Interleukin-31 targeting and other novel drugs in itch

Peter Olah, Ulrike Raap, Bernhard Homey

Article - Version of Record

Suggested Citation:
Oláh, P., Raap, U., & Homey, B. (2025). Interleukin-31 targeting and other novel drugs in itch. Annals of Allergy, Asthma, & Immunology, 136(2), 141–148. https://doi.org/10.1016/j.anai.2025.11.007

Ann Allergy Asthma Immunol 136 (2026) 141–148

Contents lists available at ScienceDirect

Review

Interleukin-31 targeting and other novel drugs in itch

Peter Olah, PhD*; Ulrike Raap, MD†,‡; Bernhard Homey, MD*

* Department of Dermatology, University Hospital Düsseldorf, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany
† Division of Experimental Allergy and Immunodermatology, Faculty of Medicine and Health Sciences, University of Oldenburg, Oldenburg, Germany
‡ University Clinic of Dermatology and Allergy, Oldenburg Clinic, Oldenburg, Germany

Key Messages

- Itch represents the most significant quality-of-life burden in a range of chronic inflammatory skin conditions.
- Biological therapies have offered increasingly effective targeted interventions for the treatment of chronic pruritus in recent years.
- Although Janus kinase inhibitors generally offer faster itch relief than biologicals, their broader effects and safety profiles may pose clinical challenges.
- The targeted blockage of interleukin-31 thus offers a promising avenue of rapid itch relief combined with broader safety margins.

ARTICLE INFO

Article history:
Received for publication September 4, 2025.
Received in revised form November 8, 2025.
Accepted for publication November 10, 2025.

ABSTRACT

Chronic pruritus is a debilitating symptom of several inflammatory skin conditions, presenting severe quality-of-life decreasing effects and major clinical challenges in terms of disease management. In the past decade, novel biological therapies have offered increasingly effective targeted interventions for the treatment of chronic pruritus, in which traditional approaches were often lacking or presented suboptimal safety profiles. However, recent advancements in the molecular characterization of sensory neuronal subsets helped to shed light on specific mechanisms of pruriception and thus have furthered our understanding of the peripheral nervous system and disease-relevant neuroimmune crosstalk. These developments have highlighted the targeting of interleukin-31, a major pruritus-associated cytokine, as a highly promising therapeutic target for chronic pruritus in inflammatory skin conditions. In this review, we therefore provide a focused overview of inflammatory conditions in which pruritus represents the major burden, the fundamental immune pathways, and sensory circuits involved, alongside the efficacies and safety profiles of novel therapies addressing chronic pruritus.

Introduction

Pruritus (or itch) is an evolutionarily vital, unpleasant sensation that provokes the specific behavior of scratching or rubbing the affected area. According to the 2025 Delphi consensus, itch can be defined as "(...) an unpleasant sensation of the skin and/or neighboring mucous membranes commonly triggering an urge to scratch," which "(...) can be triggered, worsened or improved by a broad variety of external and internal factors."[1] Indeed, it can be caused by many factors, including the following: dry skin, allergic reactions, insect bites, or chronic inflammatory skin diseases, such as atopic dermatitis (AD), prurigo nodularis (PN), bullous pemphigoid, lichen planus (LP), or psoriasis; or systemic issues such as liver or kidney disease.[2,3] Uncovering the neural pathways of itch has led to its definite distinction from pain.[4] The International Forum for the Study of Itch (IFSI) has established etiologic categories for itch, which comprise the following: dermatologic, systemic, neurologic, psychiatric diseases and mixed causes, and "other causes."[5,6] Furthermore, the IFSI distinguishes pruritus into acute and chronic based on duration: itch lasting less than 6 weeks is acute, whereas that lasting 6 weeks or more is defined as chronic pruritus.[7] The IFSI had developed a clinical

Address correspondence to: Bernhard Homey, MD, Department of Dermatology, University Hospital Düsseldorf, Moorenstr. 5, D-40225 Düsseldorf, Germany. E-mail: bernhard.homey@med.uni-duesseldorf.de.

https://doi.org/10.1016/j.anai.2025.11.007

classification specifically for chronic pruritus, subdividing it into 3 groups based on the condition of the skin at the onset of itching:

- IFSI I: Chronic pruritus on primarily lesional (inflamed or diseased) skin, meaning the itch occurs on skin already affected by a skin disease.
- IFSI II: Chronic pruritus on primarily nonlesional (normal-looking) skin, in which itch occurs without initial skin changes.
- IFSI III: Chronic pruritus with severe chronic scratch lesions, such as chronic prurigo or lichen simplex, in which the presence of extensive scratching damage makes classification into the above-mentioned groups not possible.

This classification helps guide diagnosis and treatment by identifying whether itch occurs on diseased skin or not and/or if scratching has caused secondary skin changes.

The global prevalence of pruritus is approximately 39.8% according to a large international study conducted across 20 countries in 2023.[8] The prevalence is highest among people aged 65 years and older, reaching approximately 43.3% in this group. Women tend to experience pruritus slightly more than men (40.7% vs 38.9%). The prevalence also varies geographically, being lower in Europe (35.9%) compared with North America (41.2%) and higher in Africa (45.7%). There are no significant differences between ethnic groups. In BRICS countries, the prevalence is somewhat higher than in developed countries (40.3% vs 38.7%).[8,9]

The Evolutionary Significance of Itch Sensation

Itching primarily serves as a protective mechanism that helps organisms detect and respond to potentially harmful environmental threats such as parasites, insects, and skin irritants. Itch triggers the urge to scratch, which can physically remove or dislodge irritants, toxins, venoms, or parasites from the skin surface.[10]

Moreover, scratching initiates an inflammatory response that activates the immune system locally to fight off potential infections. Mice studies have revealed that scratching increases inflammation and immune cell activity at the site of itching and helps to ward off bacterial infections, including *Staphylococcus aureus*.[11] This suggests that the pleasurable feeling associated with scratching has been evolutionarily preserved because it positively enforces this protective behavior. Itch and scratching evolved to help maintain skin homeostasis, remove harmful irritants, and boost local immune defense against infections and parasites. Although this mechanism has clear survival benefits across multiple species, the modern human environment has drastically altered its original context.[9,10]

Chronic Pruritus in Common Inflammatory Skin Diseases

Although itch is a frequent symptom associated with chronic inflammatory skin diseases, qualitative and quantitative differences exist. In fact, pruritus represents the most burdensome symptom in patients with AD or PN, 2 diseases presenting a prominent type 2 inflammatory response element.

Hence, chronic pruritus is the disease-defining symptom of AD, affecting most of patients. Peak pruritus Numerical Rating Scale (ppNRS) scores approximately 7.3 to 7.6 are recorded in recently studied large adult cohorts.[12,13] PN is defined by a mixture of type 2 (T_H2 driven) and type 3 (mainly T_H17 driven) inflammatory signatures.[14,15] Here, itching typically establishes a vicious itch-scratch cycle mediated by neuroimmune interactions which promote continuous scratching behavior that further damages the skin barrier and amplifies pruritogenic signaling.[16] The pathomechanism involves bidirectional communication between activated immune cells including eosinophils, mast cells, T_H2 cells, and peripheral sensory neurons that contribute to neuronal hyperplasia and neural sensitization in the skin (Fig 1).[16–18] This neuroimmune feedback loop is sustained by pruritogens and elevated expression of cytokine receptors including interleukin-4 receptor alpha (IL-4Rα) and IL-31Rα in cutaneous nerve endings, maintaining chronic pruritus and driving the formation of characteristic hyperkeratotic nodular lesions.[17,19] Across the above-mentioned dermatoses, chronic pruritus leads to significant sleep disturbances and impaired quality of life (QoL), with nocturnal itch contributing to difficulty falling and staying asleep.[20,21]

Considering the modalities of neuroimmune interactions in inflammatory skin diseases, itch is the most burdensome symptom in most diseases with a strong type 2 element, with profound QoL effects in severe cases. Furthermore, AD and PN represent patient populations with significantly more diverse molecular backgrounds than, for example, psoriasis.[22,23] This highlights the need for not only more personalized approaches but also precision targeting of the dominant pruritus-associated pathways in a diverse patient cohort. Here, we will focus on novel and approved systemic therapeutic targeting approaches to control chronic itch in the 2 most important pruritic inflammatory skin diseases, AD and PN.

Peripheral and Central Pathways of Itch Signaling

Itch can be broadly classified into 2 subtypes based on the initiating substance, histaminergic and nonhistaminergic (Fig 1). The former, initiated by the activation of the H_1 and H_4 histamine receptors, is characteristic of acute pruritus.[24] Nonhistaminergic itch, provoked by a multitude of exogenous or endogenous stimuli (such as microbial products, proteases, cytokines, and chemokines), lies in the background of a major proportion of chronic pruritic skin conditions, in which antihistamines consequentially demonstrate very limited efficacy.[24]

Tracing the neural pathways of itch poses several challenges, ranging from the heterogeneity of sensory neurons to the complex integration of signals at the level of the central nervous system (CNS). Briefly, activated peripheral neurons will transmit impulses to the spinal cord, in which gastrin-releasing peptide receptor–expressing excitatory interneurons in the superficial dorsal horn represent a key central relay for itch transmission, with genetic ablation of these neurons almost completely abolishing scratching behavior, while leaving pain responses intact.[25,26] In the CNS, spinothalamic and spinoparabrachial pathways for itch converge as spinal projection neurons transmit pruritic signals to both the thalamus and parabrachial nucleus, integrating sensory-discriminative and affective-motivational itch processing within supraspinal circuits[25,27] (Fig 1). The peripheral and central itch pathways may exhibit plasticity and sensitization in chronic conditions; however, due to the complexity and highly interconnected nature of central pathways, the periphery remains the main target of intervention and, in essence, provides the “battleground” in which chronic pruritus may be defeated.[28]

At this crucial, initial level represented by nerve endings, itch sensation commences in specialized peripheral sensory neurons, primarily unmyelinated C-fibers and thinly myelinated Aδ nerve fibers, which function as pruriceptors that detect and transduce pruritogenic stimuli into electrical signals transmitted to the CNS.[29,30] Two distinct subpopulations of C-fibers mediate different types of pruritus: mechanically insensitive C-fibers that respond to histamine through histamine receptor-1 activation and subsequent sensitization of transient receptor potential vanilloid-1 channels and polymodal mechanically sensitive C-fibers that are activated by nonhistaminergic pruritogens through a variety of receptors, including cytokine (eg, IL-31Rα, IL-13R1, and thymic stromal lymphopoietin receptor) and G-protein–coupled receptors (eg, protease-activated receptor-2 and mas-related G-protein coupled receptor member X2) leading to subsequent transient receptor potential vanilloid-1/transient receptor potential ankyrin-1 activation[30,31] (Fig 1). Furthermore, prostaglandins

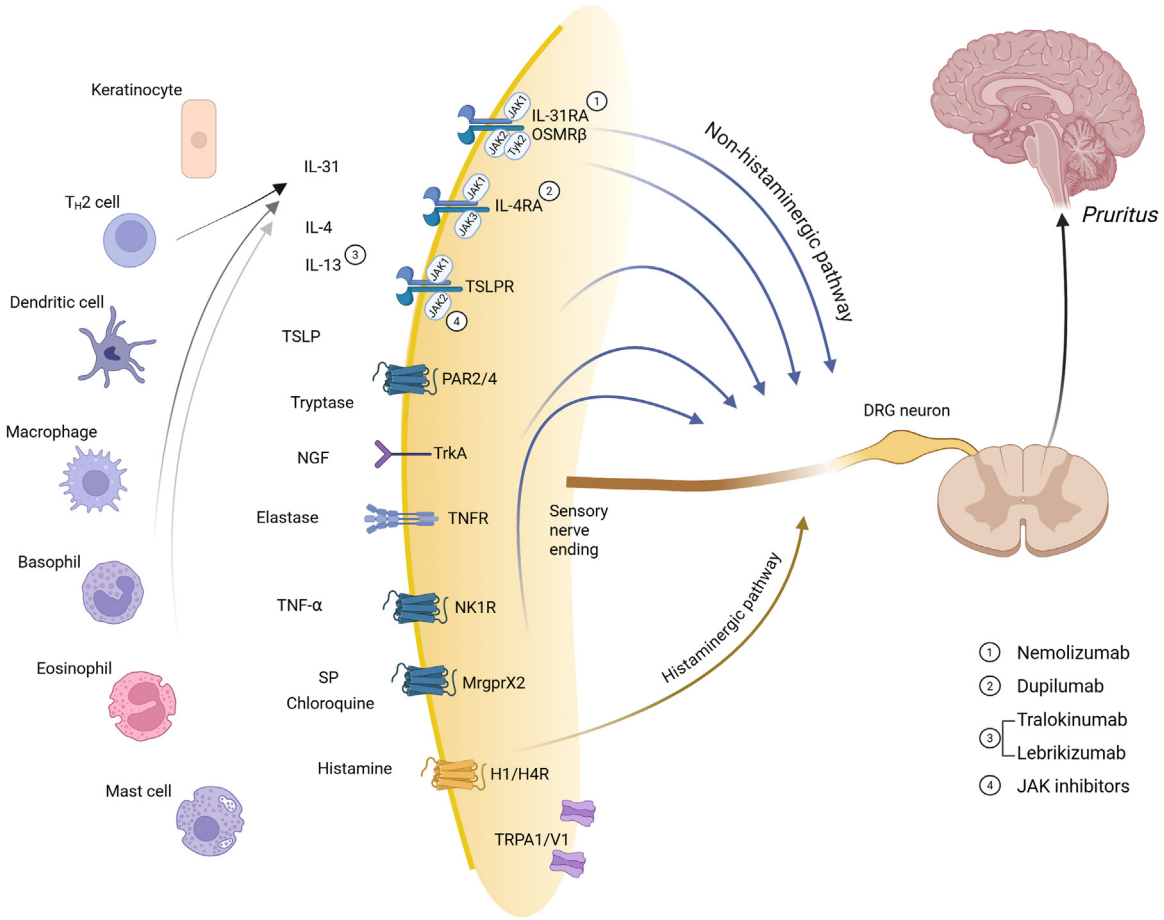

Figure 1. Schematic overview of key pruritus pathways and interventions of the monoclonal antibody and JAK inhibitor classes. DRG, dorsal root ganglion; IL, interleukin; JAK, Janus kinase; OSMRβ, oncostatin M receptor beta; PAR-2, protease-activated receptor 2; TRPA1, transient receptor potential ankyrin-1; TRPV1, transient receptor potential vanilloid-1; TSLP, thymic stromal lymphopoietin.

have been found to sensitize nerve endings and lower the threshold for common pruritogens, thereby exacerbating symptoms.[32-34] Arachidonic acid–derived mediators such as cysteinyl leukotrienes also demonstrate elevated levels in type 2 inflammation and may serve as direct pruritogens in the lesional micromilieu.[35,36] Importantly, recent single-cell sequencing studies of various mammalian dorsal root ganglion neurons have identified pruritogen receptor-enriched subsets, with the most prominent being the "non-peptidergic 3" (NP3) sensory neuronal subset, but also including the NP2 cluster.[37] It has to be noted that a clear human nomenclature for pruriceptive neuronal subsets is still pending. Moreover, molecular classification studies from, for example, mice need to be thoroughly scrutinized in terms of their applicability to human dorsal root ganglion neurons.[37-39] Despite the challenges of nomenclature and data harmonization, the NP3/NP2 subsets represent distinct populations critical for mediating itch, with a unique expression profile including IL-31Rα, oncostatin M receptor beta (OSMRβ), and brain natriuretic peptide.[37,40,41] NP3 neurons are functionally specialized for pruriception and are directly involved in itch signal transduction, making them a central node in neuroimmune crosstalk and a promising therapeutic target for pruritic skin diseases.[40]

Importantly, although IL-31 is a key cytokine able to directly activate pruriceptive neurons,[42–44] the inflammatory cytokine milieu significantly sensitizes these subsets to other pruritogens, amplifying itch signaling by lowering the excitability thresholds.[45,46]

Taking into account the interactions of the NP3 itch-conducting neuronal subset and the type 2/type 3 inflammatory cytokine milieu, IL-31 fills a unique position among the T_H2 cytokines perpetuating pruritic conditions, bridging the gap between the immune and peripheral nervous systems.[47] Although the primary cellular sources of IL-31 in the skin are CD4+ T_H2 cells, additional sources include basophils,[48] eosinophils,[49] even mast cells,[50] and, under specific conditions such as wound healing, dermal dendritic cells,[51] indicating that IL-31 production is coordinated across both adaptive and innate immune compartments in cutaneous inflammation (Fig 1). In subsequent texts, we describe the major developments in modulating this key pathway and place it in the broader context of recently developed targeted therapies in pruritic skin inflammation.

Therapeutic Targeting of Pruritic Type 2 Inflammation

In the past decade, biological therapies have fundamentally transformed the management of type 2 inflammatory skin diseases by offering highly effective, targeted interventions that significantly improve both disease control and patient QoL in which traditional treatments often fell short. Key landmarks in this process were the Food and Drug Administration approval of dupilumab for adults with moderate-to-severe AD in 2017 and PN in 2022, tralokinumab from age 12 years in AD in 2021, and the successive Food and Drug Administration approvals of nemolizumab for PN (adults) and AD (aged 12 years) in 2024. In subsequent texts, we summarize the mechanisms of action and comparative efficacy and safety profiles.

Nemolizumab

Nemolizumab is a humanized monoclonal IgG2 antibody that selectively inhibits IL-31 signaling by blocking the IL-31Rα subunit,

thereby preventing the formation of the IL-31Rα/oncostatin M receptor beta (OSMRβ) complex that mediates pruritogenic signaling through Janus kinase (JAK)/Signal transducer and activator of transcription, mitogen-activated protein kinase, and phosphoinositide-3-kinase/protein kinase B pathways.[47,52] IL-31 receptors are abundantly expressed in the dorsal root ganglia of cutaneous sensory nerves and keratinocytes, making this pathway a critical target for chronic pruritus as IL-31 directly activates unmyelinated C fibers and promotes sustained neuronal outgrowth that contributes to persistent itch sensation.[53-55] In the landmark phase IIb study, nemolizumab demonstrated dose-dependent efficacy with the 0.5 mg/kg every 4 weeks group having the greatest pruritus improvement from baseline at week 12 (−46.8% vs −21.4% with placebo, $P < .001$), establishing proof-of-concept for IL-31 receptor antagonism in AD-associated pruritus.[56] Importantly, the onset of antipruritic action was rapid, with significant improvements in pruritus scores observed as early as day 2 after the first injection in multiple phase 2 and 3 trials, demonstrating the immediate neuronal response to IL-31 pathway blockade.[57,58] Long-term extension studies revealed sustained and progressive improvements, with pruritus reductions reaching −65.9% at week 68 compared with −45.6% at week 16 in patients continuing nemolizumab therapy, indicating durable efficacy without development of tachyphylaxis.[56] In the phase III OLYMPIA 1 trial for PN, nemolizumab monotherapy achieved significantly higher rates of more than or equal to 4-point reduction in ppNRS compared with placebo at week 16 (58.4% vs 16.7%, difference 40.1%, $P < .001$), with response rates maintained at 58.3% vs 20.4% at week 24.[59] The complementary OLYMPIA 2 study in PN patients demonstrated even more pronounced efficacy, with nemolizumab 30 mg and 60 mg groups achieving −61.1% and −56.0% reductions in ppNRS, respectively, vs −18.6% with placebo at week 16 ($P < .0001$ for both doses).[60] In the phase III adolescent and adult AD studies, nemolizumab with topical therapy (Topical corticosteroid/topical calcineurin inhibitor) demonstrated superior antipruritic efficacy compared with placebo plus topical therapy, with more than or equal to 4-point ppNRS improvement achieved in 53% to 60% of patients vs 15% to 25% with placebo across different dosing regimens.[61] A comprehensive systematic review and meta-analysis of randomized controlled trials confirmed nemolizumab's consistent efficacy, revealing significant reductions in pruritus scores (weighted mean difference −18.86, 95% CI: −27.57 to −10.15, $P < .001$) across multiple studies with no significant heterogeneity in response patterns.[62] Summaries from pooled results of the original trials are provided in Table 1. The safety profile of nemolizumab is generally favorable across all age groups, with treatment-emergent adverse events occurring in 71.7% to 89% of patients but being predominantly mild to moderate in severity, with the most common events being nasopharyngitis, upper respiratory tract infection, and injection site reactions occurring in 2.2% to 8.7% of patients.[56,63] In pediatric patients aged 6 to 12 years, the safety profile was comparable to older patients, with 73.9% experiencing adverse events vs 65.1% with placebo, and notably, no adverse events led to treatment discontinuation, demonstrating acceptable tolerability across the age spectrum.[64] Long-term safety data extending to 68 weeks reveal no new safety concerns, with most treatment-emergent adverse events remaining mild and similar to those reported in shorter duration studies, overall supporting the rapid and sustained antipruritic action of nemolizumab alongside its long-term safety.[65]

Dupilumab

Dupilumab is a fully human monoclonal antibody that specifically binds to the IL-4Rα subunit, thereby blocking signaling of both IL-4 and IL-13 cytokines, key drivers of type 2 inflammation.[66,67] The dual blockade of IL-4 and IL-13 signaling pathways through their shared receptor subunit is advantageous, as these cytokines have both redundant and distinct roles in mediating pruritogenic inflammatory cascades.[67] The SOLO 1 and SOLO 2 phase III monotherapy trials revealed that 41% and 36% of adult patients, respectively, achieved a clinically meaningful more than or equal to 4-point improvement in ppNRS at week 16, compared with only 12% and 10% in the placebo group.[68] For PN, the LIBERTY-PN PRIME and PRIME2 phase III trials demonstrated that 60.0% and 37.2% of patients, respectively, achieved more than or equal to 4-point reduction in ppNRS at their primary end points (week 12 and 24), significantly exceeding placebo response rates of 18.4% and 22.0%[69] (pooled results in Table 1). A systematic literature review of patients with chronic prurigo and chronic idiopathic pruritus treated with dupilumab revealed mean time to first improvement of 5.18 ± 3.13 weeks for chronic prurigo and 2 ± 0 weeks for chronic idiopathic pruritus, with 83% of patients with chronic prurigo noticing improvement before 4 weeks of therapy.[70] Complete improvement of pruritus (time-final) occurred at a mean of 13.6 ± 12.0 weeks for patients with chronic prurigo and 14.6 ± 10.0 weeks for patients with chronic idiopathic pruritus, with 89% and 100% of patients, respectively, achieving more than 4-point NRS reduction.[70] Real-world evidence supports clinical trial findings, with up to 98% of patients achieving improvement in at least 1 AD domain including pruritus reduction at week 16, demonstrating robust effectiveness across diverse patient populations.[71] The safety profile of dupilumab in pruritus trials is generally favorable, with the most common adverse events being conjunctivitis (8.4%-22.1% vs 2.1%-11.1% with placebo), injection site reactions, and nasopharyngitis, with most conjunctivitis cases being manageable with topical treatments.[72,73] Long-term safety data extending up to 4 years reveal

Table 1
Systemic Anti-Pruritic Therapies of the Monoclonal Antibody and JAK Inhibitor Class, Alongside General Efficacy in Atopic Dermatitis and Prurigo Nodularis

Drug	Target	Disease	Study	≥4 Point improvement in ppNRS/wiNRS at week 16 [treatment % (placebo %)]
Nemolizumab	IL-31Rα	Atopic dermatitis	ARCADIA 1 and 2	43.5 (19.8)
		Prurigo nodularis	OLYMPIA 1 and 2	57.4 (18.7)
Dupilumab	IL-4Rα	Atopic dermatitis	LIBERTY-AD SOLO 1 and 2	38.5 (11)
		Prurigo nodularis	LIBERTY-PRIME 1 and 2	58.8 (19) (week 24)
Lebrikizumab	IL-13	Atopic dermatitis	ADvocate 1 and 2	42.58 (7.25)
Tralokinumab	IL-13	Atopic dermatitis	ECZTRA 1 and 2	22.5 (9.9)
Baricitinib	JAK1/2	Atopic dermatitis	BREEZE-AD 1 and 2	52.5 (15.4)
Abrocitinib	JAK1	Atopic dermatitis	JADE COMPARE	49.1 (13.8) (week 2)
Upadacitinib	JAK1	Atopic dermatitis	Measure-UP 1 and 2	63.7 (3.7)

Abbreviations: IL-13, interleukin-13; IL-31Rα, interleukin-31 receptor alpha; IL-4RA, interleukin-4 receptor alpha; JAK, Janus kinase; JADE, JAK1 Atopic Dermatitis Efficacy and Safety; ppNRS, peak pruritus Numerical Rating Scale; wiNRS, worst itch Numerical Rating Scale.

that exposure-adjusted incidence rates of conjunctivitis decrease over time (15.66 per 100 patient-years), with treatment discontinuation due to adverse events being rare.[72] The consistent efficacy and acceptable safety profile across multiple clinical trials have established dupilumab as an effective therapeutic option for patients with chronic pruritus associated with various inflammatory dermatoses.[74]

Tralokinumab

Tralokinumab is a fully human IgG4λ monoclonal antibody that specifically binds to IL-13 with high affinity, competitively blocking IL-13 interaction with both IL-13Rα1 and IL-13Rα2 receptor chains.[75,76] During phase IIb trials, tralokinumab 300 mg every 2 weeks demonstrated significant improvements in ppNRS scores compared with placebo, with patients having greater reductions in 7-day mean pruritus NRS at week 12, establishing early evidence of antipruritic efficacy.[77] The phase III ECZTRA 1 and ECZTRA 2 trials confirmed robust antipruritic effects, with significantly greater proportions of patients achieving more than or equal to 4-point reduction in weekly average worst daily pruritus NRS at week 16 compared with placebo (ECZTRA 1: 41.1% vs 17.7%, $P < .001$; ECZTRA 2: 45.8% vs 14.9%, $P < .001$).[78] Significant differences in ppNRS vs placebo were observed as early as week 2 in both ECZTRA trials, and sustained improvements were maintained to week 52 in patients continuing tralokinumab therapy.[78,79] In the adolescent phase III ECZTRA 6 trial, tralokinumab 150 mg and 300 mg every 2 weeks achieved significantly higher rates of more than or equal to 4-point reduction in ppNRS compared with placebo (23.2% and 25.0% vs 3.3%, respectively; $p < .001$ for both doses, summary in Table 1), with efficacy maintained in more than 50% of responders at week 52.[80] Real-world evidence demonstrates that patients with higher baseline pruritus scores (NRS ≥ 8) are more likely to achieve rapid therapeutic response, with clinical improvement typically observed within 4 to 6 weeks of treatment initiation, and stable disease control defined as worst daily pruritus NRS less than 3 being predictive of successful dose reduction to every 4 weeks of maintenance dosing.[81,82] Regarding the safety profile, conjunctivitis is the most common adverse event occurring in 5.4% of patients vs 1.9% with placebo, though these events are typically mild to moderate in severity and resolve during treatment, with rates potentially lower than those observed with dual IL-4/IL-13 inhibition.[83] Long-term safety data up to 2 years reveal no increase in adverse event rates with continued treatment. Real-world studies report ocular adverse events in approximately 25% of patients, but these rarely lead to treatment discontinuation, with many patients who experienced conjunctivitis with dupilumab having no recurrence or milder symptoms when switched to tralokinumab.[83,84]

Lebrikizumab

Lebrikizumab is a high-affinity IgG4 monoclonal antibody that selectively neutralizes IL-13 with slow off-rate kinetics, thereby blocking the downstream effects of IL-13 signaling with high potency and preventing the formation of the IL-4Rα/IL-13Rα1 heterodimer receptor complex.[85,86] In the phase IIb clinical trial, lebrikizumab demonstrated antipruritic efficacy with a ppNRS improvement of more than or equal to 4 points observed as early as day 2 in some of the high-dose patients vs placebo (15.3% vs 4.5%, respectively), with dose-dependent improvements maintained to week 16.[87] The phase III ADvocate1 and ADvocate2 trials confirmed these findings, revealing significant point reduction in NRS scores compared with baseline, with lebrikizumab-treated patients achieving 53.3% and 46.3% improvements respectively vs 21.4% and 18.0% with placebo at week 16[88,89] (summary in Table 1). At week 16, significantly more patients treated with lebrikizumab vs placebo achieved more than or equal to 3-point improvement in pruritus NRS from baseline, with response rates of 54.6% vs 19.2% for ADvocate1 and 49.4% vs 14.0% for ADvocate2 ($P < .001$ for both trials).[88] Long-term efficacy data from maintenance studies reveal that patients who achieved response criteria at week 16 maintained stable antipruritic effects, with 66.1% and 62.7% of patients continuing lebrikizumab every 2 weeks and every 4 weeks, respectively, maintaining more than or equal to 4-point pruritus NRS improvement with minimal fluctuations to week 52.[90] The safety profile of lebrikizumab is favorable, with adverse events being mostly nonserious and mild to moderate in severity, with conjunctivitis being the most frequently reported adverse event in lebrikizumab-treated patients (8.5%) compared with placebo (2.5%).[90] Injection site reactions occurred at low rates (2.6% lebrikizumab vs 1.5% placebo), and adverse events leading to treatment discontinuation were infrequent (2.3% lebrikizumab vs 1.4% placebo).[90] Two-year safety data demonstrate that skin and itch outcomes are maintained in prolonged treatment periods.[91]

Janus Kinase Inhibitors

Besides the rapid development of biologicals in the past decade, JAK inhibitors have also emerged as effective options for chronic pruritus. Both topical and oral JAK inhibitors have demonstrated rapid itch relief in clinical trials, with topical ruxolitinib reducing NRS itch scores by approximately 3 to 4 points within days of application.[92] Among oral agents, the selective JAK1 inhibitors upadacitinib and abrocitinib have yielded higher itch response rates and faster onset of action compared with the JAK1/2 inhibitor baricitinib, suggesting that JAK1 selectivity enhances antipruritic efficacy.[92-94] Upadacitinib achieved significant itch reduction as early as day 2 in phase II trials, and abrocitinib demonstrated sustained itch relief in 12 weeks.[95-97] Baricitinib has also been effective in reducing pruritus of unknown origin, with a recent case series reporting marked itch decrease in patients with chronic pruritus of unknown origin after 8 weeks of therapy.[98-100] Recent mechanistic studies have further elucidated that JAK1-selective inhibitors demonstrate superior antipruritic efficacy through preferential inhibition of type 2 cytokine signaling pathways, including IL-4, IL-13, and IL-31[101-103] (Table 1).

JAK inhibitors have demonstrated benefit beyond AD, including refractory pruritus in PN[100,104,105] and LP,[106,107] in which both oral and topical formulations achieved substantial itch resolution. The safety profile of JAK inhibitors in patients with pruritic skin diseases is generally acceptable but, in general, less favorable than biologicals. The most common adverse events are nasopharyngitis, acne, and transient laboratory abnormalities. Real-world evidence from dermatology-specific cohorts indicates that the cardiovascular risk profile of JAK inhibitors may be more favorable than initially suggested by studies of patients with rheumatological diseases, particularly in younger patients without extensive cardiovascular comorbidities.[108,109] Long-term monitoring requirements include regular assessment of cardiovascular risk factors, hematologic parameters, and lipid profiles, with topical formulations demonstrating minimal systemic absorption and reduced risk of systemic adverse events compared with oral agents.[110,111]

Itch Improvement During Janus Kinase Inhibition vs Biological Therapy

A direct, head-to-head comparison of phase III clinical trials between antipruritic treatments is complicated by several practical aspects, such as end points, inclusion criteria, and rescue medications, and allowed concomitant therapies vary even between CONSORT-standardized studies. However, from both clinical experience and the evaluation of matching end points between published clinical trials, it is established that JAK inhibitors typically achieve a more than or equal to 4-point improvement in itch NRS

by weeks 2 to 4 in both AD and PN, with some trials revealing significant relief as early as the first week.[99,104,112,113] Dupilumab generally reaches this threshold by week 4 in AD and by weeks 4 to 5 in PN, with maximal response rates observed at 12 to 24 weeks.[72,74,112] Head-to-head studies in AD demonstrate that JAK inhibitors upadacitinib and abrocitinib provide superior and more rapid itch relief compared with dupilumab, with a larger proportion of patients achieving early itch relief at 2 weeks and sustained advantages to 12 to 16 weeks.[114] In the Heads Up phase IIIb trial, upadacitinib achieved significantly greater improvements in itch NRS compared with dupilumab as early as week 1 (32.0% vs 8.9%, $P < .001$) and at week 16 (67.8% vs 49.6%, $P < .001$), with 56.1% vs 36.4% of patients achieving more than or equal to 4-point itch improvement.[112] However, JAK inhibitors are associated with greater risk of infections (including herpes zoster and nasal and respiratory infections), acneiform eruptions, and laboratory abnormalities,[110,111] whereas dupilumab's safety profile is dominated by conjunctivitis, local injection site reactions, and mild joint complaints, with lower risk of serious infections or systemic immunosuppression.[70,72,73] In the context of itch as the most significant burden in AD and PN, precision targeting of IL-31 signaling provides the benefit of shorter time until maximal itch NRS response rates are achieved, alongside the generally more favorable safety profile of monoclonal antibodies vs JAK inhibitors. As evidenced by the rapid decrease in ppNRS during the first week of nemolizumab administration,[56,65] blockage of IL31-RA and specific modulation of the NP3 sensory neuronal subset presents a powerful alternative for a significant percentage of patients. The exploration of combination therapies and patient subtype-specific approaches thus represents key areas of interest in the optimal future management of patients with severe, QoL-affecting pruritus.

Conclusion

The management of chronic pruritus presents a complex challenge. Experimental modeling of the involved sensory circuits can only be partial and heavily reliant on animal models, whereas in vivo data on disease status often need to rely on subjective self-reported measures. The advent of biological therapies, and specifically the targeting of key multifaceted molecules and their downstream pathways, has opened new avenues in the past decade. The blockade of the highly itch-related cytokine IL-31 provides an effective novel targeted therapy. However, due to the heterogeneity of molecular backgrounds within type 2 inflammation, the characterization of specific, unresponsive subpopulations still poses an ongoing challenge. Open questions remain on how the unique neuroanatomy of the epidermis —including the density, distribution, and dynamic remodeling of intraepidermal nerve fibers—contributes to the initiation and persistence of chronic pruritic states. It is yet unclear how impaired epidermal barriers might expose nerve endings to pruritogens, but also how cytokines sensitize nerves during chronic inflammation. In addition, the interplay between neuroimmune signaling and the adaptive structure of nerve endings in the skin may hold key insights into why pruritus becomes chronic and refractory, especially in T_H2-polarized inflammatory conditions. Nevertheless, recent therapeutic developments in targeting pruritic inflammation have resulted in a dramatic improvement of the QoL of patients with AD and PN.

Disclosures

Dr Homey has received research funding from Galderma Pharmaceuticals and participates in studies with nemolizumab. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

The study was funded by a grant of the German Research Foundation RU2690 PruSEARCH HO2092/7-1, HO2092/7-2 to Dr Homey and RA1026/3-1, RA1026/3-2 to Dr Raap.

References

1. Ständer S, Schmelz M, Lerner E, Murota H, Nattkemper L, Reich A, et al. A multidisciplinary Delphi consensus on the modern definition of pruritus: sensation and disease [e-pub ahead of print]. *J Eur Acad Dermatol Venereol*. https://doi.org/10.1111/jdv.20851, accessed September 2, 2025.
2. Weisshaar E, Kucenic MJ, Fleischer Jr. AB. Pruritus: a review. *Acta Derm Venereol Suppl (Stockh)*. 2003:(213):5–32.
3. Metz M, Grundmann S, Ständer S. Pruritus: an overview of current concepts. *Vet Dermatol*. 2011;22(2):121–131.
4. Yosipovitch G, Greaves MW, Schmelz M. Itch. *Lancet*. 2003;361(9358):690–694.
5. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol*. 2007;87(4):291–294.
6. Ständer S. Classification of itch. *Curr Probl Dermatol*. 2016;50:1–4.
7. Ständer S, Augustin M, Reich A, Blome C, Ebata T, Phan NQ, et al. Pruritus assessment in clinical trials: consensus recommendations from the International Forum for the Study of Itch (IFSI) special interest group scoring itch in clinical trials. *Acta Derm Venereol*. 2013;93(5):509–514.
8. Yosipovitch G, Skayem C, Aroman MS, Taieb C, Inane M, Hayoun YB, et al. International study on prevalence of itch: examining the role of itch as a major global public health problem. *Br J Dermatol*. 2024;191(5):713–718.
9. Butler DC, Berger T, Elmariah S, Kim B, Chisolm S, Kwatra SG, et al. Chronic pruritus: a review. *JAMA*. 2024;331(24):2114–2124.
10. Rinaldi G. The itch-scratch cycle: a review of the mechanisms. *Dermatol Pract Concept*. 2019;9(2):90–97.
11. Liu AW, Zhang YR, Chen CS, Edwards TN, Ozyaman S, Ramcke T, et al. Scratching promotes allergic inflammation and host defense via neurogenic mast cell activation. *Science*. 2025;387(6733):eadn9390.
12. Soares GB, Orfali RL, Averbach BL, Yap QV, Yosipovitch G, Aoki V. Pruritus in atopic dermatitis: a cross-sectional study of adult patients from a tertiary university hospital in São Paulo, Brazil. *An Bras Dermatol*. 2025;100(4):101093.
13. De La Cueva Dobao P, Barredo LC, Salvador JFS, Serra-Baldrich E, Pinto PH, Cano NH, et al. Patient burden and impact of moderate-to-severe atopic dermatitis in the Spanish healthcare system: the APOLO cross-sectional study. *Dermatol Pract Concept*. 2025;15(3):5538.
14. Zeidler C, Tsianakas A, Pereira M, Ständer H, Yosipovitch G, Ständer S. Chronic prurigo of nodular type: a review. *Acta Derm Venereol*. 2018;98(2):173–179.
15. Zeidler C, Ständer S. The pathogenesis of Prurigo nodularis–'Super-Itch' in exploration. *Eur J Pain*. 2016;20(1):37–40.
16. Wong LS, Yen YT. Chronic nodular prurigo: an update on the pathogenesis and treatment. *Int J Mol Sci*. 2022;23(20):12390.
17. Kwatra SG, Ständer S, Yosipovitch G, Kim BS, Levit NA, O'Malley JT. Pathophysiology of prurigo nodularis: neuroimmune dysregulation and the role of type 2 inflammation. *J Invest Dermatol*. 2025;145(2):249–256.
18. Shao Y, Wang D, Zhu Y, Xiao Z, Jin T, Peng L, et al. Molecular mechanisms of pruritus in prurigo nodularis. *Front Immunol*. 2023;14:1301817.
19. Liao V, Cornman HL, Ma E, Kwatra SG. Prurigo nodularis: new insights into pathogenesis and novel therapeutics. *Br J Dermatol*. 2024;190(6):798–810.
20. Kantor R, Dalal P, Cella D, Silverberg JI. Research letter: impact of pruritus on quality of life-a systematic review. *J Am Acad Dermatol*. 2016;75(5):885–886.e4.
21. Gwillim EC, Nattkemper L, Yosipovitch G. Impact of itch on sleep disturbance in patients with prurigo nodularis. *Acta Derm Venereol*. 2021;101(3):adv00424.
22. Cornman HL, Manjunath J, Reddy SV, Adams J, Rajeh A, Samuel C, et al. Comprehensive plasma cytokine and chemokine profiling in prurigo nodularis reveals endotypes in type 2 inflammation. *Sci Rep*. 2024;14(1):8098.
23. Fyhrquist N, Yang Y, Karisola P, Alenius H. Endotypes of atopic dermatitis. *J Allergy Clin Immunol*. 2025;156(1):24–40.e4.
24. Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. *J Allergy Clin Immunol*. 2018;142(5):1375–1390.
25. Chen XJ, Sun YG. Central circuit mechanisms of itch. *Nat Commun*. 2020;11(1):3052.
26. Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. *Nature*. 2007;448(7154):700–703.
27. Piyush Shah D, Barik A. The spino-parabrachial pathway for itch. *Front Neural Circuits*. 2022;16:805831.
28. Mahmoud O, Oladipo O, Mahmoud RH, Yosipovitch G. Itch: from the skin to the brain - peripheral and central neural sensitization in chronic itch. *Front Mol Neurosci*. 2023;16:1272230.
29. Schmelz M. How do neurons signal itch? *Front Med*. 2021;8:643006.
30. Misery L, Pierre O, Le Gall-Ianotto C, Lebonvallet N, Chernyshov PV, Le Garrec R, et al. Basic mechanisms of itch. *J Allergy Clin Immunol*. 2023;152(1):11–23.
31. Davidson S, Giesler GJ. The multiple pathways for itch and their interactions with pain. *Trends Neurosci*. 2010;33(12):550–558.
32. Lovell CR, Burton PA, Duncan EH, Burton JL. Prostaglandins and pruritus. *Br J Dermatol*. 1976;94(3):273–275.

33. Neisius U, Olsson R, Rukwied R, Lischetzki G, Schmelz M. Prostaglandin E2 induces vasodilation and pruritus, but no protein extravasation in atopic dermatitis and controls. *J Am Acad Dermatol*. 2002;47(1):28–32.
34. Yanes DA, Mosser-Goldfarb JL. Emerging therapies for atopic dermatitis: the prostaglandin/leukotriene pathway. *J Am Acad Dermatol*. 2018;78(3)(suppl 1): S71-S75.
35. Honda T, Kabashima K, Kunisawa J. Exploring the roles of prostanoids, leukotriens, and dietary fatty acids in cutaneous inflammatory diseases: insights from pharmacological and genetic approaches. *Immunol Rev*. 2023;317(1):95–112.
36. Andoh T, Haza S, Saito A, Kuraishi Y. Involvement of leukotriene B4 in spontaneous itch-related behaviour in NC mice with atopic dermatitis-like skin lesions. *Exp Dermatol*. 2011;20(11):894–898.
37. Jung M, Dourado M, Maksymetz J, Jacobson A, Laufer BI, Baca M, et al. Cross-species transcriptomic atlas of dorsal root ganglia reveals species-specific programs for sensory function. *Nat Commun*. 2023;14(1):366.
38. Shiers S, Klein RM, Price TJ. Quantitative differences in neuronal subpopulations between mouse and human dorsal root ganglia demonstrated with RNAscope in situ hybridization. *Pain*. 2020;161(10):2410–2424.
39. Bhuiyan SA, Xu M, Yang L, Semizoglou E, Bhatia P, Pantaleo KI, et al. Harmonized cross-species cell atlases of trigeminal and dorsal root ganglia. *Sci Adv*. 2024;10 (25):eadj9173.
40. Wang K, Cai B, Song Y, Chen Y, Zhang X. Somatosensory neuron types and their neural networks as revealed via single-cell transcriptomics. *Trends Neurosci*. 2023;46(8):654–666.
41. Xie K, Cheng X, Zhu T, Zhang D. Single-cell transcriptomic profiling of dorsal root ganglion: an overview. *Front Neuroanat*. 2023;17:1162049.
42. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: involvement of TRPV1 and TRPA1. *J Allergy Clin Immunol*. 2014;133(2):448–460.
43. Xu J, Zanvit P, Hu L, Tseng PY, Liu N, Wang F, et al. The cytokine TGF-β induces interleukin-31 expression from dermal dendritic cells to activate sensory neurons and stimulate wound itching. *Immunity*. 2020;53(2):371–383.e5.
44. Koumaki D, Gregoriou S, Evangelou G, Krasagakis K. Pruritogenic mediators and new antipruritic drugs in atopic dermatitis. *J Clin Med*. 2023;12(6):2091.
45. Jha MK, Han Y, Liu Z, Hara Y, Langohr IM, Morel C, et al. Type 2 cytokines pleiotropically modulate sensory nerve architecture and neuroimmune interactions to mediate itch. *J Allergy Clin Immunol*. 2025;156(4):1066–1081.e12.
46. Pogatzki-Zahn EM, Pereira MP, Cremer A, Zeidler C, Dreyer T, Riepe C, et al. Peripheral sensitization and loss of descending inhibition is a hallmark of chronic pruritus. *J Invest Dermatol*. 2020;140(1):203–211.e4.
47. Nemmer JM, Kuchner M, Datsi A, Oláh P, Julia V, Raap U, et al. Interleukin-31 signaling bridges the gap between immune cells, the nervous system and epithelial tissues. *Front Med (Lausanne)*. 2021;8:639097.
48. Raap U, Gehring M, Kleiner S, Rüdrich U, Eiz-Vesper B, Haas H, et al. Human basophils are a source of - and are differentially activated by - il-31. *Clin Exp Allergy*. 2017;47(4):499–508.
49. Kunsleben N, Rüdrich U, Gehring M, Novak N, Kapp A, Raap U. IL-31 induces chemotaxis, calcium mobilization, release of reactive oxygen species, and CCL26 in eosinophils, which are capable to release IL-31. *J Invest Dermatol*. 2015;135 (7):1908–1911.
50. Niyonsaba F, Ushio H, Hara M, Yokoi H, Tominaga M, Takamori K, et al. Antimicrobial peptides human beta-defensins and cathelicidin LL-37 induce the secretion of a pruritogenic cytokine IL-31 by human mast cells. *J Immunol*. 2010;184 (7):3526–3534.
51. Hashimoto T, Yokozeki H, Karasuyama H, Satoh T. IL-31-generating network in atopic dermatitis comprising macrophages, basophils, thymic stromal lymphopoietin, and periostin. *J Allergy Clin Immunol*. 2023;151(3):737–746.e6.
52. Orfali RL, Aoki V. Blockage of the IL-31 pathway as a potential target therapy for atopic dermatitis. *Pharmaceutics*. 2023;15(2):577.
53. Feld M, Garcia R, Buddenkotte J, Katayama S, Lewis K, Muirhead G, et al. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J Allergy Clin Immunol*. 2016;138(2):500–508.e24.
54. Taha MR, Tyring SK. Use of nemolizumab in the treatment of prurigo nodularis and atopic dermatitis. *Skin Therapy Lett*. 2025;30(3):1–3.
55. Takahashi S, Ochiai S, Jin J, Takahashi N, Toshima S, Ishigame H, et al. Sensory neuronal STAT3 is critical for IL-31 receptor expression and inflammatory itch. *Cell Rep*. 2023;42(12):113433.
56. Kabashima K, Furue M, Hanifin JM, Pulka G, Wollenberg A, Galus R, et al. Nemolizumab in patients with moderate-to-severe atopic dermatitis: randomized, phase II, long-term extension study. *J Allergy Clin Immunol*. 2018;142(4):1121–1130.e7.
57. Silverberg JI, Pinter A, Pulka G, Poulin Y, Bouaziz JD, Wollenberg A, et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol*. 2020;145(1):173–182.
58. Kabashima K, Matsumura T, Komazaki H, Kawashima M, Nemolizumab-JP01 Study Group. Nemolizumab improves patient-reported symptoms of atopic dermatitis with pruritus: post hoc analysis of a Japanese Phase III randomized controlled trial. *Dermatol Ther (Heidelb)*. 2023;13(4):997–1011.
59. Ständer S, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, et al. Efficacy and safety of nemolizumab in patients with moderate to severe prurigo nodularis: the OLYMPIA 1 randomized clinical Phase 3 trial. *JAMA Dermatol*. 2025;161 (2):147–156.
60. Yokozeki H, Murota H, Matsumura T, Komazaki H, Nemolizumab-JP11 Study Group. Efficacy and safety of nemolizumab and topical corticosteroids for prurigo nodularis: results from a randomized double-blind placebo-controlled phase II/III clinical study in patients aged ≥ 13 years. *Br J Dermatol*. 2024;191(2):200–208.
61. Silverberg JI, Wollenberg A, Reich A, Thaçi D, Legat FJ, Papp KA, et al. Nemolizumab with concomitant topical therapy in adolescents and adults with moderate-to-severe atopic dermatitis (ARCADIA 1 and ARCADIA 2): results from two replicate, double-blind, randomised controlled phase 3 trials. *Lancet*. 2024;404 (10451):445–460.
62. Liang J, Hu F, Dan M, Sang Y, Abulikemu K, Wang Q, et al. Safety and efficacy of nemolizumab for atopic dermatitis with pruritus: a systematic review and meta-regression analysis of randomized controlled trials. *Front Immunol*. 2022;13:825312.
63. Kwatra SG, Yosipovitch G, Legat FJ, Reich A, Paul C, Simon D, et al. Phase 3 trial of nemolizumab in patients with prurigo nodularis. *N Engl J Med*. 2023;389 (17):1579–1589.
64. Igarashi A, Katsunuma T, Matsumura T, Komazaki H, Nemolizumab-JP04 Study Group. Efficacy and safety of nemolizumab in paediatric patients aged 6-12 years with atopic dermatitis with moderate-to-severe pruritus: results from a phase III, randomized, double-blind, placebo-controlled, multicentre study. *Br J Dermatol*. 2023;190(1):20–28.
65. Yokozeki H, Murota H, Matsumura T. Long-term (68 weeks) administration of nemolizumab and topical corticosteroids for prurigo nodularis in patients aged ≥ 13 years: efficacy and safety data from a phase II/III study. *Br J Dermatol*. 2025;193(1):56–65.
66. McCann MR, Kosloski MP, Xu C, Davis JD, Kamal MA. Dupilumab: mechanism of action, clinical, and translational science. *Clin Transl Sci*. 2024;17(8):e13899.
67. Le Floc'h A, Allinne J, Nagashima K, Scott G, Birchard D, Asrat S, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75(5):1188–1204.
68. Silverberg JI, Yosipovitch G, Simpson EL, Kim BS, Wu JJ, Eckert L, et al. Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS. *J Am Acad Dermatol*. 2020;82(6):1328–1336.
69. Yosipovitch G, Mollanazar N, Ständer S, Kwatra SG, Kim BS, Laws E, et al. Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials. *Nat Med*. 2023;29(5):1180–1190.
70. Gael M, Adam T, Mariano-Bourin M, Bursztejn AC. Efficacy of dupilumab in chronic prurigo and chronic idiopathic pruritus: a systematic review of current evidence and analysis of response predictors. *J Eur Acad Dermatol Venereol*. 2022;36(9):1541–1551.
71. Barei F, Zussino M, Tavecchio S, Angileri L, Rizzo A, Calzari P, et al. Assessment of patient-reported outcomes at 48 months of treatment with dupilumab for severe atopic dermatitis: a single-center real-life experience with 126 patients. *Pharmaceuticals (Basel)*. 2024;17(1):117.
72. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. *J Am Acad Dermatol*. 2020;82(2):377–388.
73. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol*. 2019;181 (3):459–473.
74. Richter C, Hafner J, Schuermann M, Tanadini M, Trisconi N, Schmid-Grendelmeier P, et al. Dupilumab for chronic prurigo: case series on effectiveness, safety, and quality of life. *Dermatology*. 2023;239(5):811–817.
75. Simpson EL, Guttman-Yassky E, Eichenfield LF, Boguniewicz M, Bieber T, Schneider S, et al. Tralokinumab therapy for moderate-to-severe atopic dermatitis: clinical outcomes with targeted IL-13 inhibition. *Allergy*. 2023;78(11):2875–2891.
76. Lytvyn Y, Gooderham M. Targeting interleukin 13 for the treatment of atopic dermatitis. *Pharmaceutics*. 2023;15(2):568.
77. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol*. 2019;143(1):135–141.
78. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *Br J Dermatol*. 2021;184(3):437–449.
79. Simpson EL, Pink AE, Blauvelt A, Gooderham M, Armstrong AW, Worm M, et al. Tralokinumab efficacy over 1 year in adults with moderate-to-severe atopic dermatitis: pooled data from two Phase III trials. *Am J Clin Dermatol*. 2023;24 (6):939–952.
80. Paller AS, Flohr C, Cork M, Bewley A, Blauvelt A, Hong HC, et al. Efficacy and safety of tralokinumab in adolescents with moderate to severe atopic dermatitis: the Phase 3 ECZTRA 6 randomized clinical trial. *JAMA Dermatol*. 2023;159(6):596–605.
81. Weidinger S, Bewley A, Hong HC, Silvestre JF, Peris K, Wollenberg A, et al. Predicting success with reduced dosing frequency of tralokinumab in patients with moderate-to-severe atopic dermatitis. *Br J Dermatol*. 2025;192(3):410–419.
82. Potestio L, Patruno C, Napolitano M. Efficacy and safety of tralokinumab in real life: possible predictive rapid response factors. *Dermatitis*. 2024;35(S 1):S77–S80.
83. Simpson EL, Merola JF, Silverberg JI, Reich K, Warren RB, Staumont-Sallé D, et al. Safety of tralokinumab in adult patients with moderate-to-severe atopic dermatitis: pooled analysis of five randomized, double-blind, placebo-controlled phase II and phase III trials. *Br J Dermatol*. 2022;187(6):888–899.
84. Sebastian N, Chircop O, Clayton TH, Kreeshan FC, Hunter HJA, Warren RB. Real-world clinical experience of tralokinumab in a tertiary centre: an alternative for patients with conjunctivitis on dupilumab? *Dermatol Ther (Heidelb)*. 2025;15 (8):2275–2279.

85. Labib A, Ju T, Yosipovitch G. Managing atopic dermatitis with lebrikizumab - the evidence to date. *Clin Cosmet Investig Dermatol*. 2022;15:1065–1072.
86. Bernardo D, Bieber T, Torres T. Lebrikizumab for the treatment of moderate-to-severe atopic dermatitis. *Am J Clin Dermatol*. 2023;24(5):753–764.
87. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J, et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. *JAMA Dermatol*. 2020;156(4):411–420.
88. Yosipovitch G, Lio PA, Rosmarin D, Serra-Baldrich E, Legat FJ, Casillas M, et al. Lebrikizumab improved itch and reduced the extent of itch interference on sleep in patients with moderate-to-severe atopic dermatitis: two randomized, placebo-controlled, phase III trials. *Br J Dermatol*. 2024;190(2):289–291.
89. Simpson E, Fernández-Peñas P, de Bruin-Weller M, Lio PA, Chu CY, Ezzedine K, et al. Improvement across dimensions of disease with lebrikizumab use in atopic dermatitis: two Phase 3, randomized, double-blind, placebo-controlled monotherapy trials (ADvocate1 and ADvocate2). *Adv Ther*. 2025;42(1):132–143.
90. Stein Gold L, Thaçi D, Thyssen JP, Gooderham M, Laquer V, Moore A, et al. Safety of lebrikizumab in adults and adolescents with moderate-to-severe atopic dermatitis: an integrated analysis of eight clinical trials. *Am J Clin Dermatol*. 2023;24(4):595–607.
91. Guttman-Yassky E, Weidinger S, Simpson EL, Gooderham M, Irvine AD, Spelman L, et al. Two-year efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis: a long-term extension (ADjoin). *Dermatol Ther (Heidelb)*. 2025;15(8):2217–2232.
92. Han Y, Woo YR, Cho SH, Lee JD, Kim HS. Itch and Janus kinase inhibitors. *Acta Derm Venereol*. 2023;103:adv00869.
93. Wan H, Jia H, Xia T, Zhang D. Comparative efficacy and safety of abrocitinib, baricitinib, and upadacitinib for moderate-to-severe atopic dermatitis: a network meta-analysis. *Dermatol Ther*. 2022;35(9):e15636.
94. Nogueira M, Torres T. Janus kinase inhibitors for the treatment of atopic dermatitis: focus on abrocitinib, baricitinib, and upadacitinib. *Dermatol Pract Concept*. 2021;11(4):e2021145.
95. Simpson EL, Silverberg JI, Nosbaum A, Winthrop KL, Guttman-Yassky E, Hoffmeister KM, et al. Integrated safety analysis of abrocitinib for the treatment of moderate-to-severe atopic dermatitis from the Phase II and Phase III clinical trial program. *Am J Clin Dermatol*. 2021;22(5):693–707.
96. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet*. 2021;397(10290):2151–2168.
97. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2020;145(3):877–884.
98. Buttgereit T, Grekowitz EM, Metz M. Baricitinib rapidly and sustainably relieves a patient from chronic pruritus of unknown origin refractory to dupilumab. *JAAD Case Rep*. 2021;15:36–38.
99. Buhl T, Rosmarin D, Serra-Baldrich E, Fernandez-Peñas P, Igarashi A, Konstantinou MP, et al. Itch and sleep improvements with baricitinib in patients with atopic dermatitis: a post hoc analysis of 3 Phase 3 studies. *Dermatol Ther (Heidelb)*. 2021;11(3):971–982.
100. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T, et al. Efficacy and safety of baricitinib combined with topical corticosteroids for treatment of moderate to severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2020;156(12):1333–1343.
101. Taylor PC, Choy E, Baraliakos X, Szekanecz Z, Xavier RM, Isaacs JD, et al. Differential properties of Janus kinase inhibitors in the treatment of immune-mediated inflammatory diseases. *Rheumatology (Oxford)*. 2024;63(2):298–308.
102. Toyosawa Y, Komiya E, Kaneko T, Suga Y, Tominaga M, Takamori K. Type 2 cytokine-JAK1 signaling is involved in the development of dry skin-induced mechanical alloknesis. *J Dermatol Sci*. 2025;117(3):52–60.
103. Dogra S, Shah S, Gupta M, Sharma A, Chhabra S. Abrocitinib: a comprehensive review of its efficacy and safety in dermatology. *Indian Dermatol Online J*. 2024;15(6):930–941.
104. Kwatra SG, Bordeaux ZA, Parthasarathy V, Kollhoff AL, Alajmi A, Pritchard T, et al. Efficacy and safety of abrocitinib in prurigo nodularis and chronic pruritus of unknown origin: a nonrandomized controlled trial. *JAMA Dermatol*. 2024;160(7):717–724.
105. Mozafari N. Effective treatment of prurigo nodularis with oral tofacitinib: a case report. *Clin Case Rep*. 2025;13(3):e70287.
106. Didona D, Caposiena Caro RD, Calabrese L, D'Onghia M, Galluccio G, Di Nicola MR, et al. Use of JAK inhibitors in Lichen Planus: an update. *Medicina*. 2025;61(6):1056.
107. Motamed-Sanaye A, Khazaee YF, Shokrgozar M, Alishahi M, Ahramiyanpour N, Amani M. JAK inhibitors in lichen planus: a review of pathogenesis and treatments. *J Dermatolog Treat*. 2022;33(8):3098–3103.
108. Kraev K, Geneva-Popova MG, Hristov BK, Uchikov PA, Belova-Popova SD, Kraeva MI, et al. Examining the safety profile of Janus Kinase (JAK) inhibitors in the management of immune-mediated diseases: a comprehensive review. *Life (Basel)*. 2023;13(12):2244.
109. Beard A, Trotter SC. JAK 1-3 inhibitors and TYK-2 inhibitors in dermatology: practical pearls for the primary care physician. *J Fam Med Prim Care*. 2024;13(10):4128–4134.
110. Samuel C, Cornman H, Kambala A, Kwatra SG. A review on the safety of using JAK inhibitors in dermatology: clinical and laboratory monitoring. *Dermatol Ther (Heidelb)*. 2023;13(3):729–749.
111. Alves C, Penedones A, Mendes D, Batel Marques F. Topical Janus kinase inhibitors in atopic dermatitis: a safety network meta-analysis. *Int J Clin Pharm*. 2023;45(4):830–838.
112. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S, et al. Efficacy and safety of Upadacitinib vs Dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2021;157(9):1047–1055.
113. Bianco M, D'Oria F, Falcidia C, Foggi G, Matteodo E, Di Giulio S, et al. New and emerging biologics and Jak inhibitors for the treatment of prurigo nodularis: a narrative review. *Medicina (Kaunas)*. 2025;61(4):631.
114. Gao Q, Zhao Y, Zhang J. Efficacy and safety of abrocitinib and upadacitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a systematic review and meta-analysis. *Heliyon*. 2023;9(6):e16704.