Dermatol Ther (Heidelb)
https://doi.org/10.1007/s13555-025-01437-8

REVIEW

Emerging Therapies in the Treatment of Prurigo Nodularis: Biological Therapy and Systematic Review of Literature

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Received: March 26, 2025 / Accepted: April 24, 2025

ABSTRACT

Introduction: Prurigo nodularis (PN) is a chronic, intensely pruritic dermatosis characterized by hyperkeratotic nodules and a persistent itch–scratch cycle. Recent insights highlight the role of T helper type 2 cell (Th2)-driven immune dysregulation and neuroinflammation, with cytokines such as interleukin (IL)-4, IL-13, and IL-31 implicated in disease pathogenesis. PN is associated with significant morbidity and multiple comorbidities, and conventional therapies often yield suboptimal outcomes, underscoring the need for targeted treatments.

Methods: A systematic review was conducted using PubMed, Scopus, and Google Scholar to identify studies published from January 2020 to March 2025 on PN pathogenesis and treatment. Search terms included combinations of "prurigo nodularis," "biologic therapy," "JAK inhibitors," "IL-4," "IL-13," and "targeted therapy." Of 123 articles screened, 26 were selected on the basis of inclusion criteria prioritizing biologics, JAK inhibitors, randomized controlled trials, cohort studies, and real-world evidence.

Results: Advances in understanding the neuroimmune basis of PN have led to the development of novel therapies. Dupilumab, targeting IL-4Rα, demonstrated significant reductions in pruritus and lesion burden in phase III trials (PRIME/PRIME2) and is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Nemolizumab, an IL-31RA antagonist, received EMA approval in 2025 and shows rapid and sustained efficacy. Other promising agents include JAK inhibitors, vixarelimab (dual IL-31/oncostatin M (OSM) blockade), rocatinlimab (anti-OX40), and anti-IgE therapy with omalizumab. Biomarker-driven endotyping (e.g., eosinophilia, race-specific cytokine profiles) may refine patient selection.

Discussion: Biologics and JAK inhibitors represent a paradigm shift in PN management, offering durable relief through immune and neurogenic modulation. Dupilumab and nemolizumab emerge as first-line therapies

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Published online: 15 May 2025

with favorable safety profiles, while JAK inhibitors provide rapid relief for refractory cases. The heterogeneity of PN underscores the importance of personalized treatment approaches based on immunologic profiling.
Conclusion: Targeted therapies are revolutionizing PN treatment. Integrating clinical efficacy, immunologic endotyping, and real-world data will be pivotal to optimizing therapeutic strategies, enhancing outcomes, and personalizing care in prurigo nodularis.

Keywords: Biologic therapy; Emerging treatments; IL-4/IL-13 inhibition; IL-31 inhibition; JAK inhibitors; Neuroimmune dysregulation; Prurigo nodularis; Targeted therapy

Key Points
In prurigo nodularis (PN) pathogenesis Th2-driven inflammation and neuroimmune interactions sustain chronic itch.
This review explores emerging targeted therapies based on recent advances in PN pathophysiology.
Biologics and JAK inhibitors which target key inflammatory pathways improve PN management. Dupilumab and nemolizumab offer effective, disease-modifying treatment with robust clinical data. JAK inhibitors show rapid efficacy but need more studies for approval.
Personalized treatments and emerging biologics are under investigation. Immunologic endotyping enables personalized therapy and improved treatment outcomes.

INTRODUCTION

Prurigo nodularis (PN) is a chronic neuroimmunologic skin disorder characterized by intense, persistent pruritus lasting over 6 weeks, often leading to repeated scratching and the formation of hyperkeratotic, excoriated, or crusted nodules. These nodules typically localize symmetrically on the extensor surfaces of the extremities [1]. Patients might report additional symptoms such as pain, burning, and stinging sensations.

The prevalence of PN is higher among middle-aged and older adults, particularly in women and individuals of African descent. Epidemiological data reveal significant geographic variability, with prevalence estimates ranging from 8 to 200 cases per 100,000 individuals [2].

PN has a substantial impact on quality of life and is associated with various comorbid conditions, including dermatologic, metabolic, oncologic, neurologic, and psychiatric disorders [3]. Diagnosis is primarily based on clinical grounds (the three main criteria are a more than 6-week history of pruritus, a history of repeated scratching/friction, and skin lesions, such as nodules, papules, firm plaques with or without excoriations) [4], and supported by histopathological findings such as orthohyperkeratosis (with or without focal parakeratosis), acanthosis, dermal fibrosis, immune cell infiltrates, and neuroanatomical changes [5, 6].

Aims

This review aims to provide a comprehensive and structured analysis of emerging therapeutic strategies for PN, a complex and increasingly prominent topic in dermatology. As understanding of PN pathogenesis continues to evolve, there is a pressing need to systematically examine the underlying mechanisms and their therapeutic implications. By critically evaluating data from clinical trials and real-world studies, this review seeks to contextualize the efficacy and safety of novel agents, including biologics and Janus kinase (JAK) inhibitors. Given the heterogeneity of PN—spanning immunologic endotypes, demographic variations, and diverse comorbidities—organizing and interpreting current evidence is essential to inform personalized, evidence-based treatment strategies.

METHODS

A structured literature search was performed in PubMed, Scopus, and Google Scholar covering the period from January 2020 to the present. The following keywords and their Boolean combinations were used: "PN", "chronic prurigo", "biologic therapy", "JAK inhibitors," "IL-4," "IL-13," "IL-31," "pathophysiology," and "targeted therapy." The initial search yielded 123 articles. Titles and abstracts were screened for relevance to biologic and small-molecule inhibitor therapies in PN, with a focus on randomized controlled trials (RCTs), cohort studies, and real-world evidence. After the application of inclusion and exclusion criteria, 26 articles were selected for full-text evaluation.

Eligibility Criteria

Studies were included if they met the following criteria:

1. Study design: RCTs, cohort studies, or large case–control studies with a clear methodology.
2. Intervention: Studies evaluating biologic therapies (e.g., IL-4, IL-13, IL-31 inhibitors) or JAK inhibitors in PN treatment.
3. Outcomes assessed: Studies reporting at least one of the following: improvement in pruritus, lesion resolution, quality of life changes, safety, or long-term efficacy.
4. Language: Articles published in English.
5. Population: Studies including adult patients (>18 years old) with a confirmed diagnosis of PN based on clinical and/or histopathological criteria.

Exclusion Criteria

1. Non-peer-reviewed articles, conference abstracts.
2. Studies focusing on other pruritic conditions without specific PN data.
3. Studies with insufficient follow-up (<12 weeks) or lacking quantitative outcome measures.
4. Trials with high risk of bias (e.g., inadequate randomization, incomplete data reporting).

Data Extraction and Selection Process

Two independent reviewers (blinded to each other's assessments) screened titles and abstracts. A third reviewer resolved any discrepancies. Covidence software was used to manage the selection process, and a PRISMA flow diagram was generated to illustrate study selection (Fig. 1).

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

The patient in this manuscript has given written informed consent to publication of her case details and clinical photographs.

RESULTS

Pathogenesis and Rationale for Targeted Therapies

Traditional treatments for PN, including topical corticosteroids, calcineurin inhibitors, phototherapy, and systemic immunosuppressants (e.g., cyclosporine A, methotrexate, thalidomide), have often been limited in effectiveness, with many patients experiencing only partial relief [3, 7]. Recent insights into PN pathophysiology—particularly in cytokine dysregulation and neurocutaneous abnormalities—have led to the exploration of targeted therapies, including monoclonal antibodies and JAK inhibitors, which offer promising new approaches for more effective management.

PN pathophysiology involves complex interactions between keratinocytes, immune cells, and neural pathways that sustain the itch–scratch cycle [3]. The disease appears to be associated with Th1, Th17,Th22, and, notably, Th2 pathways [8]. Elevated levels of T helper type 2 cells (Th2), mast cells, eosinophils, and Th2 cytokines, mainly interleukin-4, -13, and

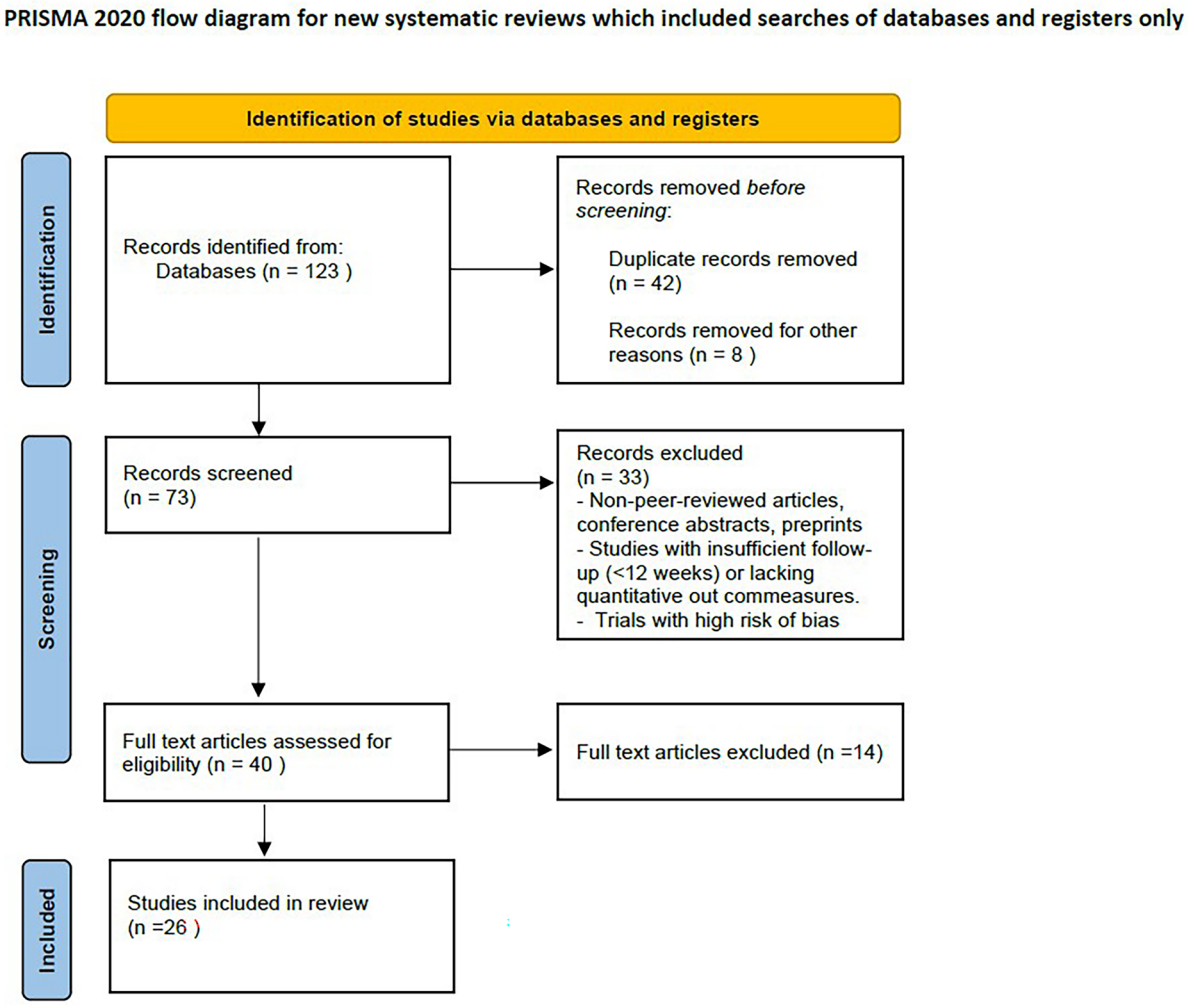

Fig. 1 PRISMA flow diagram of study selection for systematic review on emerging therapies in PN

-31 (IL-4, IL-13, IL-31), have been detected in PN lesions, contributing to inflammation, pruritus, and nodule formation.

Neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP), and nerve growth factor (NGF) are key drivers of neurogenic inflammation and pruritus in chronic prurigo nodularis (CNPG). These molecules activate sensory nerve fibers and amplify inflammation through neuroimmune interactions. IL-4 and IL-31 facilitate neuroimmune communication through receptors on dorsal root ganglia neurons, while neuropeptides like SP and CGRP contribute to inflammation via vasodilatation and mast cell degranulation. IL-31, produced by Th2 cells and other immune cells, directly stimulates sensory neurons and enhances inflammation by activating keratinocytes and immune cells. Additionally, periostin, released by keratinocytes and fibroblasts, directly modulates nerve fibers and promotes pruritogen release, contributing to the chronic itch–scratch cycle [1–3].

Oncostatin M (OSM), a member of the IL-6 cytokine family, contributes to chronic pruritus by amplifying Th2-mediated inflammation and sensory neuron activation via the OSMRβ receptor, shared with IL-31. Preclinical models demonstrate that OSM exacerbates cutaneous inflammation and itch-related behavior, whereas OSMRβ blockade attenuates Th2 cytokine expression, IgE production, and scratching. These findings underscore OSM's potential role

in pruritic disorders such as PN and highlight its relevance as a therapeutic target [9].

Transcriptomic studies indicate increased IL-4 in the skin, elevated IL-13 and IL-22 in plasma, and upregulation of oncostatin M. These cytokines exert their effects through the JAK-STAT pathway, promoting chronic pruritus. Consequently, JAK inhibitors have the potential to disrupt this signaling cascade, offering a promising therapeutic approach for PN [4].

Emerging Therapies

Dupilumab

Dupilumab is a fully human monoclonal antibody targeting IL-4 receptor alpha (IL-4Rα), a receptor shared by IL-4 and IL-13. By inhibiting these key Th2 cytokines, dupilumab has shown efficacy across Th2-mediated diseases such as atopic dermatitis and asthma [3].

In 2022, following phase 3 trials, dupilumab received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for PN treatment, demonstrating substantial reductions in pruritus and skin lesions over 24 weeks and significant quality-of-life improvements [7].

Pooled data from the LIBERTY-PN PRIME and PRIME2 trials, randomized, double-blind, placebo-controlled studies, demonstrate that dupilumab provides significant symptom relief in moderate-to-severe PN. Pruritus reduction (≥ 4-point WI-NRS decrease) was observed as early as week 2, with substantial improvements by week 12 (40.5%) and week 24 (58.8%) compared to placebo (19.0%; $P<0.0001$). Additionally, the trials reported a 37% reduction in the Peak Pruritus Numeric Rating Scale (PP-NRS) at week 12, increasing to 60% by week 24, with nearly half of patients achieving an Investigator Global Assessment (IGA) score of 0 or 1 by the study's end. Combined itch reduction and clear/almost-clear skin were achieved by 35.3% of dupilumab-treated patients at week 24, compared to 8.9% with placebo ($P<0.0001$). These results highlight dupilumab's rapid onset and sustained efficacy, supported by consistent safety data through 36 weeks, offering a transformative treatment option for PN [10].

Dupilumab safety profile is favorable, with mild adverse events such as conjunctivitis (2.7–3.9%) and herpes infections (5.2%), making it viable for a wide patient demographic [4]. A recent study by Bao et al. suggests that dupilumab may also influence circulating inflammatory mediators in patients with PN, marking a significant advancement for those unresponsive to conventional therapies [11].

Tralokinumab and Lebrikizumab

Tralokinumab and lebrikizumab are IL-13-targeting monoclonal antibodies currently under investigation for PN treatment. Tralokinumab neutralizes IL-13 by preventing its interaction with both IL-13Rα1 and IL-13Rα2, which are involved in pruritus signaling and skin barrier impairment. Lebrikizumab, another IL-13-targeting agent, prevents IL-13 from forming the IL-13Rα1/IL-4Rα receptor complex, leading to itch alleviation and epidermal hyperplasia reduction. Phase II trials in atopic dermatitis have shown rapid reduction of pruritus with both agents, accompanied by mild adverse events, including conjunctivitis and respiratory infections [3].

Both therapies hold potential for treating PN by targeting key immune pathways, although further research is needed to evaluate their efficacy in patients with PN.

Nemolizumab

Nemolizumab, a humanized monoclonal antibody targeting IL-31 receptor A (IL-31RA), inhibits a pivotal neuroimmune axis implicated in chronic pruritus and the pathogenesis of PN. By blocking IL-31 binding to its receptor on sensory neurons and keratinocytes, nemolizumab disrupts downstream JAK1/2-mediated signaling, thereby attenuating pruritus and inflammation.

Results from the phase III OLYMPIA 2 trial revealed that nemolizumab significantly reduced pruritus (≥ 4-point WI-NRS improvement in 56.3% of patients vs. 20.9% with placebo) and achieved IGA success (37.7% vs. 11.0%) at week 16. Sleep quality and overall quality of life

improved substantially. Mechanistic data from transcriptomic analyses indicate a broader disease-modifying role via downregulation of genes linked to nerve activity and neuroinflammation [12].

A 2025 systematic review and meta-analysis by Sinha et al., encompassing 859 patients across four RCTs, confirmed nemolizumab's efficacy (WI-NRS RR 3.52; IGA RR 4.40) and safety profile, with most adverse events being mild and self-limited. Though a slight increase in adverse events was noted (RR 1.11), this did not reach statistical significance. Importantly, unlike observations in atopic dermatitis, peripheral edema and asthma exacerbation were rare in PN populations [13].

As of February 2025, nemolizumab has received regulatory approval by the EMA for both atopic dermatitis and PN, marking a landmark shift in the therapeutic landscape for chronic pruritic dermatoses.

Vixarelimab

Vixarelimab (KPL-716) introduces a novel dual-cytokine inhibition strategy, targeting the β subunit of the oncostatin M receptor (OSMRβ), thereby simultaneously blocking IL-31 and oncostatin M (OSM) signaling. This mechanism addresses both pruritus and the fibrotic remodeling characteristic of PN.

In a phase IIa trial, vixarelimab achieved a ≥ 4-point WI-NRS reduction in 52.2% of patients compared to 30.8% with placebo ($p = 0.03$). Approximately 30.4% achieved an IGA score of 0 or 1 by week 8. Improvements in sleep, Dermatology Life Quality Index (DLQI), and ItchyQoL scores further underscored its impact on disease burden. Safety was favorable, with no serious adverse events or hematologic abnormalities observed. Notably, early symptom improvement was observed by week 3, with several patients experiencing ≥ 8-point WI-NRS reductions.

Comparative data suggest that vixarelimab may offer enhanced nodule clearance relative to monotherapies like nemolizumab, supporting its development in ongoing phase III trials [14].

JAK Inhibitors

Emerging therapies for PN are evolving with the advent of JAK inhibitors. Among these, upadacitinib, a selective JAK1 inhibitor, studied in various inflammatory diseases, has shown promising results in the treatment of refractory PN. Clinical studies have demonstrated that upadacitinib (15 mg daily) leads to rapid relief of pruritus and significant improvement in skin lesions, with good tolerability, even in patients with chronic renal insufficiency. In a prospective study of patients with PN refractory to other immunosuppressive therapies, the pruritus scores (NRS) and Investigator Global Assessment (IGA) significantly improved after 24 weeks of treatment, with no serious adverse events observed. This treatment primarily works by interrupting the itch–scratch cycle, modulating the JAK-STAT pathway involved in both pruritus transmission and cutaneous inflammation [15–17].

In a phase II, randomized, double-blind, placebo-controlled study, povorcitinib, another selective oral JAK1 inhibitor, demonstrated significant efficacy and safety in patients with PN. The 40-week results revealed that povorcitinib achieved meaningful improvements in itch severity (NRS4) and skin lesion resolution (IGA-TS) compared to placebo, with sustained responses during the extension period. The drug was well tolerated, with no new safety concerns emerging from prolonged treatment. These findings underscore the potential of povorcitinib as a novel therapeutic option for recalcitrant PN, paving the way for ongoing investigations in the phase III STOP-PN1 trial, designed to assess the efficacy and safety of povorcitinib and confirm these benefits in a broader population [18].

Other JAK inhibitors, such as abrocitinib and tofacitinib, have also shown positive effects in refractory PN cases, with significant reductions in pruritus and improvement in skin lesions [1].

A recent prospective study investigated the tissue expression of STAT1, STAT3, and STAT6 in PN and their correlation with tofacitinib efficacy. Findings confirmed a Th2/Th17-driven inflammation (immunohistochemical analysis revealed marked tissue expression of STAT6 in 13 patients and STAT3 in 10 patients, while STAT1 expression was seen in only 4 patients)

and demonstrated a 66.1% PGSS reduction ($p = 0.0004$) with rapid onset (11.2 days) and sustained remission (82.4%) [19].

Additionally, topical ruxolitinib, currently under investigation for PN, may offer a viable alternative for managing localized disease [8].

In conclusion, relying also on an evidence-based review recently published on management of PN with systemic Janus kinase inhibitors, systemic JAK inhibitors demonstrated promising efficacy in refractory PN. Complete resolution was highest with upadacitinib (59.5%) and tofacitinib (58.8%), though adverse events (e.g., acne, infections) occurred in 18.8% of cases. Further large-scale studies are warranted [20].

Other Promising Biologic Therapies

Omalizumab

Omalizumab, an anti-IgE monoclonal antibody approved for chronic spontaneous urticaria (CSU) and asthma, has shown promise in treating chronic prurigo (PN), particularly in nodular and papular-plaque subtypes. Case reports suggest it improves pruritus and skin lesions by targeting basophils, which play a role in PN pathogenesis. Omalizumab binds free IgE, preventing its activation of basophils, mast cells, and eosinophils, thereby reducing pruritus. Its potential benefit in PN is linked to reducing nerve growth factor release, which contributes to the itch–scratch cycle. Ligelizumab, another IgE inhibitor, is under investigation and shows similar potential for treating pruritus [3].

Rocatinlimab

Rocatinlimab is a human, non-fucosylated monoclonal IgG1 antibody targeting OX40, a co-stimulatory T cell receptor critical for effector and memory T cell activity. It disrupts the OX40-OX40L pathway, pivotal in atopic dermatitis (AD) and PN pathogenesis, by inhibiting T cell proliferation and survival, thus attenuating inflammation and disease progression. This therapeutic mechanism modulates multiple T cell subsets (Th2, Th1, Th17, Th22), reducing inflammatory cytokines such as IL-4, IL-13, and IL-22, and potentially restoring skin barrier function.

Phase 2b trials in AD demonstrated significant efficacy with rocatinlimab, achieving up to 61% reduction in EASI scores and sustained clinical benefits, with favorable safety profiles. Secondary outcomes showed improved pruritus scores and long-term disease control post treatment cessation. These findings underline its biological rationale in inflammatory dermatoses like AD and PN.

A phase III trial (NCT06527404) is underway to evaluate rocatinlimab for PN. This 52-week, multicenter, double-blind, placebo-controlled study will assess efficacy, safety, and tolerability in adults inadequately controlled by topical therapies. The primary endpoint focuses on patient-reported pruritus outcomes and overall clinical assessment at 24 weeks, reinforcing its potential as a transformative therapy [21, 22].

Benralizumab

Benralizumab is a monoclonal antibody targeting the interleukin-5 receptor alpha (IL-5Rα), approved for eosinophilic asthma, now under investigation for chronic prurigo (CPG), including PN. IL-5 plays a key role in the differentiation, activation, and survival of eosinophils—a cell type increasingly recognized as a contributor to the neuroimmune and inflammatory milieu in PN, particularly in eosinophilic endotypes.

Although phase II data in PN are pending, the therapeutic rationale for benralizumab is supported by its efficacy in other eosinophil-driven dermatoses and respiratory diseases. By inducing antibody-dependent cell-mediated cytotoxicity (ADCC), benralizumab depletes eosinophils in both circulation and tissues, potentially disrupting the itch–inflammation–fibrosis axis central to PN pathogenesis.

Extrapolations from chronic urticaria and eosinophilic gastrointestinal disorder studies further strengthen the mechanistic plausibility of benralizumab in this setting. Ongoing trials are expected to elucidate its clinical efficacy, safety, and role within an emerging endotype-specific therapeutic framework [23].

Opioid modulators such as nalbuphine, a μ-opioid receptor antagonist and κ-opioid receptor agonist, have demonstrated modest efficacy in phase IIb/III trials for PN; however, concerns persist regarding potential for habit formation and the exclusion of patients with psychiatric comorbidities. Similarly, NK1 receptor antagonists, including aprepitant and serlopitant, have failed to show consistent clinical benefit in larger trials, although they may retain a role in selected patients with predominant neurogenic itch [4, 23].

A growing body of evidence supports the use of biologics and small-molecule inhibitors for the treatment of PN. The following table summarizes the main systemic therapies currently available or under investigation, highlighting their mechanisms of action, regulatory status, routes of administration, and standard dosages (Table 1).

DISCUSSION

Prurigo nodularis is a chronic, severely pruritic dermatologic condition that profoundly impairs patients' quality of life. Traditional therapies have primarily focused on symptomatic relief, offering limited benefit in a disease characterized by complex immunologic and neurocutaneous mechanisms. Advances in PN pathogenesis research have uncovered an intricate interplay of Th2-driven immune dysregulation, neuroimmune cross talk, and cutaneous structural alterations, thus paving the way for targeted therapies aimed at disease modification rather than mere symptom control.

Monoclonal antibodies and JAK inhibitors represent a paradigm shift in PN management. Dupilumab, which inhibits IL-4 and IL-13 signaling, broadly attenuates Th2-mediated inflammation and has demonstrated significant efficacy in reducing pruritus and skin lesions. Tralokinumab, by selectively targeting IL-13, offers a more focused anti-inflammatory effect and retains a favorable safety profile, especially advantageous for patients with contraindications to broader immunosuppression.

Phase III randomized, double-blind trials have consistently shown that dupilumab significantly reduces pruritus and nodule burden, with clinical improvements evident as early as week 2 and sustained beyond 24 weeks. Its safety profile—characterized by mostly mild adverse events and the absence of new long-term safety signals—supports its role as a first-line systemic treatment for moderate-to-severe PN. Real-world data reinforce these findings; a retrospective Italian study involving 64 patients with long-standing, treatment-refractory PN demonstrated sustained clinical benefit with dupilumab [24].

Clinical response to dupilumab is further illustrated in a patient treated at the Dermatology Unit of Spedali Civili di Brescia, showing notable improvement at 16 weeks (Fig. 2).

Additional biologics with novel mechanisms of action are under investigation. The approval of nemolizumab by the EMA in February 2025 for both PN and moderate-to-severe atopic dermatitis represents a major milestone in the treatment of chronic pruritic disorders. This regulatory endorsement validates IL-31RA as a therapeutic target and highlights the pathophysiological relevance of neuroimmune signaling in PN.

Contrasting traditional anti-inflammatory approaches, nemolizumab exemplifies the precision medicine paradigm, interrupting IL-31-mediated activation of sensory neurons and keratinocytes. This specificity enables meaningful reductions in pruritus and inflammation, with a favorable safety profile, establishing nemolizumab as a rational, now formally approved first-line biologic for moderate-to-severe PN.

Importantly, nemolizumab appears to impact disease biology beyond symptom suppression. Transcriptomic analyses reveal downregulation of genes associated with neuroinflammation and neuronal activation, suggesting a potential to alter the chronic disease course. However, the relatively short follow-up periods in clinical trials and the absence of immunologic stratification underscore the need for long-term studies and biomarker-driven approaches to fully define its therapeutic potential.

Vixarelimab introduces a dual cytokine inhibition strategy by targeting OSMRβ,

Table 1 Current and emerging systemic therapies for prurigo nodularis

Drug	Standard dosage	Route of administration	Regulatory status	Mechanism of action
Dupilumab	300 mg SC every 2 weeks	Subcutaneous	*Approved* (FDA/EMA, 2022; PRIME/PRIME2 trials)	IL-4Ra antagonist (blocks IL-4 and IL-13)
Tralokinumab	300 mg SC every 2 weeks (AD)	Subcutaneous	Investigational (AD phase II trials)	IL-13 monoclonal antibody
Lebrikizumab	250 mg SC every 2 weeks (AD)	Subcutaneous	Investigational (AD phase II trials)	IL-13 monoclonal antibody
Nemolizumab	60 mg SC every 4 weeks	Subcutaneous	*Approved* (EMA, 2025; OLYMPIA 1 and 2 trials)	IL-31RA antagonist
Vixarelimab	540 mg SC loading, then 180 mg SC weekly	Subcutaneous	Phase IIa completed (NCT03816891)	OSMRβ antagonist (blocks IL-31 and OSM)
Upadacitinib	15–30 mg orally once daily	Oral	Off-label (observational cohorts)	JAK1 selective inhibitor
Povorcitinib	75 mg orally once daily	Oral	Phase III ongoing (STOP-PN1; NCT06516952)	JAK1 selective inhibitor
Tofacitinib	5 mg orally twice daily	Oral	Off-label (STAT-driven PN studies)	JAK1/3 inhibitor
Rocatinlimab	150 mg SC every 4 weeks	Subcutaneous	Phase III ongoing (NCT06527404)	Anti-OX40 monoclonal antibody
Benralizumab	30 mg SC every 4 weeks	Subcutaneous	Investigational (targeting eosinophilic PN)	IL-5RA monoclonal antibody
Omalizumab	150–300 mg SC every 4 weeks	Subcutaneous	Off-label (case reports in PN)	Anti-IgE monoclonal antibody

Systemic therapies for prurigo nodularis: mechanisms of action, regulatory status, administration route, and standard dosages. This table summarizes current and emerging systemic therapies for prurigo nodularis, grouped by pharmacological class. Dosage information is based on available clinical trial data or standard practice in related conditions (e.g., atopic dermatitis). Regulatory status reflects the most recent updates from FDA, EMA, or ongoing trial registries

SC subcutaneous, *PN* prurigo nodularis, *AD* atopic dermatitis, *JAK* Janus kinase, *IL* interleukin, *OSM* oncostatin M

thereby simultaneously blocking IL-31 and oncostatin M signaling. This dual mechanism addresses both pruritus and dermal fibrosis—hallmarks of advanced PN. Phase II trials report early and robust improvements across multiple domains, including pruritus, lesion clearance, and patient-reported outcomes. Given its broader target profile, vixarelimab may be especially valuable in patients with fibrotic or nodular-dominant phenotypes, where IL-31 inhibition alone may be insufficient.

Rocatinlimab, an anti-OX40 monoclonal antibody, modulates a range of T cell subsets implicated in PN pathogenesis, including Th2, Th1,

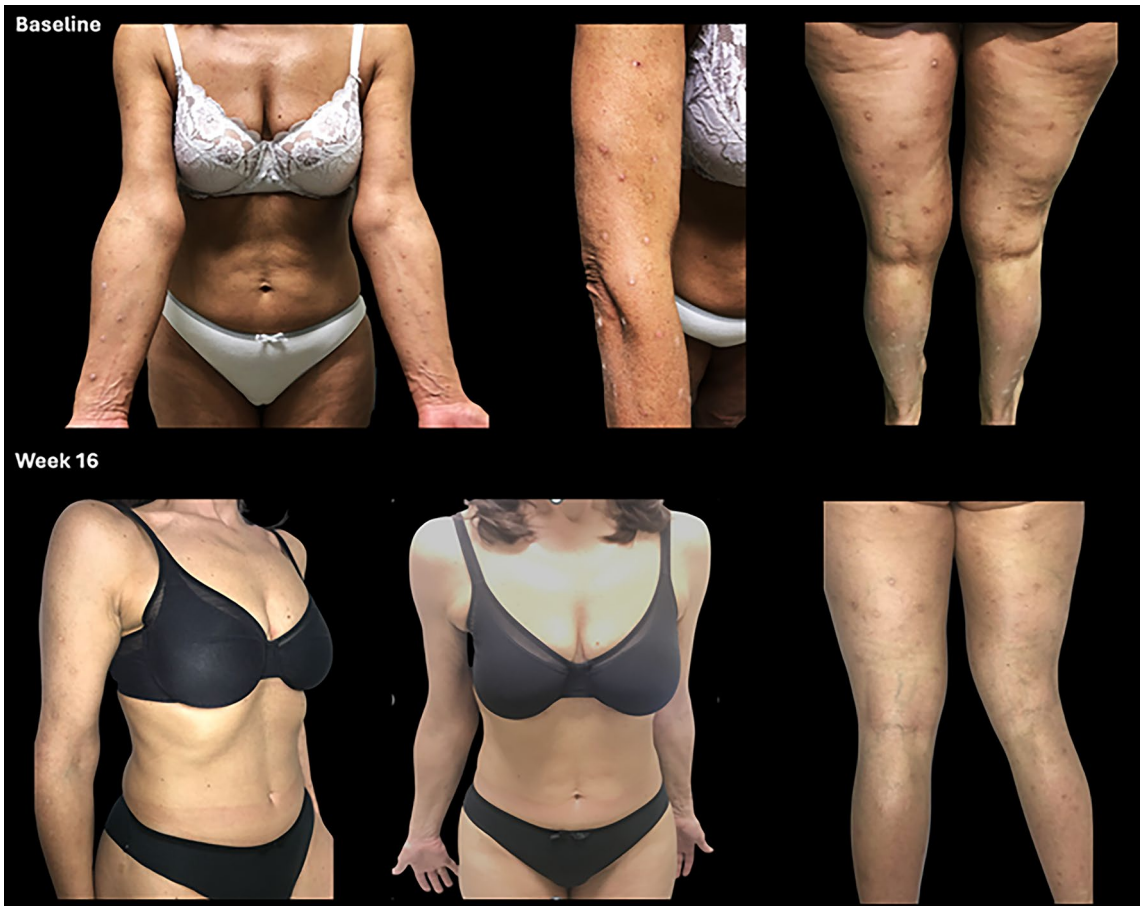

Fig. 2 Therapeutic outcome at 16 weeks following dupilumab treatment in prurigo nodularis. Clinical images demonstrate a substantial reduction in nodule number, erythema, and excoriations, accompanied by marked improvement in pruritus and overall skin condition

Th17, and Th22. Preliminary data in atopic dermatitis suggest durable disease control, justifying its further investigation in PN.

Benralizumab, targeting IL-5Rα, may offer clinical benefit in eosinophilic PN subtypes. Cornman et al. [25] have identified a subset of patients with elevated eosinophil counts, for whom benralizumab's mechanism—antibody-dependent eosinophil depletion—may be particularly effective.

JAK inhibitors, such as upadacitinib, have demonstrated efficacy in treatment-refractory PN by targeting multiple pro-inflammatory cytokines through the JAK-STAT pathway. This broad immunomodulatory activity positions JAK inhibitors as versatile options, especially for patients who fail or do not tolerate monoclonal antibody therapies.

Yew and Yeo conducted a comparative study involving 49 patients with PN treated with either dupilumab or oral JAK inhibitors [26]. Both therapies yielded significant improvements in pruritus and lesion burden, with 60% (dupilumab) and 58.3% (JAK inhibitors) achieving a ≥ 4-point itch reduction within 12–16 weeks. Notably, JAK inhibitors had a faster onset of action (3.65 vs. 10.7 weeks, $P = 0.004$). While adverse events were generally comparable, flares and infections occurred slightly more frequently in the JAK inhibitor group. Dupilumab was associated with a non-significant trend toward superior lesion resolution (40% vs. 25%).

Despite the promise of these agents, challenges remain. Long-term safety data—especially for JAK inhibitors—are limited, with potential risks including immunosuppression and thromboembolic events. Ongoing phase III trials (e.g., povorcitinib) are crucial to establish the long-term benefit–risk profiles and clarify their role in clinical practice. Real-world data will be instrumental in defining patient selection criteria, informed by comorbidities and baseline characteristics, and in guiding future clinical guidelines.

Additionally, the optimal duration of therapy, need for maintenance, and feasibility of combination regimens remain unresolved. Investigational topical therapies such as ruxolitinib offer promising localized treatment strategies that may reduce systemic exposure and associated risks.

Further comparative and combination studies are warranted to assess efficacy, safety, and treatment sequencing across drug classes.

Continued progress in understanding PN pathogenesis will likely yield new molecular targets and therapeutic options. Biomarker-driven strategies hold the potential to personalize treatment based on each patient's immunologic and neurogenic profile. Identification of molecular signatures predictive of disease phenotype and therapeutic response could enable stratification and optimize outcomes.

Recent immunoprofiling studies have deepened our understanding of disease heterogeneity. Cornman et al. [25] identified immunologic endotypes through cytokine and chemokine profiling of plasma from 56 patients with PN and 13 healthy controls. Eleven inflammatory markers were significantly elevated, including IL-6, IL-12/IL-23p40, TNFα, TSLP, MDC/CCL22, IL-10, IL-15, sVCAM-1, sICAM-1, MIP-1α/CCL3, and SAA, revealing systemic inflammation involving both Th1/Th17 and Th2 pathways.

Elevated eosinophil counts (AEC > 0.3 K/μL) were present in 32% of patients, correlating with higher levels of Th2-related cytokines (eotaxin, eotaxin-3, IL-5, MCP-1/CCL2, MCP-4/CCL13, and TSLP), TNFα, and angiogenic markers like sVCAM-1 and VEGFR-1. This Th2-high endotype may help identify candidates likely to respond to agents such as dupilumab.

Striking racial differences were also observed. African American patients exhibited lower AECs and reduced Th2 cytokine levels compared to Asian and white individuals. In a cohort of 12 patients with PN treated with dupilumab, clinical response was significantly better among those with high baseline eosinophilia, atopic history, and Asian or white ethnicity. None of the African American patients responded, whereas response rates reached 67% and 80% in Asian and white patients, respectively. These findings suggest that race and eosinophil counts could serve as practical biomarkers for treatment stratification, echoing approaches used in asthma and atopic dermatitis [25].

PN is a heterogeneous disease with varying degrees of Th2 dominance and neurogenic involvement, which may influence therapeutic responsiveness. Future research should aim to define tailored treatment algorithms that incorporate immune and neurogenic signatures, demographic variables, comorbidities, and disease chronicity. Clarifying the role of biomarker-based stratification, optimal treatment duration, and maintenance strategies will be essential for maximizing efficacy while minimizing risk. As trial data and real-world evidence continue to emerge, integrating personalized medicine principles into clinical practice will be crucial to advance the care of patients with PN.

CONCLUSION

The therapeutic landscape of PN is undergoing a transformative shift, fueled by insights into its neuroimmune pathophysiology. Biologics and small-molecule inhibitors are reshaping clinical management, offering targeted disease modification rather than symptomatic relief. Agents like dupilumab and nemolizumab have demonstrated sustained efficacy in improving pruritus, lesion burden, and quality of life. JAK inhibitors further expand treatment options, particularly for refractory cases, though long-term safety remains a concern, especially regarding immunosuppression and thromboembolic risk.

Given the immunologic and demographic heterogeneity of PN, uniform treatment strategies are inadequate. Personalized protocols, guided by biomarkers and immune endotyping, are critical for optimizing outcomes. Future research should clarify therapy duration, maintenance, and sequencing, aligning interventions with patient-specific characteristics. The integration of mechanistic insights with pragmatic clinical decision-making will be central to delivering safe, effective, and individualized care for patients with PN.

ACKNOWLEDGEMENTS

We sincerely thank the patients whose clinical data contributed to the development of this review.

Author Contributions. The authors express their gratitude to all contributors who provided valuable insights and support during the preparation of this review. We also acknowledge the efforts of the research and clinical teams whose work has contributed to the advancement of knowledge in this field. Gaetano Licata conceived the study design, contributed to the conception of the manuscript and critically revised the final draft. Mariachiara Arisi (corresponding author) coordinated the review process, contributed to the conception of the manuscript, and participated in drafting of the manuscript. Caterina Mariarosaria Giorgio conducted the literature search contributed to data analysis and interpretation of the selected studies. Cesare Ariasi and Simone Soglia participated in drafting the manuscript and contributed to the clinical contextualization of therapeutic strategies. Cesare Tomasi contributed to the methodological framework and performed statistical analysis and interpretation of the data. Sara Mezzana, Benedetta Galli, and Grazia Linda Artelli contributed to literature screening, data extraction, and drafting of sections concerning emerging therapies. Mariateresa Rossi supervised all phases of manuscript development, and provided critical revision and expert guidance throughout. Cecilia Catapano conducted the literature search, analyzed the selected articles, and authored substantial sections of the manuscript, also providing critical revision of the final draft.

Funding. The authors received no financial support for the research, authorship, and/or publication of this article.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. The authors have not conflict of interest to declare. Gaetano Licata, Mariachiara Arisi, Caterina Mariarosaria Giorgio, Cesare Ariasi, Cesare Tomasi, Simone Soglia, Sara Mezzana, Benedetta Galli, Grazia Linda Artelli, and Mariateresa Rossi have nothing to disclose. Mariateresa Rossi is an Editorial Board member of *Dermatology and Therapy*. Mariateresa Rossi was not involved in the selection of peer reviewers for the manuscript nor of the subsequent editorial decisions. Cecilia Catapano has nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The patient in this manuscript has given written informed consent to publication of her case details and clinical photographs.

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