From Refractory to Responsive: The Expanding Therapeutic Landscape of Prurigo Nodularis

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Prurigo nodularis (PN) is a chronic, severely pruritic neuroimmunologic skin disorder characterized by multiple firm hyperkeratotic nodules and intense pruritus, often leading to considerable impairment in quality of life and increased rates of depression and anxiety.[1] It is considered difficult to treat due to its complex pathogenesis, the severity and chronicity of pruritus, and the limited efficacy of conventional therapies.[2,3] The disease is driven by a self-perpetuating itch-scratch cycle, underpinned by dysregulation of both immune and neural pathways including type 2 (interleukin [IL] 4, IL-13, IL-31), Th17, and Th22 cytokines as well as neuropeptides and altered cutaneous nerve architecture.[1,3] This results in persistent severe pruritus and nodular lesions that are highly refractory to standard treatments.[1] Conventional therapies (eg, locally acting agents, phototherapy, and systemic immunomodulators and neuromodulators) have varied efficacy and notable adverse effect profiles.[3] While the approval of targeted biologics has transformed the therapeutic landscape, several other treatment options also are being explored in clinical trials. Herein, we review all recently approved therapies as well as emerging treatments currently under investigation.

Dupilumab

Dupilumab, the first therapy for PN approved by the US Food and Drug Administration (FDA) in 2022—is a monoclonal antibody that inhibits signaling of IL-4 and IL-13, key drivers of type 2 inflammation implicated in PN pathogenesis.[4,5] In 2 pivotal phase 3 randomized controlled trials (LIBERTY-PN PRIME and PRIME2),[5] dupilumab demonstrated notable efficacy in adults with moderate to severe PN. A reduction of 4 points or more on the Worst Itch Numeric Rating Scale (WI-NRS) was achieved by 60.0% (45/75) of patients treated with dupilumab at week 24 compared with 18.4% (14/76) receiving placebo in the PRIME trial. In PRIME2, the same outcome was achieved by 37.2% (29/78) of patients receiving dupilumab at week 12 compared with 22.0% (18/82) of patients receiving placebo.[5] Dupilumab also led to a greater proportion of patients achieving a substantial reduction in nodule count (≤5 nodules) and improved quality of life compared with placebo.[5,6] The safety profile of dupilumab for treatment of PN was favorable and consistent with prior experience in atopic dermatitis; conjunctivitis was the most common adverse event.[5,6]

Nemolizumab

Nemolizumab, an IL-31 receptor A antagonist, is the most recent agent approved by the FDA for PN in 2024.[7] In the OLYMPIA 1 and OLYMPIA 2 phase 3 trials,[8] nemolizumab produced a clinically meaningful reduction in itch (defined as a ≥4-point improvement in the Peak Pruritus Numerical Rating Scale score) in 56.3% (103/183) of patients at week 16 compared with 20.9% (19/91) receiving placebo. Additionally, 37.7% (69/183) of patients receiving nemolizumab achieved clear or almost clear skin (Investigator's Global Assessment score of 0 or 1 with a ≥2-point reduction) vs 11.0% with placebo (both $P<.001$). Benefits were observed as early as week 4, including rapid improvements in itch, sleep disturbance, and nodule count.[8] Nemolizumab also improved quality of life and reduced symptoms of anxiety and depression. The safety profile was favorable, with headache and atopic dermatitis the most common adverse events; serious adverse events were infrequent and similar between groups.[8]

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Abrocitinib

Abrocitinib, an oral selective Janus kinase 1 inhibitor, is an investigational therapy for PN and currently has not been approved by the FDA for this indication. In a phase 2 open-label trial, abrocitinib 200 mg daily for 12 weeks led to a 78.3% reduction in weekly Peak Pruritus Numerical Rating Scale scores in PN, with 80.0% (8/10) of patients achieving a clinically meaningful improvement of 4 points or higher. Nodule counts and quality of life also improved, with an onset of itch relief as early as week 2. The safety profile was favorable, with acneform eruptions the most common adverse event and no serious adverse events reported[9]; however, these results are based on small, nonrandomized studies and require confirmation in larger randomized controlled trials before abrocitinib can be considered a standard therapy for PN.

Cryosim-1

Transient receptor potential melastatin 8 (TRPM8) is a cold-sensing ion channel found in unmyelinated sensory neurons within the dorsal root and trigeminal ganglia.[10] It is activated by cool temperatures (15-28 °C) and compounds such as menthol, leading to calcium influx and a cooling sensation. In a randomized, double-blind, vehicle-controlled trial, researchers investigated the efficacy of cryosim-1 (a synthetic TRPM8 agonist) in treating PN.[10] Thirty patients were enrolled, with 18 (60.0%) receiving cryosim-1 and 12 (40.0%) receiving placebo over 8 weeks. By week 8, cryosim-1 significantly reduced itch severity (mean numerical rating scale score postapplication, 2.8 vs 4.3; P=.031) and improved sleep disturbances (2.2 vs 4.2; P=.031) compared to placebo. Patients reported higher satisfaction with itch relief, and no adverse effects were observed. The study concluded that cryosim-1 is a safe, effective topical therapy for PN, likely working by interrupting the itch-scratch cycle and potentially modulating inflammatory pathways involved in chronic itch.[10]

Nalbuphine

Nalbuphine is a κ opioid receptor agonist and μ opioid receptor antagonist that has been investigated for the treatment of PN.[11] In a phase 2 randomized controlled trial, oral nalbuphine extended release (NAL-ER) 162 mg twice daily provided measurable antipruritic efficacy, with 44.4% (8/18) of patients achieving at least a 30% reduction in 7-day WI-NRS at week 10 compared with 36.4% (8/22) in the placebo group. Among those who completed the study, 66.7% (8/12) of patients receiving NAL-ER 162 mg achieved significant itch reduction vs 40% (8/20) receiving placebo (P=.03). At least a 50% reduction in WI-NRS was achieved by 33.3% (6/18) of patients receiving NAL-ER 162 mg twice daily. Extended open-label treatment was associated with further improvements in itch and lesion activity. Adverse events were mostly mild to moderate (eg, nausea, dizziness, headache, and fatigue) and occurred during dose titration. Physiologic opioid withdrawal symptoms were limited and resolved within a few days of discontinuing the medication.[11]

Final Thoughts

In conclusion, PN remains one of the most challenging chronic dermatologic conditions to manage and is driven by a complex interplay of neuroimmune mechanisms and resistance to many conventional therapies. The approval of dupilumab and nemolizumab has marked a pivotal shift in the therapeutic landscape, offering hope to patients who previously had limited options[5,8]; however, the burden of PN remains substantial, and many patients continue to experience relentless itch, poor sleep, and reduced quality of life.[1] Emerging therapies such as TRPM8 agonists, Janus kinase inhibitors, and opioid modulators represent promising additions to the treatment options, targeting novel pathways beyond traditional immunosuppression.[9-11]

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