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

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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 in active CSU compared to controls, with basophil hypo-responsiveness improving in disease remission.[2,3,4] 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 al[6] with analysis of basophil parameters in patients with CSU using a larger, expanded cohort including the initial participants. We also include a sub-cohort for studies comparing histamine release (HR) and the basophil activation test (BAT) for functional phenotyping.

Study approval was granted by the Johns Hopkins University IRB. 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 histamine release (HR) and basophil activation test (BAT) assays are in the Online Repository text.

Of the 182 subjects recruited, 159 provided adequate blood samples for basophil functional phenotyping using histamine release with 71 (45%) classified as basophil responders, 55 (35%) as non-responders, and 33 (21%) as basopenics (Table E1). 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 to basophil functional classification using histamine release (%HR) profiling in 19 (58%) responders, 4 (12%) non-

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responders and 10 (30%) basopenics. Percent gated CD63 BAT demonstrated the best correlation with HR results with 0.1ug/mL anti-IgE stimulation (R^2= 0.7812, p<0.0001, Figure E1a) and with 0.01ug/mL anti-IgE stimulation (R^2= 0.8050, p<0.0001, Figure E1b). In contrast, correlation between BAT and HR by all measures was poor with 1ug/mL anti-IgE stimulation (Figure E1c).

With classification by HR as the reference standard, we also determined the frequency of proper classification of basophil functional phenotype using the BAT (Table 1). With 0.1ug/mL anti-IgE stimulation, a cut-off value ≥13 %CD63 gated BAT was 94.7% sensitive and 100% specific for the basophil responder phenotype. With 0.01ug/mL anti-IgE stimulation, a cut-off value ≥6 %CD63 gated BAT was 100% sensitive and specific. No cut-off value at 1ug/mL anti-IgE stimulation achieved sensitivity or specificity greater than 80%.

With regards to clinical parameters, similar quality-of-life impairment as assessed by total SkinDex-29 score was noted in basopenics, responders, and non-responders (Table 2). Mean of the “Emotional” domain was significantly higher for basopenics (29.6) compared to 24.1 for responders (p=0.036) and 25.3 for non-responders (p=0.041). The difference between basopenics and non-responders remained significant adjusting for confounders (Table E2). 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 to 48.5% of basopenics (p=0.012) and 47.3% of non-responders (p=0.0062) (Table 2). Adjusted odds of having shorter disease duration was 3.3 for non-responders (95% CI: 1.5, 7.5, p=0.004) and 3.7 for basopenics (95% CI: 1.4, 9.6, p=0.007) relative to responders, respectively (Table E2). More basopenics (75.8%) and non-responders (66.0%) required steroid taper(s) in the last year, compared to responders (47.1%) (p=0.0063 and p=0.047, respectively) (Table 2). Mean number/size of current hives was highest for basopenics (1.52) compared to non-responders (0.75) and to responders (0.65) (p<0.001). Mean current itch score was also highest for basopenics (3.33), compared to responders (2.23) and non-responders (1.30) (p=0.002). Finally, itch score during flares was again highest for basopenics (9.50) compared to responders (8.48) and non-responders (9.13) (p=0.035). Other clinical characteristics were similar between groups (Table E3).

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-response rise in blood basophil count.[9]

We also examined an alternate method for basophil functional phenotyping and found strong correlation between HR and %gated CD63 BAT at lower anti-IgE stimulation concentrations (0.01 and 0.1ug/mL), which has not been previously reported.[1] However, at higher anti-IgE concentration (1ug/mL), correlation was poor. This is likely because HR decreases while the dose response plateaus in BAT at supra-optimal concentrations of anti-IgE stimulation.

While BAT may be used for CSU basophil functional classification, direct measurement of HR should first be conducted in a limited sample to assure correlation of both anti-IgE dose response curves.

In addition, 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, but our remaining findings were not previously observed.[6] This may be explained by the small sample size (n=50) of the previous study. While the present study has increased power overall, limitations remain. First, the sample size for BAT vs. 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 is reported here. Future work will include longitudinal analysis to correlate basophil functional measures with disease evolution in CSU.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

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Clinical Implications

- In CSU, basopenia was associated with more severe disease while 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.

Table 1.

BAT threshold to correctly identify basophil responder (vs. non-responder) phenotype, using classification by % histamine release as gold standard

Anti-IgE concentration (ug/mL)	BAT (% gated) threshold	Sensitivity	Specificity
0.1	>=13 is responder <13 is non-responder	94.7%	100%
	>=11 is responder <11 is non-responder	100%	75%
0.01	>=6 is responder <6 is non-responder	100%	100%
1	>=17 is responder <17 is non-responder	79.0%	50%
	>=18 is responder <18 is non-responder	79.0%	75%
	>=28 is responder <28 is non-responder	63.2%	100%

Table 2.

Survey Characteristics[1], by functional basophil type

Survey Characteristic	Basopenic (n=33)	Responder (n=71)	Non-Responder (n=55)	p-value[2,3]
Total SkinDex-29 Score,				
Mean (SE)	76.1 (4.8)	65.2 (3.0)	66.4 (3.3)	0.13
SkinDex-29 Symptom Components,				
Mean (SE)	19.3 (1.0)	17.1 (0.7)	17.0 (0.8)	0.14
SkinDex-29 Functional Components,				
Mean (SE)	28.2 (2.1)	23.9 (1.2)	25.3 (1.3)	0.17
SkinDex-29 Emotional Components,				**0.024**
Mean (SE)	29.6 (10.8)	24.1 (10.0)	24.0 (9.0)	*__0.041__ **__0.036__ ***__1.0__
Years of Urticaria since first episode, n(%)				**0.044**
6 months to 2 years Between 2 to 4 years 4 or more years	**16 (48.5)** 3 (9.1) 14 (42.4)	**17 (23.9)** 13 (18.3) 41 (57.8)	**26 (47.3)** 7 (12.7) 22 (40.0)	*0.91 **__0.012__ ***__0.0062__
Steroid Tapers in Past Year, n (%)				**0.012**
0	8 (24.2)	37 (52.9)	18 (34.0)	*0.34
1 or more	**25 (75.8)**	**33 (47.1)**	**35 (66.0)**	**__0.0063__ ***__0.047__
Steroid Tapers in Lifetime, n (%)	4 (12.5)	16 (23.5)	12 (21.8)	
0 1 or more	28 (87.5)	52 (76.5)	43 (78.2)	0.45
Average score for number/size of current hives,				**<0.001**
Mean (SE)	1.52 (0.23)	0.75 (0.11)	0.65 (0.12)	*__0.001__ **__0.002__ ***__1.0__
Average score for number/size of hives durina flares, Mean (SE)	2.91 (0.19)	2.55 (0.15)	2.72 (0.15)	0.32
Current itch,				**0.002**
Mean (SD)	3.33 (0.54)	2.23 (0.32)	1.30 (0.27)	*__0.001__ **__0.12__ ***__0.14__
Itch during flare,				**0.035**
Mean (SD)	9.50 (0.22)	8.48 (0.27)	9.13 (0.26)	*1.0 **__0.050__ ***__0.21__
Wheal locations during flare,				
Mean (SD)	4.85 (0.29)	4.39 (0.20)	4.48 (0.23)	0.44
Wheal duration during flare, n (%)				
Less than 1 hour	1 (3.0)	8 (11.4)	4 (7.4)	0.32

Survey Characteristic	Basopenic (n=33)	Responder (n=71)	Non-Responder (n=55)	p-value[2,3]
1–24 hours	23 (69.7)	34 (48.6)	28 (51.9)	
Longer than 24 hours	9 (27.3)	28 (40.0)	22 (40.7)	

[1] Assessed for patients with available data (missing not shown).

[2] Overall p-value comparing the three groups is the first value displayed.

[3] Bolded data indicate values used for sub-comparisons between pairs of groups.

* indicates p-value for basopenics vs. non-responders in sub-comparisons.

** indicates p-value for basopenics vs. responders in sub-comparisons.

*** indicates p-value for responders vs. non-responders in sub-comparisons.