to differences in treatment responses.

To establish personalized treatment approaches, a thorough understanding of the underlying pathogenesis and inflammatory biomarkers is essential. Considering the pathogenesis of urticaria, the main effector cells are mast cells, which express high-affinity immunoglobulin E (IgE) receptors (FcepsilonR1-alpha=FcεRI). IgE is found in the connective tissue under the epithelial layers of the skin, mostly on mast cells, bound to FcεRI receptors and very little in the circulation as a soluble antibody. When an antigen comes into contact with a mast cell, it cross-links two or more FcεRI molecules and activates granule release from the mast cell [3]. In the case of CSU, these antigens are mainly auto allergens rather than environmental allergens, such as anti-TPO or IL-24 which constitute the basis of auto allergic CSU, while formation of IgG type autoantibodies against FcεRI or IgE are considered as autoimmune CSU [4]. Apart from this, different receptor expressions that cause

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stimulation of mast cells such as MRGPRX2 have also been detected [5,6]. Whether mast cells are activated with or without the presence of IgE, the release of mediators, such as histamine and tryptase, occurs, leading to vasodilation and heightened permeability. Tryptase is more suitable for analysis due to its slower release and longer half-life compared to histamine [5,7]. Mast cells are also sources of IL-5, TNF and eotaxin and provide recruitment and stimulation of eosinophils in urticarial lesions. Eosinophils promote allergic inflammation through the release of pro-inflammatory mediators such as eosinophil cationic protein (ECP) that cause tissue damage [8–11]. The present findings along with previous data suggest that in CSU, eosinophils trigger the activation of the coagulation pathway by expressing Tissue Factor (TF) [12–15]. This causes excessive and abnormal production of platelet-derived clotting factors such as thrombin. D-dimer is a fibrin degradation product that reflects the dynamic balance between clot formation and fibrinolysis in the coagulation pathway and has been shown to be elevated in severe and antihistamine resistant CSU [16]. D-dimer can increase vascular permeability and induce further degranulation of mast cells [17,18].

Antihistamines relieve local effects such as pruritus and urticaria plaques by blocking histamine type1 (H1) receptors, but do not block or reduce histamine release [19]. The fact that histamine is not the only mediator and mast cells are not the only cells contributing to the pathophysiology of CSU may explain the inability to suppress urticaria completely with antihistamines [20]. Patients with autoimmune CSU has been considered to be more refractory to antihistamines and markers of autoimmune CSU such as high Urticaria Activity Score (UAS), positive basophil tests, eosinopenia, basopenia, low IgE and elevated anti TPO IgG has been linked to poor response to sgAHs [21,22]. The monoclonal anti-immunoglobulin E antibody, omalizumab, is indicated in CSU that cannot be controlled despite increasing the dose of antihistamines by 4-folds. Omalizumab binds to free IgE, causing down-regulation of FcεRI receptors on basophils and mast cells and apoptosis of eosinophils [23,24]. It is also thought to prevent the activation of the extrinsic coagulation pathway by reducing D-dimer levels [25]. As in the case of antihistamine refractoriness, markers of autoimmune CSU were found to reflect poor response and/or non response to omalizumab [26]. These results indicate the existence of distinct endotypes of CSU, each displaying unique response patterns to existing treatments. This underscores the significance of precision medicine, which relies on biomarkers, in tailoring therapeutic approaches for individuals with CSU.

In recent years, there have been great efforts to find reliable biomarkers to predict the response to treatments in CSU. Among these, CRP, D-dimer, and total IgE have surfaced as the most frequently cited markers [27–29]. Beyond biomarkers for treatment response, certain studies offer evidence on biomarkers reflecting urticaria disease activity. These include low basophil count, high CRP, low eosinophil count, and elevated eotaxin levels, which serve as indicators of severe CSU [29]. Additionally, ECP levels and total tryptase levels were found higher in patients with active symptoms of urticaria compared to patients without urticaria [11,30]. However, no studies evaluated ECP and tryptase as biomarkers of disease severity and predictors of response to antihistamine or omalizumab treatment. In our study, we aimed to explore the impact of baseline levels of specific biomarkers including total IgE, tryptase, ECP, and D-dimer on the response to antihistamine and omalizumab treatments.

2. Methods

2.1. Study population

We analyzed electronic or record-based medical data from 2560 patients with chronic spontaneous urticaria (CSU) who received treatment with antihistamines or omalizumab for a minimum of 12 weeks between 2015 and 2021 at our Allergy and Clinical Immunology Department. Patients whose urticaria could not be controlled despite standard single-dose sgAHs treatment and whose patient files included information on total IgE, tryptase, ECP and D-dimer levels were considered as eligible for the study. Exclusion criteria were: missing data, isolated chronic inducible urticaria (CIndU), severe systemic and infectious disease, concomitant atopic dermatitis, neoplastic disease, pregnancy, using drugs that affect the coagulation system such as anticoagulants and antiaggregants, cardiovascular disease, using immunosuppressant drugs. Subsequently, the patients were divided into two groups: those who underwent 2–4 fold antihistamine treatments or those who received additionally omalizumab treatment for a minimum of 12 weeks (Figure 1: Flow Chart).

All patients provided written informed consent, signifying their acceptance of the prescribed treatment regimens. The study protocol received approval from our hospital's local ethics committee, under decision number 209, and was conducted in adherence to the standards of good clinical practice and the Declaration of Helsinki.

2.2. Treatment groups

The antihistamine group comprised patients who received 2–4 fold antihistamines and did not exhibit a response to a single dose of antihistamine treatment (n:421, 82%); The omalizumab group included patients who showed no response despite quadruple antihistamine treatment for a minimum of 6 months (n:88, 18%).

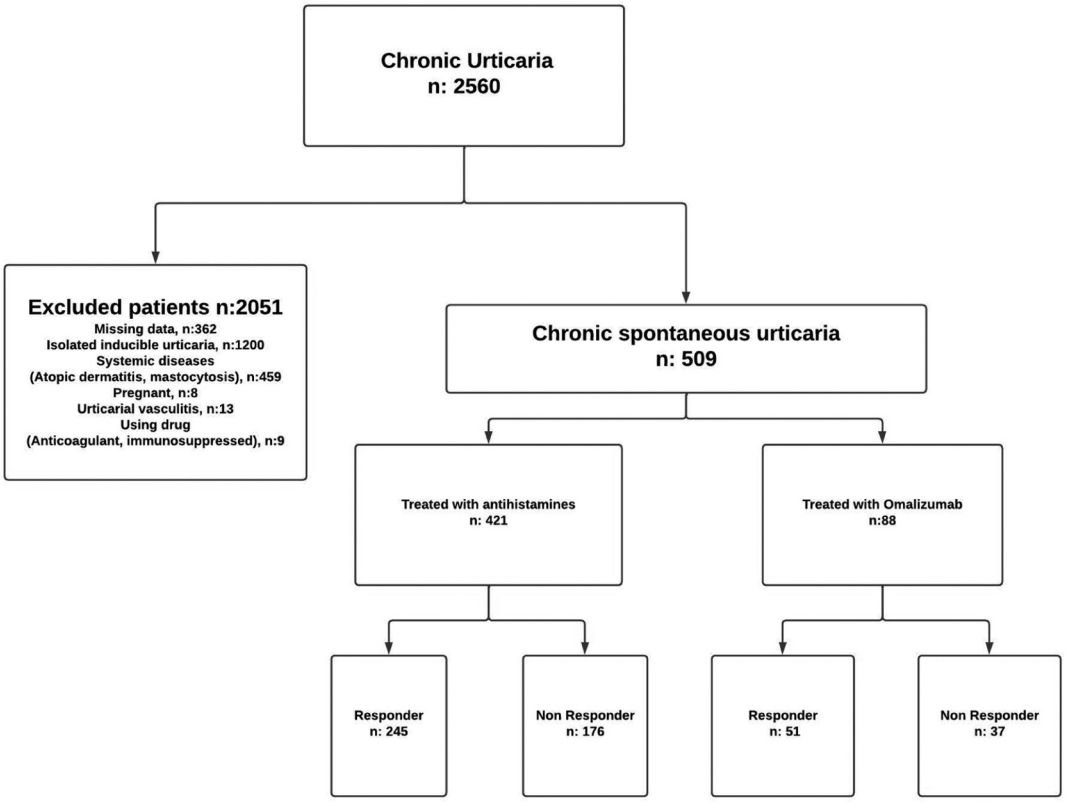


Figure 1. Flow chart of the study design.

The study population consisted of Chronic Spontaneous Urticaria patients who underwent 2–4 fold antihistamine treatments or those who received additionally omalizumab treatment for a minimum of 12 weeks.

In this group, patients who added omalizumab treatment continued to take 2–4 fold antihistamine. The omalizumab dose was 300 mg every 4 weeks.

2.3. Clinical response

Urticaria Control Test (UCT), consisting of four questions, was used to evaluate urticaria control. With these four questions, it was possible to evaluate the control of the signs and symptoms of the disease, the effect on the quality of life, the effectiveness of the treatment and the overall disease control. Patients are considered as responder if UCT ≥ 12, as non-responder if UCT < 12 after 12 weeks of treatment (Figure 1: Flow Chart) [31].

2.4. Collected data

Parameters such as age, gender, duration of disease, angioedema, obesity, hypertriglyceridemia, abdominal USG findings, H. pylori, accompanying hypothyroidism, eosinophil and basophil counts, mean platelet volume (MPV), sedimentation, CRP, ANA and anti-TPO, and total IgE, tryptase, ECP and D-dimer, were retrieved from patient files. The association of these parameters with disease activity (baseline UCT scores) in two treatment groups were assessed.

2.5. Laboratory analysis

Total IgE levels were assessed using chemiluminescent immunoassay (ImmunoCAP; ThermoFisher Scientific, Uppsala, Sweden), with values equal to or exceeding 100 kU/L considered elevated compared to the reference range established by the laboratory of the primary investigative center. Tryptase by feia method in phadiaimmunocap device, ECP; In Siemens immulite device, clia method, D-dimer, coagulometric symex cs 2500 device polish was studied with chemmulinescence method.

The following threshold values were used for inflammatory parameters in laboratory tests, serum triglyceride>;(0-150) mg/dL, antinuclear antibodies > 1:100, antithyroid peroxidase antibodies >9 IU/mL and antithyroglobulin antibodies > 4 IU/mL, total IgE >100 IU/mL, D-dimer >0.55 mg/L, Eosinophilic cationic protein:>24 ng/mL, tryptase: >11.4 ug/L, basophil :<150/µL basopenia, eosinophil: <150/µL eosinopenia, sedimentation >20 L, CRP: > It was determined as 5 mg/dL cut-off values.

2.6. Statistical analyzes

It was done using SPSS software (version 21.0 for Windows; SPSS Inc., Chicago, IL, USA). Parametric variables were presented as means and standard deviations, non-parametric variables as medians and

interquartile ranges (IQR). Number of cases and percentages were used for categorical variables. Chi-square or Fisher's exact test was used in the analysis of categorical variables. Whether the continuous variables were normally distributed or not was determined by Kolmogorov-Smirnov and histogram analysis. Normally distributed numerical variables were analyzed using Student's t-test and ANOVA. Mann-Whitney U and Kruskal–Wallis tests were used to compare numerical variables that did not show normal distribution. Correlations of numerical variables were evaluated with Spearman and Pearson tests. Binary logistic regression test was used for the analysis of risk factors affecting treatment response. A p value of 0.05 or less was considered statistically significant.

3. Results

3.1. Comparison of the treatment groups

The antihistamine group had a lower mean age compared to the omalizumab treatment group [39 (23) vs 46 (14), p = 0.009]. Although the majority in both groups were female, there was no significant gender difference between them (72% vs 75%, p = 0.655). Patients in the omalizumab group had a higher mean disease duration [12 (20) months vs 36 (40) months; p=<0.001] and UCT [6 (3) vs 5 (2); p=<0.001] than patients taking antihistamines, and were more often accompanied by angioedema (55.3% vs 71.8%, p = 0.007). However, the comorbidities were similar, with the highest frequency thyroid disease [10.8%, (n = 55)] and H. pylori associated gastritis [8%, (n = 41)].

The relationship between baseline blood eosinophil count and ECP was measured by Pearson correlation. A weak but significant positive correlation was found between these parameters [$r = 0.422$, $p < 0.001$] (Shown as figure in Supplemental data).

The relationship between baseline ECP and UCT score was measured by Pearson correlation. A very weak but significant negative correlation was found between these parameters [$r = -0.241$, $p < 0.001$] (Shown as figure in Supplemental data).

In ROC analysis, the cut-off value for ECP to predict of non-responder patients in the antihistamine group was found 38.15 ng/mL. The sensitivity of ECP measurement in determining urticaria control was calculated as 63.7% and specificity as 65% (Shown as figure in Supplemental data).

In ROC analysis, the cut-off value for D-dimer to predict of non-responder patients in the antihistamine group was found 0.605 mg/L. The sensitivity of D-dimer measurement in determining urticaria control was calculated as 50% and specificity as 22.8% (Shown as figure in Supplemental data).

Autoimmune and inflammatory markers were similar in both treatment groups, except that MPV was lower [10.30 (1.40) vs 9.50 (1.90); $p < 0.001$] in the omalizumab arm and CRP was higher [3 (5) vs 3 (4); $p = 0.024$]. Mean tryptase and D-dimer levels were within the normal range, while total IgE and ECP were found to be elevated at baseline [Total IgE 130 IU/mL (1–3552]; cut off value > 100 IU/mL; ECP = 43.81 ± 30.45; cut off value >24 ng/mL) (Table 1).

3.2. Factors affecting antihistamine treatment response

The average treatment duration for the 421 patients undergoing antihistamine treatment was 6 months, with a response rate of 58.2%. When antihistamine responder and non-responder patients were compared in terms of age, gender, accompanying angioedema autoimmunity rate, total IgE and tryptase, there was no statistical difference. However, disease duration, eosinophil count, CRP, D-dimer and ECP levels were statistically higher in non-responder patients. (Disease duration: 6 months vs 21 months, $p < 0.001$; Eosinophil count: 110/μL vs 140/μL, $p < 0.001$; CRP: 2.3 mg/dL vs 3 mg/dL, $p = 0.036$; D-dimer: 0.3 mg/L vs 0.60 mg/L, $p < 0.001$; ECP: 28.1 ng/mL vs 49 ng/mL, $p < 0.001$) (Table 2).

3.3. Factors affecting omalizumab treatment responses

The average treatment duration for the 88 patients receiving omalizumab treatment was 12 months, with a response rate of 58%. When the responder and non-responder patients were compared in terms of age, gender, BMI, disease duration, accompanying angioedema, autoimmunity rate, eosinophil, CRP, total IgE, D-dimer, tryptase, ECP, no significant differences were found (Table 2).

4. Discussion

In our study, when baseline characteristics were analysed, we found that the mean age was lower, the duration of disease was shorter, angioedema was less accompanying, UCT, MPV and CRP were higher in the antihistamine group compared to the Omalizumab group. We found that basal ECP were negatively correlated with UCT. In addition, when biomarkers were analysed in terms of response to treatment, no significant difference was observed between omalizumab responder and non-responder, whereas we observed shorter disease duration, lower eosinophil count, lower CRP, D-dimer and ECP values in antihistamine responders compared to non-responders.

Eosinophils are activated after being drawn to the inflammation site and release some mediators like this

Table 1. Baseline demographic, clinical, and laboratory features of patients with CSU undergoing antihistamine or omalizumab treatment.

	Antihistamine Group n: 421	Omalizumab Group n: 88	p value
Age, years, median (IQR)	39 (23)	46 (14)	**0.009**
Gender, female, n (%)	303 (72)	66 (75)	0.655
BMI, mean ± SD kg/m^2	27.75 ± 5.35	28.76 ± 5.95	0.184
Disease duration, months, median (IQR)	12 (20)	36 (40)	**<0.001**
UCT, median (IQR)	6 (3)	5 (2)	**<0.001**
Presence of angioedema, n (%)	226 (53.6)	61 (69.3)	**0.007**
Atopy presence, n (%)	166 (39.5)	33 (37.5)	0.782
Thyroid Disease	5 (1)	0 (0)	0.312
-Graves, n (%)	39 (9)	11 (12)	
-Hashimoto, n (%)			
Helicobacter pylori positivity, n (%)	31 (7)	10 (11.3)	0.295
Laboratory findings, median (IQR)	120 (140)	110 (130)	0.749
Eosinophil,/µL	30 (30)	30 (40)	0.108
Basophil,/µL	10.30 (1.40)	9.50 (1.90)	**<0.001**
MPV, fL	15 (18)	16.50 (19)	0.121
Sedimentation, mm	3 (5)	3 (4.1)	**0.024**
CRP, mg/dL	125 (213)	164 (318)	0.111
Total IGE, IU/mL	0.39 (0.59)	0.37 (0.52)	0.541
D-dimer, mg/L	5.64 (3.95)	6.04 (3.86)	0.483
Tryptase, µg/L	37.65 (35.15)	33.95 (29.13)	0.146
ECP, ng/mL			
Autoimmune markers	84 (19)	13 (15.7)	0.330
ANA positivity, n (%)	46 (10.9)	16 (18)	0.218
ENA positivity, n (%)	64 (15.2)	11(12.5)	0.595
Anti-TPO positivity, n (%)	48 (11.4)	4 (4.5)	0.080
Antithroglobulin positivity, n (%)			

Abbreviations: IQR: Interquartile range, SD: Standard deviation, BMI: Body mass index, UCT: Urticaria control test, MPV: Mean platelet volume, CRP: C-reactive protein, ECP: Eosinophilic Cationic Protein, ANA: Antinuclear antibodies, Anti-TPO: Anti-thyroperoxidase, ENA panel: Extractable nuclear antigen panel is a blood test that looks for antibodies to 6 or 7 different proteins in the body [anti-Ro, anti-La, anti-Sm (anti-Smith antibody) anti-RNP (anti-ribonucleoprotein), anti-Jo-1, anti-Scl70, anti-centromere].
Bold values denote statistical significance at the $p < 0.05$ level.

Table 2. The effect of clinical and laboratory parameters on antihistamine or omalizumab treatment response in individuals with CSU.

	Antihistamine Group n:421			Omalizumab Group n:88		
	Responder n:245	Non responder n:176	p value	Responder n:51	Non responder n:37	p value
Age, years, median (IQR)	39 (23)	41 (22)	0.059	43 (14)	48 (16)	0.245
Gender, female, n (%)	174 (71)	129 (73.3)	0.608	39 (76.5)	27 (73)	0.901
BMI, kg/m^2 mean±SD	27.84 ± 5.14	27.65 ± 56	0.788	28.82 ± 5.64	28.66 ± 6.46	0.914
Disease Duration, months, median (IQR)	6 (11)	21 (29)	**<0.001**	39 (41)	40 (33)	0.801
Presence of angioedema, n (%)	124 (50.6)	102 (58)	0.104	35 (68.6)	26 (70.2)	0.852
Eosinophıl/µL median (IQR)	110 (140)	140 (147.5)	**<0.001**	105 (150)	140 (105)	0.103
CRP mg/dL median (IQR)	2.30 (5.1)	3 (5.3)	**0.036**	3 (5.4)	3 (2.7)	0.823
Total Ig E IU/mL median (IQR)	121 (208)	132 (246)	0.709	160 (229)	244 (389)	0.646
D-dimer mg/L median (IQR)	0.33 (0.36)	0.60 (0.96)	**<0.001**	0.30 (0.43)	0.49 (1.42)	0.646
Tryptase µg/L median (IQR)	5.68 (3.95)	5.61 (4.01)	0.422	6.39 (4.21)	5.65 (3.83)	0.30
ECP ng/mL median (IQR)	28.1 (28.6)	49.0 (38.85)	**<0.001**	31.4 (26.75)	42.90 (27.95)	0.97

Abbreviations: IQR: Interquartile range, SD: Standard deviation, BMI: Body mass index, UCT: Urticaria control test, MPV: Mean platelet volume CRP: C-reactive protein ECP: Eosinophilic Cationic Protein Responder: UCT Score ≥ 12, non responder: UCT Score < 12.
Bold values denote statistical significance at the $p < 0.05$ level.

Eosinophil cationic protein that are toxic to tissues [32]. The ECP level is more beneficial than the blood eosinophil count, as the blood eosinophil count does not fully reflect the number of active eosinophils that can release ECP [33]. In previous studies, mean ECP serum concentrations were found to be significantly higher in patients with both acute and chronic urticaria compared to healthy subjects [11,33,34]. In the study of Lorenzo et al., in chronic urticaria, an increase in eosinophil blood values was observed only in symptomatic patients, while serum ECP levels were increased in both symptomatic and asymptomatic patients. The results of this study suggest that ECP may increase both in the active symptomatic period and in the stable period of the disease [11]. In the study conducted with Saleh AA et al. [35], it was found that serum level of eosinophil derived neurotoxin (EDN) which is an another cytotoxic secretory product significantly correlated with the severity of CSU. In our study, similar to this study, it was shown that ECP level increased as urticaria control deteriorated. Moreover, ECP was associated with treatment unresponsiveness in the antihistamine group. Therefore, in the management of patients with CSU, increasing the dose of antihistamine does not seem to be very effective if ECP is found to be high.

Considering the studies on tryptase in patients with CSU, higher tryptase levels were observed in

urticaria patients compared to the control patient group [30]. In another study, it was predicted that high tryptase may be a biomarker for the necessity of steroid treatment in chronic urticaria [36]. In our study, baseline tryptase levels were found to be within normal limits and similar in antihistamine group and Omalizumab group (5.64 ng/mL vs. 6.04 ng/mL respectively) and did not affect treatment responses.

D-dimer is a fibrin degradation product that reflects expression of tissue factor by eosinophils, activation of the coagulation cascade, and thrombin generation. D-dimer can increase vascular permeability and induce degranulation of mast cells [37]. There are studies showing that high D-dimer levels in CSU negatively affect antihistamine treatment and positively affect omalizumab treatment [13,28,38–45]. In our study, although high D-dimer was associated with antihistamine unresponsiveness, Omalizumab could not be associated with treatment response.

A review including 73 studies investigating biomarkers and predictors that are more objective than subjective parameters such as UAS and UCT scoring in evaluating treatment response in CSU is also included. it has been shown that high D-dimer and low total IgE levels are associated with omalizumab unresponsiveness [21,46]. In our study, although high D-dimer was associated with antihistamine unresponsiveness, it was observed that total IgE level did not affect omalizumab treatment. The most important reason for this may be due to the high mean total IgE levels of the patients at baseline. Because in a study conducted in 2019, it has been stated that the Total IgE level should be above 43 IU/mL in or to have an omalizumab treatment response [47]. In our study, total IgE level was higher in the omalizumab group compared to the antihistamine group.

The strengths of our study are the large number of patient populations, as well as the evaluation of both antihistamine and omalizumab treatment responses. In addition, little-known biomarkers such as Total IgE and D-Dimer as predictors, as well as new inflammatory biomarkers such as ECP and tryptase. Its weaknesses are the use of UCT, which evaluates the last 4 weeks of control, rather than the daily UAS score in the evaluation of responder status, since it is retrospective.

5. Conclusion

This study suggests that elevated ECP and D-dimer levels can be considered as a biomarker for antihistamine-resistant CSU, particularly in patients showing a moderate disease severity. In our retrospective cross-sectional study, the omalizumab and antihistaminic responder rates were observed to be similar. It has been shown that high ECP and D-dimer levels, which are new biomarkers, may be associated with antihistamine unresponsiveness. UCT was found to be negative correlated with only ECP, and UCT showed significant improvement after both treatments.

Abbreviations/Acronyms

ANA	Antinuclear antibody
Anti TPO	Antithyroid Peroxidase
BMI	Body mass index
CIndU	Chronic inducible urticaria
CRP	C-reactive protein
CSU	Chronic spontaneous urticaria
ECP	Eosinophilic Cationic Protein
EDN	Eosinophil derived neurotoxin
FcεRI	Fc-epsilon R1-alpha
IgE	Immunoglobulin E
IQR	Interquartile Range
MPV	Mean platelet volume
SD	Standard deviation
sgAHs	Second generation H1-antihistamines
UAS	Urticaria Activity Score
UCT	Urticaria control test

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