

Clinical Communications

Association of basophil parameters with disease severity and duration in chronic spontaneous urticaria (CSU)

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Clinical Implications

- In chronic spontaneous urticaria (CSU), basopenia was associated with more severe disease, whereas the basophil responder phenotype was associated with longer disease. Furthermore, the basophil activation test may be an alternative method to basophil histamine release for classifying basophil functional phenotypes in CSU.

TO THE EDITOR:

Chronic spontaneous urticaria (CSU) is characterized by ≥ 6 weeks of spontaneous, pruritic hives. Despite CSU's significant impact on quality of life, few predictors are known for the clinical course of disease. However, basophils have been shown to have unique features in CSU. First, basopenia has been linked to disease severity.^{1,2} Second, studies have demonstrated suppression of the IgE pathway to histamine release (HR) in active CSU compared with controls, with basophil hyporesponsiveness improving in disease remission.²⁻⁴ Lastly, basophils are specifically recruited to skin lesions of patients with CSU.⁵ Given their altered phenotype in disease, basophil parameters may help predict the clinical course of disease. Here we update the preliminary report from Baker et al⁶ with the analysis of basophil parameters in patients with CSU using a larger, expanded cohort including the initial participants. We also include a subcohort for studies comparing HR and the basophil activation test (BAT) for functional phenotyping.

Study approval was granted by the Johns Hopkins University Institutional Review Board. Patients ≥ 18 years of age with allergist/dermatologist diagnosis of active CSU were recruited from Johns Hopkins specialty clinics between October 2004 and September 2018. As per previous protocols,⁶ study participants underwent venipuncture and completed a written questionnaire (including urticaria severity score for current symptoms and with flares and the SkinDex-29 dermatology quality-of-life index) at each study visit, with baseline visit data presented here.^{7,8} Detailed methods for basophil HR and BAT assays are described in the Methods section of this article's Online Repository at www.jaci-inpractice.org.

Of the 182 subjects recruited, 159 provided adequate blood samples for basophil functional phenotyping using HR, with 71 (45%) classified as basophil responders, 55 (35%) as nonresponders, and 33 (21%) as basopenics (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Age, gender, and race were similar among groups. In a subset ($n = 33$) of subjects enrolled since June 2016, analysis of BAT using CD63 (% gated, mean, median) was compared with basophil functional classification using HR (%HR) profiling in

TABLE I. BAT threshold to correctly identify basophil responder (vs nonresponder) phenotype, using classification by % histamine release as the reference standard

Anti-IgE concentration ($\mu\text{g/mL}$)	BAT (% gated) threshold	Sensitivity	Specificity
0.1	≥ 13 is responder	94.7%	100%
	< 13 is nonresponder		
	≥ 11 is responder	100%	75%
	< 11 is nonresponder		
0.01	≥ 6 is responder	100%	100%
	< 6 is nonresponder		
1	≥ 17 is responder	79.0%	50%
	< 17 is nonresponder		
	≥ 18 is responder	79.0%	75%
	< 18 is nonresponder		
	≥ 28 is responder	63.2%	100%
	< 28 is nonresponder		

BAT, Basophil activation test.

19 (58%) responders, 4 (12%) nonresponders, and 10 (30%) basopenics. Percent-gated CD63 BAT demonstrated the best correlation with HR results with 0.1 $\mu\text{g/mL}$ anti-IgE stimulation ($R^2 = 0.7812$, $P < .0001$; Figure E1, A, available in this article's Online Repository at www.jaci-inpractice.org) and with 0.01 $\mu\text{g/mL}$ anti-IgE stimulation ($R^2 = 0.8050$, $P < .0001$; Figure E1, B, available in this article's Online Repository at www.jaci-inpractice.org). In contrast, a correlation between BAT and HR by all measures was poor with 1 $\mu\text{g/mL}$ anti-IgE stimulation (Figure E1, C, available in this article's Online Repository at www.jaci-inpractice.org).

With classification by HR as the reference standard, we also determined the frequency of proper classification of basophil functional phenotype using the BAT (Table I). With 0.1 $\mu\text{g/mL}$ anti-IgE stimulation, a cutoff value $\geq 13\%$ CD63-gated BAT was 94.7% sensitive and 100% specific for the basophil responder phenotype. With 0.01 $\mu\text{g/mL}$ anti-IgE stimulation, a cutoff value $\geq 6\%$ CD63-gated BAT was 100% sensitive and specific. No cutoff value at 1 $\mu\text{g/mL}$ anti-IgE stimulation achieved sensitivity and specificity greater than 80%.

With regard to clinical parameters, similar quality-of-life impairment as assessed by the total SkinDex-29 score was noted in basopenics, responders, and nonresponders (Table II). However, the mean of the "Emotional" domain was significantly higher for basopenics (29.6) compared with 24.1 for responders ($P = .036$) and 25.3 for nonresponders ($P = .041$). The difference between basopenics and nonresponders remained significant adjusting for confounders (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Basophil responders were more likely to have longer disease duration, with only 23.9% noting disease duration between 6 months and 2 years as compared with 48.5% of basopenics ($P = .012$) and 47.3% of nonresponders ($P = .0062$) (Table II). Adjusted odds of having shorter disease duration was 3.3 for nonresponders (95% confidence interval [CI]: 1.5, 7.5; $P = .004$) and 3.7 for basopenics (95% CI: 1.4, 9.6; $P = .007$) relative to responders

TABLE II. Survey characteristics[†], by functional basophil type

Survey characteristic	Basopenic (n = 33)	Responder (n = 71)	Nonresponder (n = 55)	P value ^{‡§}
Total SkinDex-29 score, mean (SE)	76.1 (4.8)	65.2 (3.0)	66.4 (3.3)	.13
SkinDex-29 symptom components, mean (SE)	19.3 (1.0)	17.1 (0.7)	17.0 (0.8)	.14
SkinDex-29 functional components, mean (SE)	28.2 (2.1)	23.9 (1.2)	25.3 (1.3)	.17
SkinDex-29 emotional components, mean (SE)	29.6 (10.8)	24.1 (10.0)	24.0 (9.0)	.024
				.041*
				.036**
				1.0***
Years of urticaria since first episode, n (%)				.044
6 mo to 2 y	16 (48.5)	17 (23.9)	26 (47.3)	.91*
Between 2 and 4 y	3 (9.1)	13 (18.3)	7 (12.7)	.012**
4 or more y	14 (42.4)	41 (57.8)	22 (40.0)	.0062***
Steroid tapers in the past year, n (%)				.012
0	8 (24.2)	37 (52.9)	18 (34.0)	.34*
1 or more	25 (75.8)	33 (47.1)	35 (66.0)	.0063**
				.047***
Steroid tapers in lifetime, n (%)				.45
0	4 (12.5)	16 (23.5)	12 (21.8)	
1 or more	28 (87.5)	52 (76.5)	43 (78.2)	
Average score for number/size of current hives, mean (SE)	1.52 (0.23)	0.75 (0.11)	0.65 (0.12)	<.001
				.001*
				.002**
				1.0***
Average score for number/size of hives during flares, mean (SE)	2.91 (0.19)	2.55 (0.15)	2.72 (0.15)	.32
Current itch, mean (SD)	3.33 (0.54)	2.23 (0.32)	1.30 (0.27)	.002
				.001*
				.12**
				.14***
Itch during flare, mean (SD)	9.50 (0.22)	8.48 (0.27)	9.13 (0.26)	.035
				1.0*
				.050**
				.21***
Wheal locations during flare, mean (SD)	4.85 (0.29)	4.39 (0.20)	4.48 (0.23)	.44
Wheal duration during flare, n (%)				
Less than 1 h	1 (3.0)	8 (11.4)	4 (7.4)	.32
1-24 h	23 (69.7)	34 (48.6)	28 (51.9)	
Longer than 24 h	9 (27.3)	28 (40.0)	22 (40.7)	

SD, Standard deviation; SE, standard error.

*Indicates P value for basopenics vs nonresponders in subcomparisons.

**Indicates P value for basopenics vs responders in subcomparisons.

***Indicates P value for responders vs nonresponders in subcomparisons.

†Assessed for patients with available data (missing not shown).

‡Overall P value comparing the 3 groups is the first value displayed.

§Bolded data indicate values used for subcomparisons between pairs of groups.

(Table E2). More basopenics (75.8%) and nonresponders (66.0%) required steroid taper(s) in the last year, compared with responders (47.1%) ($P = .0063$ and $P = .047$, respectively) (Table II). The mean number/size of current hives was highest for basopenics (1.52) compared with nonresponders (0.75) and responders (0.65) ($P < .001$). The mean current itch score was also highest for basopenics (3.33), compared with responders (2.23) and nonresponders (1.30) ($P = .002$). Finally, itch score during flares was again highest for basopenics (9.50) compared with responders (8.48) and nonresponders (9.13) ($P = .035$). Other clinical characteristics were similar between groups

(Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Strengthening previous findings, many CSU disease severity measures tracked with basopenia in our study. Specifically, basopenics reported greater use of steroid tapers in the last year, greatest current hive/itch scores and itch during flares, and highest score on the SkinDex-29 emotional component. Taken together, blood basopenia may indicate a more severe phase of disease with increased recruitment of basophils to the skin that may contribute to disease symptoms.⁵ Consistent with this theory, patients with CSU who experience clinical improvement

with omalizumab also demonstrate a dose-related rise in blood basophil count.⁹

We also examined an alternate method for basophil functional phenotyping and found a strong correlation between HR and % gated CD63 BAT at lower anti-IgE stimulation concentrations (0.01 and 0.1 µg/mL), which has not been previously reported.¹ However, at a higher anti-IgE concentration (1 µg/mL), the correlation was poor. This is likely because at supraoptimal concentrations of anti-IgE stimulation, HR decreases whereas the dose response plateaus in BAT. Although BAT may be used for CSU basophil functional classification, direct measurement of HR should first be conducted in a limited sample to assure a correlation between both anti-IgE dose response curves.

In addition, the basophil responder phenotype was associated with longer disease duration although responders may carry less disease burden than basopenics. Prolonged disease duration in responders is consistent with Baker et al's 2009 study,⁶ but our remaining findings were not previously observed. This may be explained by the small sample size ($n = 50$) of the previous study. Although the present study has increased power overall, limitations remain. First, the sample size for BAT versus HR release was limited ($n = 33$) and results should be replicated with a larger cohort. In addition, patient-reported survey characteristics may be subject to recall bias. The predominance of highly educated Caucasian patients recruited from an urban, tertiary care center may limit study generalizability. Lastly, data from the baseline study visit are reported here. Future work will include longitudinal analysis to correlate basophil functional measures with disease evolution in CSU.

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advisory board member for Genentech, Novartis, Medimmune, AstraZeneca, Pfizer, Allakos, Eli Lilly, and Gossamer Bio. The rest of the authors declare that they have no relevant conflicts of interest.

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ONLINE REPOSITORY

METHODS

Patient recruitment

Exclusion criteria included the use of systemic corticosteroids, cyclosporine, or sulfasalazine in the last month or diagnosis of concomitant urticarial vasculitis, atopic dermatitis, or physical urticaria.

Basophil histamine release (HR) assay

Density gradient sedimentation (single Percoll density centrifugation) was used to isolate blood basophils of patients from venous blood samples.^{E1,E2} Polyclonal goat antihuman IgE (0.001–1.0 µg/mL; DACI Lab, Baltimore, Md) was used in duplicate to stimulate basophils for HR in calcium-containing buffers and measured using automated fluorometry. In addition, basophils were stimulated using N-formyl-met-leu-phe (fMLP) (10^{-6} M) as a positive control for basophil degranulation as it is an independent pathway typically preserved in patients with chronic spontaneous urticaria (CSU).^{E2,E3} Supernatants were collected and analyzed via automated fluorimetry. Results are presented as the percentages of total histamine content of total cell lysates of leukocyte aliquots after spontaneous HR was subtracted. Total histamine content was defined as total histamine content released from lysed leukocytes derived from 1 mL of whole blood minus the basal level of histamine released spontaneously by basophils without stimulus (ie, in buffer). Per previously optimized protocol, HR levels to 0.1 µg/mL concentration of IgE were used to classify basophil functional phenotypes. Patients with HR $\geq 10\%$ of total histamine content were categorized as “responders,” whereas those with response $< 10\%$ were categorized as “nonresponders.”^{E2} Patients with histamine concentrations < 5 ng/mL blood leukocytes were classified as “basopenics.” Evidence of a strong correlation between blood histamine content and independent verification of basophil numbers by flow cytometry and enumeration has been shown.^{E4,E5}

Basophil activation test (BAT)

At the time of blood sampling for basophil HR, blood samples were also collected in parallel into heparinized tubes (BD vacutainer, San Jose, Calif) for flow studies. Heparinized blood was immediately incubated with either buffer alone or identical doses of anti-IgE antibody or fMLP for 30 minutes at 37°C. Samples were then washed and labeled with CD123 APC (Thermo Fisher Scientific, Grand Island, NY) and either CCR3 PE (Thermo Fisher Scientific) or CD63 PE (Beckman Coulter, Atlanta, Ga). Cells were subsequently lysed and fixed (Beckman Coulter) and then analyzed on a BD FACS Calibur flow cytometer. Basophils were gated using CCR3+, CD123+ cell subset and results expressed as both net mean fluorescence intensity and % positive relative to buffer.^{E6} Exogenous IL-3 was not added to the BAT assay buffers, in contrast to the Rauber et al^{E3} study, in order to maintain consistent conditions between the HR results and BAT results.

Written questionnaire

A 3-part survey was administered to patients on the same visit as their venipuncture.^{E1} Part 1 included demographic variables, CSU disease duration, family history of CSU, medication usage, as well as CSU-related work/school

absenteeism and hospital/emergency department (ED) visits. Part 2 was the urticaria severity score, an instrument used in previous studies of CSU to quantify wheal size and number and itching in the present time and during flares.^{E7,E8} Systemic symptoms during flares were queried, with 4 classified as being related to anaphylaxis: gastrointestinal, wheezing, palpitations, and flushing. Part 3 was the SkinDex-29 questionnaire, a validated dermatology instrument for assessing the impact of skin disease on quality of life in the past 3 months.^{E9}

Statistical analysis

Groups' means were compared using the analysis of variance test, whereas proportions of categorical variables were compared using the χ^2 test and Fisher's exact test. For results showing significant differences, *post hoc* pairwise comparisons were conducted using the Bonferroni method. Multivariable linear/logistic regression was used to adjust for potential confounders. A correlation between %HR and the BAT was assessed by linear regression. Various threshold values were tested to determine the sensitivity and specificity of BAT in identifying basophil phenotypes, with classification by %HR as the reference standard. All analyses were performed in Stata/IC 15.1 (StataCorp, College Station, Tex).

Results (Tables E1 and E3)

Clinical demographics were similar among groups (Table E1). By definition, histamine concentration per 1 mL blood leukocytes was different among the 3 groups ($P < .001$) and anti-IgE HR was higher in responders compared with nonresponders ($P < .001$). In contrast to previous studies^{E1} with smaller samples, lower fMLP HR was reported in nonresponders (29.5) compared with responders (39.6) ($P = .008$).

Mean scores for “Symptom” and “Functional” domains of the SkinDex-29 were similar between groups ($P = .14$ and $P = .17$, respectively) (Table E3). Absent days due to urticaria in the past year and lifetime were not different ($P = .43$ and $P = .87$, respectively). Frequency of hospital/ED visits for urticaria in the past year and lifetime were also not different ($P = .47$ and $P = 1.0$, respectively). No differences were seen between groups in the proportions of patients with positive personal history of allergic comorbidities ($P = .15$) or in the proportions of patients with positive family history, with roughly 15% positive in all groups ($P = 1.0$). No differences were seen among groups in any of the other (ie, nonsteroidal) medications taken for urticaria, either currently or lifetime. Lifetime requirements for one or more steroid tapers were similar ($P = .45$). The mean score of the number and size of hives during flares and the mean number of wheal locations during flares were not significantly different among groups ($P = .32$ and $P = .44$, respectively). Durations of urticarial wheals during flares were similar ($P = .32$). The mean number of systemic symptoms during a flare was not significantly different among the other groups ($P = .52$). Similarly, the mean number of anaphylaxis-type symptoms (gastrointestinal, wheezing, palpitations, flushing) was not significantly different from other groups ($P = .52$). Proportions of each of the 4 symptoms of anaphylaxis were also not different between groups ($P > .05$). In all groups, flushing was the most common anaphylaxis-associated symptom, whereas palpitations were the least common.

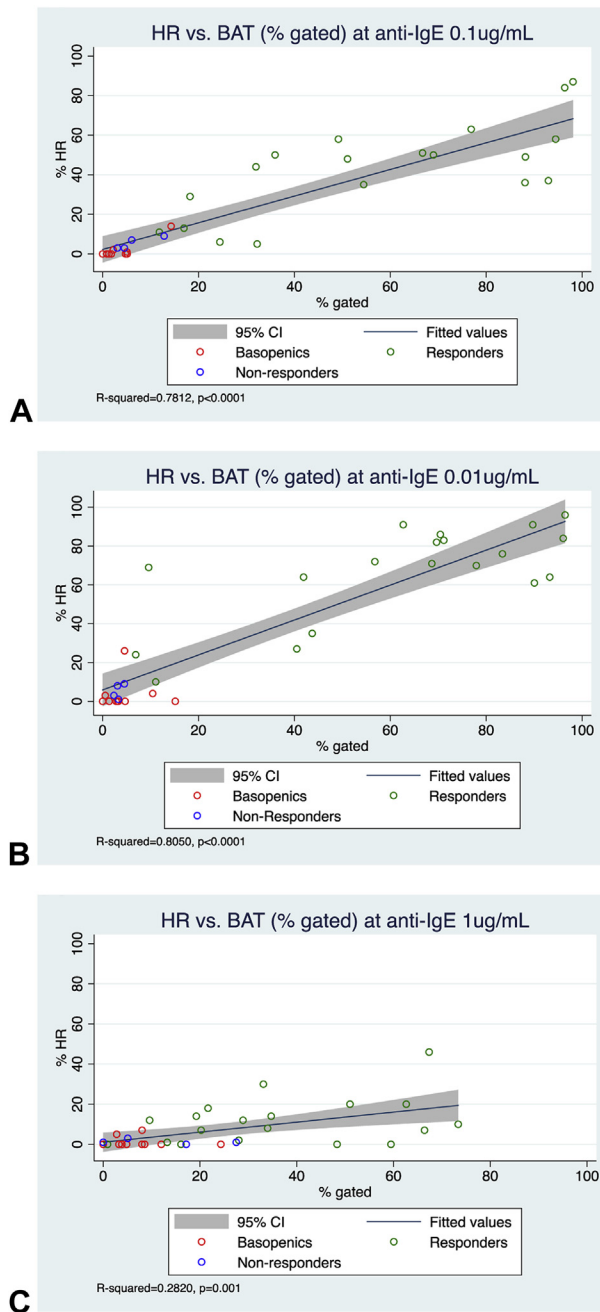


FIGURE E1. Percent histamine release (HR) versus basophil activation test (BAT), at various concentrations of anti-IgE stimuli. **A**, Gold standard for HR: anti-IgE 0.1 μ g/mL. **B**, Lower concentration: anti-IgE 0.01 μ g/mL. **C**, Higher concentration: anti-IgE 1 μ g/mL. *CI*, Confidence interval.

TABLE E1. Demographics and basophil functional characteristic

Characteristic	Basopenic (n = 33)	Responder (n = 71)	Nonresponder (n = 55)	P value
Age (y), mean (SE)	41.3 (2.2)	44.1 (1.7)	43.7 (1.8)	.607
Gender, n (%)				.419
Male	10 (30.3)	23 (32.4)	12 (21.8)	
Female	23 (69.7)	48 (67.6)	43 (78.2)	
Race, n (%)				
White/Caucasian	25 (75.8)	53 (74.7)	46 (83.6)	.885
Black/African American	6 (18.2)	8 (11.3)	5 (9.1)	
East Asian/Pacific Islander	0 (0)	1 (1.4)	1 (1.8)	
American Indian	0 (0)	0 (0)	0 (0)	
Hispanic/Latino Origin	1 (3.0)	3 (4.2)	1 (1.8)	
South Asian (Indian, etc.)	0 (0)	2 (2.8)	1 (1.8)	
Other	0 (0)	2 (2.8)	0 (0)	
Multiethnicity	1 (3.0)	2 (2.8)	1 (1.8)	
Education level, n (%)				.153
8th grade or less	0 (0)	0 (0)	0 (0)	
Any high school	0 (16.4)	10 (14.3)	9 (16.4)	
Any college graduate	24 (43.6)	37 (52.9)	24 (43.6)	
Any postgraduate	22 (40.0)	23 (32.9)	22 (40.0)	
Missing	0 (0)	1 (1.4)	0 (0)	
Histamine concentration, ng/1 mL blood leukocytes, mean (SE)	1.7 (0.2)	28.9 (1.8)	25.7 (2.3)*	<.001
Anti-IgE (0.1 µg/mL), % histamine release, mean (SE)	—	45.0 (2.7)	2.2 (0.4)	<.001
fMLP (10^{-6} M), % histamine release, mean (SE)	—	39.6 (2.6)*	29.5 (2.6)	.008

fMLP, N-Formyl-met-leu-phe; SE, standard error.

Bold indicates statistical significance ($P < .05$).

*Missing 1.

TABLE E2. Multivariable regression models adjusting for potential confounders

Characteristic	Unadjusted mean	Unadjusted <i>P</i> value	Adjusted mean*	Adjusted <i>P</i> value*		
SkinDex: emotional component						
Basopenic	(Ref.)		(Ref.)			
Nonresponder	−5.6	.014	−4.5	.046		
Responder	−5.5	.012	−4.4	.050		
Average score for number/size of current hives						
Basopenic	(Ref.)		(Ref.)			
Nonresponder	−0.87	<.001	−0.79	.001		
Responder	−0.77	.001	−0.74	.002		
Current itch						
Basopenic	(Ref.)		(Ref.)			
Nonresponder	−2.0	<.001	−1.8	.002		
Responder	−1.1	.041	−1.0	.072		
Itch during flare						
Basopenic	(Ref.)		(Ref.)			
Nonresponder	−0.37	.404	−0.50	.268		
Responder	−1.02	.017	−1.02	.020		
Characteristic	Unadjusted OR	95% CI	<i>P</i> value	Adjusted OR*	95% CI	<i>P</i> value
Disease duration <2 y						
Responder	(Ref.)			(Ref.)		
Nonresponder	2.8	(1.3, 6.1)	.007	3.3	(1.5, 7.5)	.004
Basopenic	3.0	(1.2, 7.2)	.014	3.7	(1.4, 9.6)	.007
One or more steroid tapers in the last year						
Responder	(Ref.)			(Ref.)		
Nonresponder	2.2	(1.04, 4.5)	.038	2.2	(1.02, 4.9)	.045
Basopenic	3.5	(1.4, 8.8)	.008	3.7	(1.4, 10.0)	.011

CI, Confidence interval; OR, odds ratio.

Bold indicates statistical significance ($P < .05$).

*Adjusted for age, gender, race, and education.

TABLE E3. Survey characteristics†, by functional basophil type

Survey characteristic, n (%)	Basopenic (n = 33)	Responder (n = 71)	Nonresponder (n = 55)	P value‡
Absent days in the past year, n (%)				.43
None	14 (42.4)	37 (53.6)	23 (43.4)	
1 or more	19 (57.6)	32 (46.4)	30 (56.6)	
Absent days in lifetime, n (%)				.87
None	9 (27.3)	19 (28.8)	17 (32.7)	
1 or more	24 (72.7)	47 (71.2)	35 (67.3)	
Hospital/ED visits in the past year, n (%)				.47
None	20 (60.6)	50 (70.4)	34 (61.8)	
1 or more	13 (39.4)	21 (29.6)	21 (38.2)	
Hospital/ED visits in lifetime, n (%)				1.0
None	14 (42.4)	29 (42.0)	24 (43.6)	
1 or more	19 (57.6)	40 (58.0)	31 (56.4)	
Medications ever taken for urticaria, n (%)				
Antihistamine	33 (100)	69 (97.2)	55 (100.0)	.69
Steroids	28 (84.9)	53 (74.7)	40 (72.7)	.42
Leukotrienes	16 (48.5)	27 (38.0)	31 (56.4)	.12
Dapsone	3 (9.1)	4 (5.6)	4 (7.3)	.79
Colchicine	0 (0)	1 (1.4)	3 (5.5)	.27
Sulfasalazine	3 (9.1)	16 (22.5)	8 (14.6)	.22
Antidepressants	19 (57.6)	28 (39.4)	30 (54.6)	.12
Thyroid medications	8 (24.2)	8 (11.3)	12 (21.8)	.15
Stomach acid medications	18 (62.1)	35 (60.3)	31 (70.5)	.58
Current medications for urticaria, n (%)				
Antihistamine	26 (89.7)	50 (86.2)	35 (79.6)	.47
Steroids	5 (17.2)	10 (17.2)	3 (6.8)	.25
Leukotrienes	7 (24.1)	7 (12.1)	14 (31.8)	.044
Dapsone	1 (3.5)	2 (3.5)	0 (0)	.45
Colchicine	0 (0)	0 (0)	0 (0)	—
Sulfasalazine	2 (6.9)	7 (12.1)	5 (11.4)	.87
Antidepressants	8 (27.6)	9 (15.5)	11 (25.0)	.35
Thyroid medications	1 (3.5)	5 (8.6)	9 (20.5)	.078
Stomach acid medications	6 (20.7)	14 (24.1)	16 (36.4)	.26
Family history, n (%)				
Yes	5 (15.2)	11 (15.7)	8 (14.8)	1.0
Other allergic diseases, n (%)				
Yes	4 (20.0)	18 (43.9)	9 (29.0)	.15
Systemic symptoms during flare, mean (SD)	1.82 (0.27)	1.77 (0.22)	1.46 (0.21)	.52
No. of anaphylaxis symptoms, mean (SE)	0.82 (0.13)	0.77 (0.13)	0.59 (0.10)	.44
Endorses GI symptoms, n (%)	5 (15.2)	14 (19.7)	7 (13.0)	.60
Endorses wheezing, n (%)	10 (30.3)	13 (18.3)	7 (13.0)	.14
Endorses palpitations, n (%)	1 (3.0)	8 (11.3)	2 (3.7)	.25
Endorses flushing, n (%)	11 (33.3)	20 (28.2)	16 (30.0)	.88

ED, Emergency department; GI, gastrointestinal; SD, standard deviation; SE, standard error.

†Assessed for patients with available data (missing not shown).

‡Overall P value comparing the 3 groups.

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