Original Article

Autoimmune Diseases and Low Baseline IgE in Chronic Spontaneous Urticaria: A Clinical and Therapeutic Prospective Analysis in Real-Life Clinical Practice

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What is already known about this topic? Autoimmune diseases are associated with chronic spontaneous urticaria (CSU), particularly in the autoimmune CSU subtype.

What does this article add to our knowledge? A particular biologic phenotype for patients with autoimmune disease and CSU is described with specific clinical, laboratory, and therapeutic characteristics. Total baseline IgE less than or equal to 43.8 IU/mL is detected as a biomarker of autoimmune disease in patients with CSU.

How does this study impact current management guidelines? These results suggest the need to assess autoimmune signs and symptoms in patients with CSU with low serum IgE levels. This prospective study supports the existence of an "autoimmune phenotype" in real-life clinical practice with specific clinical and laboratory characteristics.

BACKGROUND: Autoimmunity contributes to the pathogenesis of chronic spontaneous urticaria (CSU). The subtyping of CSU has revealed an autoimmune form of CSU. Despite autoimmune diseases having been associated with CSU, there are few prospective studies that have evaluated the characteristics and biomarkers of patients with CSU and autoimmune disease in a real-life practice setting.

OBJECTIVE: To evaluate the presence of specific biomarkers for the presence of autoimmune disease in CSU and to analyze the clinical and therapeutic features of patients with CSU and autoimmune disease.

METHODS: The clinical, laboratory, and therapeutic features of patients with CSU at a tertiary-level center were prospectively collected. Data obtained were compared in function of the presence/absence of autoimmune disease and typified according to IgE levels.

RESULTS: Patients with CSU who had associated autoimmune disease corresponded to middle-aged women with a common pattern of blood test findings: both low baseline IgE and high-affinity receptor of IgE expression, basopenia, eosinopenia, higher baseline erythrocyte sedimentation rate and D-dimer, increased presence of antinuclear antibodies, IgG against thyroid peroxidase, and positive autologous serum skin test result. Total baseline IgE less than or equal to 43.8 IU/mL was both the optimal cutoff to predict autoimmune disease in the CSU cohort and a significant risk factor for the presence of autoimmune disease in the regression analysis.

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Abbreviations used
aiCSU- autoimmune chronic spontaneous urticaria
ANA- antinuclear antibody
ASST- autologous serum skin test
AUC- area under the curve
CSU- chronic spontaneous urticaria
ESR- erythrocyte sedimentation rate
FcεRI- high-affinity receptor of IgE
IgG anti-TPO- IgG against thyroid peroxidase
ROC- receiver-operating characteristic
UAS-7- Urticaria Activity Score Over 7 Days
UCT- Urticaria Control Test

CONCLUSIONS: In real-life clinical practice, characteristics of patients with CSU and autoimmune disease share common features with type IIb autoimmune CSU. Total baseline IgE less than or equal to 43.8 IU/mL has been detected as a possible biomarker of autoimmune disease in patients with CSU. **(J Allergy Clin Immunol Pract 2023;11:3763-71)**

Key words: *Urticaria; Chronic; Autoimmune urticaria; Autoimmunity; IgE; IgG anti-TPO*

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a condition with an autoimmune background. It has been proposed that its pathophysiology could include type I autoimmunity (autoallergy) and type II autoimmunity (IgG autoantibodies against patients' own IgE or the high-affinity receptor [FcεRI]).[1,2] Patients with CSU may often present with autoimmune comorbidities, such as autoimmune thyroiditis.[3] To identify and define an autoimmune background in patients with CSU, different approaches have been proposed in terms of phenotypic classification. The PURIST study defined a subtype of autoimmune CSU (aiCSU) in accordance with the positivity to 3 complementary tests, including basophil activation test, autologous serum skin test (ASST), and IgG against IgE/FcεRI.[4] This study showed that patients with aiCSU presented a particular immunologic profile (lower baseline IgE and elevated IgG against thyroid peroxidase [IgG anti-TPO] levels). The definition of aiCSU, however, involves the use of some techniques that are still not available in daily clinical practice. This limitation has fostered new approaches to predict CSU phenotypes. Recently, Kolkhir et al[5] proposed the combination of high IgG anti-TPO and low IgE levels to diagnose aiCSU in clinical practice. Furthermore, Türk et al[6] classified CSU phenotypes with the use of machine learning in function of both levels of baseline IgE and levels of serological autoimmunity (antinuclear antibodies [ANAs] and IgG anti-TPO).[6] Interestingly, this group of authors defined a group, "Cluster 3," that presented with low IgE levels and high levels of serological autoimmunity. Furthermore, rationale for the association of low IgE and autoimmune disease has been suggested because of the higher risk of autoimmune disease in patients with selective IgE hypogammaglobulinemia.[7-9] In this group of patients, CSU has been depicted as the most frequent skin manifestation,[10] highlighting a possible pathogenic relevance of low IgE for the development of CSU.

The main objective of this study was to analyze the clinical, laboratory, and therapeutic features of patients with CSU and autoimmune disease, as well as to typify our cohort according to their IgE levels.

METHODS

Patients

An observational, unicentric, prospective study of adult patients with a diagnosis of CSU was conducted from January 2008 to January 2022 at the Urticaria Unit of Hospital del Mar (Barcelona). CSU was defined as recurrent wheals, angioedema, or both recurring for more than 8 weeks with unknown cause or trigger. Patients with isolated chronic inducible urticaria, urticaria vasculitis, without baseline blood test studies, or whose blood test studies had been performed under treatment with biological therapies, oral corticosteroids, and/or other immunosuppressive agents were excluded from the study. Finally, a total of 377 patients were included. Variables were collected prospectively at the first visit and during follow-up and transferred to an anonymized database. Complementary tests conducted in this study are aligned with real-life clinical practice, and were mostly performed in accordance with CSU guidelines.[11,12] It is important to note that some advanced tests that are not included in the guidelines (including FcεRI expression, ASST, and ANA) were performed in the setting of a specialized center, and in accordance with current evidence.[13-15] Ethical approval for the study was granted by the local Clinical Research Ethics Committee (2012/4913/I).

Clinical and therapeutic parameters

Demographic data (age, sex, presence of obesity defined by a body mass index [BMI] >30.0 kg/m^2), comorbidities (autoimmune, cancer, cardiopathy, pneumopathy, and psychiatric diseases), as well as targeted anamnesis and physical examination for autoimmune signs (low-grade fever, arthralgias, myalgias, abdominal pain, recurrent aphthae, xerosis, xeropthalmia, alopecia, other skin lesions apart from urticaria, fatigue, and neurological symptomatology) and symptoms were assessed in the first visit and were revisited during follow-up. If an autoimmune disease was suspected, further tests were performed depending on the clinical suspicion. The presence of a nondermatological autoimmune disease had to be diagnosed by a trained physician at our center or the patient had to present a medical document certifying the condition. Autoimmune diseases included were autoimmune thyroid disease, vitiligo, rheumatoid arthritis, celiac disease, type I diabetes mellitus, SLE, autoimmune gastritis/pernicious anemia, ankylosing spondylitis, alopecia areata, myasthenia gravis, antiphospholipid syndrome, scleroderma, dermatomyositis, primary biliary cholangitis, autoimmune hepatitis, and autoimmune adrenalitis.[16,17] "Polyautoimmunity" was defined as finding more than 1 autoimmune disease in a single patient.[18]

Clinical baseline features (baseline Urticaria Activity Score Over 7 Days [UAS-7], baseline Urticaria Control Test [UCT] score, association of angioedema and/or chronic inducible urticaria) were collected in the first visit. Variables obtained during follow-up were presence of positive ASST result, number of flares, and CSU duration.

In terms of therapeutic characteristics, it was evaluated whether 4-fold dose antihistamines, treatment with cyclosporine, and/or

TABLE I. Demographic, analytic, and therapeutic characteristics in the cohort of patients with CSU depending on the presence of autoimmune comorbidity

		Association of autoimmune disease		
		Yes	No	
Variables	Total (n = 377)	(n = 78)	(n = 299)	*P* value
Demographic and clinical characteristics				
Sex: female, n (%)	269 (71.4)	65 (83.3)	204 (68.2)	<.01
Age (y), median (IQR)	46.0 (34.0-58.0)	49.0 (38.0-65.0)	45.0 (34.0-57.0)	.064
Angioedema, n (%)	164 (43.5)	41 (52.6)	123 (41.1)	.07
CIndU, n (%)	85 (22.5)	12 (15.4)	73 (24.4)	.096
Autoimmune disease, n (%)	78 (20.7)	NA	NA	NA
Poliautoimmunity	12 (3.2)			
Cardiopathy, n (%)	66 (17.5)	14 (17.9)	52 (17.4)	>.99
Pneumopathy, n (%)	44 (11.7)	11 (14.1)	33 (11.0)	.437
Oncologic disease, n (%)	30 (8.0)	5 (6.4)	25 (8.4)	.647
Psychiatric comorbidity, n (%)	67 (17.8)	16 (20.5)	51 (17.1)	.509
Atopy, n (%)	91 (24.1)	16 (20.5)	75 (25.1)	.460
Atopic dermatitis	36 (9.5)	5 (6.4)	31 (10.4)	.388
Asthma	61 (16.2)	13 (16.7)	48 (16.1)	>.99
Rhinitis	73 (19.4)	14 (17.9)	59 (19.7)	.751
Obesity, n (%)	95 (25.2)	20 (25.6)	75 (25.1)	>.99
Baseline markers and complementary tests				
Baseline IgE (IU/mL), median (IQR)	115.0 (43.0-269.0)	33.8 (11.2-85.6)	148.0 (66.6-300.0)	<.001
Baseline IgE cutoff, n (%)				<.001
≤43.8 IU/mL	n = 96	51 (65.4)	45 (15.1)	
>43.8 IU/mL	n = 281	27 (34.6)	254 (84.9)	
FcεRI (MFI), median (IQR)	7,743.0 (3,099.0-12,970.0)	3,482.0 (1,621.0-7,253.0)	9,288.5 (4,729.5-13,995.0)	<.001
Absolute eosinophil count (10^9/L), median (IQR)	0.12 (0.06-0.25)	0.09 (0.01-0.15)	0.14 (0.07-0.26)	<.01
Absolute basophil count (10^9/L), median (IQR)	0.03 (0.02-0.05)	0.02 (0.01-0.03)	0.03 (0.02-0.05)	<.01
Eosinopenia, n (%)	52 (13.8)	24 (30.8)	28 (9.4)	<.01
Basopenia, n (%)	32 (8.5)	17 (21.8)	15 (5.0)	<.01
ESR (mm/h), median (IQR)	5.0 (2.0-12.0)	8.5 (4.3- 14.5)	4.0 (2.0-10.0)	<.001
RCP (mg/dL), median (IQR)	0.3 (0.1-0.9)	0.3 (0.1-0.9)	0.3 (0.1-0.9)	.545
D-dimer (mg/dL), median (IQR)	340.0 (210.0-565.0)	430.0 (300.0- 810.0)	330.0 (200.0- 530.0)	.002
IgG anti-TPO+, n (%)	70 (18.6)	42 (53.8)	28 (9.7)	<.001
IgG anti-TPO (IU/mL), median (IQR)	207.5 (106.5-600.0)	218.0 (108.0- 600.0)	161.0 (48.0- 527.0)	.266
ANA+, n (%)	42 (11.1)	18 (23.1)	24 (8.0)	.001
ASST+, n (%)*	112 of 189 (59.3)	33 of 41 (80.5)	79 of 148 (53.4)	.001
Therapeutic characteristics				
Use of AH4X, n (%)	252 (66.8)	65 (83.3)	187 (62.5)	.001
Omalizumab, n (%)	173 (45.9)	27 (34.6)	146 (48.8)	.043
No. of doses	20.0 (10.0-35.0)	14.0 (9.0-32.0)	21.0 (10.0-35.0)	.226
median (IQR)				
Global discontinuation for omalizumab, n (%)	66 of 173 (38.2)	16 of 27 (59.3)	50 of 146 (34.2)	.014
Discontinuation due to inefficacy, n (%)	20 of 173 (11.6)	8 of 27 (29.6)	12 of 146 (8.2)	<.001
Discontinuation due to remission, n (%)	40 of 173 (23.1)	6 of 27 (22.2)	34 of 146 (23.3)	.847
Discontinuation due to loss of follow-up, n (%)	6 of 173 (3.5)	2 of 27 (7.4)	4 of 146 (2.7)	—
Cyclosporine, n (%)	29 (7.7)	17 (21.8)	12 (4.0)	<.001
Control, n (%)	324 (85.9)	59 (75.6)	265 (88.6)	.004
Remission, n (%)	177 (46.9)	33 (42.3)	144 (48.2)	.146
Baseline UAS-7, median (IQR)	21.0 (13.0-29.0)	24.0 (14.0-29.0)	21.0 (12.5-29.5)	.297
Baseline UCT score, median (IQR)	7.0 (4.0-10.0)	6.5 (5.0-9.0)	8.0 (4.0-10.0)	.330

AH4X, 4-Fold dose of antihistamines; *ANA+*, positive ANA; *ASST+*, positive ASST; *CIndU*, chronic inducible urticaria; *MFI*, mean fluorescence intensity; *RCP*, reactive C-protein.

*ASST was performed in only 189 patients (50.1%).

TABLE II. Autoimmune diseases according to IgE levels and characteristics of patients with polyautoimmunity (n = 12)

Autoimmune disease characteristics				
Autoimmune disease (n = 78)	**Total autoimmune diseases**	**IgE ≤ 43.8 IU/mL (n = 96)**	**IgE > 43.8 IU/mL (n = 281)**	***P* value**
ATD, n (%)	48 (61.5)	30 (31.3)	18 (6.4)	<.001
Autoimmune gastritis/pernicious anemia, n (%)	9 (11.5)	8 (8.3)	1 (0.4)	<.001
Vitiligo, n (%)	5 (6.4)	4 (4.2)	1 (0.4)	.016
SLE, n (%)	5 (6.4)	4 (4.2)	1 (0.4)	.016
Rheumatoid arthritis, n (%)	5 (6.4)	3 (3.1)	2 (0.7)	.107
Celiac disease, n (%)	4 (5.1)	3 (3.1)	1 (0.4)	.053
Type 1 diabetes, n (%)	4 (5.1)	2 (2.1)	2 (0.7)	.26
Alopecia areata, n (%)	4 (5.1)	3 (3.1)	1 (0.4)	.05
Sjögren syndrome, n (%)	3 (3.8)	2 (2.1)	1 (0.4)	.10
Autoimmune adrenalitis, n (%)	2 (2.6)	2 (2.1)	0	.06
Raynaud disease, n (%)	2 (2.6)	2 (2.1)	0	.06
Scleroderma, n (%)	1 (1.3)	1 (1.0)	0	.088
Primary biliary cholangitis, n (%)	1 (1.3)	0	1 (0.4)	.56

Patients with polyautoimmunity					
Baseline IgE (IU/mL)	**AD 1**	**AD 2**	**AD 3**	**IgG anti-TPO**	**ANA**
2	ATD	Alopecia areata	Raynaud disease	+	+
2.8	ATD	Celiac disease	−	+	−
3.2	ATD	Vitiligo	Autoimmune gastritis	+	+
6.3	ATD	SLE	Rheumatoid arthritis	+	+
7.9	ATD	Autoimmune adrenalitis	−	+	+
9.2	Autoimmune gastritis	Vitiligo	−	−	+
20.9	ATD	SLE	−	+	+
28.4	Alopecia areata	Type 1 diabetes	−	+	−
34.8	ATD	Sjögren syndrome	−	+	−
43	ATD	Vitiligo	−	+	−
128	ATD	Rheumatoid arthritis	−	+	−
244	ATD	Rheumatoid arthritis	−	+	−

AD, Autoimmune disease; *ATD*, autoimmune thyroid disease.

treatment with omalizumab had occurred. If omalizumab had been administered, discontinuation and reasons for discontinuation were registered. Clinical remission and clinical control of the disease were also evaluated. Clinical remission achievement was defined as the absence of clinical symptoms during 6 months or more, independently on the possibility of posterior flares. Clinical control of the disease was defined by a UCT score of 12 or more and UAS-7 of less than 7 over 6 months.[19] To evaluate omalizumab effectiveness, treatment prescribed was at least 6 months, with at least 1 updosing at month 3, if the desired goals of UAS-7 and UCT score were not achieved.[20]

Blood test parameters

The entire cohort had the same baseline blood tests, which included total IgE, FCεRI, ANA, IgG anti-TPO, reactive C-protein, D-dimer, erythrocyte sedimentation rate (ESR), and complete blood cell count including eosinophils and basophils. FcεRI expression in blood basophils was measured by flow cytometry. We followed standard procedures to perform flow cytometry analyses.[21] FcεRI expression in basophils was assessed by mean fluorescence intensity. To ensure consistency of analysis, the same investigator processed and analyzed all samples. Baseline total IgE in serum and IgG anti-TPO levels in serum were analyzed by a chemiluminescence immunoassay with IMMULITE 2000 XPi System (Siemens, Munich, Germany). All other laboratory values were measured by automated analyzers in the local central laboratory. Eosinopenia and basopenia were defined as less than 0.05×10^9/L and 0.01×10^9/L, respectively.

Statistical analysis

Demographic characteristics of patients with CSU were reported using descriptive statistics. Because data were not normally distributed, nonparametric tests were used. Results are expressed as median and interquartile range (IQR) for quantitative variables or number and percentage for qualitative variables. The groups resulting from the presence/absence of autoimmune disease were compared using the C2 test of homogeneity (categorical variables) or the Mann-Whitney *U* test (continuous variables). If the conditions to apply the C2 test were not fulfilled, Fisher test was used. Receiver-operating characteristic (ROC) curves were generated to assess baseline IgE levels. The area under the curve (AUC) of the ROC value was calculated for the presence of confirmed autoimmune disease. When a significant cutoff value was observed, the sensitivity and specificity were presented. The descriptive analysis was repeated for the groups defined by the IgE cutoff. Multivariate analysis in the form of a logistic regression to study the impact of variables of interest (defined as those with a *P* value in the bivariate <.05) for the presence of autoimmune disease was performed. Variables that were related to the presence of an autoimmune disease (IgG anti-TPO positivity) and to the baseline levels of IgE (FcεRI expression)

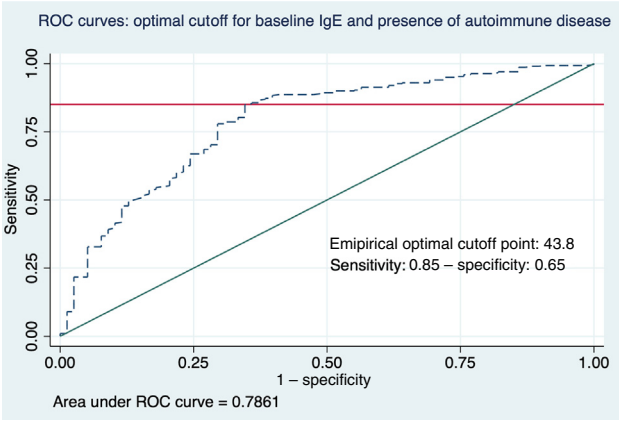

FIGURE 1. ROC curve for baseline IgE and presence of autoimmune disease. The intersection of the red line with the ROC curve indicates the optimal cutoff point. The parameters are specified in the figure.

were not included in the model. To perform the multivariate analysis, ROC curves were generated for the quantitative variables of interest (basophils, eosinophils, D-dimer, and ESR) and these variables were analyzed as categorical variables. Furthermore, a stratified analysis for autoimmune thyroid disease, IgG anti-TPO, ASST, and SLE is also presented in this article's Online Repository at www.jaci-inpractice.org. A *P* value of less than .05 was considered statistically significant. Statistical analyses were performed with Stata-17 (StataCorp, College Station, Texas).

RESULTS

Clinical characteristics

The presence of autoimmune disease (n = 78 of 377, 20.7%) was mostly linked to middle-aged (median, 49.0 years; IQR, 38.0-65.0 years) women (n = 65 of 78, 83.3%), without differences in comorbidities, presence of angioedema, or chronic inducible urticaria. Patients with CSU and autoimmune disease exhibited a high spectrum of autoimmune conditions. Autoimmune thyroid diseases were the most commonly seen (n = 48 of 78, 61.5%), followed by autoimmune gastritis/pernicious anemia (n = 9 of 78, 11.5%), vitiligo (n = 5 of 78, 6.4%), SLE (n = 5 of 78, 6.4%), rheumatoid arthritis (n = 5 of 78, 6.4%), celiac disease (n = 4 of 78, 5.1%), type 1 diabetes (n = 4 of 78, 5.1%), alopecia areata (n = 4 of 78, 5.1%), Sjögren syndrome (n = 3 of 78, 3.8%), autoimmune adrenalitis (n = 2 of 78, 2.6%), Raynaud disease (n = 2 of 78, 2.6%), scleroderma (n = 1 of 78, 1.3%), and primary biliary cholangitis (n = 1 of 78, 1.3%). The presence of polyautoimmunity was seen in 12 patients (n = 12 of 377, 3.2%). Tables I and II present the cohort features in function of the presence of autoimmune disease and autoimmune disease characteristics.

Baseline total IgE and FcεRI levels

Baseline total IgE in patients with autoimmune disease was lower (33.8 IU/mL; IQR, 11.2-85.6 IU/mL) than in patients without autoimmune disease (148.0 IU/mL; IQR, 66.6-300.0 IU/mL) ($P < .001$). Similarly, baseline levels of FcεRI were significantly lower in the autoimmune disease group (mean fluorescence intensity, 3482.0; IQR, 1621.0-7253.0) ($P < .001$).

ROC-curve analysis of IgE to predict autoimmune disease (Figure 1) revealed the optimal cutoff point at 43.8 IU/mL (AUC, 0.79; sensitivity, 0.85; specificity, 0.65).

The analysis of all patients with total baseline IgE levels less than or equal to 43.8 IU/mL indicated that 53.1% (n = 51 of 96) of the patients in this group presented with an autoimmune disease, significantly higher than the 9.6% (n = 27 of 281) of patients in the group with IgE more than 43.8 IU/mL ($P < .01$). Polyautoimmunity was significantly higher in patients with IgE less than or equal to 43.8 IU/mL ($P < .01$). The analysis of groups according to the cutoff for IgE showed that autoimmune thyroid disease, autoimmune gastritis/pernicious anemia, SLE, and vitiligo were significantly higher in patients with IgE less than or equal to 43.8 IU/mL. No differences could be found for other conditions. Patients' features according to the IgE cutoff can be found in Table III.

The stratified analysis based on ASST, thyroid autoimmune disease, IgG anti-TPO, and SLE also identified differences in terms of baseline IgE in patients who presented presence or positivity to any of the aforementioned variables. However, differences in other baseline analytic features or clinical features were not uniformly seen for all groups. Results can be seen in Tables E1-E4, in this article's Online Repository at www.jaci-inpractice.org.

Other baseline markers and complementary tests

Total eosinophil and basophil count were significantly lower in patients with associated autoimmune disease, with median values of 0.09×10^9/L and 0.02×10^9/L, respectively, and this was reiterated with the analysis of eosinopenia and basopenia according to the established limits (30.8% and 21.8%, respectively). In terms of acute-phase reactants, both higher median ESR and basal D-dimer values were found in patients with CSU and autoimmune disease ($P < .01$). However, no significant differences were found for basal reactive C-protein levels ($P = .545$). For ASST, its positivity was higher in patients with autoimmune disease (n = 33 of 41, 80.5%) ($P = .001$).

Antibody positivity for IgG anti-TPO in patients with autoimmune disease (n = 42, 53.8%) diverged from that in patients without a diagnosed autoimmune disease (n = 28, 9.7%) ($P < .01$). Total levels of IgG anti-TPO were also higher in this group, without reaching significance ($P = .266$). Similar findings were disclosed for ANAs, with an increased positivity in patients with autoimmune disease (n = 18, 23.1%) in comparison to patients without (n = 24, 8.0%).

Multivariate analysis: Logistic regression

ROC curves have been made for the continuous variables of interest (baseline basophils, baseline eosinophils, baseline D-dimer, and baseline ESR) and the presence of autoimmune disease. When evaluating all ROC curves, IgE ROC curve (Figure 1) had the best performance (AUC, 0.79), followed by basophils (AUC, 0.69), eosinophils (AUC, 0.66), ESR (AUC, 0.63), and D-dimer (AUC, 0.62). ROC curves and their parameters have been added to the Online Repository (see Figures E1-E4 in this article's Online Repository at www.jaci-inpractice.org). Furthermore, new optimal cutoffs were found for basophils (0.025), eosinophils (0.105), ESR (4.5), and D-dimer (399.5), in addition to the previously presented cutoff for baseline IgE.

TABLE III. Demographic, blood test, and therapeutic characteristics in the cohort of patients with CSU depending on the IgE cutoff

		IgE		
Variables	**Total (n = 377)**	**≤43.8 IU/mL (n = 96)**	**>43.8 IU/mL (n = 281)**	***P* value**
Demographic and clinical characteristics				
Sex: female, n (%)	269 (71.4)	82 (85.4)	187 (66.5)	<.01
Age (y), median (IQR)	46.0 (34.0-58.0)	48.0 (34.0-62.0)	45.0 (35.0-57.0)	.297
Angioedema, n (%)	164 (43.5)	50 (52.1)	114 (40.6)	.06
CIndU, n (%)	85 (22.5)	22 (22.9)	63 (22.4)	>.99
Autoimmune disease, n (%)	78 (20.7)	51 (53.1)	27 (9.6)	<.01
Poliautoimmunity	12 (3.2)	10 (10.4)	2 (0.7)	<.01
Cardiopathy, n (%)	66 (17.5)	13 (13.5)	53 (18.9)	.278
Pneumopathy, n (%)	44 (11.7)	13 (13.5)	31 (11.0)	.581
Oncologic disease, n (%)	30 (8.0)	9 (9.4)	21 (7.5)	.520
Psychiatric comorbidity, n (%)	67 (17.8)	19 (19.8)	48 (17.1)	.540
Atopy, n (%)	91 (24.1)	17 (17.7)	74 (26.3)	.127
Atopic dermatitis	36 (9.5)	8 (8.3)	28 (10.0)	.840
Asthma	61 (16.2)	14 (14.6)	47 (16.7)	.748
Rhinitis	73 (19.4)	16 (16.7)	57 (20.3)	.549
Obesity, n (%)	95 (25.2)	26 (27.1)	69 (24.6)	.684
Baseline markers and complementary tests				
Baseline IgE (IU/mL), median (IQR)	115.0 (43.0-269.0)	19.3 (7.4-34.3)	180.0 (93.3-325.0)	<.001
Baseline IgE cutoff, n (%)		NA	NA	NA
≤43.8 IU/mL	n = 96			
>43.8 IU/mL	n = 281			
FcεRI (MFI), median (IQR)	7,743.0 (3,099.0-12,970.0)	3,290.5 (1,618.0-7,087.3)	9,918.0 (5,132.5-14,843.0)	<.001
Absolute eosinophil count (10^9/L), median (IQR)	0.12 (0.06-0.25)	0.07 (0.01-0.11)	0.15 (0.08-0.26)	.02
Absolute basophil count (10^9/L), median (IQR)	0.03 (0.02-0.05)	0.02 (0.01-0.03)	0.03 (0.02-0.05)	<.01
Eosinopenia, n (%)	52 (13.8)	38 (39.6)	14 (5.0)	<.01
Basopenia, n (%)	32 (8.5)	21 (21.9)	11 (3.9)	<.01
ESR (mm/h), median (IQR)	5.0 (2.0-12.0)	8.0 (4.0-15.2)	4.0 (2.3-10.2)	<.01
RCP (mg/dL), median (IQR)	0.3 (0.1-0.9)	0.3 (0.1-0.9)	0.3 (0.1-0.9)	.526
D-dimer (mg/dL), median (IQR)	340.0 (210.0-565.0)	405.0 (250.0- 710.0)	330.0 (200.0- 525.0)	.010
IgG anti-TPO+, n (%)	70 (18.6)	37 (38.5)	33 (11.7)	<.01
IgG anti-TPO (IU/mL), median (IQR)	207.5 (106.5-600.0)	248.0 (108.0-600.0)	197.0 (105.0-703.0)	.852
ANA+, n (%)	42 (11.1)	25 (26.0)	17 (6.0)	<.01
ASST+, n (%)*	112 of 189 (59.3)	36 of 49 (73.4)	76 of 140 (54.3)	.02
Therapeutic characteristics				
Use of AH4X, n (%)	252 (66.8)	80 (83.3)	172 (61.21)	<.001
Omalizumab, n (%)	173 (45.9)	30 (31.3)	143 (50.9)	.001
No. of doses, median (IQR)	20.0 (10.0-35.0)	16.0 (7.0-32.0)	21.0 (10.0-35.0)	.146
Global discontinuation for omalizumab, n (%)	66 of 173 (38.2)	17 of 30 (56.7)	49 of 143 (34.3)	.02
Discontinuation due to inefficacy, n (%)	20 of 173 (11.6)	12 of 30 (40.0)	8 of 143 (5.6)	<.001
Discontinuation due to remission, n (%)	40 of 173 (23.1)	4 of 30 (13.3)	36 of 143 (25.2)	.162
Discontinuation due to loss of follow-up, n (%)	6 of 173 (3.5)	1 of 30 (3.3)	5 of 143 (3.5)	—
Cyclosporine, n (%)	29 (7.7)	23 (23.9)	6 (2.1)	<.001
Control, n (%)	324 (85.9)	64 (66.7)	260 (92.5)	<.001
Remission, n (%)	177 (46.9)	39 (40.6)	138 (49.1)	.157
Baseline UAS-7, median (IQR)	21.0 (13.0-29.0)	26.0 (18.0-31.0)	20.0 (12.0-28.0)	<.001
Baseline UCT score, median (IQR)	7.0 (4.0-10.0)	6.0 (4.0-8.0)	8.0 (4.0-10.5)	.067

AH4X, 4-Fold dose of antihistamines; *ANA+*, positive ANA; *ASST+*, positive ASST; *CIndU*, chronic inducible urticaria; *MFI*, mean fluorescence intensity; *RCP*, reactive C-protein.
*ASST was performed in only 189 patients (50.1%).

Multivariable analysis was performed on 349 patients to study the effect of selected variables on the presence of autoimmune disease. Variables included were IgE levels (defined by optimal cutoff), basophils (defined by optimal cutoff), eosinophils (defined by optimal cutoff), D-dimer (defined by optimal cutoff), ESR (defined by optimal cutoff), sex, and ANA positivity. ASST was not initially included in the regression model because the variable was available in only 189 patients (50.1%).

However, a second regression analysis was performed to include ASST, which is included in the Online Repository (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Logistic regression revealed that a low baseline IgE state (IgE $\leq$ 43.8 IU/mL) could be a risk factor for the presence of autoimmune disease (odds ratio, 6.0 [3.1-11.5]) ($P < .001$), as well as lower baseline basophil levels (basophils $\leq$ 0.025 10^9/L) (odds ratio, 2.7 [1.4-5.0]) ($P = .002$). All other variables did not remain statistically significant at the multivariate analysis (Table IV). The second regression analysis, which included ASST, confirmed that low IgE was an important risk factor for the presence of autoimmune disease (Table E5).

TABLE IV. Regression analysis results for the presence of autoimmune disease

Variables	OR	SE	*P* value	95% CI
IgE $\leq$ 43.8 (IU/mL)	6.0	2.0	<.001	3.1-11.5
Basophils $\leq$ 0.025 (10^9/L)	2.65	0.8	.002	1.4-5.0
Eosinophils $\leq$ 0.105 (10^9/L)	1.16	0.4	.65	0.6-2.2
D-dimer $\geq$ 399.5 (mg/dL)	1.73	0.6	.09	0.9-3.2
ESR $\geq$ 4.5 (mm/h)	1.33	0.5	.40	0.7-2.6
ANA positivity	1.50	0.6	.34	0.6-3.5
Sex: male	0.7	0.3	.33	0.3-1.5

OR, Odds ratio.

Therapeutic characteristics

In our cohort, patients with autoimmune disease needed a higher use of 4-fold dose antihistamines ($P = .001$), were more commonly treated with cyclosporine ($P < .001$), and received less commonly omalizumab ($P = .043$). Once omalizumab started, the number of doses was also lower, without reaching significance ($P = .226$). The data of the 173 patients who received omalizumab correspond to real-life clinical practice. The evaluation of omalizumab initiation showed that 6 patients started it before 2014 in the setting of an off-label use, whereas for most patients omalizumab therapy was commenced between 2014 and 2020 (n = 144, 83.2%). Omalizumab was discontinued in 66 of 173 (38.2%) because of different therapeutic results: clinical remission (n = 40 of 173, 38.2%), treatment failure (n = 20 of 173, 11.6%), or loss of follow-up (n = 6 of 173, 3.5%). Total discontinuation was higher in patients with autoimmune disease ($P = .03$), and differences were also found when discontinuation due to omalizumab inefficacy was analyzed ($P < .001$). A subanalysis of omalizumab discontinuation for relevant clinical variables showed significant differences between remission and inefficacy for IgE levels ($P < .001$), presence of autoimmune disease ($P = .03$), and basophil levels ($P = .05$), whereas no differences were found for other variables (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

Clinical control of the disease was achieved less frequently if autoimmune disease was present ($P = .004$). No differences were found in terms of discontinuation due to remission, baseline UAS-7, or baseline UCT score. In this regard, patients with IgE less than or equal to 43.8 IU/mL presented higher baseline UAS-7 ($P < .001$).

DISCUSSION

The importance of the detection of serological and/or clinical autoimmunity in the management of CSU has been reflected on its guidelines, with IgG anti-TPO considered to be a routine initial test. In addition, extended autoimmunity studies may be performed on the basis of clinical suspicion. However, the association of autoimmune diseases and CSU continues to present unanswered questions in research and daily clinical practice.

This prospective study has provided evidence indicating that a significant portion of patients had associated underlying autoimmune disease(s) either at diagnosis or during follow-up. The most common associated autoimmune disease was thyroid autoimmune disease, followed by pernicious anemia and vitiligo, whereas the most common autoimmune serologic marker was IgG anti-TPO. Consistent with these findings, previous studies have reported autoimmune comorbidities in 28% of patients with CSU, particularly autoimmune thyroid disease.[17] An increased presence of polyautoimmunity in patients already with an autoimmune disease has also been described. Furthermore, an IgE less than or equal to 43.8 IU/mL could be suggested as a risk factor for the presence of autoimmune disease in patients with CSU. Therefore, all these results may highlight the need to include targeted history and thorough examination for the presence of autoimmune signs or symptoms in all patients with CSU, at diagnosis and during follow-up. Present data could also suggest that this would be especially important for patients with low or very-low IgE or who already have an associated autoimmune disorder.

Within our cohort, patients with CSU and autoimmune disease presented laboratory results with a common pattern, characterized by low baseline IgE and low blood basophil FcεRI expression, lower basophil and eosinophil counts, higher ESR and D-dimer, higher ASST positivity, and higher positivity for ANA and IgG anti-TPO. Low total IgE has been defined as levels below 30 or 40 IU/mL.[5,22] In this study, the optimal decision cutoff to predict autoimmune disease was 43.8 IU/mL, and the median level of total baseline IgE in patients with CSU and autoimmune disease(s) was 33.0 IU/mL, both indicating low IgE state in autoimmune disease. Low baseline IgE, eosinopenia, basopenia, and IgG anti-TPO are thought to be related to type IIb autoimmunity aiCSU.[5,23,24] Furthermore, ASST is 1 of the 3 criteria that defines aiCSU. However, ASST positivity by itself had low predictive values for type IIb aiCSU against non-IIb in the PURIST study[4] and may present with false-positive results in patients with dermographism or formation of vasoactive mediators during serum preparation.[24,25] ANAs have not been suggested as a useful clinical marker, but their positivity has been described as increased in Cluster 3.[6] Therefore, the blood test pattern of patients with autoimmune disease shares common features with previously reported laboratory features of patients with diagnosed IIb aiCSU. However, it is interesting to emphasize that, at least, a significant number of patients with autoimmune disease would not fulfill aiCSU criteria because the ASST result was negative in one-fifth of the patients with autoimmune disease. This percentage could be higher because basophil activation test and test for antibodies against IgE/FcεRI were not performed. We hypothesize that aiCSU criteria alone may not reflect the complexity of the autoimmune subtype of CSU in clinical practice.

Some differences in terms of therapeutic management were observed in patients with autoimmune disease. In terms of first-line treatment, patients with autoimmune disease required more often 4-fold antihistamine dosage. This may be related to the

lower response to antihistamines seen in low IgE, IgG anti-TPO autoimmunity, elevation of ESR or D-dimer, and/or eosinopenia.[5,23,26-28] Decreased use of omalizumab with an increased prescription of cyclosporine, increased total omalizumab discontinuation, and increased failure to omalizumab were seen in this group. Low baseline IgE, with suggested predictive cutoff values ranging from 17.9 to 42.1IU/mL, can be considered as a predictor of slow response and partial response to omalizumab related to the type IIb aiCSU.[5,29,30] Therefore, it is concordant that the observation of lower IgE levels in patients with autoimmune disease present increased failure to omalizumab. Basophil levels' clinical relevance in relation to CSU phenotypes and omalizumab responsiveness[31-33] has been reinforced because in our cohort lower basophil levels were suggested as a risk factor of autoimmune disease, and lower baseline basophil levels occurred in patients who failed to respond to omalizumab. Furthermore, several other parameters related to poorer omalizumab response, such as serological autoimmunity (eg, ANA positivity and high IgG anti-TPO levels) and eosinopenia,[24,30,34,35] were also found in patients with autoimmune disease. Despite the different clinical and blood test features, there were no differences in terms of basal UAS-7 or UCT score, in opposition to previous research.[36]

This study provides additional evidence regarding the diversity of phenotypes in CSU. Moreover, similar findings between patients with CSU with autoimmune disease in our cohort and previous studies involving aiCSU or "Cluster 3" patients have been consistently observed. These shared blood test, demographic, and clinical features may shed light on the existence of a spectrum of common pathogenic traits in patients with CSU autoimmune disease(s) and patients with type IIb aiCSU. This autoimmune background in patients with autoimmune disease may lead to typical aiCSU or to a partial "aiCSU-like" phenotype that does not fulfill the established criteria, but with common phenotypic and blood test characteristics. It is normally accepted that low total IgE is related to an autoimmune pathogenesis and signature of patients with CSU,[5] even if the exact pathogenesis that explains the cause of lower IgE in patients with an autoimmune background (eg, aiCSU or patients with associated autoimmune disease) has not been precisely deciphered.[24] Further studies are needed to have a better understanding in the autoimmune pathogenesis of CSU and the common pathogenic basis with other autoimmune diseases.

Strengths and limitations

The strengths of this study include the prospective obtention of the data and the technical homogeneity of complementary tests for all patients. Some limitations are to be pointed out: its unicentric nature, the lack of triple testing for aiCSU to identify the number of patients with autoimmune disease that match with the aiCSU criteria, and the descriptive nature of the study, which impedes establishing causality. In addition, the clinical and laboratory findings associated with patients with CSU and autoimmune disease may not be entirely attributed to the pathogenesis and activity of CSU, because some have previously been described as being associated only with some autoimmune diseases.[37-40] Further studies are needed to improve our understanding on the pathogenesis of CSU and its relation to autoimmune diseases. In terms of therapeutic response, there are limitations for the interpretation of the IgE levels as therapeutic predictor *per se*, because the group with low IgE levels, also presented with positive ASST result and high frequency of anti-TPO IgG. Both ASST and IgG anti-TPO have been described as nonpredictors of response in the ASTERIA I and II studies.[41,42]

CONCLUSIONS

This study corroborates the existence of distinct laboratory and clinical characteristics among patients with CSU and autoimmune disease in a real-world clinical setting, and reinforces previous knowledge on aiCSU and autoimmunity in CSU.[43] A common spectrum of clinical, laboratory, and therapeutic characteristics of patients with autoimmune disease and CSU has been described, revealing a particular biological pattern characterized by middle-aged female women, with low total baseline IgE and low blood basophil FcεRI expression, eosinopenia, basopenia, and elevation of some inflammatory and autoimmunity markers. In real-life clinical practice, the therapeutic approach of these patients differs with an increased use of 4-fold antihistamines, an increased use of cyclosporine, and higher failure of omalizumab. Low total baseline IgE (cutoff $\leq$ 43.8 IU/mL) could be a useful biomarker to predict the presence of autoimmune diseases in clinical practice for patients with CSU. These results highlight the importance to assess at diagnosis and during follow-up autoimmune signs and symptoms in this population, especially if a low baseline IgE is detected.

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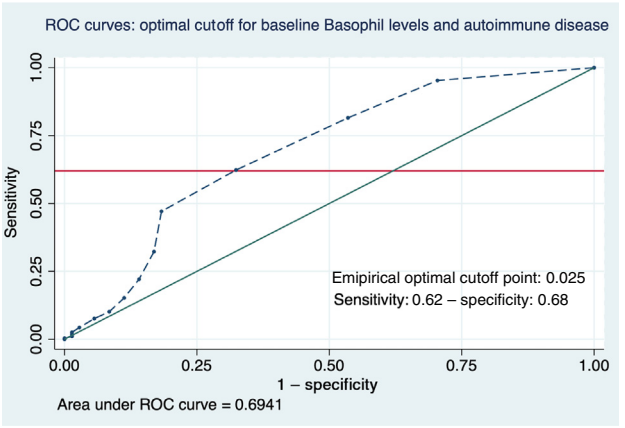

FIGURE E1. ROC curve for baseline basophil levels and presence of autoimmune disease. The intersection of the red line with the ROC curve indicates the optimal cutoff point. The parameters are specified in the figure.

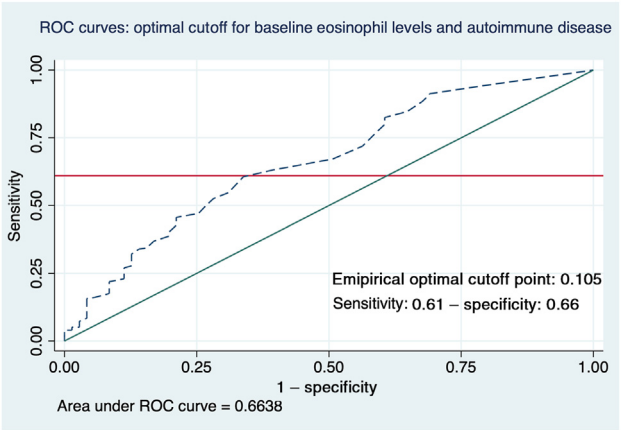

FIGURE E2. ROC curve for baseline eosinophil levels and presence of autoimmune disease. The intersection of the red line with the ROC curve indicates the optimal cutoff point. The parameters are specified in the figure.

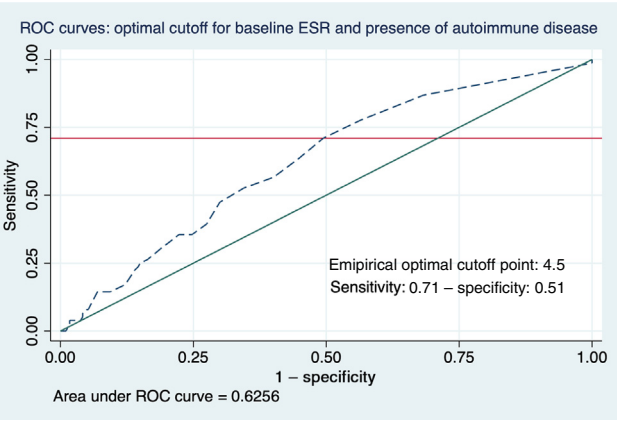

FIGURE E3. ROC curve for baseline D-dimer and presence of autoimmune disease. The intersection of the red line with the ROC curve indicates the optimal cutoff point. The parameters are specified in the figure.

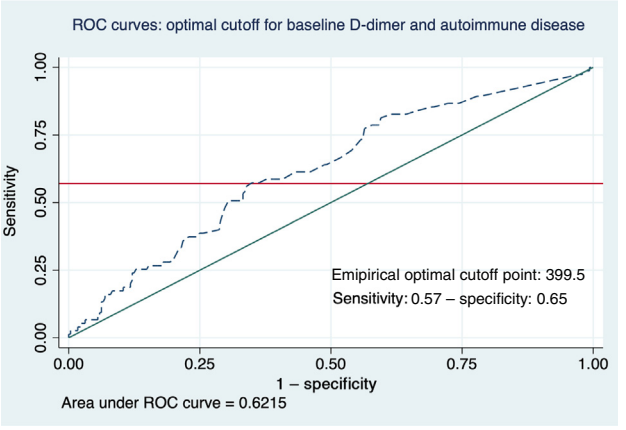

FIGURE E4. ROC curve for baseline ESR and presence of autoimmune disease. The intersection of the red line with the ROC curve indicates the optimal cutoff point. The parameters are specified in the figure.

TABLE E1. Demographic, laboratory, and therapeutic characteristics analysis for ASST

		ASST result		
Variables	**Total (n = 189)**	**Positive (n = 112)**	**Negative (n = 77)**	***P* value**
Sex: female, n (%)	142 (75.1)	89 (79.5)	53 (68.9)	.10
Age (y), median (IQR)	46 (58-38.5)	49.9 (62-39.5)	44.2 (53.5-31)	.0165
Angioedema, n (%)	85 (45.0)	54 (48.2)	31 (40.3)	.28
CIndU, n (%)	48 (25.4)	31 (27.7)	17 (22.1)	.385
Autoimmune disease, n (%)	41 (21.7)	33 (29.5)	8 (10.4)	.002
Baseline IgE (IU/mL), median (IQR)	106.5 (253-43.1)	78.7 (192.0-28.9)	186.5 (382.5-78.1)	<.001
Baseline IgE cutoff, n (%)				.019
≤43.8 IU/mL	49 (25.9)	36 (32.1)	13 (16.9)	
>43.8 IU/mL	140 (74.1)	76 (67.9)	64 (83.1)	
FcεRI (MFI), median (IQR)	7,593.0 (12,124.5-2,708.5)	6,790.0 (12,117.0-2,447.3)	8,238.0 (12,507.5-4,006.5)	.29
Absolute eosinophil count (10^9/L), median (IQR)	0.12 (0.24-0.07)	0.11 (0.20-0.04)	0.14 (0.26-0.09)	.004
Absolute basophil count (10^9/L), median (IQR)	0.03 (0.05-0.01)	0.025 (0.05-0.01)	0.04 (0.06-0.02)	.002
Eosinopenia, n (%)	31 (16.4)	26 (23.2)	5 (6.5)	.002
Basopenia, n (%)	22 (11.6)	17 (15.2)	5 (6.5)	.067
ESR (mm/h), median (IQR)	6.0 (12.0-3.0)	6.0 (12.0-3.0)	3.0 (10.8-2.0)	.254
RCP (mg/dL), median (IQR)	0.4 (1.31-0.15)	0.54 (1.5-0.14)	0.35 (1.30-0.15)	.865
D-dimer (mg/dL), median (IQR)	225 (765-210)	391 (820-200)	330 (636-215)	.368
IgG anti-TPO+, n (%)	35 (18.5)	27 (24.1)	8 (10.4)	.017
ANA+, n (%)	18 (9.5)	14 (12.5)	4 (5.2)	.13
AH4x, n (%)	109 (57.7)	69 (61.6)	40 (51.9)	.187
Omalizumab, n (%)	119 (63.0)	64 (57.1)	55 (71.4)	.065
Omalizumab global discontinuation, n (%)	50 of 119 (42.0)	30 of 64 (46.9)	20 of 55 (36.4)	.269
Discontinuation due to inefficacy, n (%)	15 of 119 (12.6)	12 of 64 (18.8)	3 of 55 (5.5)	.039
Cyclosporine, n (%)	15 (7.9)	11 (9.8)	4 (5.2)	.286
Baseline UAS-7, median (IQR)	21 (13-29)	21 (14-30)	23 (13 -30)	.885
Baseline UCT score, median (IQR)	7 (4-10)	8 (5-10)	6 (4-9)	.017

AH4X, 4-Fold dose of antihistamines; *ANA+*, positive ANA; *ASST+*, positive ASST; *CIndU*, chronic inducible urticaria; *MFI*, mean fluorescence intensity; *RCP*, reactive C-protein.

TABLE E2. Demographic, laboratory, and therapeutic characteristics analysis for IgG anti-TPO

		IgG anti-TPO		
Variables	**Total (n = 377)**	**Positive (n = 70)**	**Negative (n = 307)**	***P* value**
Sex: female, n (%)	269 (71.4)	61 (87.1)	208 (67.8)	.001
Age (y), median (IQR)	46.0 (58.0-34-0)	47 (59-35)	41.5 (53.3-26)	.011
Angioedema, n (%)	164 (43.5)	34 (48.6)	130 (42.3)	.343
CIndU, n (%)	85 (22.5)	10 (14.3)	75 (24.4)	.066
Autoimmune disease, n (%)	78 (20.7)	42 (60.0)	36 (12.8)	<.001
Baseline IgE (IU/mL), median (IQR)	115.0 (269.0-43.0)	37.5 (103.4-6.3)	139.5 (289.5-63.7)	<.001
Baseline IgE cutoff, n (%)				<.001
≤43.8 IU/mL	96 (25.5)	37 (52.9)	59 (19.2)	
>43.8 IU/mL	281 (74.5)	33 (47.1)	248 (80.8)	
FcεRI (MFI), median (IQR)	7,743.0 (12,970.0-3,099.0)	2,753.5 (8,403.5-1,613.0)	8,592.0 (13,880.0-4,839.5)	<.001
Absolute eosinophil count (10^9/L), median (IQR)	0.12 (0.25-0.06)	0.13 (0.28-0.08)	0.11 (0.24-0.06)	.86
Absolute basophil count (10^9/L), median (IQR)	0.03 (0.05-0.02)	0.03 (0.05-0.02)	0.03 (0.06-0.02)	.66
Eosinopenia, n (%)	52 (13.8)	15 (21.4)	37 (12.1)	.063
Basopenia, n (%)	32 (8.5)	11 (15.7)	21 (6.8)	.016
ESR (mm/h), median (IQR)	5.0 (12.0-2.0)	8.0 (13.0-3.5)	5.0 (10.3-2.0)	.005
RCP (mg/dL), median (IQR)	0.3 (0.9-0.1)	0.38 (1.0-0.2)	0.3 (0.9-0.12)	.12
D-dimer (mg/dL), median (IQR)	340.0 (565.0-210.0)	390 (650-290)	330 (540-200)	.043
ANA+, n (%)	42 (11.1)	12 (17.1)	30 (9.8)	.06
AH4x, n (%)	252 (66.8)	57 (81.4)	195 (63.5)	.005
Omalizumab, n (%)	173 (45.9)	26 (37.1)	147 (47.9)	.112
Omalizumab global discontinuation, n (%)	66 of 173 (38.2)	16 of 26 (61.5)	50 of 147 (34.0)	.014
Discontinuation due to inefficacy, n (%)	20 of 173 (30.3)	7 of 26 (26.9)	13 of 147 (8.8)	.015
Cyclosporine, n (%)	29 (7.7)	13 (18.6)	16 (5.2)	<.001
Baseline UAS-7, median (IQR)	21.0 (13.0-29.0)	24.0 (14.8-32.3)	21.0 (12.0-28.0)	.040
Baseline UCT score, median (IQR)	7.0 (4.0-10.0)	6.0 (4.0-9.0)	8.0 (4.0-10.0)	.172

AH4X, 4-Fold dose of antihistamines; *ANA+*, positive ANA; *CIndU*, chronic inducible urticaria; *MFI*, mean fluorescence intensity; *RCP*, reactive C-protein.

TABLE E3. Demographic, laboratory, and therapeutic characteristics analysis for autoimmune thyroid disease

		Autoimmune thyroid disease		
Variables	**Total (n = 377)**	**Present (n = 48)**	**Absent (n = 329)**	***P* value**
Sex: female, n (%)	269 (71.4)	43 (89.6)	226 (68.7)	.003
Age (y), median (IQR)	46.0 (58.0-34-0)	49 (62-39)	45 (58-34)	.204
Angioedema, n (%)	164 (43.5)	26 (54.2)	138 (41.9)	.11
CIndU, n (%)	85 (22.5)	7 (14.6)	78 (23.7)	.157
Baseline IgE (IU/mL), median (IQR)	115.0 (269.0-43.0)	35.1 (128-7.5)	134.5 (289.5-53.6)	<.001
Baseline IgE cutoff, n (%)				<.001
≤43.8 IU/mL	96 (25.5)	30 (62.5)	66 (20.1)	
>43.8 IU/mL	281 (74.5)	18 (37.5)	263 (79.9)	
FcεRI (MFI), median (IQR)	7,743.0 (12,970.0-3,099.0)	2,706 (8,375-1,069)	8,474 (13,558.8-4,143)	<.001
Absolute eosinophil count (10^9/L), median (IQR)	0.12 (0.25-0.06)	0.09 (0.16-0.01)	0.13 (0.26-0.07)	.905
Absolute basophil count (10^9/L), median (IQR)	0.03 (0.05-0.02)	0.02 (0.03-0.01)	0.03 (0.05-0.02)	>.99
Eosinopenia, n (%)	52 (13.8)	13 (27.1)	39 (11.9)	.004
Basopenia, n (%)	32 (8.5)	11 (22.9)	21 (6.4)	<.001
ESR (mm/h), median (IQR)	5.0 (12.0-2.0)	8.0 (12.5-3.5)	5.0 (11.0-2.0)	.023
RCP (mg/dL), median (IQR)	0.3 (0.9-0.1)	0.34 (0.66-0.17)	0.31 (0.91-0.12)	.414
D-dimer (mg/dL), median (IQR)	340.0 (565.0-210.0)	465 (745-310)	330 (540-200)	.004
IgG anti-TPO+, n (%)	70 (18.5)	36 (75.0)	34 (10.3)	<.001
ANA+, n (%)	42 (11.1)	9 (18.8)	33 (10.0)	.07
AH4x, n (%)	252 (66.8)	41 (85.4)	211 (64.1)	.003
Omalizumab, n (%)	173 (45.9)	18 (37.5)	155 (47.1)	.220
Omalizumab global discontinuation, n (%)	66 of 173 (38.2)	10 of 18 (55.6)	56 of 155 (36.1)	.128
Discontinuation due to inefficacy, n (%)	20 of 173 (30.3)	5 of 18 (27.8)	15 of 155 (9.7)	.039
Cyclosporine, n (%)	29 (7.7)	9 (18.8)	20 (6.1)	.006
Baseline UAS-7, median (IQR)	21.0 (13.0-29.0)	24 (13-30)	21 (13-29)	.483
Baseline UCT score, median (IQR)	7.0 (4.0-10.0)	7.5 (5-10)	7 (4-10)	.970

AH4X, 4-Fold dose of antihistamines; *ANA+*, positive ANA; *CIndU*, chronic inducible urticaria; *MFI*, mean fluorescence intensity; *RCP*, reactive C-protein.

TABLE E4. Demographic, laboratory, and therapeutic analysis for SLE

		SLE		
Variables	**Total (n = 377)**	**Present (n = 5)**	**Absent (n = 372)**	***P* value**
Sex: female, n (%)	269 (71.4)	4 (80.0)	265 (71.2)	>.99
Age (y), median (IQR)	46.0 (58.0-34-0)	64.0 (65.5-43.0)	46.0 (58.0-34.0)	.161
Angioedema, n (%)	164 (43.5)	3 (60.0)	161 (43.3)	.656
CIndU, n (%)	85 (22.5)	0 (0)	85 (22.8)	.592
Baseline IgE (IU/mL), median (IQR)	115.0 (269.0-43.0)	29.3 (60.5-13.6)	118.0 (271.8-44.7)	.033
Baseline IgE cutoff, n (%)				.016
≤43.8 IU/mL	96 (25.5)	4 (80.0)	92 (24.7)	
>43.8 IU/mL	281 (74.5)	1 (20.0)	280 (75.3)	
FcεRI (MFI), median (IQR)	7,743.0 (12,970.0-3,099.0)	5,869 (6,640.5-2,426.5)	7,906.5 (13,174.0-3,276.3)	.170
Absolute eosinophil count (10^9/L), median (IQR)	0.12 (0.25-0.06)	0.08 (0.1-0)	0.12 (0.25-0.07)	.351
Absolute basophil count (10^9/L), median (IQR)	0.03 (0.05-0.02)	0.02 (0.04-0.02)	0.03 (0.05-0.02)	.91
Eosinopenia, n (%)	52 (13.8)	2 (40.0)	50 (13.4)	.142
Basopenia, n (%)	32 (8.5)	0 (0)	32 (8.6)	>.99
ESR (mm/h), median (IQR)	5.0 (12.0-2.0)	5.0 (11.5-3.0)	5.0 (12.0-2.0)	.936
RCP (mg/dL), median (IQR)	0.3 (0.9-0.1)	0.5 (2.3-0.2)	0.3 (0.9-0.1)	.776
D-dimer (mg/dL), median (IQR)	340.0 (565.0-210.0)	390 (1,730-270)	340.0 (570.0-210.0)	.45
IgG anti-TPO+, n (%)	70 (18.5)	3 (60.0)	67 (18.0)	.046
ANA+, n (%)	42 (11.1)	5 (100)	37 (9.9)	<.001
AH4x, n (%)	252 (66.8)	4 (80)	248 (66.7)	>.99
Omalizumab, n (%)	173 (45.9)	0	173 (46.5)	—
Cyclosporine, n (%)	29 (7.7)	1 (20)	4 (1.1)	.065
Baseline UAS-7, median (IQR)	21.0 (13.0-29.0)	14.5 (14.0-16.5)	21.0 (13.0-29.0)	.219
Baseline UCT score, median (IQR)	7.0 (4.0-10.0)	5.0 (4.0-7.0)	7.0 (4.0-10.0)	.246

AH4X, 4-Fold dose of antihistamines; *ANA+*, positive ANA; *CIndU*, chronic inducible urticaria; *MFI*, mean fluorescence intensity; *RCP*, reactive C-protein.

TABLE E5. Regression analysis results (including ASST) for the presence of autoimmune disease

Variables	**OR**	**SE**	***P* value**	**95% CI**
IgE ≤ 43.8 (IU/mL)	8.7	4.3	<.001	3.3-22.9
Basophils ≤ 0.025 (10^9/L)	1.65	0.8	.28	0.7-4.1
Eosinophils ≤ 0.105 (10^9/L)	1.50	0.7	.40	0.6-3.8
D-dimer ≥ 399.5 (mg/dL)	1.31	0.6	.56	0.5-3.2
ESR ≥ 4.5 (mm/h)	1.87	0.9	.19	0.7-4.8
ANA positivity	1.12	0.7	.85	0.3-4.1
ASST positivity	1.22	0.7	.67	0.5-3.2
Sex: male	0.8	0.4	.63	0.2-2.3

OR, Odds ratio.

TABLE E6. Omalizumab discontinuation: Analysis of remission vs failure

Variables	**Remission (n = 40)**	**Failure (n = 20)**	***P* value**
Autoimmune disease, n (%)	6 (15)	8 (40)	.03
IgE, median (IQR)	207.5 (101.8-361)	29 (10.2-44)	<.001
Basophils, median (IQR)	0.04 (0.02-0.06)	0.01 (0.003-0.03)	.05
IgG anti-TPO, n (%)	6 (15)	7 (35)	.08
ANA positivity, n (%)	3 (7.5)	4 (20)	.21
Sex: male, n (%)	8 (20)	5 (25)	.74
Age, median (IQR)	44.5 (37.8-60.3)	52.5 (38.3-62)	.24
ASST positivity, n (%)	18 of 35 (51.4)	12 of 15 (80)	.06