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Type 2 Inflammation and Its Role in Dermatologic Diseases

Raj Chovatiya[1,2] | Jason E. Hawkes[3] | Douglas DiRuggiero[4] | Leigh Ann Pansch[5] | Elizabeth Simcox[6] | Tayler Gonzalez[7]

[1]Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois, USA | [2]Center for Medical Dermatology and Immunology Research, Chicago, Illinois, USA | [3]Oregon Medical Research Center, Portland, Oregon, USA | [4]Skin Cancer and Cosmetic Dermatology Center, Rome, Georgia, USA | [5]Dermatologists of Central States (DOCS Dermatology), Cincinnati, Ohio, USA | [6]Regeneron Pharmaceuticals Inc., Tarrytown, New York, USA | [7]Sanofi, Cambridge, Massachusetts, USA

Correspondence: Tayler Gonzalez (tayler.gonzalez@sanofi.com)

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ABSTRACT

Atopic dermatitis, prurigo nodularis, and chronic spontaneous urticaria are immune-mediated, inflammatory skin conditions characterized by intense itch and disease-specific skin lesions. Despite their different clinical presentations, the three diseases are unified by an aberrant type 2 immune response involving type 2 cytokines, immune cells, and sensory nerves that may underlie their shared clinical manifestations of inflammation and pruritus. The chronic nature of these conditions is associated with significant impairment in patients' quality of life and psychological disorders, such as anxiety and depression. This article reviews type 2 inflammation and its role in atopic dermatitis, prurigo nodularis, and chronic spontaneous urticaria, focusing on the pathophysiologic drivers of type 2 inflammation in each dermatologic condition. Understanding the shared immune mechanisms that underlie these seemingly distinct skin diseases and other concomitant inflammatory conditions is critical for applying therapeutic interventions targeting the type 2 immune pathway.

1 | Introduction

Chronic inflammation is driven by abnormal or dysregulated immune responses, often triggered by complex interactions between intrinsic and environmental factors. Under normal physiological circumstances, the role of type 2 inflammation is to provide defense against multicellular parasitic pathogens and environmental irritants, toxins, and allergens. However, aberrant type 2 immune signaling is associated with several inflammatory conditions, such as atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and chronic obstructive pulmonary disease. Recently, dysregulated type 2 inflammation has been identified as contributing to other skin conditions beyond AD, specifically prurigo nodularis (PN) and chronic spontaneous urticaria (CSU). In all three skin diseases, an aberrant type 2 immune response leads to intense itch and skin lesions, which are often chronic and can significantly impact the quality of life. However, despite their shared type 2 pathophysiology, the clinical presentations of AD, PN, and CSU diverge, with distinct patterns of skin manifestations and clinical courses.

This review aims to provide an overview of type 2 inflammation and its contribution to AD, PN, and CSU. Specifically, we highlight the role of immune cells and cytokines that contribute to disease activity and progression. We also explore the therapeutic rationale for targeting the type 2 inflammatory axis to modulate the immune dysregulation in AD, PN, and CSU.

2 | Overview of the Immune System

The human immune system consists of innate and adaptive responses. The innate immune system recognizes molecular

patterns shared by many pathogens. It provides an initial, rapid, non-specific immune response, whereas the adaptive immune system targets specific invading pathogens and provides long-term immune protection through immunologic memory [1]. Activation of the adaptive immune system is a highly orchestrated process involving various signals from the innate system to confer the specific host response through clonal selection [2]. While immune responses can be categorized in several ways, they are conventionally grouped into three major modules based on shared activity and functions, distinguished by the involvement of specific innate and adaptive immune cells and cytokines (Figure 1; Supporting Information) [3].

Type 1 immunity predominantly targets intracellular pathogens, including viruses, intracellular bacteria, and transformed cancer cells. It is mediated by T helper (Th) type 1 cells, T cytotoxic (Tc) cells, and group 1 innate lymphoid cells (ILC1s). Infected or malignant cells are eliminated through the release of proinflammatory cytokines, such as interferon (IFN), interleukin (IL)-12, and tumor necrosis factor (TNF) [4].

Type 2 immunity provides defense against parasites, mainly helminths, and diverse environmental threats, including toxins and irritants. It is driven by Th2 cells, Tc2 cells, group 2 ILCs (ILC2s), and mast cells, which release alarmins and signature cytokines (IL-4, IL-5, IL-13, and IL-31). In turn, type 2 cytokines recruit effector cells, such as eosinophils and basophils, and promote further Th2 polarization, keratinocyte hyperproliferation, and B cell class switching to immunoglobulin E (IgE), IgG, and IgA. Type 2 immune mechanisms aim to eliminate parasites by triggering expulsion (e.g., the itch/scratch reflex) and fibrosis (e.g., wound repair) [5].

Type 3 immunity mainly protects against extracellular fungi and bacteria. Its main cellular components are group 3 ILCs (ILC3s), Th17, and Tc17 cells, which produce IL-17 and IL-22 cytokines. IL-17 cytokines stimulate the production of a broad array of proinflammatory proteins secreted by keratinocytes, including antimicrobial peptides and IL-36 [6]. This results in the recruitment of neutrophils and activation of other immune cells to protect against pathogens through phagocytosis and tissue inflammation [3].

Under normal physiologic conditions, the various types of immune responses serve protective roles and have multiple layers of regulatory mechanisms. However, chronic inflammation and inflammatory diseases can arise when immune responses become dysregulated. Dysregulated type 1 immunity contributes to psoriatic arthritis, rheumatoid arthritis, Hashimoto thyroiditis, and multiple sclerosis [3, 7]. Dysregulated type 2 immunity can contribute to various chronic inflammatory diseases, including AD, allergic rhinitis, allergic asthma, PN, CSU, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis [8, 9]. Type 3 diseases include plaque psoriasis and ankylosing spondylitis [6, 10].

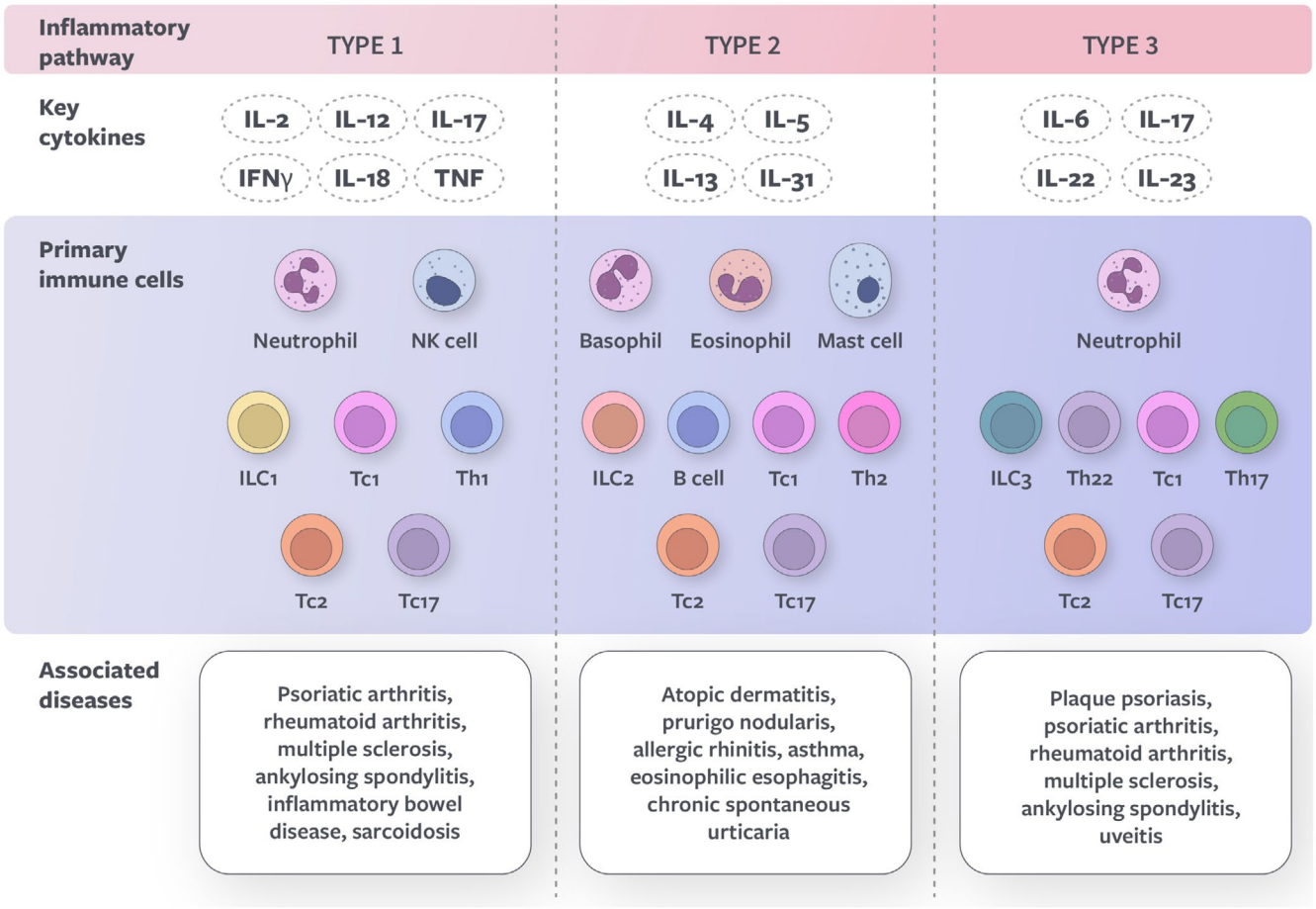

FIGURE 1 | Overview of types 1, 2, and 3 immune responses. IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; NK, natural killer; Tc, T cytotoxic cell; Th, T helper cell; TNF, tumor necrosis factor.

3 | The Role of IL-4 and IL-13 in Type 2 Inflammation

Type 2 immunity is characterized by the expression of type 2 cytokines (IL-4, IL-5, IL-13, and IL-31), crucial in regulating immune responses to allergens, irritants, and parasites. This occurs in concert with innate cells, adaptive cells, cutaneous neurons, and keratinocytes that perpetuate the polarization of a type 2 immune response. Type 2 cytokines and their receptors are widely expressed among cell types from both the innate and adaptive arms of the immune system [11–15]. In AD, PN, and CSU, type 2 cytokines are critical mediators of inflammation at both the systemic and local tissue levels and employ the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway to exert their effect through direct receptor binding (see Supporting Information) [16].

IL-4 and IL-13 are the two primary effector cytokines in type 2 immunity. They share some functions but are not identical or interchangeable. Both IL-4 and IL-13 promote IgE production, mast cell and basophil activation and degranulation, fibrotic tissue remodeling, skin barrier dysfunction, and microbiome imbalance [17–21]. In addition, IL-4 and IL-13 act on receptors in sensory neurons, increasing their sensitivity to several pruritogens [22]. IL-4, but not IL-13, is essential for Th2 cell differentiation and polarization, further amplifying the systemic inflammatory response through the release of IL-4, IL-5, IL-13, and IL-31 [19, 20, 23, 24]. In contrast, IL-13 has a role in peripheral immunity as an effector cytokine in end-organ tissues [25]. It contributes to skin pathology by promoting collagen deposition [17, 21]. IL-4, IL-13, and IL-5 control eosinophil recruitment and trafficking into tissue, whereas IL-5 also controls eosinophil survival and differentiation [19, 20]. IL-31 is primarily produced by differentiated T lymphocytes and mediates itch sensations upon binding to its receptor IL-31RA, expressed on various cell types, including sensory neurons, keratinocytes, and immune cells [24, 26]. In addition, IL-31 may contribute to inflammation, skin barrier dysfunction, and fibrosis [26, 27].

Activating immune cells and enhancing immune cell trafficking to tissues amplify type 2 inflammation and establish a chronic and persistent disease phenotype [8, 18]. Continued activation of type 2 immunity may lead to the emergence of resident memory T lymphocytes and long-term changes in the immune response.

4 | Neuroimmune Interactions

Immune cells, neurons, and cytokines work together to perpetuate the chronic inflammatory state at the tissue level. In the localized tissue microenvironment, the proximity of immune cells and sensory neurons fosters dynamic crosstalk, enabling reciprocal stimulation and modulation of inflammatory pathways. The interaction between nerves, mast cells, T cells, eosinophils, and other immune cells triggers the release of proinflammatory mediators such as histamines and cytokines, promoting itch, pain, and inflammation. Additionally, sensory neurons can be activated by alarmins (IL-33, thymic stromal lymphopoietin; see Supporting Information) produced by keratinocytes. Activated sensory neurons release neuropeptides, such as substance P (see Supporting Information), which further activate immune cells and promote chronic inflammation [8, 9, 20, 28, 29].

Recent therapeutic strategies have revealed that targeting mediators of type 2 inflammation can alleviate various dermatologic conditions previously thought to have different disease drivers. AD, PN, and CSU are distinct skin conditions with disease-specific signs and symptoms, but they share an intricate crosstalk between sensory cells and type 2 immune cells. It is now appreciated that sensory neurons play a crucial role in relaying signals, generating their molecular messengers that impact surrounding immune components in the skin. However, this shared pathophysiology manifests uniquely in each disorder. In AD and PN, the itch is persistent, with primary skin lesions reflective of the itch-scratch cycle. In contrast, itch and pain in CSU fluctuate with the transient nature of urticarial lesions and leave no residual skin changes upon resolution. Unraveling the intricacies of type 2 inflammation in AD, PN, and CSU enhances our understanding of the immune response and holds promise for therapeutic interventions targeting their common elements.

5 | Atopic Dermatitis

AD is a debilitating systemic disease characterized by recurrent eczematous lesions, skin barrier disruption, and intense pruritus [30]. AD usually develops in childhood and often persists into adulthood [31], with an estimated prevalence of 11.8% in the US pediatric population [32] and 7.3% in the US adult population [33]. AD pathogenesis involves a complex interplay of genetic and environmental factors. Genetic predisposition to AD can derive from mutations in genes related to skin barrier function (e.g., *FLG* and *LOR*) and immune response regulation (e.g., *CARD14* and *TLR* genes) [34]; such genetic variations may increase susceptibility to environmental triggers such as irritants, allergens, and pathogens [35, 36].

Patients with AD experience a multidimensional disease burden that can have a significant impact on quality of life. The persistent itch and pain can lead to sleep disturbances, reduced productivity, and absenteeism from work and school [37–39]. These effects, together with the distress caused by visible skin lesions, can strongly contribute to mental health disorders such as anxiety and depression [37]. Moreover, AD is often associated with comorbidities such as allergic conditions, skin infections, and cardiovascular diseases [40].

Type 2 cytokines are key drivers of the pathophysiology of AD (Figure 2). Disruption of the epithelial barrier triggers the release of alarmins (see Supporting Information), which act as early soluble signals to stimulate the polarization of a type 2 immune response [42, 43]. Type 2 inflammation leads to the activation of immune effector cells, which infiltrate the skin and perpetuate the inflammatory response. Elevated Th2 cytokines result in the downregulation of antimicrobial peptides and barrier proteins in keratinocytes, weakening the skin defenses and increasing the risk of infections [44, 45]. IL-4 and IL-13 have sensitized neurons to a range of pruritogens (e.g., IL-31 and histamine),

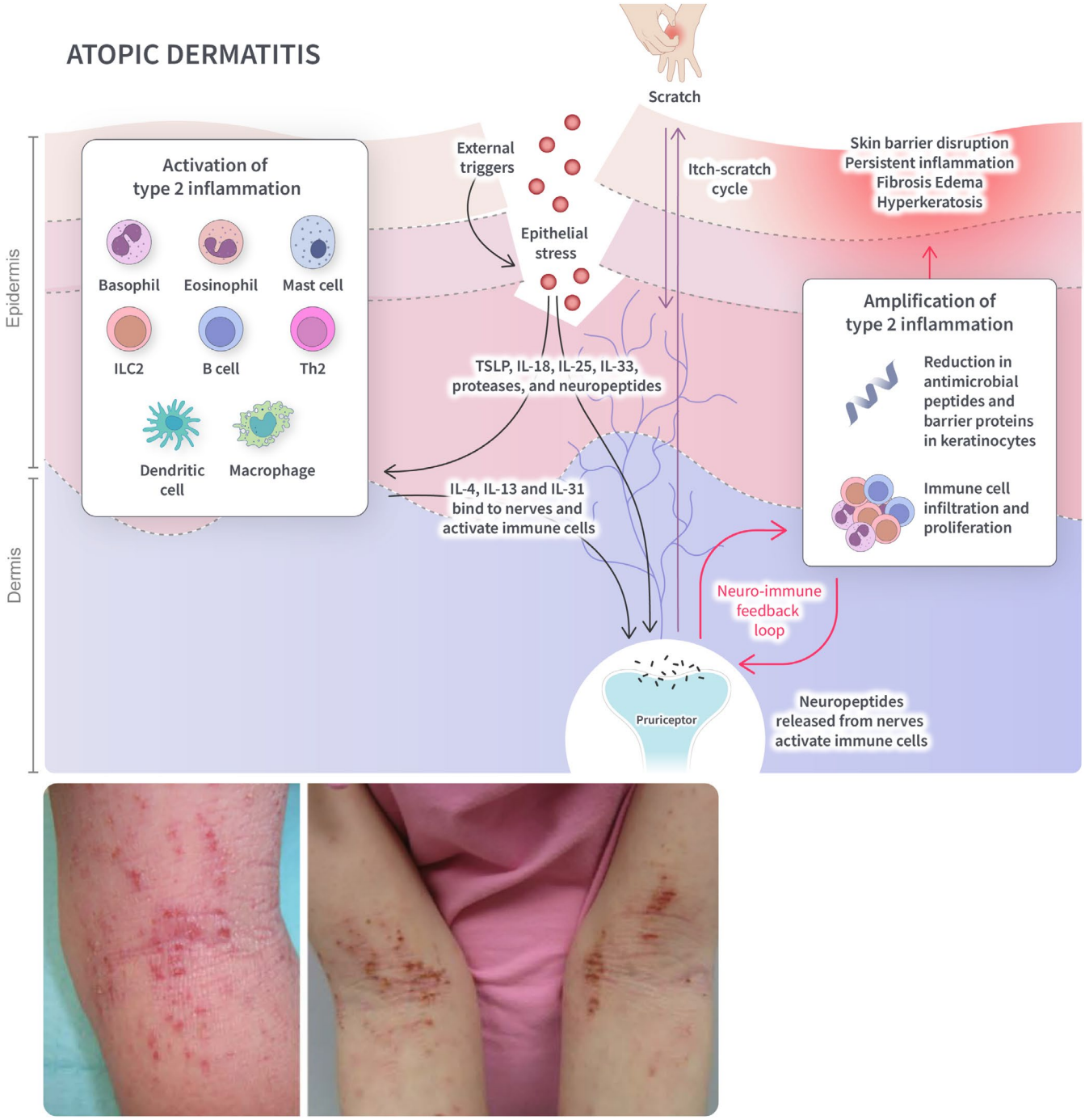

FIGURE 2 | Overview of type 2 inflammation in AD. Skin barrier disruption triggers the release of alarmins (IL-25, IL-33, TLSP), which stimulate a type 2 immune response. Type 2 cytokines (IL-4 and IL-13) activate immune cells and sensitize neurons to pruritogens, leading to an itch-scratch cycle. A neuro-immune feedback loop results in the amplification of type 2 inflammation and further skin barrier disruption through scratching. IL, interleukin; ILC, innate lymphoid cell; Th, T helper cell; TSLP, thymic stromal lymphopoietin. *Source:* Siegfried et al. [41].

resulting in chronic itch [22, 46]. Furthermore, a feedback loop occurs where IL-4, produced by Th2 cells and potentially mast cells and basophils, acts on Th2 cells to trigger the production of IL-31, along with more IL-4 and IL-13 [19, 23, 47]. Scratching can also further disrupt the epithelial barrier and lead to a continued increase in alarmin production by keratinocytes, thereby promoting disease chronicity in the skin [47].

The chronic inflammatory signaling driven by type 2 cytokines and immune effector cells can lead to maladaptive responses. Persistent scratching can give rise to epidermal thickening (lichenification) and excoriations [42]. Skin barrier function is further disrupted, resulting in a vicious cycle of increased susceptibility to irritants and allergens, inflammation, and skin barrier dysfunction [30]. In addition, a dysfunctional skin barrier is often associated with alterations in the skin microbiome and increased colonization by *Staphylococcus aureus* [48]. The overgrowth of *S. aureus* can trigger inflammatory responses in keratinocytes through the activation of pattern recognition receptors and promote the release of toxins, further aggravating

the epidermal barrier disruption, lesion chronicity, and susceptibility to infections [48, 49].

Emollients and moisturizers are pivotal in managing AD to restore skin barrier function and thereby reduce inflammatory signals produced by activated keratinocytes [50, 51]. Topical corticosteroids, available in various potency levels, may further alleviate inflammation and pruritus by modulating immune responses in the skin. However, prolonged use can lead to skin atrophy, so their application requires non-continuous treatment and monitoring [51, 52]. Non-steroidal anti-inflammatories such as topical calcineurin inhibitors (e.g., tacrolimus and pimecrolimus), topical JAK inhibitors (e.g., ruxolitinib), topical phosphodiesterase 4 inhibitors (e.g., crisaborole and roflumilast) and aryl hydrocarbon receptor modulators (e.g., tapinarof) offer an alternative for sensitive areas such as the face, neck, and genitals [50–55]. In cases of moderate-to-severe AD unresponsive to topical treatments, phototherapy or systemic medications, such as oral immunosuppressants, may be considered. Traditional immunosuppressive agents used to treat AD include azathioprine, cyclosporine, and methotrexate; however, these medications require close laboratory monitoring due to their narrow therapeutic index, multiple drug–drug interactions, and the potential for serious side effects, including kidney or liver injury, bone marrow suppression, pulmonary fibrosis, and hypertension [51, 56, 57].

More recently, injectable biologics (e.g., dupilumab, tralokinumab, lebrikizumab, and nemolizumab) have demonstrated efficacy and safety in the treatment of moderate-to-severe AD [51, 57–62]. Dupilumab, the first biologic approved for the treatment of AD, modulates the type 2 immune response and inflammation through dual inhibition of IL-4 and IL-13 by blocking the IL-4Rα subunit [51, 57]. Tralokinumab and lebrikizumab reduce the inflammatory response associated with AD through inhibition of IL-13 [58, 59]. In contrast, nemolizumab inhibits the signaling of IL-31 by blocking IL-31Rα and is therefore effective at reducing pruritus and inflammation [60–62]. However, the ability of nemolizumab to adequately suppress type 2 inflammatory circuits in the skin through the inhibition of IL-31 signaling alone has not been fully elucidated. Additional clinical studies are needed to compare the clinical significance of IL-31 blockade versus selective blockade of IL-4 and/or IL-13 signaling in primary cutaneous conditions.

For patients who are not responsive to biologics and other systemic therapies, oral JAK inhibitors have emerged as an efficacious alternative, though more studies are needed to assess their long-term safety [63, 64]. JAK inhibitors alleviate AD symptoms by blocking the JAK/STAT signaling pathway, which is involved in intracellular signaling pathways for a broad range of inflammatory cytokines and growth factors [57, 63, 64]. Finally, early clinical studies exploring the OX40 receptor and its ligand (OX40L) as therapeutic targets for AD have recently shown promise [65–67]. OX40, primarily expressed on the surface of activated T cells, modulates immune responses by promoting T-cell survival and proliferation [67–69]. OX40L belongs to the TNF superfamily and is primarily expressed on antigen-presenting cells, such as dendritic and B cell populations [70]. By targeting the OX40/OX40L pathway, novel drugs such as rocatinlimab (anti-OX40), telazorlimab (anti-OX40), and amlitelimab (anti-OX40L) aim to regulate memory and regulatory T-cell responses, thereby reducing the inflammation and immune dysfunction observed in AD [65–67, 69].

6 | Prurigo Nodularis

PN is a chronic inflammatory skin condition with an estimated prevalence of 72 out of 100,000 individuals in the U.S. adult population [71]. The diagnosis of PN is based on the following clinical features: firm, itchy lesions that can present as nodules, papules, or plaques, generally with a bilateral distribution on the arms and trunk and sparing areas that are hard to reach; chronic pruritus lasting 6 weeks or more; history and/or signs of repeated scratching, picking, or rubbing [72–74]. PN primarily affects middle-aged to older patients (50 years of age and older) [75]. PN signs and symptoms (intense itch, skin lesions, bleeding of excoriated lesions, scars with skin dyspigmentation) [72, 76, 77] can have a severe impact on patients' quality of life and are associated with sleep disturbance, absenteeism from work, symptoms of depression and anxiety, and a feeling of shame and helplessness [72, 78].

The exact pathophysiology of PN is still being elucidated. However, PN is thought to occur due to neuronal dysfunction, sensitization to itch, and the subsequent development of an itch-scratch cycle [72]. Activation of sensory neurons through neuronal dysfunction and scratching may trigger the release of neuropeptides (see Supporting Information), which activate immune cells (Figure 3). Immune cell activation and the subsequent release of type 2 (IL-4, IL-13, and IL-31) and type 3 (IL-17) proinflammatory cytokines are likely to promote the development of chronic inflammation [9, 79–81]. The stimulation of fibroblasts by IL-4 and IL-13 may promote dermal fibrosis through extracellular matrix deposition, fibroblast proliferation, and myofibroblast differentiation [82]; furthermore, IL-4 and IL-13 are thought to trigger the production of periostin, which enhances itch and contributes to dermal fibrosis [83, 84]. Periostin acts on keratinocytes to induce the production of proinflammatory cytokines, further driving chronicity [83]. In addition, the stimulation of sensory neurons by IL-4, IL-13, and IL-31 induces persistent itch [9, 81]. Chronic neurogenic inflammation and immune cell infiltration may lead to fibrotic nodules and epidermal hyperplasia, further exacerbated by the itch-scratch cycle [72, 80, 85].

Treatment options for PN typically involve a multifaceted approach tailored to the patient's symptoms and underlying factors, often combining topical and oral systemic therapies [74]. Topical corticosteroids or calcineurin inhibitors may be applied directly to affected areas to alleviate itching and reduce inflammation [74]. Phototherapy and off-label systemic medications, such as gabapentinoids and antidepressants, may be considered for more widespread and persistent cases to modulate the neural pathways associated with itch and the development of PN [74, 86, 87]. In more severe cases that are resistant to other treatments, immunosuppressive medications such as oral corticosteroids, methotrexate, cyclosporine, or azathioprine may be considered, although their potential risks and long-term side effects must be carefully evaluated [86, 87].

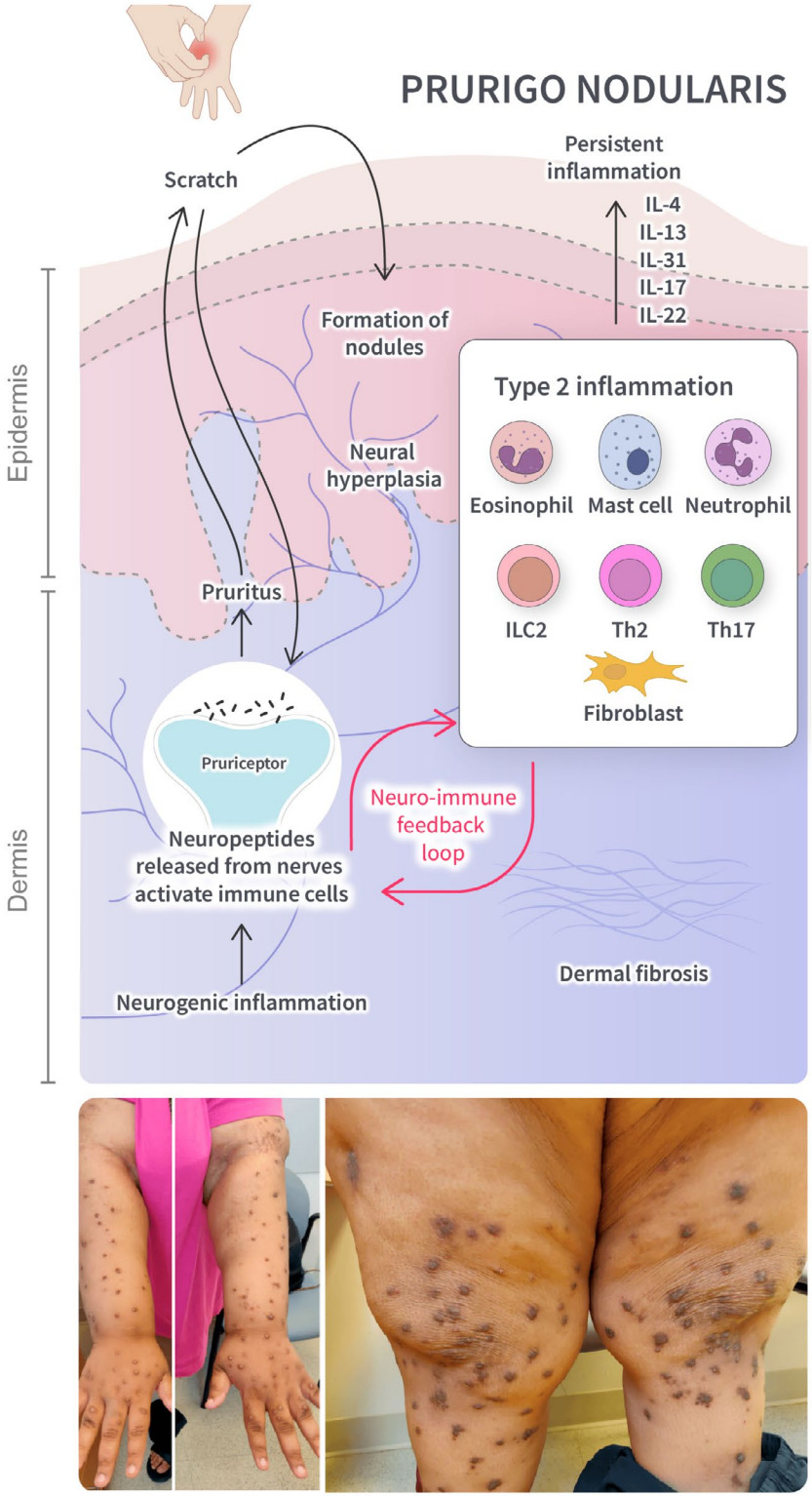

FIGURE 3 | Overview of type 2 inflammation in PN. Neurogenic inflammation triggers the release of neuropeptides, which activate immune cells. This leads to the release of type 2 cytokines, resulting in itch and chronic inflammation. Persistent scratching may lead to the formation of nodules. IL-4 and IL-13 stimulate fibroblasts, promoting dermal fibrosis. IL, interleukin; ILC, innate lymphoid cell; Th, T helper cell. *Source:* Kwon et al. [73].

Dupilumab, which inhibits the signaling of cytokines IL-4 and IL-13, is the first approved systemic therapy for adults with PN [88, 89]. Treatment with dupilumab in two phase 3 trials led to significant improvements in multiple aspects of PN, with a safety profile consistent with its known safety profile [89]. Nemolizumab, also approved for PN, targets the IL-31 receptor and has been associated with improvements in PN lesions and pruritus in phase 2 and 3 trials [88, 90, 91]. Furthermore, JAK inhibitors abrocitinib and upadacitinib have shown promise for managing PN, offering another targeted approach to interrupt

type 2 inflammatory pathways [92–94]. The potential benefits of selective blockade of IL-17 or IL-23 for treating PN are not yet known but may be useful in a subset of PN patients with increased IL-17 signaling in PN lesions.

7 | Chronic Spontaneous Urticaria

CSU is a chronic, heterogeneous, inflammatory condition characterized by recurrent transient, itchy wheals (hives), with or without angioedema, for more than 6 weeks without an identifiable trigger [95–97]. CSU differs from chronic inducible urticaria, induced by a definite trigger (e.g., cold, pressure, or ultraviolet exposure), and acute urticaria, defined by a duration of less than 6 weeks [97]. CSU and chronic inducible urticaria can occur simultaneously in the same patient.

CSU affects all age groups, with a higher incidence in 20- to 40-year-olds and a prevalence of 0.08%–0.11% in the United States [97, 98]. In adults, CSU is twice as common in women than in men [98]. Despite the self-remitting nature of the disease, many patients with CSU experience a prolonged disease course that can last for more than 5 years [99]. The appearance of CSU lesions is unpredictable and associated with anticipatory fear, debilitating itch, impaired sleep, and occasional skin pain or a burning sensation [97, 100]. Furthermore, CSU is often accompanied by comorbid autoimmune diseases (e.g., vitiligo, autoimmune thyroiditis) and, to a lesser extent, atopic conditions (e.g., AD, asthma) [97, 100]. CSU strongly affects patients' quality of life and is linked to psychosocial disorders, such as depression and anxiety [97, 101].

While the pathogenesis of CSU is not fully understood, activation of the mast cell through various autoimmune mechanisms is central to this condition [102, 103]. CSU clinical manifestations are driven by mast cell degranulation and the subsequent release of histamines, followed by leukotrienes, prostaglandins, and proinflammatory cytokines (IL-4, IL-13, IL-31) [102–104]. Mast cell degranulation in CSU may occur via IgE-dependent (type I autoimmunity/autoallergic) as well as IgE-independent pathways (type IIb autoimmunity); in the IgE-dependent pathway, autoallergens induce cross-linking of IgE antibodies bound to the high-affinity IgE receptor (FcεRI) on the surface of mast cells, whereas the IgE-independent pathway may involve the presence of IgG autoantibodies directed against IgE and FcεRI [102–104]. The release of inflammatory mediators leads to vasodilation, increased extravasation, activation of sensory skin nerves, and the recruitment of immune cells [103, 104]. In addition to mast cells, the pathogenesis of CSU involves a perivascular infiltrate of inflammatory cells, including T lymphocytes (predominantly Th2), basophils, and eosinophils [102].

Type 2 inflammation is thought to contribute to the pathophysiology of CSU through multiple processes (Figure 4). IL-4 is a key driver of differentiating naïve T lymphocytes from Th2 cells [19, 103]. IL-4 and IL-13 promote B-cell activation and IgE production and enhance autoantibody-mediated mechanisms, as well as trafficking of type 2 immune cells to the site of inflammation [19, 102–104]. At the neuroimmune axis, IL-4 and IL-13 activate and sensitize nerves to a range of pruritogens, including histamines and IL-31 [19, 102, 105]. Released neuropeptides from activated neurons potentially act as ligands by binding to MRGPRX2 receptors on cutaneous mast cells, leading to further activation and release of various inflammatory mediators [97, 102]. Collectively, these effects may lead to mast cell hyperactivity and contribute to a continuous cycle of neuroimmune inflammation [97, 102, 103].

Treatment of CSU can pose a challenge due to the recurrent and unpredictable nature of the disease. CSU treatment options aim to prevent new skin lesions, alleviate symptoms, and improve the patient's quality of life [96, 106, 107]. Nonsedating antihistamines, such as second-generation H_1-antagonists, are the first-line treatment for CSU [106–108]. Many patients, however, do not achieve symptom control with H_1 antihistamines, even after up-dosing [109]. Omalizumab, an anti-IgE monoclonal antibody, is approved for antihistamine-refractory cases [110], but approximately 25% of these patients remain symptomatic [111, 112]. Dupilumab has recently been approved for CSU in Japan, Brazil, and the United Arab Emirates and is currently under regulatory review for CSU in the US and EU, following phase 3 clinical trials [112, 113]. Recent clinical studies with Bruton's tyrosine kinase (BTK) inhibitors, such as remibrutinib and rilzabrutinib, have shown promise in patients who are refractory to H_1 antihistamines, supporting the rationale for interrupting type 2 inflammatory pathways and mast cell activation, respectively, in the management of CSU [114, 115]. Phase 2 clinical studies evaluating oral remibrutinib showed a rapid onset of action, clinical efficacy, and a favorable safety profile over 52 weeks [114, 116]; these treatment characteristics were validated in the early analysis of phase 3 clinical studies [117, 118]. Oral BTK inhibition as a treatment for CSU will be further explored in planned phase 3 clinical trials for rilzabrutinib. A variety of other novel mechanisms of action, including blockade of c-KIT and siglec-6 receptors on mast cells, are currently being evaluated and will potentially expand CSU treatment options.

8 | Shared Pathophysiology of Atopic Dermatitis, Prurigo Nodularis, Chronic Spontaneous Urticaria, and Beyond

AD, PN, and CSU are distinct inflammatory conditions with unique clinical presentations. Yet, they are unified by an interplay of cellular and molecular factors that modulate type 2 inflammation and neuroimmune interactions, which lead to their shared clinical manifestations of inflammation, pruritus, epidermal barrier dysfunction, and primary skin lesions. Dysregulation of sensory nerves is implicated in itch and neurogenic inflammation across the three conditions [42, 72, 85, 97, 102]. The interplay of dysregulated modules in neurons, cytokines, mediators, and immune cells at the epidermis and dermis contributes to the unique clinical manifestations observed in each condition.

The shared thread of a skewed, overactive type 2 immune response and neurosensitization may explain the common co-occurrence of allergic and atopic inflammatory conditions. AD is a prevalent comorbidity in patients with PN [73, 76] and is often associated with a personal or family history of asthma and allergic rhinitis [40]. Furthermore, the predisposition to allergic responses and increased levels of IgE antibodies seen in AD and asthma are also observed in CSU [119, 120].

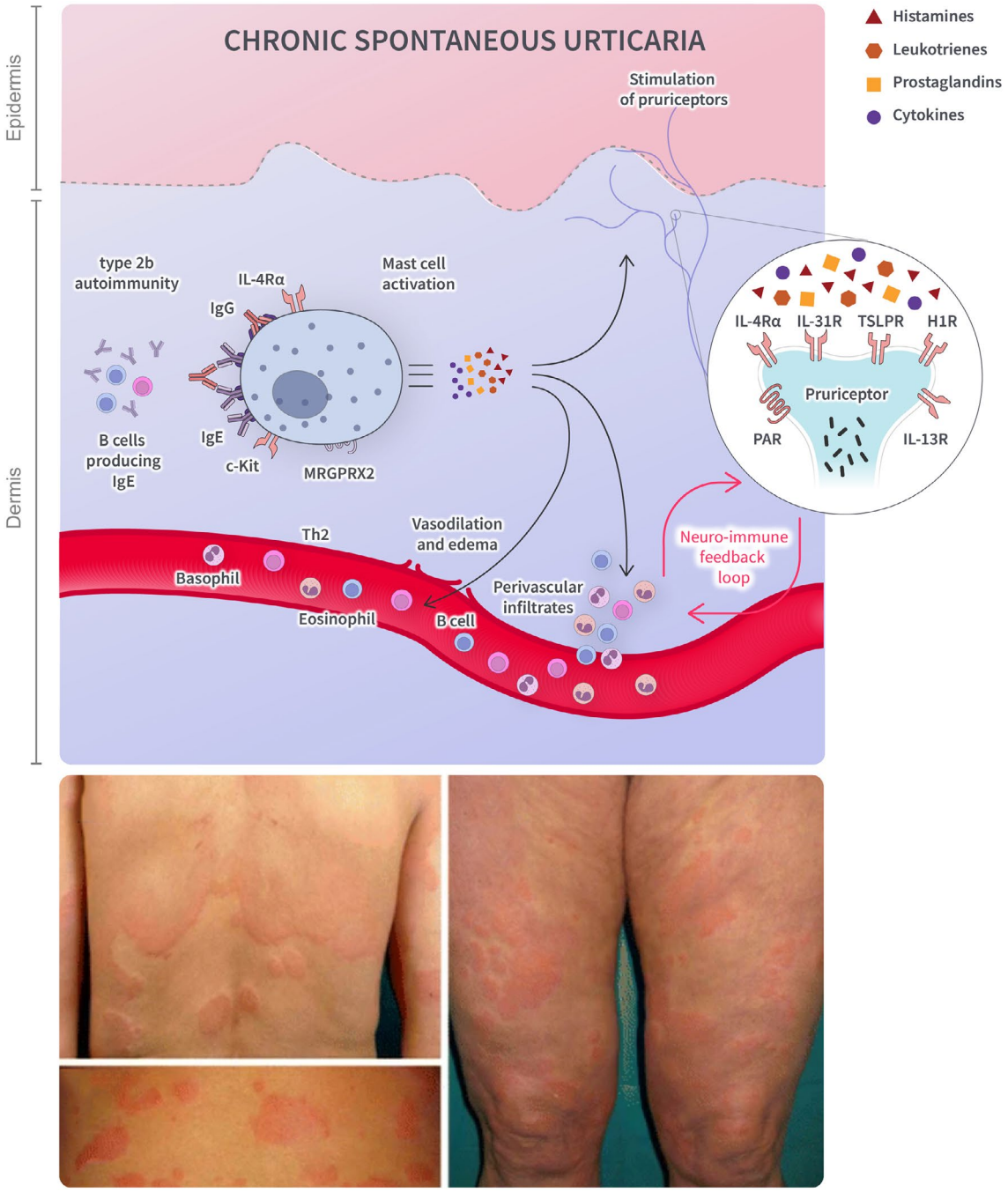

FIGURE 4 | Overview of type 2 inflammation in CSU. Mast cell degranulation is induced by IgE antibodies binding to high-affinity IgE receptors on the mast cell surface and/or by IgG antibodies targeting IgE and high-affinity IgE receptors. Mast cell activation leads to the release of histamines, followed by leukotrienes, prostaglandins, and cytokines. The release of inflammatory mediators results in the recruitment of immune cells, vasodilation, and activation of skin nerves. A perivascular infiltrate of inflammatory cells is also thought to drive clinical manifestations of CSU. BTK, Bruton's tyrosine kinase pathway; H, histamine; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; MRGPRX2, mas-related G-protein coupled receptor member; X2, PAR protease-activated receptor; R, receptor; SYK, spleen tyrosine kinase pathway; Th, T helper cell, TSLP, thymic stromal lymphopoietin. *Source:* Marzano et al. [95].

In addition to AD, PN, and CSU, type 2 immune circuits may contribute to the pathogenesis of other dermatological conditions, such as bullous pemphigoid, lichen planus, Grover's disease, and chronic pruritus of unknown origin. In bullous pemphigoid, type 2 inflammatory cytokines (particularly IL-4, IL-5, and IL-13) are thought to drive the recruitment of mast cells and eosinophils, contributing to blister formation [121]. The immunological pathways underlying lichen planus and Grover's disease are poorly understood, though both are considered mixed inflammatory conditions involving type 1 and 2 immune mechanisms [122–124]. Several cases of cutaneous lichen planus and Grover disease have been responsive to dupilumab [124–128], suggesting a potential role of type 2 immune responses in the pathogenesis of both conditions. The number of published cases reporting the potential clinical benefits of type 2 blockade in numerous dermatologic and nondermatologic immune conditions is rapidly growing, with

multiple biologic agents available to clinicians. These findings highlight the complex interplay between type 2 immunity and diverse clinical manifestations, underscoring the need for further research into type 2 inflammation across different diseases.

A deeper understanding of the type 2 pathway has led to novel therapies targeting shared mechanisms in various type 2 inflammatory conditions (Table 1). Targeting multiple co-occurring conditions with a single therapy can simplify treatment regimens and enhance patient outcomes. For instance, dupilumab modulates the immune response by inhibiting IL-4 and IL-13 signaling and has demonstrated efficacy in AD, PN, CSU, asthma, eosinophilic esophagitis, chronic obstructive pulmonary disease, and chronic rhinosinusitis with nasal polyps and is currently being evaluated in bullous pemphigoid, chronic pruritus of unknown origin, and pruritus of lichen simplex chronicus [88, 112, 113, 129–135]. Omalizumab targets IgE and is used for asthma, CSU, chronic rhinosinusitis with nasal polyps, and food allergies [110, 136, 137] but was not successful in AD trials [138]. Similarly, while effective in AD, biologics targeting only IL-13 (e.g., tralokinumab, lebrikizumab) did not significantly improve severe asthma and chronic obstructive pulmonary disease [139–142]. Nemolizumab, an anti-IL-31R biologic, has demonstrated efficacy in the management of AD and PN but had paradoxical effects of AD and asthma exacerbation in a subset of patients [61, 62, 143], leading to questions about its ability to regulate type 2 inflammation in the skin alone. This highlights the many unanswered questions in elucidating the functions of the different type 2 cytokines and immune cells. For example, are there distinct types of mast cell stimuli that induce various types of mast cell mediators, leading to differences in itch modalities (histaminergic vs. nonhistaminergic)? What are the long-term implications of underlying systemic type 2 inflammation on human health? Could the regulation of IL-4 in Th2 polarization and/or the dual inhibition of IL-4 and IL-13 influence immune processes locally and systemically, providing a more comprehensive approach to managing type 2 inflammatory conditions? What are the unique immunological and biological functions of IL-4 alone? Is IL-4 more relevant than IL-13 in type 2 inflammation? Future investigations into shared pathways rather than distinct disease states likely hold the key to understanding AD, PN, CSU, and many other type 2 inflammatory conditions.

TABLE 1 | Approved therapeutics targeting type 2 immune responses.

Drug	Mechanism	Approved indications
Dupilumab	Anti-IL-4/IL-13	Atopic dermatitis
		Prurigo nodularis
		Asthma
		Eosinophilic esophagitis
		Chronic rhinosinusitis with nasal polyps
		Chronic obstructive pulmonary disease
Omalizumab	Anti-IgE	Chronic spontaneous urticaria
		Asthma
		Chronic rhinosinusitis with nasal polyps
		Food allergies
Tralokinumab, Lebrikizumab	Anti-IL-13	Atopic dermatitis
Nemolizumab	Anti-IL-31	Atopic dermatitis
		Prurigo nodularis
Abrocitinib, Upadacitinib	JAK1 inhibitor	Atopic dermatitis

9 | Concluding Remarks

Immune dysregulation can contribute to several chronic inflammatory conditions. Although AD, PN, and CSU are distinct clinical entities, they are all characterized by chronic itch and skin lesions that significantly affect quality of life. Unveiling the complexity of type 2 immunity has fueled the clinical development of advanced, targeted therapies that inhibit key elements within this immune pathway. Such therapies have transformed our ability to alleviate the disease burden of several type 2 inflammatory diseases while simultaneously setting new disease clearance and tolerability standards. Current challenges lie in understanding the intricate and non-linear nature of type 2 immune responses, identifying disease biomarkers that predict clinical responses to specific therapies, developing treatment regimens that restore immune tolerance and/or induce disease remission, and assessing long-term patient outcomes.

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Conflicts of Interest

Raj Chovatiya has served as an advisor, consultant, speaker, and/or investigator for AbbVie, Amgen, Apogee Therapeutics, Arcutis Biotherapeutics, Argenx, Aslan Pharmaceuticals, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Dermavant, Eli Lilly, FIDE, Formation Bio, Galderma, Genentech, GSK, Incyte, L'Oréal, LEO Pharma, Nektar Therapeutics, Novartis, Opsidio, Pfizer, RAPT Therapeutics, Regeneron Pharmaceuticals Inc., Sanofi, Sitryx, and UCB. Jason Hawkes has served as an advisor, consultant, speaker, medical board member, and/or counselor for Apogee Therapeutics, Arcutis Biotherapeutics, Boehringer Ingelheim, Blueprint Medicines, Bristol Myers Squibb, Boxer Capital LLC, Galderma, Institute for Systems Biology (ISB), International Psoriasis Council, Janssen, LEO Pharma, National Psoriasis Foundation, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, Sun Pharma, Takeda, and UCB. Douglas DiRuggiero has served as an advisor, consultant, and/or speaker for AbbVie, Amgen, Arcutis Biotherapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Galderma, Incyte, Janssen, LEO

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Data Availability Statement

Data sharing does not apply to this article, as no datasets were generated or analyzed.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.