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# Unveiling the role of neutrophils in chronic spontaneous urticaria: Beyond mast cells

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## Abstract

Mast cells and eosinophils are considered pivotal contributors to the pathogenesis of chronic spontaneous urticaria (CSU). However, emerging evidence suggests that neutrophils also play a central role. Cutaneous mast cells and macrophages orchestrate the recruitment of neutrophils through the regulation and activation of diverse processes, including heightened local vascular permeability and chemokine release. Studies have demonstrated increased activation and elevated levels of neutrophil-related cytokines in CSU patients. Moreover, neutrophils have been proposed as antigen-presenting cells during the late-phase reaction of immunoglobulin E-mediated allergy and have been associated with the expression of calcitonin gene-related protein and vascular endothelial growth factor in CSU. Histopathological analysis of lesional skin in CSU patients revealed significantly higher eosinophil and neutrophil counts than unaffected skin. However, the extent of neutrophil infiltration in the skin does not appear to correlate with the number of neutrophils in peripheral blood. The utility of the neutrophil-lymphocyte ratio as a marker for disease activity or remission in CSU remains inconclusive. Neutrophil-targeted therapy may confer benefits for CSU patients who exhibit resistance to antihistamines. Omalizumab has demonstrated its ability to reduce neutrophil counts, the neutrophil-lymphocyte ratio, and the neutrophil-monocyte ratio in peripheral blood. While dapsone and colchicine are recommended as alternative treatment options for CSU, their evidential support from published studies remains limited. Inhibitors targeting interleukin-1 and neutrophil-related cytokines have been proposed as potential therapeutic interventions for patients exhibiting neutrophil predominance. Further research is warranted to gain deeper insights into the involvement of neutrophils in CSU and to explore potential therapeutic interventions.

**Key words:** Chronic spontaneous urticaria, Mast cells, Neutrophils, Peripheral blood, Skin

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Mast cells and eosinophils are considered pivotal contributors to the pathogenesis of chronic spontaneous urticaria (CSU). However, emerging evidence suggests that neutrophils also play a central role and neutrophil-targeted therapy may confer benefits for CSU patients. This article was aimed to review an important role of neutrophils in CSU.

## *Neutrophil biology and functions*

Neutrophils, also known as polymorphonuclear leukocytes (PMNs), constitute the most abundant leukocyte population in the circulation.[1] Their production arises from multipotent hematopoietic stem cells in the bone marrow, which undergo unipotent differentiation to form granulocytes. Among the cytokines involved in granulocytic proliferation, granulocyte colony-stimulating factor (G-CSF) holds particular importance. The release of mature neutrophils from the bone marrow relies on the expression of CXCL2 and the cell membrane receptors CXCR2 and CXCR4. In normal homeostasis, only a small fraction of neutrophils, approximately 1–2%, are mobilized into circulation, despite constituting approximately 70% of all leukocytes.[1]

Maintaining the balance of cytokine networks, chemokines, inflammatory mediators, and adhesion molecules is essential for neutrophil trafficking from the bone marrow to the bloodstream.[2] Factors such as B1 and B2 integrins contribute to neutrophil retention, while endotoxin and tumor necrosis factor-alpha (TNF-α) regulate their release. Furthermore, phagocyte-derived interleukin (IL)-23 and T lymphocyte-derived IL-17 play roles in regulating neutrophil production.[1] Neutrophils typically circulate in the blood for a half-life of approximately 6–12 hours[1] before undergoing circadian frequency-driven disappearance.[3] It has been reported that up to $10^{11}$ neutrophils are released into the bloodstream daily.[4] The leukocyte adhesion cascade aids in the mobilization of neutrophils to sites of infection or inflammation, facilitated by adhesion receptors, E- and P-selectins, expressed by endothelial cells near the affected sites, resulting in neutrophil adhesion.[1] Subsequently, neutrophils transmigrate to peripheral tissues with the assistance of chemoattractants such as formyl-methionyl-leucyl-phenylalanine (fMLP) and anaphylatoxin C5a, fulfilling their designated functions.[5,6]

Upon completing their antimicrobial tasks within target tissues, neutrophils undergo apoptosis. Resident macrophages and dendritic cells assist in clearing apoptotic neutrophils through phagocytosis.[1] Senescent neutrophils upregulate the expression of CXCR4, enabling their return to the bone marrow for final elimination.[7] The phagocytosis of apoptotic neutrophils triggers an anti-inflammatory response, resulting in a reduction in IL-23 production by macrophages. Consequently, levels of IL-17 and G-CSF decline, leading to a reduction in granulopoiesis.[8]

Neutrophils demonstrate both phenotypic and functional heterogeneity, exhibiting variations in membrane molecule and cytokine expression depending on the specific tissues in which they are located.[9-13] For instance, neutrophils that express the CCR7 receptor,[14] macrophage-1 Ag, integrin LFA-1, and the chemokine receptor CXCR4 play roles in facilitating neutrophil trafficking and migration to afferent lymphatics, thereby contributing to T-cell activation.[15] Another subpopulation of circulating neutrophils, characterized by $CD49d^{+}$ $VEGFR1^{high}$ $CXCR4^{high}$ phenotypes, possesses the ability to promote angiogenesis.[16]

## *Neutrophil recruitment to the skin*

Mast cells and macrophages residing in the skin play a pivotal role in initiating the recruitment of neutrophils by orchestrating various processes, including the modulation of local vascular permeability and the release of chemokines. Numerous mediators participate in the recruitment of neutrophils to sites of active inflammation. These include bacterial components (such as endotoxins, exotoxins, and capsule fragments), anaphylatoxins C3a and C5a from the complement pathway, TNF-α, IL-1, CXCL8/IL-8, IL-17, IL-36, leukotriene B4, lipocalin-2 (LCN2), platelet-activating factor, kallikrein, matrix metalloproteinases, and myeloperoxidase inhibitors.[17-19] Platelets and neutrophils themselves can also contribute to recruiting neutrophils to the tissue. Neutrophils release neutrophil extracellular traps (NETs), which are intracellular structures released into the extracellular environment.[6] The formation of NETs has been observed in both infectious and chronic inflammatory conditions. Notably, the lesional skin of patients with Schnitzler's syndrome has shown evidence of NET formation, whereas this phenomenon has not been observed in patients with CSU or in healthy controls.[20] For a comprehensive understanding of neutrophil biology and its recruitment to the skin, please refer to **Figure 1**.

## *Interactions between mast cells and neutrophils*

Mast cells are acknowledged as crucial contributors to inflammation and tissue remodeling in IgE-mediated diseases.[21] They produce a wide array of inflammatory mediators and signaling molecules that play essential roles in both innate and adaptive immunity.[22,23] Previous investigations have indicated that mast cells also play a regulatory role in the recruitment of neutrophils, thereby facilitating the efficient initiation of innate immune responses. Moreover, in cases of acute inflammation, mast cells are activated by adaptive immune responses to promote the accumulation of neutrophils within the affected tissues. In IgE-dependent late-phase reactions (LPRs) and T-cell-mediated delayed-type hypersensitivity reactions, mast cells exert control over neutrophil recruitment through the action of TNF-α and macrophage inflammatory protein 2.[24,25]

## *Evidence for the involvement of neutrophils in CSU*

The infiltration of neutrophils in urticarial skin lesions of patients with CSU was initially discussed in the early 1990s by Sanchez and Benmamán.[26] Their study of 36 patients with chronic urticaria (CU) classified histopathological patterns into three types: neutrophilic, lymphocytic, and mixed. Notably, no vasculitis was observed in the biopsy specimens of these patients.

Sabroe et al[27] examined biopsy specimens from spontaneous wheals presenting for different durations (< 4 hours and > 12 hours) and uninvolved skin in 22 CSU patients. They found that neutrophil and eosinophil accumulation occurred in the early phase of wheal evolution, with subsequent persistent eosinophil activation in CSU patients.

In a study by Kay et al,[28] paired biopsies from lesional and nonlesional skin were taken from 8 CSU patients and 9 control subjects. The lesional skin of the CSU patients exhibited significantly higher levels of eosinophils, neutrophils, CD31+ endothelial cells, and CD31+ blood vessels than uninvolved skin, suggesting a connection between inflammatory cells and vascular leakage. It is worth noting that the uninvolved skin of the CSU patients showed significantly elevated eosinophils, CD31+ endothelial cells, and CD31+ blood vessels, but not neutrophils, compared to the control subjects.

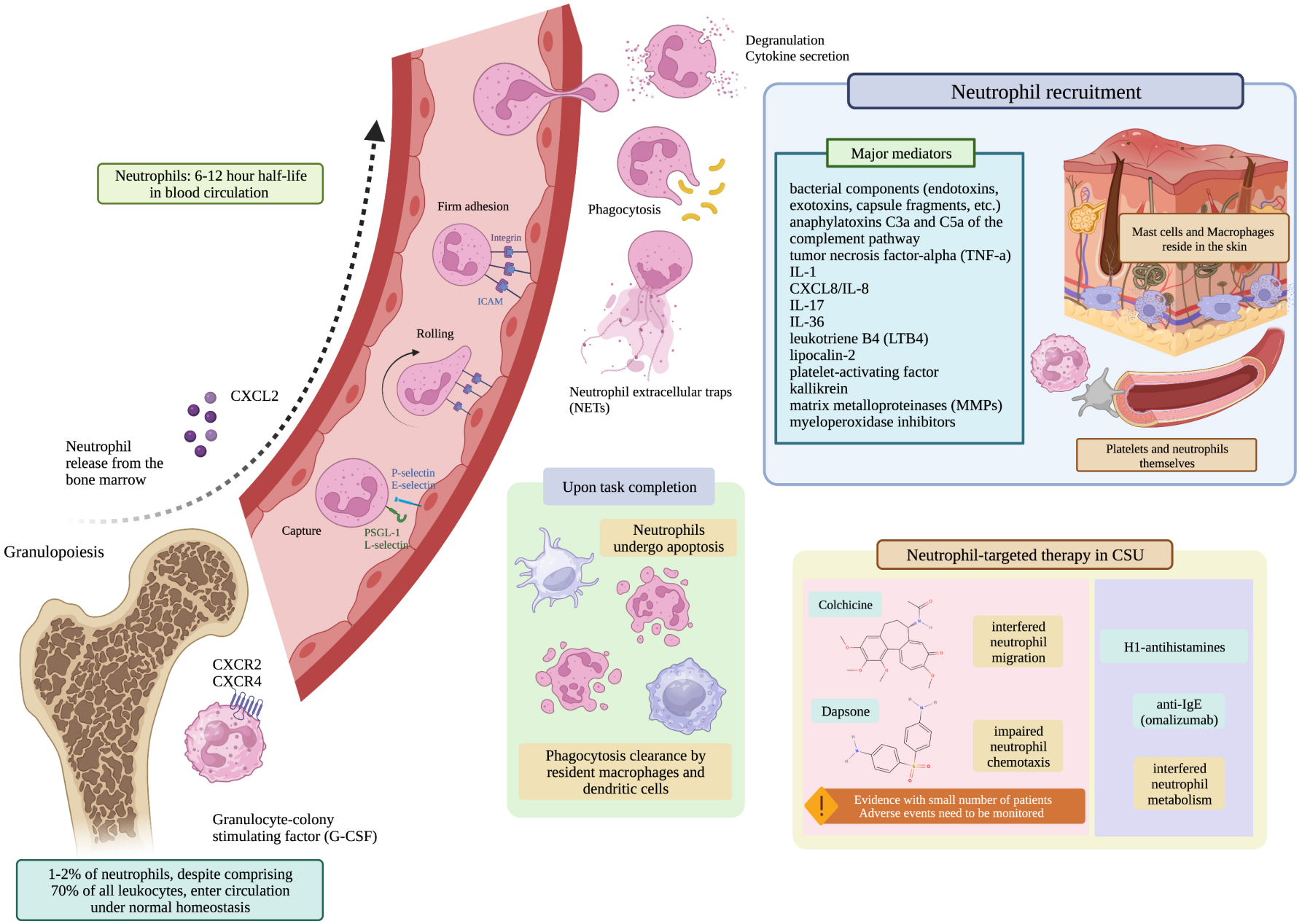


**Figure 1. Neutrophil biology and recruitment to the skin with potential neutrophil-targeted treatment in chronic spontaneous urticaria.**

(Created with BioRender.com)

**Abbreviations:** CXCL2; chemokine (C-X-C motif) ligand 2, CXCR2; C-X-C motif chemokine receptor 2, CXCR-4; C-X-C chemokine receptor type 4; CXCL8; C-X-C motif chemokine ligand 8, ICAM; intercellular adhesion molecule, PSGL-1; P-selectin glycoprotein ligand-1, IL; interleukin, Ig; immunoglobulin

Rojanapremsuk et al[29] reported a predominance of eosinophils (72%) and neutrophils (28%) in 18 CU patients with positive anti-IgE receptor antibodies. Among 19 CU patients with negative anti-IgE receptor antibodies, eosinophil and neutrophil predominance was observed in 53% and 47% of patients, respectively.

Grattan et al[30] also documented the presence of neutrophil infiltration within and around small dermal blood vessels in autologous serum-induced wheals in patients with chronic autoimmune urticaria. However, this observation did not demonstrate a significant correlation with wheal formation. In another study involving skin biopsies from 28 patients with CU who tested positive in autologous serum skin tests, dense neutrophil infiltration, a mixed subclass distribution of Th1 and Th2 lymphocytes, and the involvement of CXCR3 and CCR2 chemokines were observed.[31] An investigation utilizing skin biopsies from 8 patients with CSU demonstrated increased expression of Th2-initiating cytokines (IL-33, IL-25, and thymic stromal lymphopoietin), which may contribute to mast cell activation, inflammation, and vascular leakage in CSU.[32]

In another study involving serial biopsies of 5 patients with CSU, perivascular neutrophils and eosinophils were observed as early as 30 minutes after the procedure.[33] Within 2 hours, T lymphocyte numbers increased, with a predominance of CD4+ T cells over CD8+ T cells. While neutrophils were cleared within 48 hours, eosinophils and lymphocytes persisted. This inflammatory process resembled the LPR of IgE-mediated hypersensitivity reactions in atopic individuals.[33]

CSU patients were found to exhibit significant increases in intradermal neutrophils, eosinophils, basophils, and macrophages, as well as CD3+, CD4+, CD8+, and CD25+ T cells, following a cutaneous allergen challenge when compared with healthy control patients.[34] **Figure 2** shows the histopathological findings for our CSU patient. Dermal edema and an inflammatory infiltrate comprising lymphocytes, eosinophils, neutrophils, and nuclear dust were observed, indicating an active immune response. However, no evidence of vasculitis was detected.

## *Roles of neutrophils in CSU*

Trinh et al[35] investigated neutrophil activation and the levels of related cytokines in 191 patients with CU and compared them to 89 healthy controls. They reported significantly elevated levels of serum LCN2, TNF-α, IL-6, and IL-10 in CU patients. LCN2, an innate immunity component, is released from neutrophils upon their activation.[35] Trinh and colleagues incubated different concentrations of LCN2 with PMNs to investigate the chemotactic effect of LCN2. They found that LCN2 effectively suppressed fMLP-induced neutrophil migration in a dose-dependent manner. Moreover, an inverse correlation was observed between serum LCN2 levels and disease activity, as assessed by the urticaria activity score. Notably, refractory CU patients exhibited significantly lower LCN2 levels than those who responded to treatment.

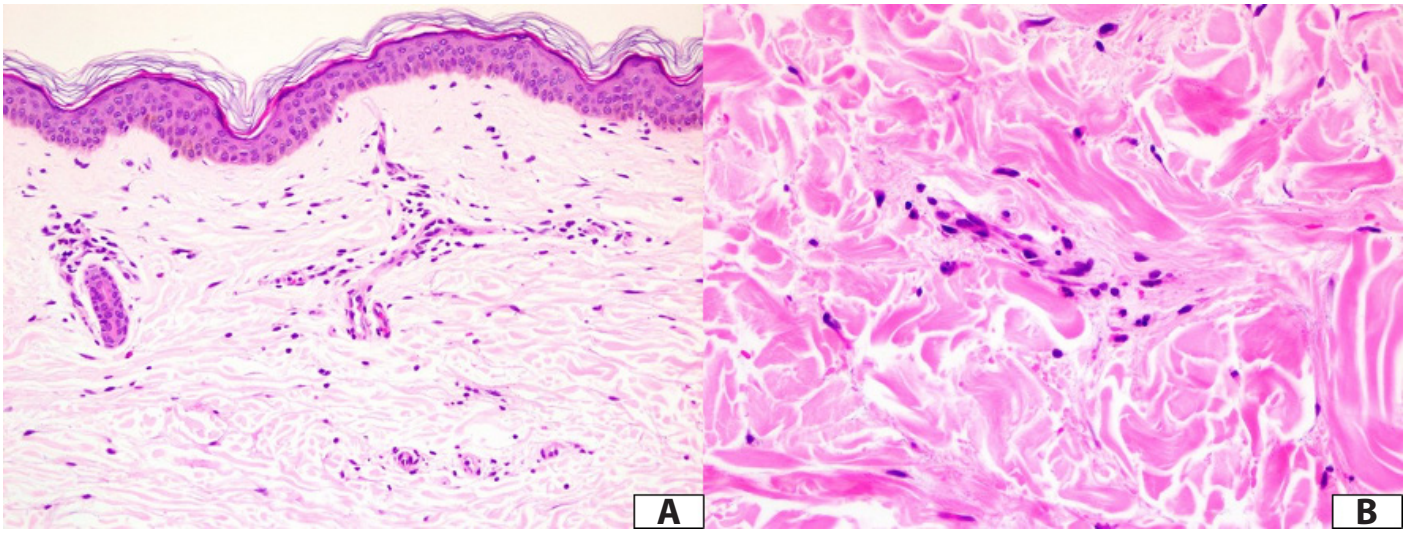


**Figure 2. Histopathological findings of skin lesions on the right arm of a male patient aged 38 years old.**
**(A)** Hematoxylin and eosin staining revealed superficial perivascular infiltration and dermal edema with an inflammatory infiltrate composed of lymphocytes, eosinophils, neutrophils, and nuclear debris. No evidence of vasculitis was observed. (Original magnification ×100)
**(B)** At higher magnification (×400), the inflammatory infiltrate consisting of lymphocytes, eosinophils, neutrophils, and nuclear debris can be clearly visualized, indicating the presence of an inflammatory response in the skin lesions.

Choi et al[36] examined neutrophil activation and related cytokines in patients with acetylsalicylic acid (ASA)-induced acute and CU. They found higher serum levels of myeloperoxidase and IL-18 in patients with ASA-intolerant CU than in normal controls. These findings provide evidence for the involvement of neutrophil activation and related cytokines in the pathogenesis of ASA-induced urticaria.

In the involved skin of patients with CSU, increased levels of basophils, macrophages, and T cells contribute to mast cell activation, leading to the release of IL-8 and eotaxin. These chemotactic factors play a role in recruiting neutrophils and eosinophils to the affected sites.[18,19,28,37] A study by Ying et al[34] demonstrated that skin biopsy specimens from IgE-mediated allergy LPR displayed a similar profile of inflammatory cell infiltration to those observed in CSU patients. Polak et al[38] proposed a novel role for neutrophils as antigen-presenting cells in LPR of IgE-mediated allergy.

Kay et al[39] observed a significant increase in the expression of calcitonin gene-related protein (CGRP) and vascular endothelial growth factor (VEGF) in lesional skin compared to nonlesional skin in patients with CSU. This finding indicates the involvement of CGRP and VEGF in the induction of whealing and tissue edema.[39] Notably, CGRP is expressed by neutrophils and eosinophils. The observed increase in inflammatory cells, vascular leakage, and the enhanced expression of CGRP and VEGF, which are characteristic features of LPR, have been proposed as a model for understanding CSU.[39]

## *Is there a correlation between the presence of neutrophils in skin tissue and neutrophilia/neutropenia or other laboratory tests in patients with CSU?*

Sugita et al[40] conducted a study involving 35 CSU patients and demonstrated the presence of neutrophils, eosinophils, and mononuclear cells in lesional skin. Among the 35 patients, 33 (94%) exhibited apparent neutrophil infiltration, with neutrophils being the predominant cell type in 5 cases. However, no correlation was observed between neutrophil infiltration in the skin and peripheral blood cell counts.

In a retrospective study by Martins et al,[41] 93 CSU patients were evaluated, and two histological groups were identified. The first group showed a predominance of neutrophils or eosinophils (42.4%), while the second group exhibited a predominance of lymphocytes (57.6%). However, no significant correlation was found between these histological groups and laboratory tests for serum vitamin D levels, antithyroperoxidase, antithyroglobulin, antinuclear antibodies, rheumatoid factor, D-dimer, serum complement levels (C3, C4), C-reactive protein, erythrocyte sedimentation rate, mean platelet volume, thyroid-stimulating hormone, and serum IgE levels.

## *What is the clinical significance of neutrophilia or neutropenia in CSU?*

The clinical relevance of neutrophilia or neutropenia in CSU remains inconclusive due to the limited data available.[42-44] Several studies have explored the neutrophil-lymphocyte ratio (N/L ratio) as a potential marker for disease severity. Actas Karabay et al[45] found that the N/L ratio was significantly higher in CSU patients (n = 50) than in healthy controls (n = 50). However, a study by Ertas et al[44] did not observe a significant difference in the N/L ratios of 143 CSU patients and 132 controls. When considering disease severity, Actas Karabay et al[45] found no significant difference in the N/L ratios of patients with mild to moderate CSU, patients with severe CSU, and healthy controls. Similarly, Akca et al[43] reported no significant correlation between the N/L ratio and disease severity assessed by the urticaria activity score. However, Ertas et al[44] demonstrated a significant decrease in neutrophil counts and the N/L ratio following omalizumab treatment.

In the pediatric population, Karaman et al[42] examined the N/L ratio in 80 patients with CSU. They found that the absolute neutrophil count in CSU patients with disease remission ($4.3 \pm 2.0 \times 10^3/\mu L$) was significantly lower than that in patients without disease remission ($5.3 \pm 2.0 \times 10^3/\mu L$). The absolute lymphocyte count was slightly higher ($3.3 \pm 1.3 \times 10^3/\mu L$) in patients with disease remission, although the difference was not statistically significant. Thus, they suggested that the N/L ratio could be a marker for CSU disease remission.

## *Is there a role for neutrophil-targeted therapy in the treatment of CSU?*

Currently, mast cell-targeted therapy, such as H1-antihistamines and anti-IgE (omalizumab), is widely recognized as effective in treating CSU.[46-49] An *in vitro* study demonstrated that antihistamines (loratadine and desloratadine) predominantly induced neutrophil apoptosis upon cell contact, suggesting that antihistamines probably interfered with neutrophil metabolism.[50] Akdogan et al[51] demonstrated a substantial reduction in peripheral blood neutrophil counts, particularly in the first 3 months, in CSU patients treated with omalizumab. Similarly, Onder et al[52] reported a statistically significant reduction in neutrophil count, N/L ratio, and neutrophil/monocyte ratio after 12 weeks of omalizumab treatment.

Dapsone (4-4′-diaminodiphenylsulfone), a sulfone derivative, inhibits neutrophil function by impairing neutrophil chemotaxis.[53] Colchicine, an alkaloid drug, exerts anti-inflammatory effects primarily by interacting with microtubules, interfering with neutrophil migration.[54] A double-blinded, placebo-controlled study conducted by Morgan et al[55] demonstrated the efficacy of dapsone in the treatment of 22 patients with antihistamine-refractory CSU.

In a prospective randomized nonblinded clinical trial conducted by Engin et al,[56] the addition of low doses of dapsone to antihistamines resulted in a persistent decrease in disease activity in patients with CSU, suggesting the potential for prolonged remission. Criado et al[53] conducted a study involving 22 patients with antihistamine-refractory CU, of whom 14 were identified as having CSU. Adding dapsone, combined with antihistamines or colchicine, improved treatment outcomes in CSU patients. Remarkably, 16 of the 22 patients remained free of urticaria even after a discontinuation period of 2 years. Additionally, a prospective study and a retrospective review demonstrated the benefits of dapsone, either as a single agent or in combination with other treatments, in patients with antihistamine-refractory CSU.[57,58]

However, it is essential to note that the small number of patients studied limits evidence supporting the use of dapsone and colchicine. It is crucial to monitor adverse events associated with dapsone, particularly hemolysis and dapsone syndrome. Currently, the International European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA2LEN), the European Dermatology Forum (EDF; EuroGuiDerm), and the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) recommend sulphones (dapsone and sulphasalazine) as the alternative treatment option for CSU +/- delayed pressure urticaria, while colchicine is recommended as the alternative treatment option for CSU.[59]

With emerging evidence linking neutrophils to the pathogenesis of CSU, the question arises as to whether targeted therapy specifically directed at neutrophils can offer potential benefits. Wanderer et al[60] have also proposed the potential of targeted therapy focusing on IL-1 to treat neutrophil-predominant urticaria.

## *Unanswered questions and conclusions*

Several questions regarding the roles of neutrophils in CSU still need to be answered, including their precise pathogenesis, their potential as biomarkers, and their therapeutic implications. Investigating whether IL-1 inhibitors or inhibitors targeting other neutrophil-related cytokines have potential roles in managing neutrophil-predominant urticaria is essential. Therefore, further studies are warranted to address these questions, which will contribute to developing more effective and safer therapeutic options for patients with antihistamine-refractory CSU.

## *Conflict-of-interest declarations*

All authors have no conflicts of interest to declare relevant to the contents of this article.

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