

Immunotargets and Therapy for Prurigo Nodularis

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Abstract: Prurigo nodularis is a chronic inflammatory skin disease consisting of severely pruritic nodules that can be very debilitating for patients. The basis of this skin condition is immunological dysregulation and neural amplification, driven by T-lymphocytes, mast cells, eosinophilic granulocytes, macrophages, and cytokines mediating itchy processes. Further complicating this already taxing diagnosis is the lack of approved treatment and consensus on management; although there are off-label treatments utilized as therapy. Immunomodulators are the cornerstone of treatment for PN, and additional novel therapies targeting key players in the immunological cascade are currently undergoing investigation. In this review, we will highlight targets of the immune cascade and explore current immunomodulating treatments as well as immunotherapies on the horizon for the management of prurigo nodularis.

Keywords: prurigo nodularis, pathogenesis, immunotherapy, treatment, IL-31 inhibitors, IL-4 antagonists, oncostatin inhibitor, JAK inhibitor

Introduction

Prurigo nodularis (PN) is a chronic inflammatory condition of the skin. It classically presents as single or multiple, intensely pruritic, symmetrically distributed nodules on the trunk or extremities that are firm, flesh-to-red colored, and hyperkeratotic in appearance.¹⁻³ This pruritic, recalcitrant condition potentiates a vicious itch-scratch cycle that defines and exacerbates the disease.⁴ In fact, PN is amongst the itchiest of skin conditions.⁵ PN is a distinct entity; however, it may also occur in the setting of other itchy conditions such as atopic dermatitis (AD), which is the most frequent concurrent skin dermatitis, and other inflammatory skin disorders, pruritic systemic etiologies, neuropathic, and psychiatric disorders.^{1,6} PN profoundly negatively affects quality of life in patients, including a significant health, mental health, and economic burden.⁷⁻⁹

It has been estimated that there are approximately 87,634 cases of PN and 125,322 ambulatory care visits per year.^{10,11} Another estimate suggests that the prevalence of PN is approximately 36.7 to 148.53 per 100,000 persons.¹² Additionally, PN poses a significant health-care burden due to the increased prevalence of comorbidities and increased utilization of specialty care.¹³

The exact pathophysiology of PN is not entirely understood. However, studies in the past have shown that the underlying mechanism of PN may be due to an interplay between immunological dysfunction and neural dysregulation.¹⁴ Currently, there are no approved treatments for PN by the Food and Drug Administration (FDA).² However, the use of immunotargeting therapies may provide benefit for patients with PN given the current understanding of its inflammatory mechanism. Previously, the mainstay treatment for PN was immunosuppressants such as steroids; however, there are numerous other immunomodulating treatments that have been utilized to treat PN as of late.^{1,4} Additionally, treatment with novel therapies, including biologics and small molecules, that directly target key players in the PN immunologic cascade are currently being investigated.¹⁵ In this review, we aim to discuss the pathogenesis of PN and examine the current and future systemic immune therapies.

Background

The pathobiological mechanism of PN is comprised of both a heightened inflammatory response and amplified neuronal circuitry.^{1,3,14} Evaluation of the dermis and epidermis has revealed that there are numerous changes that occur within PN lesions. Nearly all skin cells are affected by PN, including keratinocytes, mast cells, dendritic cells, endothelial cells, eosinophils, collagen fibers, and nerve fibers.¹⁶

Epidermal changes include hyperplasia, thickened orthohyperkeratosis, focal parakeratosis, and hypergranulosis.^{1,3,14,16} Within the dermis, histopathological studies show dense infiltrates consisting of T lymphocytes, mast cells, and eosinophilic granulocytes.^{1,3,14,16} In correspondence with the upregulated inflammatory cells, several pro-inflammatory and pruritic cytokines have also been identified in PN lesions. These include Th2-associated cytokines such as interleukin (IL) 31 and IL-4, both recognized as itchy cytokines thought to underly many pruritic conditions;¹⁴ the IL-31 axis has been found to correlate with intense itch in PN patients.¹⁷ IL-31 binds to heterodimeric IL-31 receptor A (IL-31RA) and oncostatin M (OSM) beta receptor found on keratinocytes, nerves, and eosinophils. The binding of IL-31 to its respective receptors mediates the activation of JAK 1, JAK 2, and STAT 3 predominantly.¹⁸ The subsequent downstream effect increases the sensation of pruritus and scratching behavior. The number of dermal IL-31+ cells and dermal IL-31RA+ cells has been found to be increased in PN lesioned skin and correlates with intense itch in these patients.¹⁸ The main dermal cells that express IL-31 in PN are T cells and macrophages, while the major cells expressing IL-31RA are mast cells and macrophages.¹⁸

Another itch mediator associated with the Th2 inflammatory response is extracellular matrix protein, periostin; one study analyzed PN lesions and found that periostin was upregulated in the dermis as well as significantly correlated with itch intensity in these patients.¹⁹ Additional cytokines implicated in the PN immunologic cascade include tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides.^{1,3,14,16} Eosinophil cationic protein and neuropeptides are amongst the granules released by eosinophilic granulocytes, in addition to eosinophil derived neurotoxin, eosinophil protein X, and major basic protein.^{1,3,14,16} Neurotoxicity may be promoted by eosinophil cationic protein and eosinophil protein X, which are significantly increased in lesions of PN.¹⁴

There are a few changes that occur to nerves within PN lesions. Some of these changes are mediated by neuropeptides. The common neuropeptides found to be upregulated in PN lesions include nerve growth factor (NGF), substance P (SP), and calcitonin gene-related peptide. NGF binds to receptor, tyrosine receptor kinase A (TrkA). NGF may regulate nerve cell growth, survival, and differentiation, potentially explaining findings of increased papillary dermal nerve fibers in immunohistochemical studies.²⁰ The finding of increased dermal nerve fibers appears to play a large role in the pathogenesis of PN, epitomizing the coaction of immunomodulators and nerve plasticity.^{1,3,14,16} Interestingly, nerve density was diminished in epidermal evaluation of PN lesion, but displayed recovery in healing nodules, suggesting that perhaps mechanical irritation from the itch-scratch cycle may be the cause of epidermal nerve hypoplasia. SP, produced and released by neurons, binds to neurokinin-1 receptors (NK1R), some of which are found in the skin.¹ This reaction elicits a neural inflammatory response by propagating vasodilation, plasma extravasation, and degranulation of mast cells.¹

Another cellular pathway that is associated with PN is Th17. Although many allergic skin conditions favor Th1 and Th2 cellular pathways, it is emerging that Th17 also plays a role in different phenotypes of inflammatory skin conditions.²¹ Cytokine IL-23 acts on Th17 cells to increase IL-17 release.²² Expression of IL-17 plays a key role in psoriatic conditions and is associated with other itchy, inflammatory skin conditions such as atopic dermatitis, hidradenitis suppurativa, pemphigus, and systemic sclerosis.^{22,23} Wong et al reported that Th17 were upregulated in lesioned PN skin and that IL-17 induced keratinocyte expression of vasodilator and histamine-independent itch inducer, endothelin-1 (ET1).²⁴

Treatment of PN is difficult because there are no approved FDA treatments and lack of clear guidelines; it requires multimodal management considering the complexity and intractable nature of the disease.²⁵ The treatment modalities currently used for PN target the underlying immune and neural dysregulation, such as local agents, phototherapy, systemic neuromodulating treatments, and systemic immunomodulatory agents.^{1,4,26} Topical and intralesional corticosteroids, anesthetics, calcineurin inhibitors (ie, pimecrolimus, tacrolimus), vitamin D derivatives (ie, calcipotriene), and

capsaicin are amongst the regional therapies that are often first employed in the stepwise management of PN.^{1,4,26} Narrowband ultraviolet B light (NBUVB) and psoralen plus ultraviolet A light (PUVA) are two types of phototherapies that can also be introduced as a first- or second-line choices of treatment. In PN cases that are refractory to these treatments, systemic therapies are the next step. Neuromodulating therapies include gabapentinoids, NK1R antagonists (ie, aprepitant, serlopitant), mu-opioid antagonists (ie, naltrexone), mu-opioid antagonist/kappa-opioid agonist (ie, butorphanol), selective serotonin reuptake inhibitors (SSRIs) (ie, paroxetine, fluvoxamine), serotonin and norepinephrine reuptake inhibitors (SNRIs) (ie, duloxetine), and thalidomide.^{1,4,26} One randomized controlled trial evaluated the use of NK1R antagonist, serlopitant, in patients with PN and found that it reduced pruritus in refractory PN and overall well tolerated, with most common adverse effects including nasopharyngitis, diarrhea, and fatigue.²⁷ Lastly, systemic immunomodulating therapies include oral corticosteroids, methotrexate, cyclosporine, and azathioprine.^{1,4,26} Currently, other promising systemic immunotherapies targeting key players in PN inflammation are being evaluated and undergoing Phase II and II trials, such as IL-4 inhibitors, IL-31 antagonists, anti-OSM beta receptors, receptor tyrosine kinase KIT inhibitors, and janus kinase (JAK) inhibitors (Table 1).^{1,4,15,26,28,29}

Current Immunotherapeutics Used for PN

Corticosteroids

As PN is a skin condition that is a result of aberrant immune processes, systemic immunosuppressants such as corticosteroids are a choice of treatment, especially in intractable cases.³⁰ Corticosteroids are immunomodulators primarily by altering signal transduction pathways of inflammatory processes via binding of the glucocorticoid receptor.^{31,32} This transrepression mechanism is thought to underly the anti-inflammatory efficacy of corticosteroids.^{31,32} For the treatment of PN, systemic corticosteroids are not preferred due to broad immunosuppression and adverse effects; however, they may be employed to curb severe acute flares of the disease when other treatments fail. Ultimately, the use of oral corticosteroids is limited by its significant side effect profile, consisting of osteoporosis, muscle atrophy, eye impairment, diabetes mellitus, and hypertension amongst others.³³ For the treatment of PN, alternative immunosuppressant agents such as cyclosporine, methotrexate, or emerging biologic/small molecule treatments are preferred.¹

Methotrexate

Methotrexate (MTX), a folic acid antagonist, has immunomodulatory properties which decrease pruritus through an unknown mechanism. It has proven efficacy and a good tolerance profile in other inflammatory dermatoses including atopic dermatitis, psoriasis, and bullous pemphigoid.³⁴ Two studies have highlighted its efficacy for use in PN as monotherapy.³⁵ One retrospective review of 13 patients with treatment resistant PN taking 7.5–20 mg MTX weekly for 6 months reported a $\geq 75\%$ decrease in PN lesion involvement and pruritus severity in 10 of 13 patients.³⁶ Another study of 39 PN patients taking 5–25 mg weekly showed lesion improvement for 91% of patients and pruritus improvement in 89% of patients after 3 months.³⁴ When combined with alitretinoin, MTX demonstrated near-complete or complete remission of PN in 5 of 6 patients who were refractory to MTX alone, suggesting that MTX (10–20 mg per week) and alitretinoin (10–30 mg per day) could be a potential treatment option for patients with difficult-to-treat PN.³⁷

Adverse effects of MTX occur as a result of its antifolate properties. Nausea and fatigue at treatment initiation are common. Other symptoms indicative of toxicity include mucositis, diarrhea, skin rashes, pancytopenia, transaminitis, and acute kidney injury.³⁸ Pulmonary fibrosis is one concern when using MTX; however, one systematic review found that it is unlikely that MTX causes pulmonary fibrosis and instead the finding is related to underlying disease.³⁹ Alternative studies suggest that pulmonary fibrosis is increased in patients treated with MTX;⁴⁰ therefore, more research is required for a definitive understanding of this pathology and it is advisable to monitor these symptoms nonetheless. Additionally, the use of MTX raises the concern of malignancy and many cancers such as stomach cancer, colorectal cancer, prostate cancer, ovarian cancer, malignant melanoma, and lung cancer have demonstrated an increased risk with MTX therapy.⁴¹ Skin cancer such as squamous cell carcinoma was found to be increased in MTX-treated groups when compared to placebo as well.⁴² Likewise, it is unclear if the relationship between MTX and carcinogenicity is causal but it should be

Table I A Summary of the Existing Systemic Immunomodulating Therapies and the Investigational Systemic Immunomodulating Therapies

Systemic Immunomodulating Treatments	Mechanism of Action	Efficacy	Safety	Cost (+, ++, +++)
Corticosteroids	Glucocorticoid receptor modulation	<ul style="list-style-type: none"> • Can curb severe, acute flares of PN 	<ul style="list-style-type: none"> • Common adverse effects include osteoporosis, muscle atrophy, eye impairment, diabetes mellitus, and hypertension 	+
Methotrexate	Folic acid antagonist	<ul style="list-style-type: none"> • $\geq 75\%$ decrease in PN lesion involvement • Decreased pruritus severity in majority of patients 	<ul style="list-style-type: none"> • Antifolate properties • Nausea • Fatigue • Toxicity consisting of include mucositis, diarrhea, skin rashes, pancytopenia, transaminitis, and acute kidney injury 	+
Cyclosporine	Calcineurin inhibitor	<ul style="list-style-type: none"> • 92.9% demonstrated significant improvement in itch in one clinical trial • Majority of patients achieve remission of PN 	<ul style="list-style-type: none"> • Altered renal and hepatic functions • Gingival hyperplasia • Gastric upset • Neuropathy • Hypertension 	+
Azathioprine	6-MP prodrug	<ul style="list-style-type: none"> • Substantial reduction in itch • Skin lesion clearance following 2–3 months of treatment 	<ul style="list-style-type: none"> • Transaminitis • Gastrointestinal upset • Azathioprine hypersensitivity • Myelosuppression • Infection 	+
Investigational Systemic Immunomodulating Therapies	Mechanism of Action	Efficacy	Safety	Cost (+, ++, +++)
Dupilumab	IL-4 inhibitor	<ul style="list-style-type: none"> • IGA score improvement in 63.2% of patients following 16 weeks of treatment • Significant reduction in itch 	<ul style="list-style-type: none"> • Mild side effect profile • Most common adverse effects include conjunctivitis, nasopharyngitis, injection site reactions, and skin infections 	+++
Nemolizumab	IL-31 inhibitor	<ul style="list-style-type: none"> • Significant reduction in itch in 53% of patients • Reduction in lesion severity 	<ul style="list-style-type: none"> • Mild and uncommon side effects • Most common adverse effects include abdominal pain, diarrhea, and musculoskeletal symptoms 	+++
Vixarelimab	OSM beta receptor antagonist	<ul style="list-style-type: none"> • Average pruritus reduction of 70% following 8 weeks of treatment • Significantly improved nodules 	<ul style="list-style-type: none"> • Well-tolerated with no serious adverse events • All adverse effects are mild and transient 	+++

(Continued)

Table 1 (Continued).

Systemic Immunomodulating Treatments	Mechanism of Action	Efficacy	Safety	Cost (+, ++, +++)
CDX-0159	Tyrosine kinase KIT receptor inhibitor	Limited data	Limited data	+++
Abrocitinib	Selective JAK 1 inhibitor	<ul style="list-style-type: none"> Decreased pruritus in non-PN skin conditions in as early as a few days following treatment 	<ul style="list-style-type: none"> Common side effects include upper respiratory infections, headache, nausea, and diarrhea Increased risk of herpes-related infection and acne 	+++
Tofacitinib	Selective JAK 1 and JAK 3 inhibitor	<ul style="list-style-type: none"> Reduced PN lesions by 50% Complete resolution of pruritus 	<ul style="list-style-type: none"> Overall, well tolerated The most common adverse effects are headache and nausea 	+++

Notes: + = low cost. ++ = medium cost. +++ = high cost.

Abbreviations: PN, prurigo nodularis; IGA score, Investigator Global Assessment; JAK, janus kinase; 6-MP, 6-mercaptopurine.

considered when administering MTX.⁴⁰ Adverse events may be reduced with folic acid or folinic acid supplementation, though folinic acid may affect efficacy of treatment.⁴³ According to an expert panel consensus in 2020, methotrexate for difficult-to-treat PN should be given in doses of 7.5–15 mg orally weekly, starting at 7.5 mg for 2 weeks, then increasing by 2.5–5.0 mg weekly as needed.²⁵

Cyclosporine

Cyclosporine is a calcineurin inhibitor most likely improving pruritus through IL-2 signaling modulation.³⁵ Two studies have examined its effectiveness in PN. One was a clinical trial of 14 patients with refractory PN who took 3–5 mg/kg of oral cyclosporine daily.⁴⁴ Thirteen of 14 patients (92.9%) demonstrated significant improvement in itch with the maximal effect occurring after 2 weeks to 12 months. A retrospective chart review of 8 patients taking 2–4 mg/kg of cyclosporine revealed remission in 6 patients and partial improvement in 1 patient with an average improvement time of 3 weeks (the final patient was lost to follow-up).⁴⁵ The most frequent adverse effects are altered renal and hepatic functions, gingival hyperplasia, gastric upset, diarrhea, hypertrichosis, neuropathy, hypertension, temporary serum lipid elevation, and weight gain, though side effects are usually tolerable in PN cases.⁴⁴ More severe adverse effects such as immunosuppression and malignancy can also occur with cyclosporin treatment.⁴⁶ Cyclosporin is currently recommended as first-line systemic therapy for severe, chronic, refractory PN with a plan to transition to topical or phototherapy after 3–6 months.⁴⁵ According to an expert panel consensus in 2020, cyclosporine should be started at 3 mg/kg daily for 2–4 weeks, then increased by 0.5–1.0 mg/kg daily every 2–4 wk as tolerated.²⁵

Azathioprine

Azathioprine is a synthetic purine analog derived as a 6-mercaptopurine (6-MP) prodrug resistant to immediate catabolism. Azathioprine is cleaved into 6-MP and an imidazole derivative methylnitroimidazole by sulphydryl-containing compounds and then enzymatically converted into active toxic purine analogs 6-thioguanine nucleotides and metabolites. It can then be incorporated into the replicating DNA and de novo pathway of purine synthesis, causing blockage of DNA and purine synthesis.⁴⁷ As lymphocytes lack a salvage pathway and rely on de novo synthesis of purines, they are particularly susceptible to azathioprine resulting in the inhibition of T and B cell proliferation.⁴⁸

Azathioprine has been shown to be efficacious at treating pruritus, including those with PN. In a retrospective review of 96 patients for azathioprine treatment in chronic intractable pruritus, azathioprine reduced itch from an average visual analog scale itch score of 9.25/10 to 1.625/10.⁴⁹ Lear et al reported 2 patients with severe PN were responsive to azathioprine 50 mg twice daily, with marked improvement in skin appearance and pruritus after 2–3 months of

continuous usage. Remission was achieved regardless of whether there was a family background of atopy.⁵⁰ However, azathioprine use was not curative, as recurrence of PN appeared a few months after treatment termination.

Adverse side effects of azathioprine are common. For the treatment of chronic pruritus, 65% of patients experienced adverse effects and 33% underwent complete drug withdrawal. The most common adverse effects reported were transaminitis, gastrointestinal upset (nausea, diarrhea, epigastric pain), azathioprine hypersensitivity, myelosuppression, and infection. Transaminitis and myelosuppression were transient in some cases and normalized with a drug holiday or adjusted dose. The most concerning side effect was a relative increase in lymphoproliferative malignancy or nonmelanoma skin cancer, although the risk is low in individuals with limited risk factors.^{49,50} Additionally, patients with thiopurine methyl transferase deficiency are at increased risk of severe azathioprine toxicity and prior analysis for this genotype should be evaluated to reduce risk of adverse effects.⁵¹

Current guidelines for treatment of PN with azathioprine is 50–200 mg of oral azathioprine daily. Patients may be initiated with 50 mg of oral azathioprine with gradual increase by 50 mg daily every 2–4 weeks as tolerated.²⁵

Novel Immunotherapy in PN

Anecdotal reports indicate monoclonal antibody and small molecules are effective in PN, and investigational studies proving the same are in progress. Namely, these therapies include IL-4 antagonist dupilumab, IL-31 inhibitor nemolizumab, anti-OSM beta receptor vixarelimab, tyrosine kinase KIT receptor inhibitor CDX-0159, and JAK inhibitor abrocitinib (Figure 1).

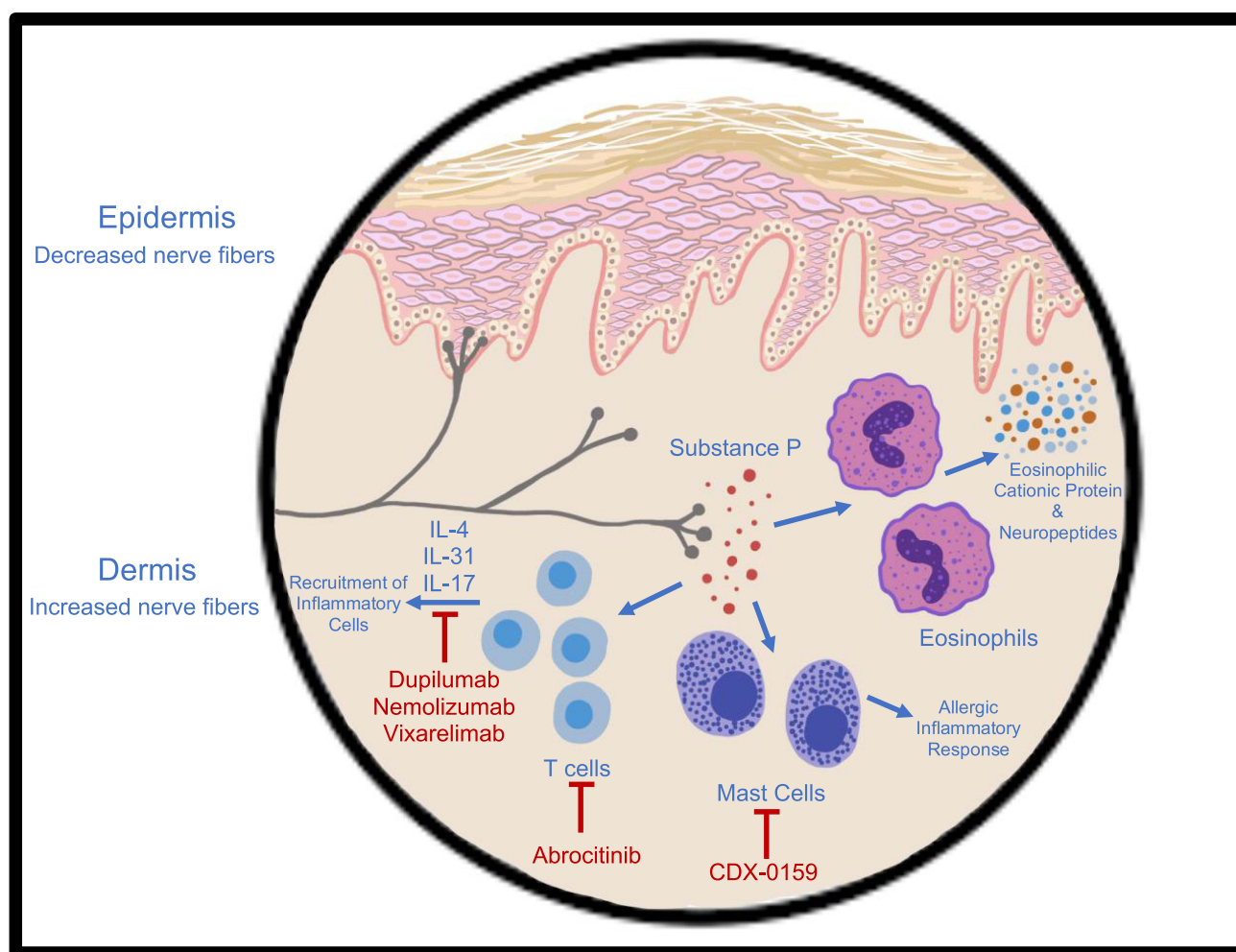


Figure 1 A summary of the pathogenesis of prurigo nodularis and the targets of novel immunotherapies dupilumab, nemolizumab, vixarelimab, CDX-1059, and abrocitinib.

Dupilumab is now the systemic drug of choice for AD. Its primary mechanism of action is monoclonal antibody inhibition of the IL-4 receptor alpha subunit, which prevents binding of IL-4 and IL-13 and thus downregulates the pro-inflammatory and pruritic signaling pathway. As PN has demonstrated a type-2 inflammatory response involving these cytokines, as well as an overlap with AD, blockade of this receptor can decrease the progression of PN and curb symptoms such as severe itch. Current literature points to numerous successful cases that support the efficacy of dupilumab for PN.^{52–62} Importantly, the clinical response of itch reduction was efficacious in many cases.^{63,64} Many reports also endorse the prevention of new nodules and the reduction of current lesion size. One cohort study on 16 PN patients receiving dupilumab reported that 50% achieved complete resolution of pruritus and lesions, 41.7% had partial resolution, and only one patient demonstrated no response and subsequently discontinued treatment following 6 months.⁶⁵ At 12 months, the number of patients with complete resolution increased.

Dupilumab was reported to be efficacious for recalcitrant PN and PN-phenotypic AD in a few case reports as well.^{66–68} A retrospective cohort study evaluating dupilumab for refractory PN reported an improvement in Investigator Global Assessment (IGA) scores in 63.2% of patients following 16 weeks of treatment, and evidence of continued benefit for up to 52 weeks while remaining on treatment.⁶⁹ As of late, there are two Phase III clinical trials underway that will investigate dupilumab for PN in randomized, double-blind, placebo controlled studies.^{70,71} One of these studies has reported preliminary data consistent with significant reduction of itch and lesions in PN patients with long-term treatment of dupilumab.⁷² Overall, dupilumab is well tolerated long term, with rare and mild adverse reactions, such as conjunctivitis, nasopharyngitis, injection site reactions, and skin infections.^{73–75} The current treatment guideline for the indication of PN is a 600 mg induction dose, followed by 300 mg maintenance dose every 2 weeks.²⁶

IL-31 is another cytokine associated with the Th2 immune cascade that is specifically correlated with intense pruritus in certain skin conditions, including PN.¹⁸ Dampening the IL-31 axis may mitigate the itch-scratch cycle in PN patients and help reduce the inflammatory response.^{76,77} Therefore, it is thought that blockade of IL-31 receptors, IL-31RA and OSM beta receptor, can be beneficial for PN patients.

Nemolizumab is a monoclonal antibody that inhibits IL-31RA. One phase II randomized, double-blind clinical trial was conducted over a 12-week trial where nemolizumab was administered subcutaneously every 4 weeks in patients with moderate-to-severe PN and pruritus.⁷⁸ Results revealed that average itch numerical rating scores (NRS) were significantly reduced by about 53%. Additionally, a reduction in lesion severity was also reported. Adverse effects reported in this study were mild and uncommon, consisting of abdominal pain, diarrhea, and musculoskeletal symptoms. This initial evaluation of nemolizumab for the treatment of PN was promising in helping reduce pruritus in PN patients, with a rapid onset within 48 hours of the first dose.⁷⁹ One study evaluated the transcriptome of PN patients after treatment with nemolizumab and found that following 12 weeks, downstream inflammatory factors were decreased and reflective of transcriptome changes.⁸⁰ Longer and larger studies are necessary to better explore the use of the IL-31RA inhibitor in PN patients. Currently, there are 4 clinical trials that are assessing the efficacy and safety of nemolizumab for treatment of PN.^{81–84}

Vixarelimab works by inhibiting the IL-31 signaling pathway by antagonizing the OSM beta receptor. This is an effective treatment due to the role of IL-31 in PN pathogenesis. One phase II clinical trial evaluating this mechanism of treatment reported that vixarelimab demonstrated improvement in PN signs and symptoms, with an average pruritus reduction of 70% by week 8 of treatment as well as significantly improved nodules as early as week 4.^{85,86}

CDX-0159 is a human monoclonal antibody that inhibits tyrosine kinase KIT receptors. This receptor is pivotal in the treatment of PN because it is involved in mast cell regulation and the initiation of allergic inflammatory processes.⁸⁷ One of the upregulated cells in PN lesions is mast cells. CDX-0159 is being evaluated for efficacy and safety in treating PN in one clinical trial presently.⁸⁸ The janus kinase-signal transducer and activator (JAK STAT) pathway upregulates CD4 T cells as well as numerous inflammatory cytokines and has been recognized for immune pathogenesis in other skin conditions such as atopic dermatitis.⁸⁹ Although there is less available information on the use of tyrosine kinase inhibitors and JAK inhibitors, they may serve as good treatment choices for PN. One study evaluated the JAK STAT pathway in prurigo nodules to determine if this inflammatory pathway may be prevalent in the disease.⁹⁰ The results reported that STAT 2 and 3 were upregulated in PN lesions, as well as corresponding cytokines of Th2, Th17, and Th22. STATs are intracellular transcription factors that propagate extracellular signals from JAK receptors to the nucleus.⁹⁰

Numerous cytokines activate the JAK response. Th1, Th2/Th17/Th22, and Th2 cellular pathways are mediated by STAT 1, 3, and 6, respectively.⁹⁰ Therefore, the use of JAK inhibitors may be effective at decreasing disease progression. One case report demonstrates the efficacy of oral tofacitinib, a JAK 1 and JAK 3 inhibitor, in minimizing skin lesions by 50% and completely diminishing pruritus in a patient with intractable PN.⁹¹ Another case series examining the treatment of topical tofacitinib showed a meaningful reduction in itch in 2 patients with PN.⁹² Additionally, JAK inhibitors decrease pruritus in certain skin conditions.⁹³ One of these skin conditions include AD; AD-related clinical trials demonstrate that JAK inhibitor abrocitinib has a mild side effect profile.⁹⁴ At this moment, JAK 1 inhibitor abrocitinib and drug INCB054707 are small molecule treatments that are currently being studied for the treatment of PN in clinical trials.^{95,96} Although not yet explored, the implication of IL-17 in PN pathogenesis may lend itself to future therapies that can diminish Th17 inflammation.

Conclusion

Prurigo nodularis is a challenging complex inflammatory skin condition. Studies on PN have disclosed that the inflammatory response is mostly Th2 mediated and comprised of T lymphocytes, mast cells, macrophages and eosinophilic granulocytes, in addition to inflammatory and pruritic cytokines such as IL-4, IL-13, and IL-31.^{1,3,14,16} Current immunotherapeutic treatments for PN aim to decrease this immune response, including systemic corticosteroids, MTX, cyclosporine, and azathioprine. Promising new drugs include biologic monoclonal antibody treatments and small molecule therapies for the treatment of this extremely bothersome condition. These include IL-4 antagonists, IL-31 inhibitors, tyrosine kinase KIT receptor antagonists, and JAK inhibitors. The treatment of PN requires a multifaceted approach and the use of systemic immunomodulators will play a large role.

Disclosure

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