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PII: S2213-2198(21)00162-8

DOI: <https://doi.org/10.1016/j.jaip.2021.01.034>

Reference: JAIP 3411

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 8 December 2020

Revised Date: 30 December 2020

Accepted Date: 20 January 2021

Please cite this article as: Roh YS, Khanna R, Patel SP, Gopinath S, Williams KA, Khanna R, Pritchard T, Sutaria N, Choi J, Alphonse MP, Kwatra MM, Kwatra SG, Circulating blood eosinophils as a biomarker for variable clinical presentation and therapeutic response in patients with chronic pruritus of unknown origin, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.01.034>.

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Circulating blood eosinophils as a biomarker for variable clinical presentation and therapeutic response in patients with chronic pruritus of unknown origin

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Keywords: chronic; pruritus; unknown; origin; idiopathic; generalized; itch; eosinophils

Funding Sources: This article has no funding source.

Conflict of Interest: Dr. Shawn G. Kwatra is on the advisory board for Abbvie, Galderma, Incyte Corporation, Pfizer Inc., Regeneron Pharmaceuticals, and Menlo Therapeutics, and has received grant funding from Pfizer Inc., Galderma, and Kiniksa Pharmaceuticals. He is also a recipient of a Dermatology Foundation Medical Dermatology Career Development Award. This research is supported by a grant from the National Institute of Health T32AR074920-01A1. The other author(s) have no conflicts of interest to declare.

Publication Status: The content in this manuscript has not been published or submitted for publication elsewhere. All authors have contributed significantly and are in agreement with the content of the manuscript.

IRB Status: IRB approval was obtained from the Johns Hopkins University School of Medicine.

Word Count: 997/1000

References: 8/9

Tables: 1

Figures: 1

Online Repository Tables: 2/2

Clinical Implications: We classify CPUO patients with and without increased circulating blood eosinophils, highlighting clinically significant differences in these phenotypes. CPUO patients with increased eosinophils responded favorably to immunomodulatory therapy, while CPUO patients without increased eosinophil counts saw greater improvement with gabapentin therapy.

Chronic pruritus is a distressing symptom associated with a significant reduction in quality of life.¹ Patients undergo an extensive diagnostic workup to search for underlying dermatologic, systemic, neurologic, or psychiatric conditions. In real-world practice, a specific causal disease process often is not

identified, and patients are diagnosed with chronic pruritus of unknown origin (CPUO). Unfortunately, there is little guidance for managing CPUO, presenting a significant clinical challenge.² We propose a clinical approach to subclassify CPUO patients by utilizing circulating blood eosinophils as a biomarker of variable clinical presentation and therapeutic response. We hypothesized that patients with vs. without increased circulating blood eosinophils would more likely experience itch reduction with immunomodulators versus gabapentinoids, respectively.

With approval of the Johns Hopkins Medicine Institutional Review Board, we conducted a single-center retrospective analysis of 40 CPUO patients treated at the Johns Hopkins Itch Center from June 2017 to October 2020. We conducted a retrospective chart review to collect demographic information, medical history, laboratory data, itch characteristics, and treatment data. Patients with an absolute eosinophil count >0.30 K/mm³ or eosinophil percentage $>4\%$ in the peripheral blood^{3,4} prior to treatment initiation were identified as having increased circulating blood eosinophils.

Patients with dermatological disease, systemic conditions, active or recent (<3 years) history of malignancy that could contribute to chronic pruritus were excluded. Patients with serum creatinine, total bilirubin, alanine or aspartate aminotransferase greater than twice the upper limit of normal were also excluded. Patients with symptoms that corresponded to any recognized neuropathic itch subtypes (e.g., brachioradial pruritus and notalgia paresthetica) were excluded. Patient records included a questionnaire of validated clinical scales, including the 24-hour Worst Itch Numerical Rating Scale (WI-NRS), Dermatology Life Quality Index (DLQI), Itchy Quality of Life (ItchyQoL) score, 5D Itch Scale, Skindex-29, and Beck's Depression Inventory (BDI).⁵ History of back pain was self-reported by the patient. Treatment effect was self-reported by the patient, using WI-NRS. Treatment effect was recorded as unknown if treatment-specific response data were unavailable. Stata 15 was used to conduct χ^2 and Student's t-tests with statistical significance defined at $p < 0.05$.

For confirmatory analyses, we obtained data from TriNetX (TriNetX, Inc., Cambridge, MA), a multinational research network of 45 healthcare organizations representing over 63 million patients. We queried the de-identified dataset for adults with diagnosis of pruritus (ICD-10-CM code: L29), with vs. without increased circulating blood eosinophils ($>4\%$ or >0.30 K/mm³) within 3 months of pruritus diagnosis. We obtained demographic information and performed propensity score matching, and

compared spinal and atopic comorbidities within 1 year prior to pruritus diagnosis. We also queried the dataset for adult patients with pruritus with and without a history of spinal comorbidities, performed propensity score matching, and compared eosinophil counts within 3 months of pruritus diagnosis.

Demographics, itch characteristics, and treatments from the chart review are reported in Table 1. Of the 40 CPUO patients, 17 (42.5%) had increased circulating blood eosinophils (Table 1). The average age of CPUO patients with increased circulating eosinophils was greater than that of patients without increased circulating eosinophils ($p=0.005$). A total of 35.3% of patients with increased eosinophils had history of neurological disease compared to 69.6% of patients without increased eosinophils ($p=0.031$).

The majority of patients had pruritus over 1-10 years with insufficient response to antihistamines and topical corticosteroids (Table 1). Gabapentin therapy was started in 52.9% of patients with increased circulating eosinophils and 73.0% of patients without increased blood eosinophils. Among patients without increased circulating eosinophils, 64.7% reported symptom improvement with gabapentin compared to 22.2% of patients with increased blood eosinophils ($p=0.010$). Mean WI-NRS dropped from 8.75 ± 0.36 to 4.39 ± 0.94 ($p<0.001$) among patients without increased circulating eosinophils taking gabapentin (Figure 1). Most patients with increased blood eosinophils (77.8%) reported no change in symptoms with gabapentin. Immunomodulators (methotrexate, oral or intramuscular steroids, or dupilumab) were prescribed to 82.4% of patients with increased circulating eosinophils and 26.1% of patients without increased blood eosinophils. Immunomodulators led to symptom improvement in 71.4% of patients with increased circulating eosinophils and resulted in no change in symptoms for 66.7% of patients without increased blood eosinophils ($p=0.001$). Mean WI-NRS decreased from 8.57 ± 0.69 to 4.00 ± 0.79 ($p=0.008$) in patients with increased blood eosinophils treated with immunomodulators.

For the confirmatory analysis, 85,512 patients and 123,692 patients were identified with a diagnosis of pruritus with and without increased blood eosinophils within 3 months of pruritus diagnosis, respectively (Table E1). After propensity score matching adjusting for age, sex, race, and ethnicity, among 85,054 patients of each group, more pruritic patients without increased blood eosinophils reported low back pain ($p=0.003$), cervicalgia ($p=0.0218$), and radiculopathy ($p<0.0001$) within 1 year prior to pruritus diagnosis. Pruritic patients with increased eosinophils were more likely to have background atopic dermatitis and asthma ($p<0.001$). We also identified 176,330 patients and 496,610 patients with

pruritus, with and without spinal comorbidities (Table E2). Patients with spinal comorbidities had lower eosinophil counts within 3 months of pruritus diagnosis, and higher odds of having non-elevated eosinophils ($p < 0.0001$).

Our results suggest that CPUO patients without increased circulating eosinophils are more likely to benefit from gabapentin compared to CPUO patients with increased circulating eosinophils. Furthermore, our results highlight that CPUO patients with increased blood eosinophils are older and likely have immune-mediated etiology, as suggested by favorable treatment results with immunomodulators. Finally, our confirmatory analysis provides further evidence that pruritic patients without increased circulating blood eosinophils are more likely to carry spinal comorbidities, suggesting an etiological role for neural sensitization in their itch.

While the pathophysiology of CPUO is poorly understood, we propose that CPUO patients may be subclassified into either a Th2 predominant phenotype, mediated by proinflammatory cytokines including IL-4, IL-13, and IL-31^{6,7} and more responsive to immunomodulators⁸, or a distinct clinical phenotype likely mediated by neural sensitization and more responsive to neuromodulators.

Limitations of this study include its retrospective nature and small sample size. Future clinical trials on CPUO should consider stratifying patients by circulating blood eosinophils to ensure a homogeneous study population and accurately assess therapeutic response. Additional studies are also needed to uncover additional novel endotypes of the CPUO population.

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FIGURES

Figure 1: Response to treatment stratified by presence of increased circulating blood eosinophils (absolute eosinophil count >0.30 K/mm or eosinophil percentage >4% in the peripheral blood)

1a: Percent of patients with symptom improvement with immunomodulatory therapy; 1b:

Percent of patients with symptom improvement with gabapentin therapy; 1c: Change in mean itch WI-NRS with suggested therapy based on circulating blood eosinophils

Table 1: Patient demographics, itch characteristics, and therapies with and without increased circulating blood eosinophils (absolute eosinophil count >0.30 K/mm or eosinophil percentage >4% in the peripheral blood)

	All CPUO(n=40)	With increased circulating blood eosinophils (n=17)	Without increased circulating blood eosinophils (n=23)	p-value
PATIENT DEMOGRAPHICS				
Age, years, mean (se)	65.6 (2.3)	72.8 (2.4)	60.3 (3.2)	p=0.005
Gender				
Female, n(%)	27 (67.5)	10 (58.8)	18 (73.9)	p=0.314
Male, n(%)	13 (32.5)	7 (41.2)	6 (26.1)	
Race, n(%)				
White	33 (82.5)	14 (82.4)	19 (82.6)	p=0.291
African American	5 (12.5)	1 (5.9)	4 (17.4)	
Other	2 (5.0)	2 (11.8)	0 (0)	
Background atopic history ¹ , n(%)	13 (32.5)	5 (29.4)	8 (34.8)	p=0.720
Back pain, n(%)	19 (47.5)	6 (35.3)	13 (56.5)	p=0.184
Neurological Disease ² , n(%)	22 (55.0)	6 (35.3)	16 (69.6)	p=0.031
Psychiatric disease ³ , n(%)	23 (57.5)	9 (52.9)	14 (60.9)	p=0.616
INITIAL ITCH CHARACTERISTICS				
WI-NRS, mean (se)	8.59 (0.23)	8.35 (0.38)	8.77 (0.28)	p=0.374
DLQI Score, mean (se)	11.42 (1.37)	9.00 (1.22)	13.50 (2.22)	p=0.103
ItchyQoL Total Score, mean (se)	76.40 (3.39)	75.70 (5.21)	76.87 (4.60)	p=0.870
5D Itch Scale, mean (se)	20.50 (0.77)	19.50 (0.73)	21.17 (1.18)	p=0.299
Duration	3.40 (0.26)	3.33 (0.46)	3.44 (0.30)	p=0.836
Degree	3.77 (0.11)	3.75 (0.18)	3.78 (0.15)	p=0.908
Direction	4.00 (0.15)	3.83 (0.27)	4.11 (0.18)	p=0.379
Disability	3.90 (0.22)	4.00 (0.37)	3.84 (0.29)	p=0.738
Skindex 29 Total, mean (se)	90.48 (5.02)	83.33 (7.29)	94.06 (6.56)	p=0.323
Beck's Depression inventory, mean (se)	13.71 (1.99)	11.00 (2.09)	15.64 (3.02)	p=0.258
THERAPY				
Antihistamine, n(%)	26 (65.0)	13 (76.5)	13 (56.5)	p=0.191
Improvement in symptoms	9 (34.6)	5 (38.5)	4 (30.8)	p=0.447
No change in symptoms	9 (34.6)	3 (23.1)	6 (46.2)	
Unknown effect	8 (30.8)	5 (38.5)	3 (23.1)	
Topical Steroid, n(%)	34 (85.0)	15 (88.2)	19 (82.6)	p=0.622
Phototherapy, n(%)	19 (47.5)	8 (47.1)	11 (47.8)	p=0.962
Gabapentin, n(%)	26 (65.0)	9 (52.9)	17 (73.9)	p=0.169
Improvement in symptoms	13 (50.0)	2 (22.2)	11 (64.7)	p=0.010
No change in symptoms	10 (38.5)	7 (77.8)	3 (17.7)	
Unknown effect	3 (11.0)	0 (0)	3 (17.7)	
Immunomodulator ⁴ , n(%)	20 (50.0)	14 (82.4)	6 (26.1)	p<0.001
Improvement in symptoms	10 (50.0)	10 (71.4)	0 (0)	p=0.001
No change in symptoms	4 (20.0)	0 (0)	4 (66.7)	
Unknown effect	6 (30.0)	4 (28.6)	2 (33.3)	

¹Atopic history was defined as having at least two out of three atopic conditions (atopic dermatitis, allergic rhinitis, or asthma).

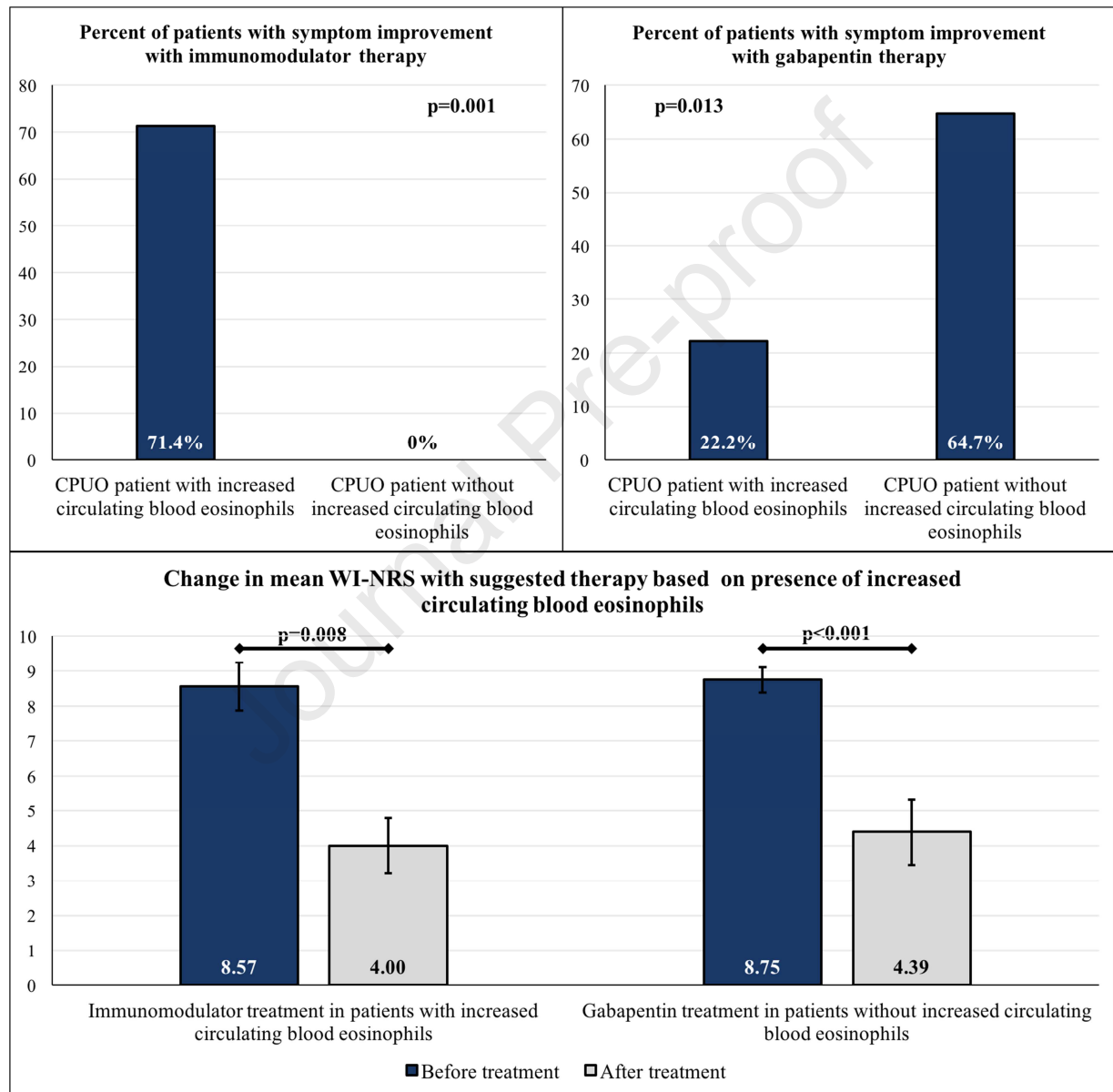
²Neurological disease included epilepsy, neurogenic bradycardia, multiple sclerosis, pain disorders, and spinal disease.

³Psychiatric disease included anxiety, depression, and mania.

⁴Immunomodulators included methotrexate, oral and intramuscular corticosteroids, and dupilumab.

FIGURES

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