

Hematologic parameters as biomarkers for antihistamine and omalizumab resistance in chronic spontaneous urticaria

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ABSTRACT

Background: Biomarkers of resistance to H_1 -antihistamines (AH) and omalizumab in chronic spontaneous urticaria (CSU) are still a matter of debate.

Objective: To identify clinical and laboratory attributes of the patient that may be predictive of AH and omalizumab resistance in CSU.

Methods: We conducted a retrospective observational study by using the electronic patient record data base of patients with CSU and of sex- and age-matched controls. Patients with CSU were divided into three study groups: the CSU group, patients who responded to AHs; the antihistamine-resistant CSU (AH-CSU) group, patients refractory to a fourfold AH dose; and the control group, composed of a random sample of age- and sex-matched subjects, with a case-control ratio of 1:2. The patients in the AH-CSU group treated with omalizumab were compared according to the response or resistance to omalizumab.

Results: A total of 106 subjects in the AH-CSU group, 483 in the CSU group, and 1198 in the control group were compared. Both AH-CSU (112.7 ± 43.1 kU/mL) and CSU (129.5 ± 52.4 kU/mL) groups were associated with higher plasma total IgE levels than control group (103.2 ± 49.5 kU/mL; $p < 0.001$). The AH-CSU group was characterized by a higher plasma high-sensitivity C-reactive protein level (6.4 ± 3.7 mg/L) than the CSU group (4.3 ± 1.4 mg/L; $p < 0.001$) and the control group (3.1 ± 1.8 mg/L; $p < 0.001$). The AH-CSU and CSU groups were characterized by a lower mean $\pm$ standard deviation basophil counts (0.18 ± 0.16 cells $\times 10^9$ /L and 0.19 ± 0.11 cells $\times 10^9$ /L, respectively) than the control group (0.22 ± 0.09 cells $\times 10^9$ /L; $p < 0.001$). The mean platelet volume was higher in the AH-CSU group (11.2 ± 0.3 fL) than in the CSU group (11.1 ± 0.4 fL; $p = 0.002$) and in the control group (10.3 ± 0.4 fL; $p < 0.001$). There were no significant differences in the mean levels of lymphocytes, monocytes, eosinophils, basophils, and platelets, and the rates of eosinopenia and basopenia between the patients in the AH-CSU group who responded to and those who were resistant to omalizumab.

Conclusion: This study provided additional data of interest to examine the pathophysiologic role of low-grade inflammation and basopenia in patients with CSU and resistant to AHs and omalizumab.

(Allergy Asthma Proc 42:e17–e24, 2021; doi: 10.2500/aap.2021.42.200088)

Chronic spontaneous urticaria (CSU) is a heterogeneous mast cell-mediated disease characterized by the recurrence of elapsing wheals or angioedema, or both, for > 6 weeks.¹ CSU is a relatively common disease, with an estimated prevalence of $\sim 1\%$ in the general population worldwide.² Although H_1 -antihistamines (AH) have long been the standard of care in CSU, up to 50% of patients with CSU remain uncontrolled at approved doses.¹ Nearly 25% of patients with CSU remain symptomatic even on a fourfold higher dose of second-generation H_1 -antihistamines, and they have antihistamine resistant CSU (AH-CSU).³ Add-on treatment with omalizumab is a

second-line therapy in AH-CSU.¹ Despite their principal role in the pathogenesis of CSU, histologic studies have not convincingly demonstrated quantitative or qualitative abnormalities in the dermal mast cells *via* histopathology.⁴

The inflammatory infiltrate of urticarial wheals plays a major role in the pathogenesis of CSU. This is supported by the consistently positive therapeutic effects of systemic corticosteroids. The perivascular infiltrate of CSU skin lesions mainly contains T lymphocytes with a Th0 cytokine profile to generate interleukin 4, interleukin 5, and interferon γ .⁵ In early (< 4 hours duration) skin lesions seen in $\sim 15\%$ of patients with CSU, an intense perivascular neutrophilic infiltrate without vasculitis is observed.⁶ Along with neutrophilic infiltration, eosinophil infiltration is also found in urticarial wheals in a minority of patients with CSU.⁷

Moreover, infiltrating eosinophils and microvascular alterations with increased mast cell numbers sometimes are observed in nonlesioned skin. This similarly suggests that nonlesioned skin is primed for whealing.⁸ A reduction in the peripheral blood basophil count is known in some patients with CSU.⁹ Moreover,

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The authors have no conflicts of interest to declare pertaining to this article

No external funding sources reported

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basopenia is frequently associated with abnormalities in the Fc ϵ R1 signaling pathway and with the presence of functional immunoglobulin G (IgG) anti-Fc ϵ R1 autoantibodies in CSU, which signifies recruitment of circulating basophils into lesioned skin.^{10,11}

Kolkhir *et al.*¹² recently identified eosinopenia to be present in ~10% of a cohort of 1259 patients with CSU; 81% of patients with eosinopenia also had basopenia. Moreover, eosinopenia was associated with high disease activity, autoimmunity, and poor response to treatment.¹² A previous study showed that the clinical and laboratory attributes of low-grade systemic inflammation may be prognostic to omalizumab resistance (OmR) in AH-CSU.¹³

The neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) are important systemic inflammation markers. Studies reported that NLR and MLR were abnormally increased and associated with prognosis in several autoimmune diseases.^{14,15} In this study, we aimed to determine the hematologic parameters, including NLR, PLR, MLR, eosinophil-lymphocyte ratio (ELR), and basophil-lymphocyte ratio (BLR) in subjects with AH-CSU compared with CSU and healthy controls. We also aimed to investigate these parameters in the subjects with AH-CSU according to the response to omalizumab therapy.

METHODS

Subjects and Setting

The subjects in the CSU group were retrospectively collected from consecutive adult patients (ages ≥ 18 years) referred to our outpatient allergy clinic from the Ashdod region (Ashdod, Israel) during 24 months and based on a diagnosis of urticaria with > 6 weeks' duration, and a good response to second-generation H₁-antihistamine monotherapy at conventional doses.

To retrospectively identify patients with AH-CSU, we used the electronic patient record (EPR) data base of the Leumit Health Care Services (LHS), a health maintenance organization that covers ~730,000 residents of Israel. The LHS has implemented an EPR system that facilitates a data base with comprehensive information on the insured population and resource utilization, such as demographic data, records of clinical visits, laboratory tests performed at a single centralized laboratory, and diagnostic codes by using the *International Classification of Diseases, 9th Revision, Clinical Modification*. This data base was used to obtain information on diagnoses and laboratory results by cross-linking data by using a unique patient identifier. Data capture was performed by using IBM Cognos (Ottawa, Ontario, Canada) 10.1.1 BI Report Studio software. The results of the queries were downloaded

into Microsoft Excel One Microsoft Way Redmond, Washington, U.S.(version 14) spreadsheets for analysis.

We included all patients with an electronically documented diagnosis of CSU from 2014 to 2018 with severe refractory disease and a fourfold H₁-antihistamines. The subjects had to have been treated with omalizumab 300 mg every 4 weeks for at least 24 weeks without concomitant montelukast, systemic steroids, or cyclosporine at community allergology centers of the LHS from December 2014 to May 2018. These subjects were in the AH-CSU group. Complete response (CR) was defined as the reduction of the baseline urticarial activity score by $\geq 90\%$, partial response by $\geq 30\%$ to $<90\%$, and OmR by $<30\%$ at 24 weeks. The control group was composed of a random sample of age- and sex-matched subjects from the EPR data base of the LHS with a case-control ratio of 1:2. The randomization was performed by using the Epi Info version 6 software (Atlanta, GA) by using simple random sampling.

Comorbidities were identified by specific *International Classification of Diseases, 9th Revision, Clinical Modification* diagnostic codes registered by the attending board-certified physicians. The exclusion criteria included a diagnosis of any active infectious, isolated chronic inducible (physical) urticaria, inflammatory and autoimmune diseases (except thyroid autoimmunity), malignancy, and pregnancy. This study was approved by the Asaf-haRofe Medical Center and LHS Institutional Review Committee.

Assessment of Hematologic Parameters

Blood samples were collected from 8 to 10 A.M. after an overnight fast. In patients with AH-CSU, the hematologic parameters were measured before starting omalizumab treatment. Peripheral blood absolute eosinophil and basophil counts were measured at the LHS central laboratory by using the automated Cell Dyn 1800 counter (Abbott Hematology, IL) for the determination of a complete blood cell count. Eosinopenia was defined as $< 0.05 \times 10^9$ cells/L.¹⁶ Basopenia was defined as basophils $< 0.01 \times 10^9$ cells/L.¹⁷ Serum samples were analyzed for total IgE levels by using the immunometric assay of the Immulite 2000 system (Diagnostic Products Corporation (DPC); Global Siemens Healthcare, Erlangen, Germany).

Statistical Analysis

Continuous variables were expressed as a mean $\pm$ standard deviation (SD). One-way analysis of variance) and Bonferroni *post hoc* examinations were carried out for comparisons among the three groups (CSU, AH-CSU, and control). Categorical variables were compared *via* the Pearson χ^2 test. A *p* value of <0.05 and a Bonferroni adjustment of $p < 0.0125$ were considered significant. All statistical analyses were

performed by using SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL).

RESULTS

Demographic and Clinical Characteristics of the Subjects

The study included the Jewish and Arab population of Israel. Age and sex as well as clinical and laboratory data for 106 subjects with AH-CSU, 483 subjects with CSU, and 1198 control subjects are shown in Table 1. There were no significant differences for sex, age, and body mass index among the three study groups. The AH-CSU group had more cases of hypothyroidism (17 [16.4%]) than the control group (113 [9.4%]; $p=0.004$). The mean $\pm$ SD urticarial activity score at baseline in the AH-CSU group was slightly higher (4.5 ± 0.2) than in the CSU group (4.1 ± 0.4 ; $p<0.001$).

Laboratory Characteristics of the Subjects

Both AH-CSU (112.7 ± 43.1 kU/mL) and CSU (129.5 ± 52.4 kU/mL) groups had higher mean $\pm$ SD plasma total IgE levels than the control group (103.2 ± 49.5 kU/mL;

$p<0.001$). The difference between the plasma total IgE levels in the AH-CSU and CSU groups was statistically significant ($p=0.002$) (Table 2). The AH-CSU group had higher mean $\pm$ SD plasma high-sensitivity C-reactive protein levels (6.4 ± 3.7 mg/L) than did the CSU (4.3 ± 1.4 mg/L; $p<0.001$) and control groups (3.1 ± 1.8 mg/L; $p<0.001$) (Table 2).

The mean levels of WBC were within normal limits in the patients in the AH-CSU, CSU, and control groups. There were significant differences in the mean $\pm$ SD levels of neutrophils, lymphocytes, monocytes, and eosinophils among the study groups. The mean $\pm$ SD basophil counts in AH-CSU (0.18 ± 0.16 cells $\times 10^9$ /L) and CSU groups (0.19 ± 0.11 cells $\times 10^9$ /L) were characterized by lower mean $\pm$ SD basophil counts than in the control group (0.22 ± 0.09 cells $\times 10^9$ /L; $p<.001$). More cases of basopenia were observed in the AH-CSU group (26 [24.5%]) than in the CSU (64 [13.2%]; $p=0.006$) and control groups (57 [4.8%]; $p<0.001$).

The mean $\pm$ SD BLR was higher in the AH-CSU group (0.07 ± 0.06) and the CSU group (0.08 ± 0.03) than in the control group (0.09 ± 0.03 ; $p<0.001$). No significant differences were observed between the AH-CSU and CSU groups in BLRs. The mean levels of

Table 1 Demographic and clinical data of the study groups

	Study Group			p Value			
	Antihistamine Resistant CSU (n = 106)	CSU (n = 483)	Control (n = 1198)	p1*	p2#	p3§	p4¶
Women, n (%)	71 (66.9)	315 (65.2)	773 (64.5)	0.138	0.363	0.303	0.393
Age, mean $\pm$ SD, y	41.2 $\pm$ 9.7	42.7 $\pm$ 10.5	42.1 $\pm$ 10.2	0.306	0.161	0.362	0.279
Duration of CSU, mean $\pm$ SD, months	16.1 $\pm$ 3.4	16.7 $\pm$ 3.6	0	<0.001	0.103	<0.001	<0.001
BMI, mean $\pm$ SD, kg/m ²	27.1 $\pm$ 3.8	27.5 $\pm$ 3.2	27.2 $\pm$ 3.4	0.217	0.245	0.998	0.096
Baseline UAS, mean $\pm$ SD,	4.5 $\pm$ 0.2	4.1 $\pm$ 0.4	0	<0.001	<0.001	<0.001	<0.001
12 weeks UAS, mean $\pm$ SD	4.3 $\pm$ 0.4	1.8 $\pm$ 0.7	0	<0.001	<0.001	<0.001	<0.001
Angioedema, n (%)	27 (35.3)	163 (33.8)	4 (0.33)	<0.001	0.098	<0.001	<0.001
Concomitant physical urticaria, n (%)	19 (18.1)	84 (17.4)	24 (2.0)	<0.001	0.083	<0.001	<0.001
Comorbidities, n (%)							
Allergic rhinitis	20 (18.8)	83 (17.2)	211 (17.6)	0.916	0.343	0.375	0.416
Asthma	12 (11.6)	41 (8.5)	104 (8.7)	0.631	0.198	0.204	0.449
Rheumatologic disorders	3 (2.8)	15 (3.1)	39 (3.2)	0.835	0.439	0.327	0.306
Hypothyroidism	17 (16.4)	68 (14.1)	113 (9.4)	0.006	0.310	0.036	0.004
Arterial hypertension	21 (19.8)	89 (18.4)	217 (18.1)	0.907	0.372	0.337	0.440
Diabetes mellitus	8 (7.5)	40 (8.3)	98 (8.1)	0.357	0.328	0.091	0.147

CSU = Chronic spontaneous urticaria; SD = standard deviation; BMI = body mass index; UAS = urticarial activity score.

*Analysis of variance among the study groups.

#A χ^2 test between the antihistamine-resistant CSU group and the CSU group.

§A χ^2 test between the antihistamine resistant CSU group and the control group.

¶A χ^2 test between the CSU group and the control group.

platelet counts were not different among the subjects in the AH-CSU, CSU, and control groups. The mean $\pm$ SD mean platelet volume (MPV) was higher in the AH-CSU group (11.2 ± 0.3 fL) than in the CSU group (11.1 ± 0.4 fL; $p=0.002$) and the control group (10.3 ± 0.4 fL; $p<0.001$) (Table 2).

Demographic, Clinical, and Laboratory Characteristics of AH-CSU according to the Response to Omalizumab

The demographic and clinical characteristics of the AH-CSU group according to the omalizumab treatment response are listed in Table 3. Of the 106 subjects in the AH-CSU group, 63 had a CR to omalizumab, 27 had a partial response, and 16 were OmR. The subjects with OmR AH-CSU were characterized by a higher mean $\pm$ SD white blood cell (WBC) count (9.1 ± 2.8 cells $\times 10^9$ /L) and NLR (2.38 ± 0.69) than the subjects with a CR (6.5 ± 3.8 cells $\times 10^9$ /L [$p=0.012$] and 1.81 ± 0.54 [$p=0.004$], respectively). There were no significant differences in the mean levels of lymphocytes, monocytes, eosinophils, basophils, platelets, or between ELR, MLR, BLR, and PLR, and the rates of eosinopenia and basopenia between the subjects with AH-CSU responding to omalizumab and those who were OmR. (Table 3). The mean $\pm$ SD MPV was higher in the subjects with OmR AH-CSU (11.2 ± 0.2 fL) than in the subjects with omalizumab-responsive AH-CSU (10.9 ± 0.3 fL; $p<0.001$) (Table 3).

DISCUSSION

This study showed that the subjects with AH-CSU had lower basophil counts, lower plasma total IgE levels, basopenia, and high high-sensitivity C-reactive protein levels. We found no difference in eosinophil counts or eosinopenia rates among the subjects in the antihistamine-responsive CSU, AH-CSU, and control groups nor in the subjects with AH-CSU who responded to omalizumab or who were OmR. Our results disagreed with a recently published study that reported that eosinopenia is associated with high activity of CSU and poor response to antihistamines and omalizumab.¹²

Kolkhir *et al.*¹² studied 1259 patients with CSU: 129 (10.2%) had a blood eosinophil count of <0.05 cells $\times 10^9$ /L. In our study, the eosinopenia rate in both subjects in the CSU group and those in the control group was 4.8%. The incidence rate of eosinopenia has not been studied in large-scale epidemiologic studies of varying ethnicities. Eosinopenia was observed in $\sim 5\%$ of the general population in a previous study of the CALIBER (cardiovascular disease by using linked bespoke studies and electronic health records) cohort study in the United Kingdom.¹⁸

Eosinophils normally account for only a small part of the peripheral WBCs ($<3\%$), and their numbers in circulation are regulated by several immunologic mechanisms.¹⁹ Although a dysbalanced T-helper type 2 response is often associated with eosinophilia and/or eosinophil-mediated tissue damage, eosinopenia is a hematologic phenomenon that is mainly observed in some infectious diseases, malignancies, endocrine diseases, and treatment with catecholamines and corticosteroids.^{20,21} Several investigators have proposed that eosinopenia is caused by acute stress.²² Another explanation for eosinopenia is that the eosinophils migrate to tissues in patients with CSU¹⁹; later studies confirmed eosinophil infiltration in CSU lesions²³ and in uninvolved skin.⁸

The different results for eosinopenia in CSU between our study and the study by Kolkhir *et al.*¹² may be related to differences in the patient population and timing of the blood collection. Therefore, larger prospective multicenter studies are needed to determine whether eosinopenia could be a predictive biomarker for CSU severity and treatment outcome. Another finding of our study was that basopenia might be a biomarker of CSU resistance to high-dose antihistamines but not to omalizumab treatment. Remarkably, a lower blood basophil count, lower BLR, and higher rates of basopenia were observed in the subjects with AH-CSU when the subjects in the CSU and control groups were compared; there was no difference in these parameters between the subjects with AH-CSU who responded to omalizumab and those who were OmR.

Basopenia was first described 5 decades ago as a biomarker of CSU.²⁴ The basophil numbers were recognized to be inversely related to CSU activity¹⁰ and CSU severity.²⁵ Basopenia might be due to the recruitment of basophils to skin tissues because basophils were found in both lesioned and nonlesioned skin biopsy specimens of patients with CSU.²⁶ Basopenia in subjects with CSU is also related to autoimmunity.⁹ In one study, omalizumab treatment in patients with CSU-elevated mean peripheral blood basophil counts as early as the first 8 days of treatment reversed a mechanism that recruits basophils to the skin and suppressed their IgE receptor pathway.²⁷ Nevertheless, several recent studies investigated the connection of blood basophil counts with treatment outcomes in patients with CSU on omalizumab treatment.^{28–30} A recent study showed that omalizumab led to an increased percentage of basophils in blood and induced a rapid and sustained decline in Fc ϵ RI expression on the surface of basophils, but these effects could not predict the response to omalizumab treatment.³¹

Several studies^{32,33} assumed that high-sensitivity C-reactive protein and MPV blood levels might be biomarkers of CSU activity, and we measured and compared them in the subjects with CSU who responded to and those

Table 2 Laboratory data of study groups*

	Study Group			p Value			
	Antihistamine Resistant CSU (n = 106)	CSU (n = 483)	Control (n = 1198)	p1#	p2§	p3¶	p4
Total IgE level, mean ± SD, kU/mL	112.7 ± 43.1	129.5 ± 52.4	103.2 ± 49.5	<0.001	0.002	0.046	<0.001
hs-CRP level, mean ± SD, mg/L	6.4 ± 3.7	4.3 ± 1.4	3.1 ± 1.8	<0.001	<0.001	<0.001	<0.001
TSH level, mean ± SD, µg/dL	2.6 ± 1.2	2.4 ± 1.1	2.5 ± 0.9	0.065	0.084	0.269	0.057
White blood cells, mean ± SD, cells ×10 ⁹ /L	7.4 ± 3.7	7.2 ± 4.3	6.9 ± 3.5	0.171	0.322	0.072	0.069
Neutrophils, cells ×10 ⁹ /L	4.8 ± 1.3	4.8 ± 1.1	4.7 ± 1.3	0.279	0.518	0.207	0.058
Lymphocytes, cells ×10 ⁹ /L	2.6 ± 1.3	2.5 ± 1.4	2.5 ± 1.3	0.735	0.484	0.429	0.994
Neutrophil-lymphocyte ratio, mean ± SD	1.76 ± 0.73	1.81 ± 0.78	1.79 ± 0.75	0.785	0.531	0.680	0.624
Eosinophils, mean ± SD, cells ×10 ⁹ /L	0.35 ± 0.16	0.36 ± 0.19	0.35 ± 0.14	0.485	0.287	0.501	0.147
Eosinophils <0.05 cells ×10 ⁹ /L, n (%)	5 (4.7)	23 (4.8)	59 (4.9)	0.987	0.492	0.461	0.443
Eosinophil/lymphocyte ratio, mean ± SD	0.17 ± 0.14	0.18 ± 0.15	0.17 ± 0.12	0.352	0.514	0.959	0.076
Basophils, mean ± SD, cells ×10 ⁹ /L	0.18 ± 0.16	0.19 ± 0.11	0.22 ± 0.09	<0.001	0.425	<0.001	<0.001
Basophils < 0.01 cells ×10 ⁹ /L, n (%)	26 (24.5 %)	64 (13.2 %)	57 (4.8 %)	<0.001	0.006	<0.001	<0.001
Basophil-lymphocyte ratio, mean ± SD	0.07 ± 0.06	0.08 ± 0.03	0.09 ± 0.03	<0.001	0.049	0.001	<0.001
Monocyte, mean ± SD, cells ×10 ⁹ /L	0.31 ± 0.15	0.32 ± 0.13	0.31 ± 0.13	0.359	0.471	0.549	0.153
Monocyte-lymphocyte ratio, mean ± SD,	0.11 ± 0.03	0.13 ± 0.04	0.11 ± 0.04	0.231	0.133	0.324	0.216
Platelets, mean ± SD, cells ×10 ⁹ /L	268 ± 131	271 ± 128	267 ± 124	0.995	0.824	0.937	0.558
MPV, mean ± SD, fL	11.2 ± 0.3	11.1 ± 0.4	10.3 ± 0.4	<0.001	0.002	<0.001	<0.001
Platelet-lymphocyte ratio, mean ± SD	117.2 ± 32.5	119.1 ± 29.2	116.7 ± 31.2	0.320	0.517	0.869	0.131

CSU = Chronic spontaneous urticaria; SD = standard deviation; IgE = immunoglobulin E; hs-CRP = high-sensitivity C-reactive protein; TSH = Thyroid stimulating hormone; MPV = mean platelet volume.

*For the definition of eosinopenia and basopenia, we used cutoff values of $<0.05 \times 10^9/L$ and $<0.01 \times 10^9/L$, respectively.

#Analysis of variance among the study groups.

§A χ^2 test between the antihistamine-resistant CSU group and the CSU group.

¶A χ^2 test between the antihistamine-resistant CSU group and the control group.

|| A χ^2 test between the CSU and control groups.

resistant to antihistamines and omalizumab. Biomarkers of low-grade inflammation such as CRP and MPV are known to be associated with disease severity in CSU.^{32,33} Nevertheless, MPV cutoff has not been validated in CSU so far, and a difference of 0.2 fL of MPV is very small, to consider the use of the MPV level as a prognostic

factor. Acer *et al.*³⁴ recently reported other biomarkers of low-grade inflammation such as NLR and PLR decrease in patients with CSU after 3 months of omalizumab treatment. Another group reported that NLR decreases whereas MPV increases in patients with CSU after 12 weeks of omalizumab treatment. However,

Table 3 Clinical and laboratory parameters of 106 patients treated with omalizumab for antihistamine-resistant CSU*

	Complete Response (n = 63)	Partial Response (n = 27)	No Response (n = 16)	p Value			
				p1#	p2§	p3¶	p4
Age, mean ± SD, y	39.8 ± 11.7	42.1 ± 13.4	40.3 ± 8.1	0.694	0.415	0.872	0.629
BMI, mean ± SD kg/m ²	27.2 ± 2.5	27.5 ± 3.1	29.4 ± 2.3	0.014	0.629	0.002	0.039
Women, n (%)	41 (65.1)	18 (66.7)	11 (68.8)	0.901	0.884	0.782	0.981
Duration of CSU, mean ± SD, months	16.4 ± 3.9	18.1 ± 5.2	15.9 ± 3.2	0.146	0.091	0.637	0.134
Angioedema, n (%)	23 (36.5)	11 (40.1)	7 (43.7)	0.841	0.704	0.594	0.846
Baseline UAS, mean ± SD	5.4 ± 0.3	5.5 ± 0.3	5.5 ± 0.2	0.301	0.151	0.211	0.999
12 weeks UAS, mean ± SD	0	2.6 ± 0.9	5.1 ± 0.4	<0.001	<0.001	<0.001	<0.001
Laboratory tests							
Total IgE, mean ± SD, kU/mL	146 ± 94	159 ± 72	109 ± 85	0.196	0.522	0.156	0.046
hs-CRP, mean ± SD, mg/L	3.4 ± 10.1	6.7 ± 7.5	10.3 ± 8.2	0.022	0.131	0.014	0.149s
WBC count, mean ± SD, cells ×10 ⁹ /L	6.5 ± 3.8	7.3 ± 3.6	9.1 ± 2.8	0.039	0.355	0.012	0.094
Neutrophils, mean ± SD, cells ×10 ⁹ /L	4.8 ± 1.3	4.9 ± 1.1	5.6 ± 1.2	0.072	0.727	0.028	0.058
Lymphocytes, mean ± SD, cells ×10 ⁹ /L	2.6 ± 1.4	2.5 ± 1.1	2.3 ± 1.1	0.675	0.727	0.399	0.567
Neutrophil-lymphocyte ratio, mean ± SD	1.81 ± 0.54	1.88 ± 0.42	2.38 ± 0.69	0.009	0.550	0.004	0.022
Eosinophils, mean ± SD, cells ×10 ⁹ /L	0.34 ± 0.11	0.31 ± 0.15	0.32 ± 0.14	0.566	0.292	0.541	0.829
Eosinophils < 0.05 cells ×10 ⁹ /L, n (%)	3 (4.8 %)	1 (3.7 %)	1 (6.2 %)	0.929	0.408	0.411	0.360
Eosinophil-lymphocyte ratio, mean ± SD	0.14 ± 0.04	0.13 ± 0.07	0.14 ± 0.06	0.692	0.394	0.971	0.636
Basophils, mean ± SD, cells ×10 ⁹ /L	0.18 ± 0.15	0.17 ± 0.19	0.18 ± 0.16	0.963	0.791	0.998	0.861
Basophils <0.01 cells ×10 ⁹ /L, n (%)	15 (23.8 %)	7 (25.9 %)	4 (25.0 %)	0.976	0.416	0.461	0.473
Basophil-lymphocyte ratio, mean ± SD	0.07 ± 0.03	0.07 ± 0.07	0.08 ± 0.04	0.756	0.899	0.374	0.604
Monocyte, cells ×10 ⁹ /L, n (%)	0.29 ± 0.14	0.32 ± 0.13	0.31 ± 0.11	0.594	0.344	0.597	0.798
Monocyte-lymphocyte ratio, mean ± SD	0.11 ± 0.03	0.12 ± 0.04	0.11 ± 0.04	0.428	0.194	0.949	0.432
Platelets, mean ± SD, 10 ⁹ cells/mL	259 ± 132	263 ± 128	277 ± 121	0.884	0.894	0.622	0.725
MPV, mean ± SD	11.2 ± 0.2	11.1 ± 0.2	10.9 ± 0.3	<0.001	0.032	<0.001	0.012
Platelet-lymphocyte ratio, mean ± SD	117.2 ± 32.5	119.1 ± 29.2	114.7 ± 31.2	0.997	0.792	0.781	0.643

CSU = Chronic spontaneous urticaria; SD = standard deviation; BMI = body mass index; UAS = urticarial activity score; IgE = immunoglobulin E; hs-CRP = high-sensitivity C-reactive protein; WBC = white blood cell; MPV = mean platelet volume.

*For the definition of eosinopenia and basopenia, we used cutoff values of $<0.05 \times 10^9/\text{L}$ and $<0.01 \times 10^9/\text{L}$, respectively.

#Analysis of variance among the study groups.

§A χ^2 test between the complete response group and the partial response group.

¶A χ^2 test between the complete response group and the omalizumab-resistant group.

|| A χ^2 test between the partial response group and the omalizumab-resistant group.

there was no significant difference in the PLR after omalizumab treatment.³⁵

We found no difference in the WBC count, lymphocyte count, NLR, MLR, ELR, and PLR between the subjects with CSU who responded or those who were resistant to antihistamines; nevertheless, the WBC count and NLR were higher in the subjects with AH-CSU who were OmR. The lack of differences in the levels of blood lymphocytes and eosinophils could explain the absence of a difference in the ELR between the study groups. Because basophil levels were lower in the AH-CSU group, we observed a similar lower level of BLR in the AH-CSU group. For that reason, we considered evidence of basopenia to be a sufficient prognostic factor for antihistamine resistance in CSU and that there is no need for additionally measuring ELR and BLR.

The mean total IgE blood level has also been proposed to be a biomarker of disease activity in CSU, but the results are inconsistent.^{13,36} In this study, the AH-CSU group was characterized by lower total IgE blood levels than the antihistamine-responsive CSU group; we found no difference in this parameter between the subjects with omalizumab-responsive and those with OmR AH-CSU. This finding contradicted recent publications that showed that a lower total IgE level was related to a poor omalizumab response,^{37,38} in agreement with other studies that did not confirm this previous observation.^{39,40} Some limitations of the study need to be addressed. First, as a retrospective study, it may have information bias because of possible inaccurate clinical records, loss to follow-up, and missing data. Second, the study included a heterogeneous study population with a potential of selection bias.

CONCLUSION

We can speculate that in patients with AH-CSU who were not responding to omalizumab, basophils might have intrinsic abnormalities in the Fc ϵ RI signaling pathway. The mechanisms implicated in basophil activation and/or recruitment in this population should be explored in future studies.

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