ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Chronic spontaneous urticaria: correlation of basophil counts with disease control and response to anti-IgE therapy

Urticária crônica espontânea: correlação dos valores de basófilos com o controle da doença e a resposta à terapêutica anti-IgE

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ABSTRACT

This retrospective study aimed to investigate the relationship between peripheral blood basophil counts and response to treatment with omalizumab in patients with chronic spontaneous urticaria (CSU). Most patients included in the study had a normal basophil count, but a significant correlation was found between a low basophil count and daily use of antihistamines still required to control symptoms. This suggests the potential utility of basophil count as a prognostic marker of response to anti-IgE monoclonal antibody therapy in CSU.

Keywords: Urticaria, basophils, biomarkers, omalizumab.

RESUMO

Este estudo retrospectivo procurou investigar a relação entre os níveis de basófilos periféricos em doentes com urticária crônica espontânea (UCE) em tratamento com omalizumab e a sua resposta terapêutica. Dos pacientes incluídos, a maioria apresentou níveis normais de basófilos, mas uma correlação significativa foi encontrada entre valores baixos de basófilos e o uso diário de anti-histamínicos ainda necessários para controle sintomático, colocando a hipótese da potencial utilidade destes como marcador prognóstico na UCE na resposta à terapêutica monoclonal anti-IgE.

Descritores: Urticária, basófilos, biomarcadores, omalizumab.

Introduction

Chronic spontaneous urticaria (CSU) is characterized by the presence of wheals with or without angioedema, which occur daily or almost daily for more than 6 weeks.[1] Mechanisms that have a probable role in the pathogenesis of CSU include autoimmunity, autoallergy, complement pathway, coagulation pathway, and chronic infections.[2-4] Despite the known prevalence and impact of CSU on patients' quality of life, this condition remains poorly understood, making effective management a clinical challenge.[2]

The underlying pathogenesis of CSU has been predominantly centered on the activation of skin mast cells through multiple potential mechanisms.[1] Although CSU is not triggered by specific environmental allergens, IgE antibodies play a role in sensitizing mast cells and basophils to respond to endogenous and exogenous stimuli. Autoantibodies directed against self-antigens, such as IgE or IgE receptors, may be involved in the activation of mast cells and basophils in CSU.[2,5] It is widely accepted that mast cells become activated and subsequently release mediators, such

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as histamine, that elicit symptoms of itching, induce vasodilation, and recruit other immune cells to lesional skin sites.[2] Growing evidence suggests the involvement of IgE and IgE receptor (FcεRI) activation in the pathophysiology of CSU, as demonstrated by the efficacy of monoclonal IgG anti-IgE antibodies in mitigating or resolving skin symptoms. Updated guidelines currently recommend omalizumab, an anti-IgE monoclonal antibody, for patients with CSU refractory to the maximum daily dose of antihistamines for more than 4 weeks.[1]

There is a keen interest in further elucidating the role of IgE-bearing cells in the manifestation of CSU, including mast cells and basophils. The exact contributions of basophils to disease are currently being explored owing to improvements in tools to isolate roles for basophils.

Basophils can produce histamine, leukotrienes, C4, and cytokines such as interleukin (IL)-4, IL-13, and IL-31 in response to IgE receptor activation.[5,6] However, the role of basophils in CSU extends beyond that of mere effector cells; accumulating evidence suggests their involvement in orchestrating the chronicity of the disease.[7] Basophils exhibit plasticity in their phenotypic and functional profiles, with studies demonstrating their ability to sustain mast cell activation and to promote T-cell polarization toward a Th2 cytokine profile, perpetuating the inflammatory cascade underlying CSU.[5,8,9]

Therefore, we aimed to evaluate peripheral blood basophil counts in a cohort of patients with CSU receiving anti-IgE monoclonal antibody therapy and to investigate a possible correlation of basophil counts with disease control and response to anti-IgE therapy.

Methods

Study design

This single-center retrospective observational study was conducted in the Allergy and Clinical Immunology Department of a tertiary care hospital. All adult and pediatric patients receiving anti-IgE monoclonal antibody therapy for CSU for at least 12 months were included.

This paper was written considering ethical and legal principles and in accordance with the recommendations of the Declaration of Helsinki of the World Medical Association.

Outcomes

The following outcome measures were assessed:

– Pretreatment serum basophil counts and other serological markers (eosinophils, C3, C4, total IgE levels) in all patients with CSU receiving anti-IgE monoclonal antibody therapy.

– Correlation of basophil counts with response to anti-IgE treatment (omalizumab) using control scores – Urticaria Control Test (UCT) and Weekly Urticaria Activity Score (UAS7) – and with disease control based on need for medication other than omalizumab.

Statistical analysis

Data were analyzed using SPSS, version 27.0. The Kolmogorov-Smirnov test was used to analyze continuous variables. The chi-square test (χ^2) and Mann-Whitney U test were used to determine differences in the distribution of nominal and continuous variables, respectively. Statistical significance was considered at $p < 0.05$.

Results

A total of 26 patients were included, with a median age of 38.7 years (SD, 15.8; range 10-66 years). Most participants were female (76.9%). The median age at symptom onset was 24.8 years, and the mean (SD) duration of omalizumab treatment was 20.36 (10.54) months.

Angioedema occurred in 30.8% of patients, and the most common sites of involvement were the face (15.4%), lips and/or tongue (8.7%), upper or lower extremities (4.3%), and genitals (2.4%).

In our cohort of 26 patients with CSU, a subset still requires pharmacological intervention for symptom control. Currently, 11 patients (42.3%) are on standard anti-IgE treatment alone (ranging from every 4 weeks to every 8 weeks) and 15 (57.7%) need at least 1 antihistamine daily (median of 2.6 antihistamines daily). Four patients (15.4%) are receiving oral corticosteroids, while 2 patients (7.7%) are still maintained on cyclosporine therapy at a maximum dose of 3 mg/kg. More than one-third of patients (34.6%) had been on immunosuppressive therapy (cyclosporine or daily oral corticosteroids) before starting omalizumab treatment.

Five patients had concomitant inducible urticaria: 2 (7.7%) had delayed pressure urticaria, 2 (7.7%) had symptomatic dermographism, and 1 (3.8%) had cholinergic urticaria.

Allergic rhinitis was the most common atopic comorbidity, affecting 10 patients (38.5%), followed by asthma in 6 patients (23.1%) and food allergies in 3 patients (11.5%).

Before treatment, 16 patients (61.5%) had a normal peripheral blood basophil count, 9 (34.6%) had a decreased basophil count, and 1 (3.8%) had an increased basophil count. Results are displayed in Table 1.

Basophil counts were slightly associated with IgE levels (p=0.049, r=0.13). No association was found between basophil counts and eosinophils, C3, C4,

Table 1
Patients' characteristics, laboratory values, and disease control scores

Pretreatment anti-IgE therapy basophil count	Normal	Decreased	Increased	p-value	Spearman coefficient, r
Patients (n)	16	9	1		
Sex (n)					
Female	12	7	1	0.312	0.15
Age, years					
Median (IQR)	39 (15-67)	34 (5-13)	23	0.971	-0.53
Angioedema (n)	5	2	1	0.457	0.48
Total IgE (kU/L)					
Median (IQR)	226 (66-983)	169 (91-630)	62	0.049*	0.13
Eosinophils (cells/µL)					
Median (IQR)	87.3 (25-620)	56.2 (15-520)	45	0.691	-0.03
C3 (mg/dL)					
Median (IQR)	122 (85-175)	113 (77-168)	111	0.125	-0.32
C4 (mg/dL)					
Median (IQR)	32 (22-45)	31 (18-41)	40	0.091	0.22
Atopy					
Asthma (n)	3	3	1	0.211	
Rhinitis (n)	5	5	0	0.394	
Food allergy (n)	2	0	0	0.934	
Daily antihistamines (n)	2 (0-4)	3 (0-4)	1	0.025*	0.837
UAS7 score					
Median (IQR)	7.1 (0-19)	5.4 (2-17)	5	0.670	0.32
UCT score					
Median (IQR)	14.3 (10-16)	14.7 (11-16)	14	0.521	0.07

UAS7 = Weekly Urticaria Activity Score; UCT = Urticaria Control Test.
* Statistical significance (p<0.05).

duration of anti-IgE therapy, or the latest patients' UAS7 and UCT scores (disease control).

Regarding atopy, there was no statistically significant association between pretreatment basophil counts and presence or severity of atopic comorbidities.

A statistically significant association was found between pretreatment peripheral blood basophil counts and the daily number of antihistamines still taken by the patients (p=0.025, r=0.837).

Discussion

The results showed that most patients (61.5%) had a normal peripheral blood basophil count before omalizumab treatment, whereas 34.6% had a decreased basophil count; only 1 patient had an increased pretreatment basophil count.

There was no significant association between basophil counts and other laboratory parameters such as eosinophils, C3, C4, duration of anti-IgE therapy, or disease control scores (UAS7 and UCT). Furthermore, basophil counts were not significantly associated with the presence or severity of atopic comorbidities, but they were slightly associated with IgE levels (p=0.049, r=0.13). However, an intriguing finding emerged from this study in that peripheral blood basophil counts were significantly associated with the daily number of antihistamines required to achieve disease control while on omalizumab treatment, where higher basophil counts correlated with greater reliance on antihistamines for symptom management. Alongside a strong correlation (r=0.837), these results underscore the potential utility of basophil count as a prognostic marker of treatment response and disease severity in CSU.

Decreased blood basophil counts have been correlated with increased symptoms of itching and hives in a subset of patients with CSU and antihistamine resistance.[10,11] A longitudinal study of patients with CSU with repeated basophil and clinical symptom evaluations demonstrated that interval increases in circulating basophil numbers were correlated with reductions in patient-reported CSU symptoms as measured by control scores.[12]

In a large-scale study, blood samples from patients with antihistamine-refractory CSU enrolled in omalizumab phase III trials were examined at baseline and after 12 weeks of therapy. An omalizumab dose-dependent improvement in clinical symptoms was observed that was mirrored by a similar pattern of increase in blood basophil counts.[13]

Recently, the use of antihistamine therapy has been reported to increase basophil numbers following symptom improvement.[14] These studies support that improvement in skin symptoms is associated with reduced basophil migration to the skin and increased circulating basophil numbers, which may serve as a potential biomeasure of clinical improvement.

Study limitations

Despite its contributions, this study has several limitations that warrant consideration. Firstly, the relatively small sample size may limit the generalizability of the findings and increase the risk of type II errors. Additionally, the retrospective nature of the study design and reliance on pre-existing patient data may introduce biases and confounding factors that could impact the validity of the results. Furthermore, the study's focus on peripheral blood basophil counts overlooks the functional aspects of basophil activation and degranulation, which could provide deeper insights into their role in CSU pathogenesis and treatment response. Lastly, the cross-sectional design of the study precludes the establishment of causality and warrants further longitudinal investigations to validate the observed associations.

Conclusion

While the study did not find a direct correlation between basophil counts and disease control or response to anti-IgE monoclonal antibody therapy in patients with CSU, it identified a significant association between basophil counts and daily requirement of antihistamines while still on omalizumab. This highlights the potential of peripheral blood basophil count as a predictive marker for treatment response and disease severity in CSU. Further research is warranted to elucidate the mechanistic underpinnings of this association and validate its clinical utility in larger cohorts of patients with CSU. Ultimately, understanding the role of basophils in CSU pathogenesis and treatment response may pave the way for personalized treatment approaches and improved outcomes for patients with this condition.

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