

BRIEF COMMUNICATION

Interval shifts in basophil measures correlate with disease activity in chronic spontaneous urticaria

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Abstract

Chronic spontaneous urticaria (CSU) significantly impacts the quality of life of those affected through symptoms of pruritus and recurrent skin lesions. In active CSU disease, reduced IgE-mediated basophil histamine release (HR) and basopenia are observed. We sought to examine the relationship between interval changes in basophil measures and shifts in patient-reported disease impairment. Simultaneous symptom and basophil evaluations were completed at two sequential study visits, and interval changes in measures were compared between visits for each subject ($n = 38$). These measures included Skindex-29, current itch and hives scores, total leukocyte histamine content (an indirect measure of blood basophil presence), and basophil HR in response to anti-IgE and formyl-methionine-leucine-phenylalanine. Overall, interval improvements in disease measures in CSU subjects were associated with increased basophil numbers (total leukocyte histamine content) and IgE-mediated HR. This suggests these measures are potential biomarkers for CSU disease improvement and further implicates a role for basophils in CSU.

Chronic spontaneous urticaria (CSU) impairs the quality of life of those affected through symptoms of pruritus and recurrent skin lesions (1). In active CSU disease, reduced IgE-mediated basophil histamine release (HR) and basopenia are observed (2–5), and these features improve during disease remission (4, 6). Based on the observations of altered basophil phenotypes in CSU, we explored the relationship between interval shifts in blood basophil measures relative to changes in disease activity measures.

Material and methods

Adults with active CSU (ages 18–75) were recruited into an IRB-approved observational study between 2004 and 2012 at the Johns Hopkins Asthma and Allergy Center (6, 7). Following informed consent, each participant completed a disease activity survey and underwent venipuncture during a routine clinic visit. Individuals who participated in this observational study on two visits were included (Fig. S1). Individuals on antihistamines and leukotriene receptor antagonists were included, but those taking sulfasalazine, mycophenolate, cyclosporine, omalizumab, dapsone, or recent corticosteroids were excluded due to their potential impact on basophil measures (8–11). Subjects in disease remission, defined as no

symptoms and no urticaria-directed medications for 2 months, were also allowed to participate if they had a previous visit during active disease.

Assessments of CSU disease activity included reports of current itch, current hives, and Skindex-29 (7). The Skindex-29 is a quality-of-life instrument utilized to assess the impact of skin diseases on the quality of life in three domains: physical, emotional, and functional symptoms (range 29–145, 29 = no impairment). Itch was reported on a 10-point visual analog scale, with 0 meaning absence of itch and 10 meaning the maximum itch possible. Hives were reported on a 4-point scale (0 = no hives, 1 = 1–10 small hives [<3 cm], 2 = 10–50 small hives or 1–10 large hives, 3 = >50 small hives or 10–50 large hives, 4 = covered with hives). Both itch and hive scores reflected current symptoms at the time of the study visit.

Basophil studies were performed as previously described (6, 11) and included the following: total blood leukocyte histamine content (TLHC)—an indirect measure of blood basophil number and presence (12); HR in response to 0.01–1 μ g/ml polyclonal goat anti-human IgE (DACI Lab; Baltimore, MD, USA) and 1 μ mol formyl-methionine-leucine-phenylalanine (fMLP; Sigma-Aldrich, St. Louis, MO, USA); and spontaneous HR.

Table 1 Chronic spontaneous urticaria subject characteristics at time of enrolment visit ($n = 38$)

Age (median years, range)	43.55 (21.57–71.8)
Female (%)	68.4
Race/Ethnicity (%)	
Caucasian	78.9
African American	13.2
East Asian	2.6
Hispanic	2.6
South Asian	2.6
Other	2.6
Medication Utilization ($n = 23$, %)	
Antihistamines (H1 ± H2)	100
Leukotriene Receptor Antagonists	0
Tricyclic Antidepressants	30.4
Thyroid Replacement Therapy	8.7
Disease Survey Scores (mean, range)	
Skindex-29	67.3 (29–123)
Current Itch	2.2 (0–10)
Current Hives	0.9 (0–4)
Baseline cellular data	
Spontaneous Histamine Release (median %, range)	4.0 (0.7–78.8)
Total Leukocyte Histamine Content (median ng/ml, range)	23.98 (0.48–76.75)

Interval changes in disease activity and basophil measures between two sequential visits were compared. Prism version 4.00 was utilized for statistical analysis. A Spearman's rank order correlation test was used for the analysis of interval changes in subjective assessment and basophil measures. A Wilcoxon signed-rank test was used for comparisons between active and remission groups. A P -value of <0.05 was considered significant.

Results

Thirty-eight CSU subjects meeting criteria were analyzed (Fig. S1). Subject baseline characteristics are detailed (Table 1). The median time interval between the two study visits was 204 days. The average Skindex-29 score at entry was 67.3 ± 25.1 , supporting a significant impairment in quality of life. At the baseline visit, itch was 2.2 ± 2.8 on a 10-point scale, and baseline hives were 0.9 ± 1.1 on a 4-point scale.

In our analysis (Table 2), a net interval reduction in disease impairment, as measured by the Skindex-29, was inversely correlated with an interval rise of *in vitro* basophil HR in response to $0.1 \mu\text{g/ml}$ anti-IgE (Spearman's $\rho [r_s] = -0.4185$, $P = 0.0089$). This dose of anti-IgE has been demonstrated to be the optimal dose for IgE-mediated basophil HR in previous studies (13). There was no significant correlation between IgE-mediated basophil HR and shifts in measures of current hives or itch. In contrast, interval increases in TLHC, a measure of basophil number and presence in the bloodstream, were inversely correlated with interval reductions in both hives ($r_s = -0.3980$, $P = 0.0133$) and itch scores ($r_s = -0.3894$, $P = 0.0157$), but not with Skindex-29. Spontaneous HR and fMLP-mediated basophil HR were not correlated with changes in Skindex-29, hive, or itch scores.

During the study, a subset of six subjects entered remission (Fig. S2). Basophil HR was higher in remission than in active disease in response to $0.1 \mu\text{g/ml}$ anti-IgE ($37.7 \pm 28.3\%$ vs $4.7 \pm 5.1\%$, $P = 0.0313$). The mean TLHC trended higher in remission for these six subjects ($28.32 \pm 8.9 \text{ ng/ml}$ vs $17.6 \pm 17.9 \text{ ng/ml}$, $P = 0.16$). There was no significant difference between fMLP-mediated HR in remission compared to active disease ($23.67 \pm 13.0\%$ vs $22.8 \pm 12.5\%$), or in spontaneous HR ($3.85 \pm 4.0\%$ vs $5.3 \pm 3.1\%$).

Discussion

It is well recognized that IgE-mediated basophil HR is reduced during active CSU (4, 11, 13–15); however, the relationship between this measure and disease activity is less clear. In this study, interval increases in IgE-mediated basophil HR were correlated with reductions in patient-reported disease impairment as measured by Skindex-29. Consistent with past studies, subjects who entered full disease remission also had an increase in IgE-mediated basophil HR (6). The mechanism behind reduced IgE receptor basophil responsiveness in active CSU remains unknown. Altered protein levels of Src-homology 2-containing inositol phosphatases (SHIPs), which regulate IgE receptor signaling, have been reported in the basophils of active CSU subjects (11).

Past studies have described basopenia as a unique feature of active CSU (2–4, 6), and increased blood basophil counts have been noted in relation to improving disease activity scores (8). We found that interval increases in blood basophil

Table 2 Comparison of symptoms to basophil measures (38 visit comparisons)

Symptom outcomes	Stimulated histamine release ($0.01\text{--}1 \mu\text{g/ml}$ anti-IgE or fMLP)				Spontaneous histamine release	Total leukocyte histamine content
	$0.01 \mu\text{g/ml}$	$0.1 \mu\text{g/ml}$	$1 \mu\text{g/ml}$	fMLP		
Skindex-29	$r_s = -0.2368$ $P = 0.1523$	$r_s = -0.4185$ $P = 0.0089$	$r_s = -0.2896$ $P = 0.0821$	$r_s = -0.2475$ $P = 0.1398$	$r_s = -0.0732$ $P = 0.6623$	$r_s = -0.1271$ $P = 0.4470$
Hives	$r_s = -0.0701$ $P = 0.6759$	$r_s = -0.1280$ $P = 0.4436$	$r_s = -0.0583$ $P = 0.7317$	$r_s = -0.1182$ $P = 0.4858$	$r_s = -0.1426$ $P = 0.3930$	$r_s = -0.3980$ $P = 0.0133$
Itch	$r_s = -0.2192$ $P = 0.1861$	$r_s = -0.2192$ $P = 0.1861$	$r_s = -0.3243$ $P = 0.0502$	$r_s = -0.3072$ $P = 0.0644$	$r_s = -0.0527$ $P = 0.7534$	$r_s = -0.3894$ $P = 0.0157$

presence and number, as measured indirectly by TLHC, were correlated with interval reductions in current measures of disease activity (itch and hives). In a subset of subjects who entered remission, blood basophil presence was higher than in active disease. In contrast, long-term CSU disease impairment, as measured by Skindex-29, was better reflected in the degree of basophil IgE receptor responsiveness. These findings support the view that basopenia reflects the exit of basophils from the bloodstream to participate in CSU skin lesions and symptoms of pruritus. The recruitment pathways for basophil migration to lesional skin sites in CSU have not been identified.

Given the unique phenotype of basophils observed in CSU disease, there is a clear rationale for exploring the relationship between interval shifts in these basophil measures relative to the measures of CSU disease activity. At present, there are no available biomeasures that accurately reflect the course of CSU disease or a patient's response to medication. These basophil measures could potentially be used in combination with clinical activity measures to verify and predict

short- and long-term CSU disease activity trends. Additional studies are needed to investigate the use of these measures as potential biomarkers.

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Conflict of interest

The authors declare that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

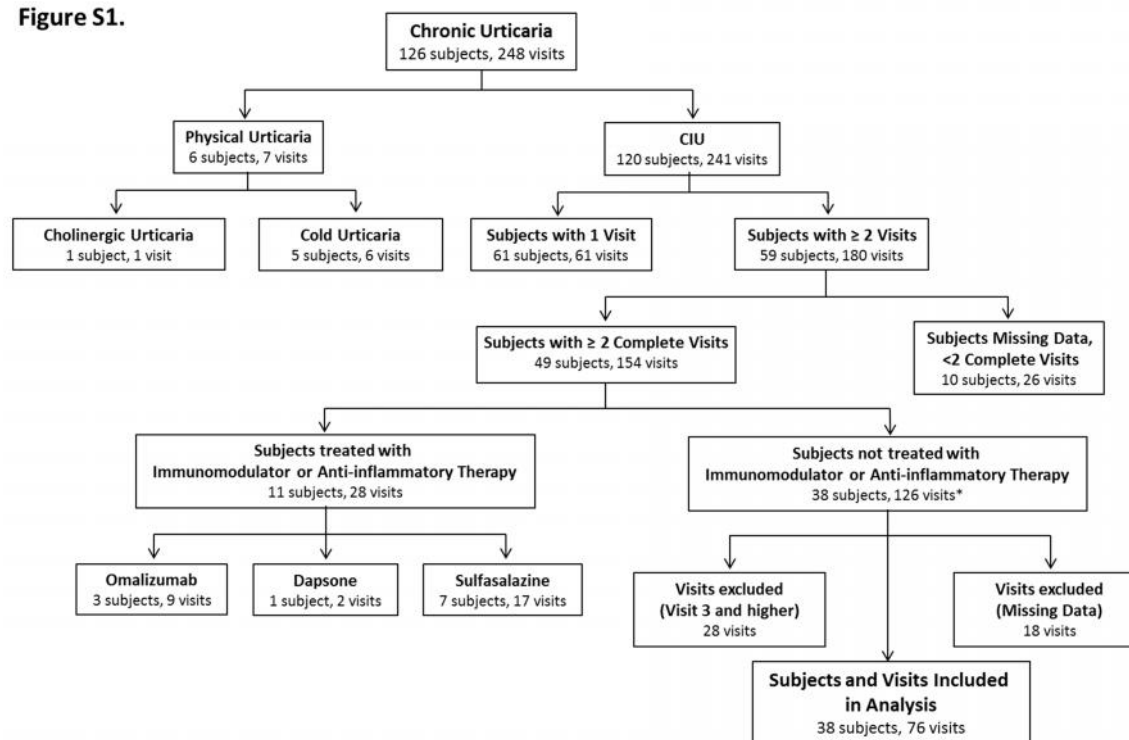
Figure S1. Patient selection.

Figure S2. Basophil measures in CSU subjects with active disease who entered remission.

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Figure S1.



*One subject started omalizumab after completing 3 visits, data from subsequent study visits after starting omalizumab (4 visits) were excluded from analysis.

Figure S2.

