Review Article:

Management of Prurigo Nodularis: a review

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Abstract

Prurigo nodularis is a chronic condition of the skin that presents with highly pruritic inflammatory nodules. It may occur alone, or with other skin & systemic diseases. Persistent itching in prurigo nodularis interfere with daily activities and leads a burden on patents well beings. Disruption of neurologic and immunologic function with upregulation of IL-4, IL-31 and neuropeptides are key factors regarding its pathology. Several topical agents (e.g., local corticosteroid, calcineurin inhibitors, calcipotriene, capsaicin, ketamine) & systemic neuro modulators (e.g., gabapentin, pregabalin, paroxetine, aprepitant, naltrexone) and immune modulators (e.g. Methotrexate, cyclosporine, azathioprine, biologics) have been studies to overcome this distressing condition. In addition, maintenance of skin hydration, stress relief and management of associated condition found promising for sustained response to therapy. Recently FDA has approved dupilumab for prurigo nodularis treatment.

Keywords: Prurigo nodularis, Pruritus, neuro modulator, immune modulator.

Background

Prurigo nodularis (PN) is a chronic inflammatory condition of the skin characterized by presence of intensely itchy nodules. This chronic pruritic condition is further exacerbated by repeated scratching, thus a vicious itch-scratch cycle is develop.[1] Though PN may present as an isolated condition, is frequently associated with other skin and systemic disorders.[2-4] Atopic dermatitis is commonly found with PN.[5] Other dermatosis that may associated with PN are xerosis cutis, epidermolysis bullosa, mycosis fungoides, post herpetic neuralgia etc..[6-7] In addition, systemic disease, such as renal and hepatic impairment, diabetes, malignancy, psychiatric disease, human immunodeficiency virus (HIV) and other infections may associate with PN.[1]

Diagnosis of PN is usually made clinically. Chronic, paroxysmal or continued pruritus with itchy excoriated nodules, papules and plaques that involving symmetrically the extensor extremities are typical presentation of PN, may also appear on abdomen and upper back.[7] Patients with PN should carefully evaluate to determine the severity of disease, and its impact on patients' quality of life.[8] laboratory work up help to determined other coexisting systemic disease.[7] Complete blood count, liver and renal function should measure in all patients.[9,10] In addition, laboratory markers for diabetes, thyroid disease, HIV, hepatitis B & C and other infectious etiology are performed if risk factors present. Histopathological evaluation of PN helps to support the diagnosis and excludes other dermatosis. Additional screening for malignancy and other diseases is considered if any suggestive features exist.[8]

The pathogenesis of PN is not fully understood. Studies define that, neural & immunologic dysregulation are the causal factors.[11] Nerves changes within PN lesions are regulated by some neuropeptides. In PN lesions there are increased expression of Substance P (SP), nerve growth factor and calcitonin gene-related peptides. These neuropeptides play a role in pruritic cycle through mast cells, eosinophil, effects on kappa- and mu- opioid receptors and endorphin.[5] Dysregulation of these neuropeptides leads nerve plasticity and an increased dermal nerve fiber density, even though these changes may occur due to frequent scratching behavior.[1]

Histopathological studies of PN lesions reveals within the

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dermis there are dense infiltrates of T lymphocytes, eosinophilic granulocytes and mast cells.[1] In PN there is upregulation of cytokines release from Th2 cells such as IL- 4, IL-13, IL-31 and increase histamine, prostaglandin, tryptase, eosinophil catanionic protein and neuropeptides.[1,11] The IL- 31 axis correspond with marked pruritus (1). IL 31 binds to IL-31 receptor A (IL-31RA) and oncostatin M (OSM) beta receptor located on keratinocytes, eosinophil and nerves. Binding of IL-31 to its receptors facilitates the activation of JAK1, JAK2 and STAT3 pathways.[12] All these increases pruritus perception and scratching habits in PN.[5]

Treatment modalities

Management of PN constitute significant challenges, as there is lack of proper treatment guidelines, as well as due to intractable and chronic nature of the disease (8). Different modalities of treatments are available include local moisturizers, topical & systemic therapy. Both neuro and immune modulators are helpful to treat PN.[5] Decision of therapy usually influenced by severity of disease, existing underling cause, comorbidities and risk benefit ratio.[13] Regarding antihistamine therapy, effect on treatment of PN is not conclusive. Some case series found good response with a combination of non-sedating at day time and sedating at night while other studies dose not recommended.[6,8]

General measures

Lifestyle modifications and behavioral therapies are cornerstone in the management of PN. Maintaining of proper skin hydration is essential. Frequent application of moisturizer helps to restore the skin barrier. Avoidance of pruritogenic stimuli such as- prolonged bathing and over drying, skin irritant- wool clothing's is necessary.[14] Habit reversal therapy is needed to break the itch-scratch cycle.[15]

Local therapeutic agents

Topical capsaicin, ketamine, lidocaine and amitriptyline that target the neural component are effective to relief pruritus.[8] Though, studies found short term response with this treatment.[16-17]

Topical corticosteroids, Vitamin D derivatives-calcipotriene, calcineurin inhibitors (CNI) includes tacrolimus & pimecrolimus, are initially use to treat PN (5). They exert their actions through immunomodulatory effects.[6] Studies found good response with 0.1% betamethasone valerate.[18] Significant response was found with applications 0.1% pimecrolimus cream twice daily for 8 weeks.[19] CNI may use as an alternative of topical steroid where prolong therapy is needed.[6]

A small RCT compared efficacy between calcipotriene & betamethasone valerate 0.1%, found greater efficacy with calcipotriene. [20]

For thicker lesions, IL triamcinolone acetonide (TA) is preferred. Combination of IL steroid & cryotherapy showed improved response.[21] Telangiectasia, hypo & hyperpigmentation may occur with the application of local steroid.[8]

Phototherapy

Narrow band ultraviolet B (NBUVB), psoralen ultraviolet A (PUVA), and UVA monotherapy have been used to treat PN. Ultraviolet lights decreased itch through anti-inflammatory effects.[22] UVB radiations also reduces NGF & IL-31.[23] Phototherapy is particularly helpful in patient with extensive PN with comorbidities.[6] Studies describes significant relief of itch with NBUVB therapy with an average quantity of 23.88±26.00 J/cm2.6 The combinations of NBUVB and PUVA showed better response in compared with PUVA alone.[22] Excimer LASER is an option for localized PN.[6] Among topical corticosteroid and excimer laser, excimer laser proved more effective.[23-24]

Gabapentin and Pregabalin

Patient with PN showed a good response with gabapentin and pregabalin.[25-26] M Mazza at al. described significant improvement after three months of therapy with pregabalin.[26]

SSRI and TCA

Paroxetine, Fluvoxamine and Amitriptyline have demonstrated efficacy in the management of PN.[26-27] A pilot study by Zalaudek et al found good response with Amitriptyline, dose schedule was 60 mg daily for 3 weeks, followed by 30 mg daily for 2 weeks and then 10 mg daily for 1 week. Side effects were tolerable.[26] Standeret al described efficacy for Paroxetine 20 mg/day in PN.[28]

Neurokinin 1 receptor (NK1r) antagonist

Aprepitant and Serlopitant are two NK1r antagonists. Studies found substantial improvement with Aprepitant.[6] A case control study by K. Agelopulos at al. revealed reduction of pruritus by four weeks treatment with oral Aprepitant (80 mg/day).[29] Some studies also described the use of topical aprepitant 1% gel.[30] Stander et all found significant improvement with daily 5 mg Selopitant for 8 weeks.[31]

Methotrexate

The immunomodulatory properties of MTX cause relief of pruritus.[4] In a study, 13 patients received weekly doses ranging from 7.5 -20 mg of MTX for a duration of 6 months and 10 patients experienced remarkable improvement.[32] Mariam Al Zaabi successfully treated a case of refractory PN with MTX for 3 months.[33] MTX induced nausea, fatigue & other adverse effects can be minimized by folic or folinic acid supplementation.[5] The recommended oral weekly dosage of methotrexate in PN is 7.5 to 15 mg. The starting dose is 7.5 mg for two weeks, followed by weekly increments of 2.5 to 5 mg.[8]

Cyclosporine

Cyclosporine is effective for refractory PN. A clinical trial in 14 patients with a daily dose of 3-5 mg/kg of oral cyclosporine showed significant improvement Maximum response developed after 2 weeks to 12 months therapy.[34] In a study by Wiznia at all, eight patients were treated with 2-4 mg/kg of cyclosporine, six patients experienced a significant reduction of symptoms, indicating a successful remission.[35] Despite the possibilities of side effects, the majority of patients tolerate this drug well (34). According to expert panel, recommended dose of cyclosporine is 3 mg/kg daily for 2-4 weeks, followed by escalation of dose by 0.5-1mg/kg daily at every 2-4 weeks.[8] Recently, cyclosporine is considered as a first line drug for chronic refractory PN.[5]

Azathioprine

Study describes relief of pruritus with azathioprine therapy.[5] In a case report two patients were treated with azathioprine 50 mg twice daily for severe PN, good improvement was foundafter 2-3 months.[36] However, more studies are required to determine the effects. Adverse effects, such as- gastrointestinal upset, altered liver function, infection and myelosuppression are common with Azathioprine.[5] Regular monitoring and dose adjustment are helpful to minimize toxicity. Dose of azathioprine for management of PN is 50-200 mg/day.[8]

Opioid receptor modulating drugs

Pruritus perception is partly regulated by opioid receptors. Activation of kappa- opioid receptor leads to attenuation of pruritus, while activated mu-opioid receptor intensify itch perception.[37] Naltrexone, a mu-opioid receptor antagonist, showed significant antipruritic effect in PN patients.[1] In one study 18 patients with chronic pruritus were treated with naltrexone. The drug dose was oral 50 mg/day and mean duration was 66 days. Though these patients were unresponsive to other treatments, 89% patients showed symptomatic improvement, marked improvement was seen in 50%, while 33% patients were nearly cured.[38] Another trial conducted on 65 patients found similar improvement.[1] Although gastrointestinal and neurological adverse effects were observed in some patient, was resolved within 2 weeks.[38] Trial with Nalfurafine, a kappa- receptor agonist, in patients with uremic pruritus, with an oral dose of 2.5 and 5 microgram/day for 14 days and intravenous infusion of 5 microgram thrice weekly for 2 weeks showed good response.[37] Nalbuphine and Butorphanol are dual kappa- receptor agonist and mu-receptor antagonist, showed efficacy for treatment of PN in few case reports.[6]

Thalidomide and Lenalidomide

In PN, thalidomide and lenalidomide exert their action through neurotoxic effect. In refractory prurigo nodularis, studies found significant improvement with Thalidomide. Although, these medicines are very effective, various side effects limits their use in PN.[6,39]

Biologics

Nemolizumab: Nemolizumab, an IL-31 RA monoclonal antibody, that binds with IL-31 RA and inhibit IL-31 induced inflammatory cascades and pruritus.[1] In a double -blind clinical trial by Ständer et at al., nemolizumab was administrated subcutaneously at 0.5 mg/kg every 4 weeks for 12 weeks. Within 48 hours of first dose, there was significant reduction of symptoms. Side effects related to nemolizumab was mild and tolerable.[40] Gastrointestinal and musculoskeletal adverse effects were found. A molecular study assessed the transcriptome in patients with PN after treatment with nemolizumab for 12 weeks & found downstream of inflammatory mediators.[1]

Dupilumab: Dupilumab, a monoclonal antibody, is FDA approved treatment of chronic resistant PN.[41] It inhibits both IL-4 & IL-13 by binding with IL-4 Ra that is shared by the IL-4 & IL-13 receptor complex.[42] In a retrospective cohort study, patients with refractory PN were treated with Dupilumab and 63.2% of patients showed good improvement after 16 weeks of therapy.[43] Tanis R et al treated a refractory case of PN with initial 600 mg subcutaneously, followed by 300 mg at 2 weeks interval. After 8 weeks, reduction of lesions size & symptoms was observed.[43] Dupilumab is a well-tolerated drug with mild side effects.[5] Current dose of dupilumab for PN is 600 mg subcutaneously as induction, followed by 300 mg at 2 weeks interval for maintenance.[8]

Emerging therapy: Cannabinoids are neuromodulators, have been studies for treatment of refractory pruritus, more studies are needed to determined its effects in PN treatment.[1,8,44] Few study found mycophenolate mofetil, an immune modulator, is beneficial for treatment of pruritus & PN.[45] Vixarelimab is a OSM beta receptor antagonist, found effective for treatment of PN.[5,46] Aborcitinib, a selective JAK1 inhibitor and Tofacitinib, selective JAK 1 and JAK 3 inhibitor, both showed efficacy in treatment of prurigo nodularis.[5,47-48])

Table I: Various antipruritic treatment modelities in patients with prurigo nodularis[8]

Therapy	Mechanism of action	Recommended dose	Side effects	Level of evidence (LOE)
Local corticosteroid Topical, IL injection	Anti-inflammatory	0.1% betamethasone valerate twice daily for 4 weeks. (18) I5-20 mg/ml IL Triamcinolone acetonide (TA) with 0.05-0.1 mL/lesions	Hypopigmentation, hyperpigmentation, telangiectasia	2b
Calcineurin inhibitors: Tacrolimus Pimecrolimus	Immunomodulation	0.1% tacrolimus twice daily 1% pimecrolimus twice daily for 8 weeks. (19)		2b
Calcipotriene	Immune mediated	Apply twice daily for 8 weeks (24)	Skin irritation	1b
Capsaicin	Substance P depletion	4-6 times daily for 2 weeks to 10 months (16)	Erythema, burning sensation, pruritus	2b
Ketamine, lidocaine, amitriptyline	neuronal	5-10% ketamine, 5% lidocaine and 5% amitriptyline 3times daily (17)	Redness, burning, itching	4
Cryotherapy with IL		Cryotherapy followed by IL TA 10 mg/ml (21)	none	5
Phototherapy: UVB PUVA	Anti-inflammatory	UVB for10 weeks (23) PUVA+/- UVB (22)	Transient erythema, burning, blisters	1b
Gabapentin	Neuromodulato	300mg/day, titrated up to 1200 mg/day. (25)	drowsiness	5
Pregabalin	Neuromodulato	75 mg/day for 3 months (26)	Dizziness, sedation	2b
Paroxetine	SSRI	10 mg/days for 3 days, then 20 mg/day, may increase up to 60 mg/day (28)	Gi upset and CNS abnormalities	2b
Amitriptyline	TCA	60mg/day-3weeks, 30mg/day-2week,10mg/day for 1 week (26)	Reduced concentration	2b
Aprepitant,	NK1r antagoni	Aprepitant 80mg/day for 4 weeks (29)	Vertigo, nausea	2b
Serlopitant	NK1r antagoni	Serlopitant 5 mg/day for 8 weeks (31)	Fatigue, pharyngitis, diarrhea	1b
Methotrexate	Immunomodulator: Folic acid antagonist	7.5-20 mg/week (8)	Nausea, fatigue, elevated transaminase, myelosuppression	4
Cyclosporine	Immunomodulator: Calcineurin inhibitor	3-5 mg/kg (8)	Gingival hyperplasia, HTN, gastrointestinal upset	4
Azathioprine	Anti-inflammatory	50 mg twice daily (8)	Infection, myelosuppression, gastrointestinal upset, malignancy	5
Naltrexone	Mu-opioid receptor antagonist	50 mg/day (38)	Anorexia, fatigue constipation	4
Thalidomide	Neurotoxic effects	50/100 mg/day (39)	Teratogenicity, Peripheral neuropathy	4
Nemolizumab	IL-31 inhibitor	0.5mg/kg every four weeks in subcutaneous route (8)	Gastrointestinal upset, musculoskeletal problem	1b

PUVA: psoralen plus ultraviolet A, UVB: ultraviolet B, *LOE (level of evidence) rating and criteria: 1a, systematic review of RCTs; 1b, individual RCT; 2a, systematic review of cohort studies; 2b, individual cohort study; 3a, systematic review of case-control studies; 3b, individual case-control study; 4, case series and poor-quality cohort and case-control studies; 5, case reports or expert opinion. RCT, randomized controlled trial.

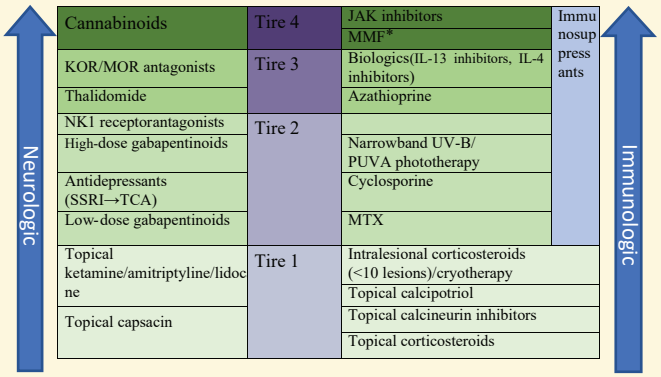

fig 1. PN treatment ladder. This ladder addresses both immunologic and neurologic mechanism (8).SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UVB, ultraviolet B; PUVA, psoralen plus ultraviolet A;IL-31, Interleukin 31; JAK, Janus kinase; KOR, k-opioid receptor; MOR,μ-opioid receptor; NK1, neurokinin 1; *Investigational therapies

Conclusion

PN is a chronic distressing skin condition. Adequate treatment with neuro & immune modulators in a step-wise pattern, as well as proper skin care & behavioral therapy, helps to relieve pruritus. Further studies are needed to establish a proper treatment guideline.

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