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 ORIGINAL ARTICLE

Interleukin-31 in Atopic Dermatitis and Prurigo Nodularis: Pathophysiology, Neuroimmune Mechanisms, and Clinical Efficacy of Nemolizumab

Naiem T. Issa MD PhD,[a,b] Shawn Kwatra MD,[c,d] Ali Shahbaz MD,[e] Leon Kircik MD[f]

[a]Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL
[b]George Washington University School of Medicine and Health Sciences, Washington, DC
[c]Department of Dermatology, University of Maryland School of Medicine, Baltimore, MD
[d]Maryland Itch Center, University of Maryland School of Medicine, Baltimore, MD
[e]Texas A&M School of Medicine, Austin, TX; Westlake Dermatology & Cosmetic Surgery, Austin, TX
[f]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University School of Medicine, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY; DermResearch, PLLC, Louisville, KY; Skin Sciences, PLLC Louisville, KY

ABSTRACT

Interleukin-31 (IL-31) is a central mediator in atopic dermatitis (AD) and prurigo nodularis (PN), functioning both as the principal pruritogenic cytokine, driving itch through direct neuronal activation via the IL-31RA/OSMRβ signaling axis, and as a key immunological amplifier that sustains Th2 polarization by promoting continued IL-4 and IL-13 production. Beyond these neuroimmune effects, IL-31 disrupts epidermal barrier integrity and acts directly on dermal fibroblasts to drive collagen synthesis and extracellular matrix remodeling, contributing to the lichenification of chronic AD and the hyperkeratotic nodule formation that defines PN. This narrative review integrates the mechanistic biology of IL-31 across both conditions with the clinical evidence base for nemolizumab, a humanized monoclonal antibody targeting IL-31RA, examining phase 3 trial data, long-term extension outcomes, translational biomarker evidence, and emerging real-world experience.

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INTRODUCTION

Atopic dermatitis and prurigo nodularis represent the two most burdensome pruritic inflammatory skin diseases encountered in clinical dermatology. While distinct in morphology, chronicity, and epidemiology, both conditions are united by a common pathophysiologic axis: type 2 immune dysregulation, peripheral neuronal sensitization, collagen deposition resulting in lichenification or nodule formation, and the relentless itch-scratch cycle that profoundly impairs quality of life. At the molecular center of this axis sits interleukin-31, a cytokine that has earned the designation "the itchy cytokine" for its potent, direct pruritogenic activity.[1]

Over the past decade, the biology of IL-31 has been systematically characterized across its receptor signaling machinery, cellular sources, downstream immunologic and neuronal effects, and epidermal consequences. Simultaneously, the therapeutic potential of interrupting IL-31 signaling has been validated through an extensive clinical development program for nemolizumab, a subcutaneously administered humanized monoclonal antibody targeting IL-31RA. The convergence of this mechanistic understanding with robust clinical evidence across two indications provides a unique opportunity to synthesize what is known about IL-31 and to contextualize the therapeutic implications of targeting its receptor.

This manuscript provides an integrated review of IL-31 pathophysiology in AD and PN and the clinical efficacy of nemolizumab across both indications, with attention to skin clearance, pruritus control, sleep restoration, long-term durability, and translational biomarker insights. A discussion section contextualizes these findings within the broader biologics landscape, addresses the mechanistic significance of key clinical observations, and outlines priority areas for future investigation.

Contextualizing Interleukin-31 in Atopic Dermatitis

Epidemiological Context and the Role of Type 2 Inflammation

Atopic dermatitis is a chronic, relapsing inflammatory skin disease characterized by intense pruritus, barrier dysfunction, and dysregulated immune activation. It affects up to 20% of children and approximately 10% of adults worldwide, imposing substantial burdens on quality of life and healthcare systems.[2] The pathogenesis of AD is multifactorial, involving genetic

susceptibility, environmental triggers, cutaneous barrier defects, and a skewed immune response dominated by type 2 inflammation, with contributions from Th1, Th17, and Th22 pathways depending on disease stage and patient demographics.[2]

Within this immunologic milieu, IL-31 has emerged as a pivotal effector cytokine linking type 2 immune activation to pruritus, barrier compromise, and neuroimmune dysregulation.[1,3]

Molecular Biology and Receptor Signaling

IL-31 is a four-helix bundle cytokine belonging to the IL-6 family, produced predominantly by activated CD4+ T helper type 2 (Th2) cells, as well as by mast cells, basophils, dendritic cells, macrophages, and eosinophils.[1,3] It signals through a heterodimeric receptor complex composed of IL-31RA and OSMRβ, activating downstream JAK1/JAK2-mediated STAT1, STAT3, STAT5, and MAPK/PI3K pathways.[4,5] This signaling cascade orchestrates a broad spectrum of downstream effects in immune cells, sensory neurons, and epithelial tissues.[5]

The IL-31RA/OSMRβ receptor complex is expressed on a diverse array of cell types highly relevant to AD pathobiology, including dorsal root ganglion (DRG) sensory neurons, keratinocytes, fibroblasts, eosinophils, basophils, and macrophages.[1,6] This broad receptor distribution underpins IL-31's capacity to simultaneously modulate itch sensation, skin barrier integrity, and immune activation, three hallmarks of AD pathogenesis.[3,5]

IL-31 and Pruritus: Neuroimmune Mechanisms

The role of IL-31 in pruritus induction is one of the most well-characterized aspects of its biology in AD. Peripheral sensory neurons, particularly unmyelinated C-fibers and Aδ-fibers expressing IL-31RA, are directly activated by IL-31, leading to the release of neuropeptides and the transmission of itch signals to the central nervous system.[3,4] Elevated IL-31 levels in the skin and serum of patients with AD correlate strongly with disease severity, pruritus intensity, and lesional burden, supporting its role as both a biomarker and effector of itch.[2,3]

A landmark mechanistic study elucidated a previously unrecognized pathway by which IL-31 drives itch in AD.[4] Their work demonstrated that IL-31 stimulates the release of brain natriuretic peptide (BNP) from DRG neurons, which then acts on gastrin-releasing peptide receptor (GRPR)-expressing spinal neurons to relay itch signals centrally. This IL-31–BNP–GRPR axis represents a key neuronal circuit through which peripheral cytokine signaling is translated into the perception of itch.[6] Furthermore, IL-31 sensitizes sensory neurons, lowering the threshold for activation by other pruritogens such as histamine and substance P, thereby amplifying itch responses in already-sensitized AD skin.[3,4]

Nemmer et al (2021) further characterized IL-31 signaling as a molecular bridge between the immune system, peripheral nervous system, and epithelial compartment.[5] Their work highlighted that in addition to direct neuronal activation, IL-31 suppresses keratinocyte differentiation markers such as filaggrin and loricrin, contributing to the compromised epidermal barrier that is characteristic of AD. This barrier dysfunction permits greater allergen penetration, further sustaining immune activation and IL-31 production in a self-perpetuating pathogenic cycle.[5]

The IL-31-Generating Network in Atopic Dermatitis

IL-31 production in AD does not occur in isolation but emerges from a complex cellular network that amplifies Th2-skewed inflammation. Hashimoto et al (2023) systematically characterized this network, identifying macrophages and basophils as critical cellular sources of IL-31 in lesional AD skin.[7] Their study demonstrated that thymic stromal lymphopoietin (TSLP), a key epithelial alarmin released in response to barrier disruption, directly induces IL-31 production from macrophages and synergizes with periostin, an extracellular matrix protein, to amplify IL-31 secretion from basophils.[7]

This network model positions TSLP and periostin as upstream regulators of IL-31 in AD, integrating epithelial barrier cues with innate and adaptive immune responses.[7] Periostin is itself upregulated by Th2 cytokines such as IL-4 and IL-13 in the AD skin, creating a self-reinforcing loop in which type 2 inflammation drives periostin expression, which in turn potentiates IL-31 release and pruritus.[4,7] TSLP, acting through its receptor on basophils and innate lymphoid cells, also directly activates these populations to produce IL-31, further amplifying the itch-immune axis.[7]

In addition to Th2 cells, basophils, and macrophages, mast cells represent another significant cellular source of IL-31 in AD lesional skin.[1,3] IgE-mediated mast cell activation—a key feature of atopic sensitization—triggers IL-31 release, providing a mechanism by which allergen exposure directly translates into pruritus via cytokine-mediated neuronal activation.[3] Taken together, this IL-31-generating network illustrates the convergence of innate and adaptive immune pathways on a single, itch-mediating cytokine.[1]

IL-31 and Epidermal Barrier Dysfunction

Beyond its neuronal effects, IL-31 exerts direct actions on keratinocytes that compound the epidermal barrier defects characteristic of AD. IL-31 stimulates keratinocyte proliferation while simultaneously suppressing the expression of key structural proteins, including filaggrin, loricrin, and involucrin, components essential for normal cornification and barrier function.[5] The resulting barrier insufficiency increases transepidermal water loss, promotes microbial colonization (particularly by *Staphylococcus aureus)*, and heightens cutaneous immune reactivity.[5] This keratinocyte-mediated mechanism creates a bidirectional amplification loop: barrier dysfunction drives IL-31 production from immune cells, while IL-31 further impairs the barrier, sustaining disease chronicity.[4,5]

Contextualizing Interleukin-31 in Prurigo Nodularis

Overview and Pathophysiological Framing

Prurigo nodularis is a severely pruritic, chronic inflammatory skin disorder characterized by the formation of hyperkeratotic nodules, predominantly on the extensor surfaces of the extremities and trunk. It disproportionately affects middle-aged to older adults and is associated with substantial psychological morbidity, including depression, anxiety, and sleep disturbance.[8] PN is mechanistically distinct from AD in several important ways, though both diseases share a Th2-skewed immune profile and elevated IL-31 signaling. The pathogenesis of PN involves intense neuroimmune dysregulation—characterized by dermal nerve fiber hypertrophy, neuropeptide hypersecretion, and immune infiltration—that drives a self-perpetuating itch-scratch cycle culminating in nodule formation.[9,10]

Recent advances in transcriptomic profiling, single-cell RNA sequencing, and biologic clinical trials have substantially advanced understanding of IL-31's role in PN, collectively positioning IL-31 and its receptor as both key drivers of itch-associated neuroimmune dysregulation and validated therapeutic targets in this historically treatment-resistant disease.[10-12]

Transcriptomic Architecture of PN: IL-31 at the Neuroimmune Interface

A landmark transcriptomic study characterized PN skin using bulk RNA sequencing, revealing a distinct molecular signature that differentiates PN from AD despite their overlapping clinical and immune features.[11] PN lesional skin demonstrated marked upregulation of IL-31, IL-31RA, and OSMRβ compared to both healthy controls and AD skin, underscoring the particular prominence of the IL-31 signaling axis in PN pathobiology. This study also provided the first transcriptomic evidence of nemolizumab's mechanism of action, demonstrating that IL-31RA blockade significantly reversed the neuronal and epithelial gene expression abnormalities in PN, including upregulation of differentiation markers and downregulation of neuroimmune activation signatures.[11] Critically, genes associated with neuronal activation and axonal signaling—including those encoding neuropeptides, ion channels, and receptors for pruritogens—were significantly elevated in PN lesional skin, and nemolizumab treatment normalized a substantial portion of these neuronal gene expression changes.[11] This transcriptomic evidence substantiates the concept that IL-31 in PN is not merely a downstream effector of immune activation but an active driver of peripheral nerve sensitization and structural neural remodeling.[11,12]

Single-cell RNA sequencing analysis further refined the cellular landscape of PN in comparison to AD.[10] Disease-specific differences in the composition and transcriptional states of immune and stromal cell populations were demonstrated, with PN exhibiting a more pronounced fibroblast activation signature, greater dermal macrophage infiltration, and distinct keratinocyte subpopulation profiles relative to AD. The IL-31 signaling axis appeared particularly prominent in the PN neuroimmune compartment, consistent with the more severe neural phenotype observed in PN skin histology.[10]

IL-31 and Neural Remodeling in Prurigo Nodularis

One of the defining pathological features of PN that distinguishes it from AD is the presence of marked neural hypertrophy and altered innervation patterns in lesional skin. Liao et al provided an updated mechanistic framework for PN pathogenesis, emphasizing the central role of IL-31 in driving both immune activation and neural remodeling.[9] In PN, dermal sensory nerve fibers—particularly substance P-expressing C-fibers—are hypertrophied and hypersensitized, a phenomenon that correlates with itch intensity and nodule burden.[7,9] IL-31 directly binds IL-31RA expressed on these sensory nerve fibers, triggering neuronal activation, neuropeptide release, and downstream spinal cord sensitization.[12]

A pivotal study directly examined the relationship between IL-31 and itch intensity in PN at the tissue level.[7] Using immunohistochemical analysis of PN nodular biopsies, they demonstrated that IL-31 protein expression, OSMRβ expression, and itch intensity scores were closely and significantly correlated in dermal tissue, providing direct tissue-level evidence that IL-31 signaling at the neuroimmune interface is a primary determinant of itch severity in PN.[7]

Biomarker Evidence: Nemolizumab-Mediated Modulation in PN

A detailed mechanistic analysis of skin and serum biomarker changes in patients with moderate-to-severe PN treated with nemolizumab provided some of the most direct evidence for IL-31's role in PN neuroimmune and epithelial dysfunction.[12] Nemolizumab treatment resulted in significant reductions in biomarkers of type 2 immune activation, including serum IL-31, periostin, and TARC/CCL17, as well as biomarkers of neural activation such as substance P and neurofilament light chain. These changes were accompanied by normalization of epidermal barrier gene expression, including recovery of filaggrin and involucrin, mirroring findings in AD but with a magnitude of neuronal biomarker change that was notably greater in PN.[12]

The reduction in neurofilament light chain, a marker of neuronal damage and axonal degeneration, following nemolizumab treatment is particularly noteworthy, because it suggests that blocking IL-31RA may not only attenuate acute neuronal activation but also limit ongoing neural injury in this disease.[12] Nemolizumab also significantly downregulated IL-22 and IL-17A in PN lesional skin, cytokines elevated in chronic PN that contribute to hyperkeratotic nodule formation via keratinocyte hyperproliferation.[12] This finding implies that IL-31 signaling in PN may indirectly sustain a broader inflammatory milieu beyond the type 2 axis, potentially through neurogenic amplification of the immune response.[9,12]

Psychodermatological Dimensions of IL-31 in PN

The psychodermatological burden of PN is substantial and is closely linked to the severity and chronicity of itch—a symptom centrally mediated by IL-31.[8] Issa et al provided a comprehensive clinicopathological overview of PN, emphasizing that the chronic, intractable nature of pruritus in PN contributes directly to the high rates of depression, anxiety, and suicidal ideation observed in this population.[8] The itch-scratch cycle in PN is not merely a physical phenomenon but is compounded by central sensitization, sleep deprivation, and neuropsychiatric comorbidities that perpetuate the disease course. Given that IL-31 is a primary mediator of the intractable itch driving this psychosocial burden, therapeutic targeting of IL-31RA has demonstrated promise not only in reducing itch scores but also in improving patient-reported quality of life, sleep quality, and anxiety and depression metrics in clinical trials.[9,12]

Comparative IL-31 Biology: Shared Features and Disease-Specific Distinctions

Despite their distinct clinical phenotypes, AD and PN share a convergent IL-31-driven pathophysiologic core (Figures 1 and 2). Both diseases are characterized by elevated IL-31 levels in lesional skin and peripheral blood, Th2-skewed immune polarization with upregulation of IL-4 and IL-13, and expression of the IL-31RA/OSMRβ

FIGURE 1. Cellular and Tissue-Level Mechanisms of IL-31 in Atopic Skin Disease. In the epidermis, a disrupted barrier, characterized by impaired tight junctions, defective filaggrin, *S. aureus* colonization, and allergen penetration, provides a stimulus for keratinocyte-derived cytokines and Th2 cell activation. IL-31 released from Th2 cells acts on eosinophils, macrophages, dendritic cells, and basophils to amplify type 2 inflammation through IL-4, IL-5, IL-9, and IL-13. In the dermis, IL-31 acts directly on sensory nerve fibers to increase neurite extension and quantity while promoting regeneration of peripheral nerve endings; opposing effects include attenuation of neurodegeneration and neuronal cell death. In the deep dermis and subcutaneous layer, IL-31 stimulates dermal fibroblasts to increase fibrosis, collagen synthesis, and extracellular matrix deposition. Together, these compartment-specific effects explain the chronic, self-reinforcing nature of itch, inflammation, and tissue remodeling observed clinically in atopic dermatitis and related conditions.

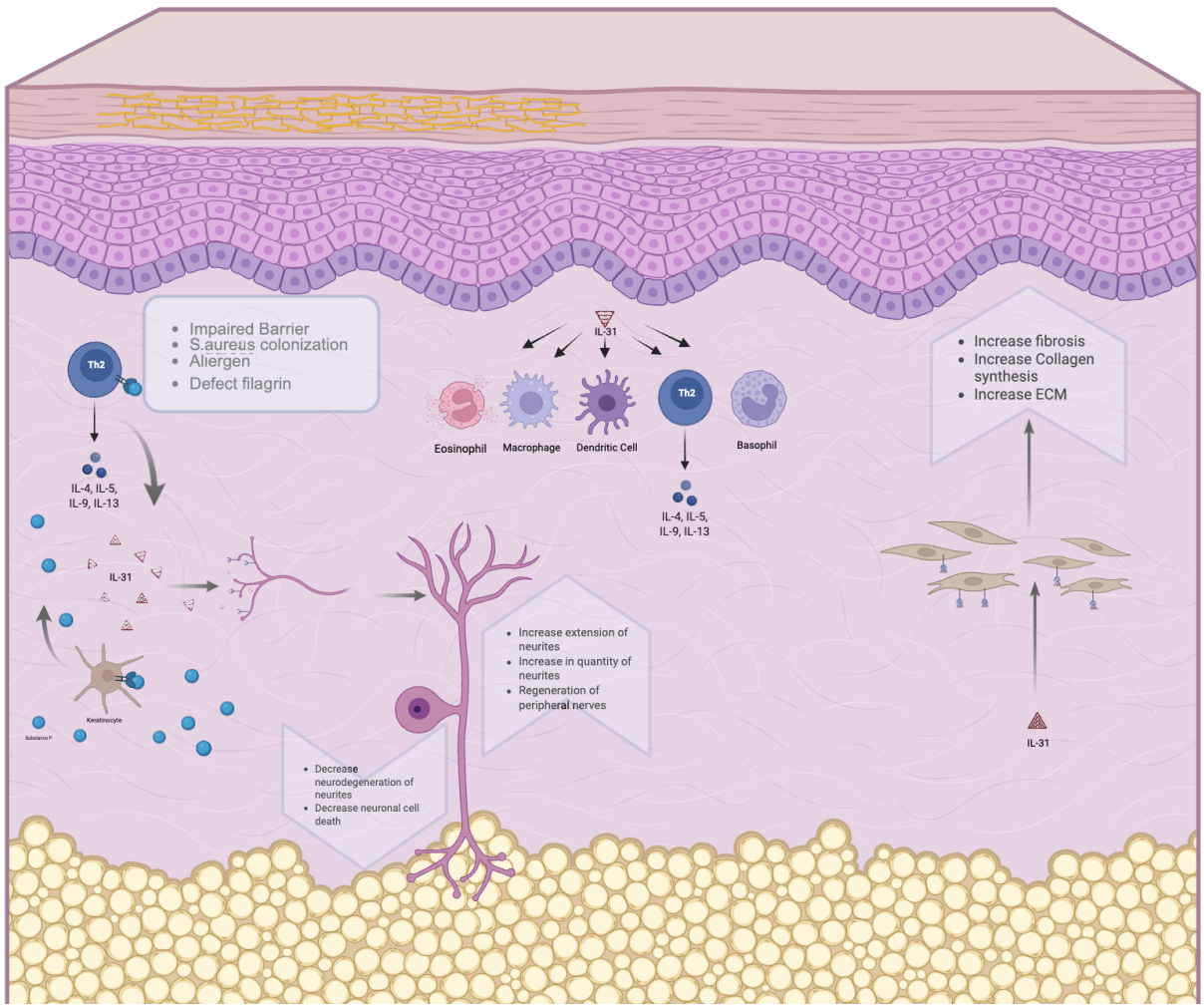
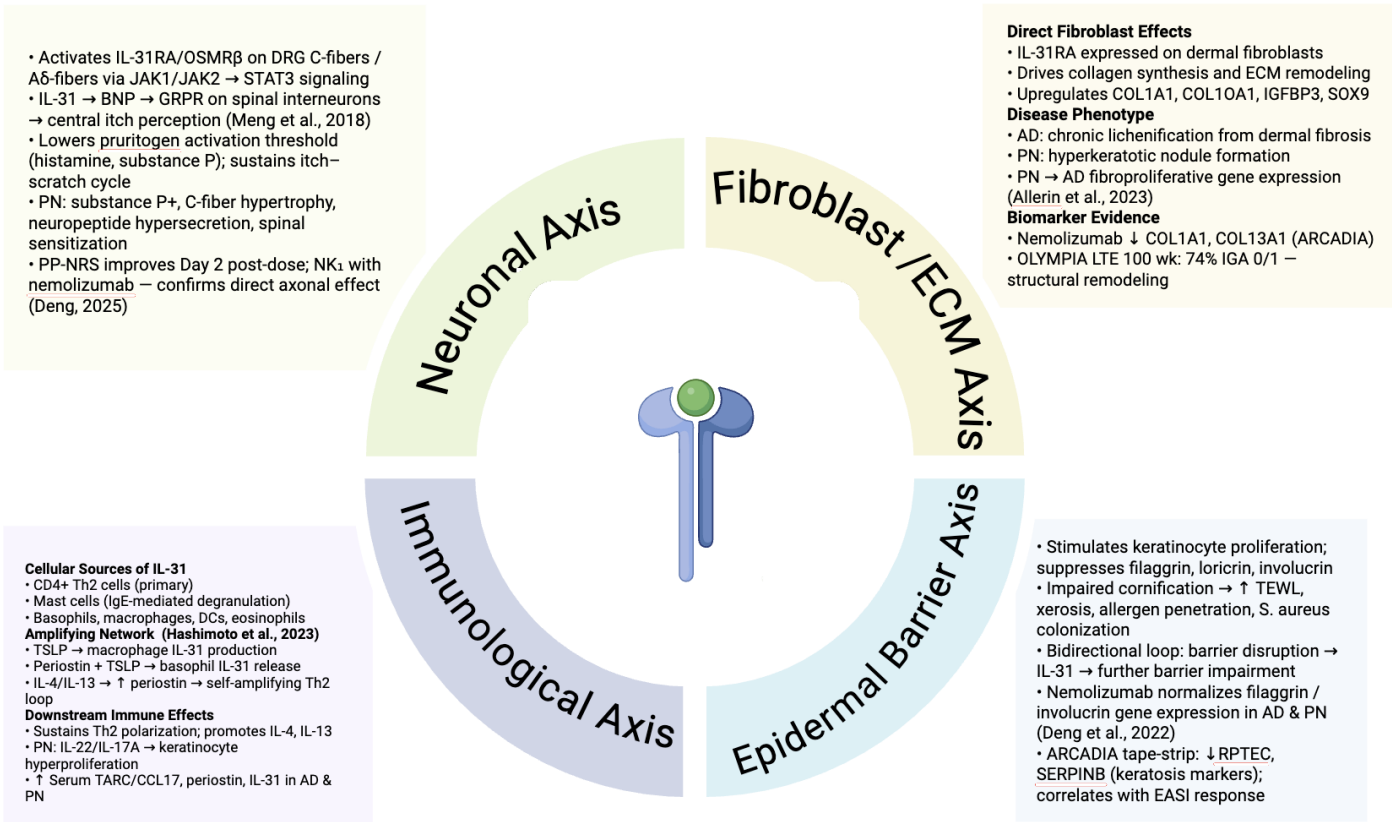


FIGURE 2. Four Biological Pillars of IL-31 Signaling in Atopic Dermatitis and Prurigo Nodularis. IL-31 signals through the IL-31RA/OSMRβ heterodimer to drive pathology across four interconnected effector axes. The Neuronal Axis activates DRG C- and Aδ-fibers via JAK1/JAK2→STAT3, lowers pruritogen thresholds, and in PN promotes C-fiber hypertrophy, substance P hypersecretion, and spinal sensitization. The Immunological Axis is sustained by Th2-derived IL-4/IL-13 and amplified through a TSLP–periostin feed-forward loop engaging macrophages, basophils, and eosinophils. The Epidermal Barrier Axis suppresses filaggrin, loricrin, and involucrin, creating a bidirectional cycle of barrier disruption and further IL-31 release. The Fibroblast/ECM Axis drives collagen synthesis and upregulates COL1A1, COL10A1, IGFBP3, and SOX9, resulting in lichenification in atopic dermatitis (AD) and hyperkeratotic nodule formation in PN. Clinical and biomarker evidence from the ARCADIA and OLYMPIA trials confirms that blockade of all four axes with nemolizumab (anti-IL-31RA monoclonal antibody) produces durable structural remodeling alongside itch relief.



receptor complex on sensory neurons, keratinocytes, and immune effector cells.[1,3,11] In both conditions, IL-31 directly activates peripheral C-fiber neurons via the IL-31RA/OSMRβ axis, triggering the release of neuropeptides and sustaining a pathological itch-scratch cycle.[3,4] Epidermal barrier dysfunction manifested by downregulation of filaggrin, loricrin, and involucrin is present in both diseases and is compounded by direct IL-31 signaling on keratinocytes.[5,12] Furthermore, IL-31 acts on dermal fibroblasts in both AD and PN to promote collagen synthesis and extracellular matrix remodeling, contributing to the structural skin changes of lichenification in AD and nodule formation in PN that define the chronic disease state.[9,10] Beyond structural remodeling, IL-31 stimulates dermal fibroblasts to produce CCL11 (eotaxin-1), a potent eosinophil chemoattractant, at levels several times higher than those of unstimulated fibroblasts, thereby driving eosinophil trafficking and infiltration into lesional skin.[13] Eosinophil degranulation products, in turn, upregulate IL-6 and IL-8 expression in fibroblasts, establishing a bidirectional IL-31-driven fibroblast-eosinophil amplification loop that perpetuates type 2 inflammation in both AD and PN.[13] The shared upstream cellular sources of IL-31, including Th2 cells, mast cells, basophils, and macrophages, are similarly operative in both diseases, and the TSLP/periostin amplification network that potentiates IL-31 production has been documented in both conditions.[7,12] These commonalities provide the biological rationale for nemolizumab's efficacy across both indications and underscore IL-31 as a unifying therapeutic target in Th2-driven pruritic dermatoses.

While IL-31 is elevated and pathologically relevant in both AD and PN, several lines of evidence suggest quantitative and qualitative differences in its role across these two diseases. IL-

31RA and OSMRβ expression are markedly higher in PN lesional skin compared to AD, and dermal IL-31 protein levels correlate more strongly with itch intensity in PN than in AD.[7,11] The neural hypertrophy and neuropeptide upregulation characteristic of PN are more pronounced than in chronic AD, suggesting that IL-31 in PN drives a more advanced and structurally entrenched program of neuronal remodeling.[9,10] Furthermore, PN demonstrates stronger upregulation of fibroproliferative and extracellular matrix remodeling genes compared to AD, consistent with the clinical phenotype of indurated, hyperkeratotic nodules rather than the eczematous plaques of AD.[9] These distinctions have important clinical implications: they predict that the magnitude of neuronal biomarker modulation following IL-31RA blockade will be greater in PN than in AD, and they suggest that nemolizumab's anti-fibroproliferative and neural remodeling effects may be particularly prominent in PN.[12]

Nemolizumab—Clinical Efficacy Across AD and PN Indications

Mechanism of Action and Therapeutic Rationale

Nemolizumab is a subcutaneously administered humanized monoclonal antibody that selectively targets IL-31RA, thereby interrupting IL-31 signaling and attenuating downstream pruritogenic and neuroimmune responses. By blocking the receptor rather than the cytokine itself, nemolizumab inhibits signaling from both IL-31 and oncostatin M, providing broader pathway inhibition.[4] Its mechanism of action positions it uniquely as an anti-itch biologic that also exerts effects through regulation of multiple disease processes, including immunologic and neuronal pathways, a duality consistent with the dual immunoneural pathobiology of AD and PN.

Nemolizumab in Atopic Dermatitis: Phase 3 and Long-Term Evidence

Trial Design and Patient Population

The ARCADIA program comprised two replicate, randomized, double-blind, placebo-controlled, phase 3 trials (ARCADIA 1: NCT03985943; ARCADIA 2: NCT03989349) conducted across international sites. Together, the trials enrolled 1,728 adolescents and adults (aged ≥12 years) with moderate-to-severe AD, defined by an Investigator's Global Assessment (IGA) score ≥3, an Eczema Area and Severity Index (EASI) score ≥16, body surface area involvement ≥10%, and a Peak Pruritus Numerical Rating Scale (PP-NRS) score ≥4. Importantly, enrollment required a documented inadequate response to TCS therapy defined as failure to achieve adequate disease control despite treatment with a stable, protocol-specified TCS regimen during a mandatory 2- to 4-week run-in period prior to randomization, thereby confirming that all enrolled patients represented an actively treated but insufficiently controlled population. Patients were then randomized 2:1 to receive nemolizumab (60 mg loading dose followed by 30 mg subcutaneously every 4 weeks (Q4W)) or placebo, with concomitant background TCS therapy with or without topical calcineurin inhibitors (TCI) permitted throughout the trial. At week 16, patients who achieved a clinical response were re-randomized into one of three blinded maintenance groups: (1) continuing nemolizumab 30 mg monthly, (2) de-escalating to nemolizumab 30 mg every 8 weeks, or (3) switching to placebo. Patients were then followed through week 48 to assess durability and optimal maintenance dosing. Patients who completed the pivotal period through week 48 were eligible to enroll in the ARCADIA open-label long-term extension (LTE), with outcomes reported up to two years of total treatment.[14,15]

Skin Clearance: From Pivotal Period to Two-Year Outcomes

Both ARCADIA trials met their co-primary endpoints at week 16 with statistical significance. In ARCADIA 1, IGA 0/1 (clear or almost clear) was achieved by 36% of nemolizumab-treated patients vs 25% in the placebo group, and EASI-75 was attained by 44% vs 29%. ARCADIA 2 demonstrated concordant results: IGA 0/1 in 38% vs 26%, and EASI-75 in 42% vs 30% (Figure 3A).[14] These findings are particularly notable given that all patients were pre-treated with active topical therapy. IL-31 blockade further improved skin clearance responses, which deepened substantially with continued treatment. Skin clearance responses deepened substantially with continued treatment. By week 104 of the LTE, IGA 0/1 was achieved in 62.6% of patients with previous nemolizumab experience (PNE) and in 58.2% of those with no prior nemolizumab exposure (NNE). EASI-75 was attained by 88.2% (PNE) and 85.4% (NNE) at two years (Figure 3B).[15,16] This trajectory of deepening skin clearance reflects the cumulative immunologic benefit of sustained IL-31RA blockade, and the comparable outcomes between PNE and NNE cohorts confirm that later initiation of therapy does not compromise the ceiling of achievable response.

Pruritus Control and Sleep Restoration

A PP-NRS improvement of ≥4 points, the threshold for a clinically meaningful within-patient change, was achieved in 45% of nemolizumab patients vs 18% of placebo patients in ARCADIA 1, and in 48% vs 21% in ARCADIA 2 at week 16.[14] Itch relief was rapid: a pooled analysis of ARCADIA 1 and 2 demonstrated statistically significant separation in PP-NRS responder rates as early as day 2 post-dose.[16] An itch-free or near itch-free state (PP-NRS ≤2) was achieved by week 16 in 33% (ARCADIA 1) and 36% (ARCADIA 2) of nemolizumab-treated patients vs 15% in both placebo arms. Sleep disturbance was similarly improved, reflecting the downstream benefit of itch suppression on nocturnal well-being.[14]

These benefits were durable and continued to deepen over two years of LTE follow-up. At week 104, VAS Pruritus ≤2 was achieved in 69.6% of PNE patients and 67.2% of NNE patients. VAS sleep loss improvement of ≥4 points was attained in 70.8% (PNE) and 68.9% (NNE) at two years, reinforcing that the holistic quality-of-life benefits of IL-31 pathway blockade are not only maintained but amplified with long-term continuous therapy (Figure 2B).[15]

Nemolizumab in Prurigo Nodularis: Phase 3 and Long-Term Evidence

Trial Design and Patient Population

The pivotal phase 3 program for PN consisted of OLYMPIA 1 and OLYMPIA 2, two replicate, randomized, double-blind, placebo-controlled trials. OLYMPIA 1 enrolled 286 adults with moderate-to-severe PN (duration ≥6 months, IGA ≥3, PP-NRS ≥7, ≥20 bilateral nodules) across 77 sites in 10 countries, with a 24-week treatment period.[17] OLYMPIA 2 enrolled 274 patients with a similar profile over a 16-week treatment period.[18] In both trials, patients were randomized 2:1 to nemolizumab—administered as a 60 mg loading dose followed by Q4W subcutaneous injections (30 mg for patients <90 kg; 60 mg for patients ≥90 kg)—or placebo, as monotherapy without concomitant immunosuppressive or topical therapies. Patients completing the pivotal period were eligible to continue into the OLYMPIA-LTE and the Japanese phase II/III extension, providing durability data up to 100 and 68 weeks, respectively.[17-20]

Skin Clearance: Pivotal to Long-Term Outcomes

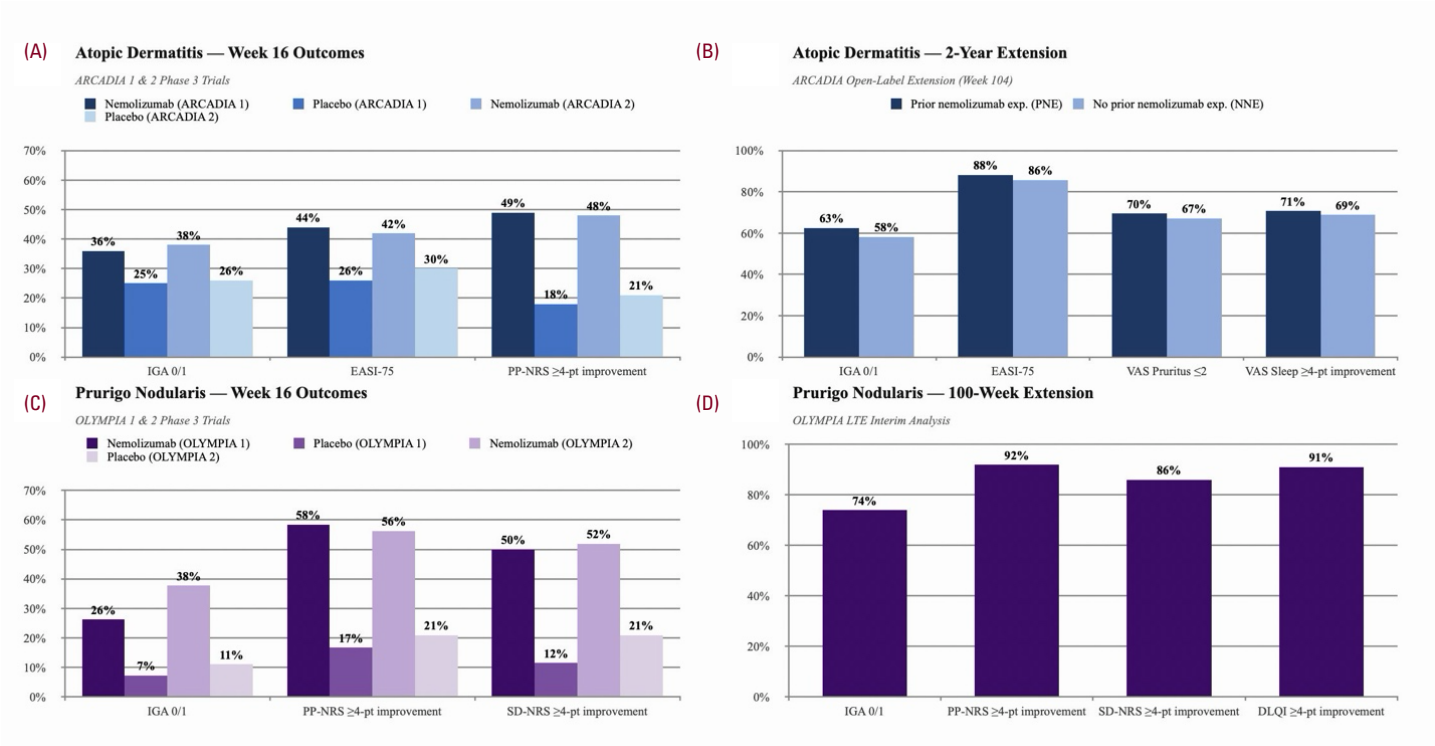
OLYMPIA 1 and OLYMPIA 2 each met their co-primary endpoints with statistical significance. At week 16, IGA 0/1 was achieved in 26.3% of nemolizumab-treated patients vs 7.3% of placebo patients in OLYMPIA 1, and in 37.7% vs 11.0% in OLYMPIA 2 (Figure 3C).[17,18] These results established nemolizumab as the first biologic with regulatory approval for PN in the United States, addressing a significant unmet therapeutic need in a condition long characterized by treatment-refractory, intractable itch.

The skin clearance benefit expanded substantially with extended treatment. At the OLYMPIA-LTE interim analysis at 100 weeks, 74% of patients achieved IGA 0/1, and greater than 75% lesion healing was observed in 84%—an outcome that underscores the drug's capacity not merely to suppress pruritus but to remodel the structural nodular pathology that defines this disease.[19] Data from the Japanese phase II/III extension demonstrated sustained IGA improvements through 68 weeks of combined nemolizumab and TCS treatment, with a ≥50% reduction in daily TCS use observed over the extension period, reflecting an important corticosteroid-sparing benefit.[20]

Pruritus Control and Sleep Restoration

A PP-NRS ≥4-point improvement was achieved in 58.4% of nemolizumab patients vs 16.7% of placebo patients in OLYMPIA 1, and in 56.3% vs 20.9% in OLYMPIA 2 (Figure 3C).[17,18] Itch relief emerged with unexpected speed: a pooled analysis of OLYMPIA 1 and 2 (N=560) demonstrated statistically significant PP-NRS

FIGURE 3. Clinical Efficacy of Nemolizumab in Atopic Dermatitis and Prurigo Nodularis: Phase 3 and Long-Term Extension Outcomes. (A) Week 16 co-primary endpoint outcomes from the ARCADIA 1 and 2 Phase 3 trials comparing nemolizumab to placebo in atopic dermatitis. (B) Sustained efficacy at week 104 in the ARCADIA open-label extension among patients with and without prior nemolizumab exposure. (C) Week 16 co-primary and key secondary endpoint outcomes from the OLYMPIA 1 and 2 Phase 3 trials comparing nemolizumab to placebo in prurigo nodularis. (D) Long-term co-primary and key secondary endpoint outcomes at 100 weeks of continuous nemolizumab from the OLYMPIA long-term extension interim analysis.



responder rates as early as day 2 post-injection (P<0.001).[16] An itch-free or near itch-free state (PP-NRS ≤2) was achieved at week 16 by 34.2% vs 4.2% (OLYMPIA 1) and 35.0% vs 7.7% (OLYMPIA 2; both P<0.001).[17,18] Sleep disturbance, assessed by the Sleep Disturbance Numerical Rating Scale (SD-NRS), improved significantly in both trials, with ≥4-point improvements in 50.0% (OLYMPIA 1) and 51.9% (OLYMPIA 2) vs 11.5% and 20.9% for placebo, respectively (Figure 3C).[17,18]

The durability of itch suppression was confirmed in long-term extension data. At the 100-week OLYMPIA-LTE interim analysis, 92% of patients achieved PP-NRS ≥4-point improvement, 86% achieved SD-NRS ≥4-point improvement, and Dermatology Life Quality Index (DLQI) ≥4-point improvement was observed in 91% (Figure 3D).[19] In the Japanese extension, PP-NRS reductions deepened from –61.1% at week 16 to –78.6% (30 mg) and –76.5% (60 mg) by week 68, with no evidence of disease relapse upon nemolizumab continuation.[20] Together, these data trace a consistent therapeutic arc: rapid itch suppression from day 2, clinically meaningful itch-free states by week 16, and progressive deepening of all pruritic, sleep, and quality-of-life endpoints through two years—establishing nemolizumab as the most comprehensively validated therapy in PN to date.

Translational Biomarker Evidence: Mechanistic Insights from ARCADIA Transcriptomics

A late-breaking analysis presented at the European Academy of Dermatology and Venereology (EADV) 2024 Congress by Guttman-Yassky et al provided transcriptomic insights from tape-strip biopsies in ARCADIA trial participants, offering mechanistic evidence to complement the clinical efficacy data.[21] Nemolizumab significantly downregulated pruritus-related biomarkers including TRPM1, TRPV3, and OSMR, as well as hyperplasia and fibrosis markers such as KRT6C, SERPINB, COL1A1, COL12A1, IGFBP3, and SOX9. Improvements in EASI, DLQI, and PP-NRS were significantly correlated with modulation of Th17/Th22 (S100A7, S100A8, S100A9, S100A12, IL36G, PI3) and Th1 markers (CCL2, MX1, OASL), suggesting that IL-31 pathway blockade exerts broader immune-modulating effects beyond direct itch suppression.

Particularly notable was the observation that patients with more severe baseline pruritus demonstrated stronger downregulation of Th2 (IL4R, CCL17), Th1 (CCL3/4, CXCL8), and Th17 (CXCL1, IL17RA, PI3) pathway markers following nemolizumab treatment. This dose-response relationship between baseline itch severity and degree of immune modulation underscores the mechanistic rationale for nemolizumab in patients most heavily burdened by pruritus and may inform future strategies for patient selection and therapeutic sequencing.

The speed of antipruritic response with nemolizumab—consistently preceding measurable changes in inflammatory biomarkers across both AD and PN trials—supports the hypothesis that IL-31-mediated itch is substantially driven by direct neuronal sensitization rather than secondary to inflammation alone.[4,5] This mechanistic insight has important implications for understanding the biology of chronic itch and for the design of future antipruritic therapies targeting the neuroimmune interface.[1]

Real-World Experience

Complementing the robust phase 3 clinical trial data, an emerging body of real-world evidence has begun to characterize the effectiveness, safety, and tolerability of nemolizumab in routine clinical practice, predominantly from Japan given its earlier regulatory approval for AD (March 2022) and PN (September 2023). Of note, the dosing of nemolizumab in AD in Japan is different (60 mg every 4 weeks without a loading dose) from that in the United States (30 mg every 4 weeks with a 60 mg loading dose). In the first published real-world post-marketing study of nemolizumab for AD, Miyawaki et al conducted a single-center retrospective analysis of patients with moderate-to-severe AD treated in clinical practice, reporting a mean percent change in EASI score of –55% at month 4—a magnitude that exceeded the –45.9% improvement observed in the Japanese phase 3 trial—an observation the authors attributed to frequent concomitant use of topical corticosteroids, moisturizers, tacrolimus, and delgocitinib ointment in the real-world setting.[22] Laboratory analyses at six months demonstrated significant reductions in lactate dehydrogenase, while IgE, eosinophil counts, and TARC levels did not show statistically significant change. Discontinuation due to AD exacerbation occurred in 2 of 15 patients (13%) after one month of therapy.[22] Building upon these findings, Sugiyama et al provided a detailed real-world analysis of cutaneous adverse events in a larger single-center cohort of 40 patients, identifying cutaneous reactions as the most prevalent treatment-emergent adverse event.[23] Notably, older age, longer disease duration, elevated baseline serum TARC levels, and a trunk-dominant clinical phenotype emerged as independent predictors of more severe cutaneous adverse events, offering clinically actionable data to inform patient selection and monitoring strategies.[23] However, these findings were not corroborated by a larger multicenter retrospective study by Sasaki et al, which evaluated 219 patients across 13 Japanese institutions and found that nemolizumab-associated cutaneous eruptions showed no significant association with baseline disease severity, TARC levels, eosinophil counts, or IgE levels.[24] Sasaki et al concluded that reliable predictive biomarkers for cutaneous adverse events remain absent, underscoring the need for close clinical monitoring during the early induction period regardless of baseline patient profile.[24] In PN, Mima et al reported the first real-world post-marketing efficacy data, demonstrating that 90.9% of patients achieved a ≥4-point PP-NRS improvement at week 24, substantially exceeding the approximately 57% responder rate observed in the OLYMPIA pivotal trials—while treatment-emergent adverse events, predominantly cutaneous in nature, occurred in 39.5% of patients and were associated with significantly lower drug survival rates; importantly, early PP-NRS improvement during induction was identified as a reliable predictor of long-term treatment outcomes.[25]

DISCUSSION

The findings reviewed in this manuscript converge on a unifying biological narrative: IL-31 is not merely one cytokine among many in the inflammatory milieu of AD and PN, but the principal molecular fulcrum connecting type 2 immune activation, peripheral neuronal sensitization, epidermal barrier dysfunction, and dermal fibroblast-driven fibroproliferation in both diseases.[26] The therapeutic corollary of this biology—that targeted blockade of IL-31RA would produce rapid, multi-domain clinical benefit—has now been rigorously validated across four replicate phase 3 trials, multiple long-term extension cohorts, and an emerging body of post-marketing real-world data. The synthesis of these mechanistic and clinical observations warrants careful interpretation within the broader context of pruritic disease management and the evolving biologics landscape.

IL-31 as a Mechanistic Unifier Across Two Distinct Diseases

One of the most important insights to emerge from the body of research reviewed here is the mechanistic commonality between AD and PN at the level of IL-31 signaling, despite their considerable clinical and histopathological differences. AD is an eczematous disease characterized by spongiotic inflammation, barrier insufficiency, and Th2/Th22 polarization, while PN is a neurocutaneous disease defined by neural hypertrophy, nodular fibrosis, and a more complex immune landscape incorporating elements of Th2, Th1, and Th17 activation.[9-11] Yet both diseases are driven, at least in part, by the same IL-31–IL-31RA signaling axis acting on the same population of sensory neurons.[1,3,5] This shared effector mechanism provides a rational basis for nemolizumab's efficacy across both indications and suggests that IL-31-mediated itch may represent a common final pathway through which diverse inflammatory stimuli produce the subjective experience of chronic pruritus.

The quantitative differences in IL-31 signaling between AD and PN—with PN demonstrating substantially higher IL-31RA and OSMRβ expression and stronger correlations between dermal IL-31 and itch intensity—have important implications for patient selection and response phaseprediction.[7,11] These data suggest that the burden of IL-31 pathway activity may be a determinant of nemolizumab response magnitude, a hypothesis supported by the ARCADIA transcriptomic late-breaking analysis showing that patients with more severe baseline pruritus (PP-NRS >7) exhibited stronger downregulation of Th2, Th1, and Th17 immune markers following treatment.[21] Prospective validation of baseline IL-31 signaling burden as a predictive biomarker, whether assessed via serum IL-31, tissue IL-31RA expression, or transcriptomic profiling, represents a priority for future investigation and could meaningfully inform therapeutic sequencing decisions.

Mechanistic Significance of Early Itch Response

The consistently observed onset of itch relief as early as day 2 post-dose across all 4 phase 3 trials—in both AD and PN—merits particular discussion, as it offers one of the clearest windows into the neuronal mechanism of IL-31-mediated pruritus.[16] Conventional anti-inflammatory biologics such as dupilumab (anti–IL-4Rα) or tralokinumab (anti–IL-13) typically produce meaningful itch reduction over weeks, consistent with their primary mechanism of attenuating type 2 inflammatory cytokine signaling upstream of neuronal activation. By contrast, nemolizumab's antipruritic effect at day 2—preceding any measurable change in inflammatory biomarkers—is consistent with direct blockade of IL-31RA on peripheral sensory neurons, interrupting itch signal transmission independently of immune cell modulation.[1,4,5] This neuronal mechanism of action distinguishes nemolizumab pharmacodynamically from other approved biologics for these indications.

This early neuronal effect has practical clinical implications. For patients with severe, refractory pruritus—in whom sleep deprivation, neuropsychiatric morbidity, and quality-of-life impairment are most pronounced—the prospect of meaningful itch relief within days of initiating therapy may have direct benefits on treatment adherence, patient-physician therapeutic alliance, and downstream psychodermatological outcomes.[8] Real-world data suggesting that early PP-NRS improvement during induction predicts long-term treatment durability further supports a paradigm in which early itch response serves as both a surrogate for mechanism engagement and a practical treatment monitoring tool in clinical practice.[25]

Contextualizing Nemolizumab Within the Biologics Landscape

In AD, nemolizumab joins dupilumab, tralokinumab, and lebrikizumab as approved biologics, and it is important to contextualize where IL-31RA blockade fits within this increasingly crowded space. Unlike IL-4Rα and IL-13 antagonists, which primarily suppress the upstream Th2 cytokine environment driving immune and epidermal abnormalities, nemolizumab acts directly on the neuronal and epithelial effector compartments, a mechanistic distinction that may translate into clinical complementarity. The ARCADIA transcriptomic data showing that nemolizumab modulates Th17/Th22 and Th1 pathway markers, beyond its primary Th2 target, further suggest that IL-31 signaling in AD has broader immunomodulatory consequences than previously appreciated.[21]

In PN, nemolizumab holds the distinction of being one of the first biologics with regulatory approval in the United States, addressing a disease that lacked any approved systemic therapy for decades.[17,18] Prior to its approval, patients were managed with off-label regimens including dupilumab, systemic immunosuppressants, and neuromodulatory agents such as gabapentin and pregabalin, none of which addressed the neuroimmune pathobiology of PN with

mechanistic precision.[9] The approval of nemolizumab therefore represents a paradigm shift not only in therapeutic options but in the conceptualization of PN as a targetable neuroimmune disease.

Real-World Evidence: Corroboration, Divergence, and Clinical Implications

The emerging real-world data from Japan add an important translational dimension to the clinical trial evidence base, though their interpretation requires appropriate methodological caution. The post-marketing studies available to date are predominantly retrospective, and limited by sample size, reflecting the early stage of nemolizumab's commercial availability outside of trial settings.[22-25] Despite these limitations, the directional consistency between real-world and trial outcomes is reassuring. The observation that real-world EASI improvements in AD exceeded those of the Japanese phase 3 trial, attributed by Miyawaki et al to optimized concomitant topical therapy, highlights a potentially important difference in how nemolizumab is deployed in practice vs trials where background topical regimens may be more intensively managed.[22] This finding has practical implications for treatment protocols and suggests that maximizing concomitant topical therapy may augment nemolizumab's skin-clearance effects beyond what was observed in the controlled trial setting.

For the PN indication, Mima et al's finding that early PP-NRS response during induction predicts long-term drug survival further supports the clinical utility of structured early response assessment at approximately 4 to 8 weeks as a guide to ongoing treatment decision-making.[25]

Limitations and Future Directions

Several limitations warrant acknowledgment. Available real-world data are exclusively from Japan, where patient demographics, dosing, and concomitant treatment patterns may differ from European or North American populations; broader international registries are needed. The durability of nemolizumab's neuromodulatory effects beyond 2 years, particularly its capacity to reverse neural remodeling in PN, remains uncharacterized, and head-to-head comparative effectiveness trials against dupilumab in both indications are absent. Future priorities include validating serum IL-31 and tissue IL-31RA expression as predictive biomarkers for treatment response, investigating combination strategies with dupilumab or JAK inhibitors for patients with refractory disease, and examining IL-31's pathogenic role in related pruritic conditions such as chronic prurigo, chronic spontaneous urticaria, and bullous pemphigoid.

CONCLUSIONS

Interleukin-31 occupies a unique and central position in the pathobiology of both atopic dermatitis and prurigo nodularis, simultaneously directing pruritus via direct neuronal activation, perpetuating epidermal barrier dysfunction, and amplifying type 2 immune responses through a complex, self-reinforcing cellular network. While IL-31 is pathologically relevant in both diseases, transcriptomic and biomarker data establish that its role in PN is quantitatively more prominent—characterized by greater upregulation of IL-31RA and OSMRβ, more severe neural remodeling, and stronger tissue-level correlations between dermal IL-31 and itch intensity—than in AD. These distinctions carry mechanistic and therapeutic significance, predicting that IL-31RA blockade may yield particularly marked neuronal and anti-fibroproliferative benefits in PN.

Nemolizumab has fulfilled its promise as a neuroimmune biologic across 4 replicate phase 3 trials, multiple extension studies, and an emerging body of real-world post-marketing experience. The drug has consistently demonstrated rapid, robust, and durable improvements in skin clearance, pruritus, and sleep disturbance in both AD and PN. Real-world data from Japan suggest that effectiveness in clinical practice may meet or exceed trial benchmarks, particularly when nemolizumab is used alongside optimized topical regimens. Early identification of clinically actionable predictors of adverse events and treatment response, including baseline pruritus severity, trunk-dominant phenotype, and early PP-NRS improvement during induction, further supports the prospect of individualized therapeutic decision-making. As the biologic landscape for pruritic inflammatory dermatoses continues to mature, nemolizumab's established efficacy, mechanistic depth, and rapidly accruing real-world evidence position IL-31RA blockade as a cornerstone therapeutic strategy for patients with moderate-to-severe AD and PN who remain inadequately controlled on topical therapy.

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AUTHOR CORRESPONDENCE

Naiem T. Issa MD PhD
E-mail:..... Drnaiemissa@gmail.com