Treatments for prurigo nodularis (PN) have had some success and are primarily targeted at reducing itch in an effort to reduce lesions. Oftentimes these treatment modalities are combined with adjuvant therapy—frequently antihistamines—to maximize the anti-pruritic effect.

With limited disease, topical and intralesional corticosteroids are considered first-line therapy. While the evidence for steroidal benefit is relatively sparse, a randomized control trial of 12 patients found that patients treated with betamethasone 0.1% under occlusion (as a tape) for four weeks had a statistically significant decrease in itch as compared to patients treated with an over-the-counter anti-itch cream containing feverfew.

Interestingly, calcipotriol therapy may be superior to treatment with topical steroids. In a trial of patients with bilateral disease, calcipotriol applied to one leg was noted to decrease lesion count and size to a greater extent than betamethasone 0.1% applied to the fellow leg. Supporting this, in cases of steroid-resistant PN, there is evidence of topical vitamin D efficacy.

Calcineurin inhibitors have also been used as an alternative topical treatment. In a study of 20 patients treated with tacrolimus or pimecrolimus, patients reported an average 53 percent reduction in itch after an average of 7.3 months of therapy. Notably, these drugs may have inadequate skin penetration, as they were found to have a limited effect on large lesions.

Topical capsaicin can be of further consideration and studies have shown its efficacy in reducing itch and resolving skin lesions. Unfortunately, the efficacy of this topical is dependent on application four to six times daily, and patient adherence should be considered.

“Currently research on the efficacy of different phototherapy modalities with respect to one another is lacking, however, PUVA, narrow-band UVB (NB-UVB), broad-band UVB (BB-UVB), and excimer laser have been shown to reduce pruritus and improve the appearance of lesions.”

**GENERALIZED OR RECALCITRANT DISEASE**

For patients with generalized or recalcitrant disease, phototherapy and systemic medication may be of benefit. The success of phototherapy has been attributed to a reduction of calcitonin gene-related peptide positive nerve fibers in both the epidermis and the dermis, which are thought to contribute to pruritus and inflammation, respectively. Currently, research on the efficacy of different phototherapy modalities with respect to one another is lacking, however, PUVA, narrow-band UVB (NB-UVB), broad-band UVB (BB-UVB), and excimer laser have been shown to reduce pruritus and improve the appearance of lesions. There is some evidence of the efficacy of combined phototherapy. In a study by Hammes et al, patients were randomized to PUVA or PUVA in combination with excimer laser. While there was no statistical difference in the number of subjects achieving complete or partial PN remission in each group, subjects receiving combination
therapy required 30 percent less PUVA radiation. This is beneficial in that reduction of PUVA may lower the risk of long-term side effects of PUVA therapy, including squamous cell carcinoma.

While phototherapy is efficacious in many patients with PN, an important limitation is the necessity of in-office treatment, and systemic medication may be a more practical treatment option for some patients. Thalidomide, lenalidomide, cyclosporine, and methotrexate are systemic therapies that have been shown to improve pruritus and the appearance of PN lesions. In a review of 106 patients with PN treated with thalidomide or lenalidomide, with most treated for less than a year, 76 (71.7 percent) were found to have significant improvement as determined by a marked reduction in pruritus and nodules. Unfortunately, the use of this category of medication is limited due to the development of peripheral neuropathy in 36.8 percent of treated patients. Lenalidomide may be preferred to thalidomide, as its different molecular structure may confer a reduced risk. Alternatively, a lower dose of thalidomide may be considered, as this has been shown to improve the safety profile while maintaining effective treatment.

Cyclosporine is a calcineurin inhibitor that suppresses the release of cytokines from T-cells. This medication may exhibit its effects by down regulating IL-31, a cytokine linked to pruritus and known to be highly expressed in PN lesions. In a case series of 14 patients with refractory PN, 13 patients had a good clinical response with a 40 percent or greater reduction in pruritus, and 10 patients had rapid improvement of their skin lesions. Unfortunately, half of the patients experienced side effects, including hypertension, creatinine elevation, and gingival hyperplasia. Because of this medication’s narrow therapeutic index, it is necessary to monitor renal and hepatic function as well as blood counts in patients taking the drug.

Methotrexate, a folate antagonist, has been shown to improve PN lesions, likely due to suppression of cytokines. In a study of 13 patients treated with low dose methotrexate, 10 patients were found to have a greater than 50 percent reduction in the number of excoriated nodules after therapy. While one patient in the cohort experienced elevated liver enzymes, leading to temporary discontinuation of methotrexate, the medication was otherwise well tolerated. A more recent study of methotrexate in 39 patients with refractory PN noted similar efficacy and found that a majority of patients had complete remission following six and 12 months of therapy.

**THE PIPELINE**

New medications are in the pipeline for treating PN. A recent phase II trial of serlopitant, an antagonist of neu-rokinin receptor 1 (NK1R), randomized 257 patients with chronic pruritus to treatment with three different strengths of medication or placebo. Patients treated with serlopitant had significantly reduced pruritus as compared to placebo after six weeks of treatment. Patients treated with the 5mg dose had the greatest improvement in pruritus with 53 percent of patients having a 4cm decrease in the visual analogue scale for itch as compared to only 26 percent of patients treated with placebo. The efficacy of this medication is attributed to the disruption of substance P binding to cutaneous NK1, a pathway that was been shown to induce itch. A recent study further supported the efficacy of serlopitant in PN and found that the medication significantly decreased itch severity as compared to placebo (p<0.05). (Abstract “Serlopitant May Stop the Itch of Prurigo Nodularis” Stander). Serlopitant has generally been well tolerated with nasopharyngitis, diarrhea, and fatigue as the most commonly reported adverse events.

Cannabinoids may also treat PN by reducing pruritus. Vast numbers of cannabinoid receptors 1 and 2 are known to be located on cutaneous nerve fibers. N-palmitoylethanolamine (PEA), an endogenous neurotransmitter, binds these receptors and has been shown to relieve pruritus. In an observational study of 13 patients with PN treated with topical PEA, nine patients had improvement in pruritus and 11 had an improvement in their skin status after an average of 2.6 months of therapy. Notably, three of these patients had complete healing of their skin without pruritus following treatment.

Future studies are needed to assess the efficacy of cytokine modulation to treat PN. Nemolizumab and dupilumab, respective inhibitors of IL-31 and IL-4/13, have been effective in reducing pruritus in patients with atopic dermatitis and similar symptomatic reduction has been demonstrated with baricitinib and tofacitinib, two Janus kinase inhibitors. Currently, there is no clinical data for PN, though the prospect of itch reduction is promising. Moreover, if PN truly is a variant of atopic dermatitis, or even just closely related, the promising pipeline of atopic dermatitis therapies may be applicable to this rarer disease.

**“While phototherapy is efficacious in many patients with PN, an important limitation is the necessity of in-office treatment and systemic medication may be a more practical treatment option for some patients.”**
MORE HOPE THAN EVER

While the underlying cause of PN remains incompletely understood, with new understanding of itch mechanisms, the immune system, and the pathophysiology of the closely-related atopic dermatitis, there is more hope than ever for treating and unraveling the mysteries of the pathogenesis of PN.

Disclosure: Dr. Lio has served as a consultant and speaker for Regeneron/Sanofi-Genzyme, an advisor for Menlo Therapeutics, a consultant for AbbVie, and a consultant for Franklin BioScience. Ms. Treister has no relevant disclosures.

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