New Horizons in Our Understanding of Prurigo Nodularis and Its Management

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Prurigo nodularis (PN) was first accurately described more than a century ago by Hyde and Montgomery as chronic itchy nodules commonly noted in symmetric distribution on extensor sites of limbs, upper back, and abdomen.[1] For decades, PN patients were among the most challenging to treat. They suffer from intractable itch that affects their sleep dominates their daily life activities and causes many psychological comorbidities such as mood disorders including anxiety, stress, and depression. In the last decade, significant advances in our understanding of the pathophysiology of PN have been achieved suggesting this condition involves mainly type 2 immune dysregulation and abnormal neural sensitization, which led to the development of new targeted treatments. In September 2022, dupilumab, an IL4R alpha inhibitor that blocks IL4, and IL 13 cytokines became the first FDA-approved medication for PN. New treatments such as Nemolizumab, an IL31R inhibitor that blocks the itchy cytokine IL31 have successfully completed phase 3 trials.[2-3] Other studies targeting type 2 cytokines and mast cells are undergoing phase 2 trials. Drugs that target the neural system using kappa opioid receptor agonists (KOR) have shown promising results.[4] In the current issue of JDD, United States (US) experts in the field of itch, prurigo nodularis and psychodermatology provide a comprehensive review of the state of the art knowledge of PN, its pathophysiology, its comorbidities, and management. Issa et al discuss the clinical pathological overview as well as psychodermatological perspectives of the disease.[5] Issa et al provide an in-depth review of recent advances in the pathophysiological aspects of this disease including transcriptomic and single cell studies that explain the role of type 2 T helper (TH2) cells in PN.[5] Moreover, Issa et al. explain that nodules and scars are developed due to upregulation of gene expression signatures of papillary fibroblasts involved in fibrosis, extracellular matrix organization, and increase in extracellular matrix protein Periostin which has shown to be highly associated with itch in PN.[6]

Another important topic that Issa et al addressed in this article is the interplay between the dermatological and the psychological aspects of PN. The severity of pruritus of PN, as well as the disfiguring skin lesions and stress, may have profound negative effects on feelings of shame and stigmatization and overall mental health.[5] Furthermore, the neural sensitization of itch in PN is also highly associated with other neural sensitization disorders of pain, such as fibromyalgia, interstitial cystitis, and irritable bowel syndrome.[7] Psychiatric conditions are significantly more prevalent in individuals with PN, for example, patients with PN have a more than six-fold chance of having body dysmorphic disorder (BDD). The authors highlight the importance of identifying those patients with neuropsychiatric comorbidities who may need more aggressive treatment and early intervention.

Kwatra et al discuss the burden of systemic comorbidities and sequelae in PN.[8] Kwatra et alanalyzed large databases of patients in the US to find an increased prevalence from age 30 and above and higher comorbidities of PN in depression, chronic kidney disease, diabetes, congestive heart failure, COPD, atopic dermatitis, and HIV.[8] All patients with PN were found to have a higher all-cause mortality. African American patients are 3.4 times more likely to have PN than White patients and have greater systemic inflammation and higher mortality rates than Whites.[10] Furthermore, patients have a higher lifetime financial burden due to multiple doctor visits.

Elmariah et al reviews the current treatments and emerging therapies for PN.[9] The authors highlight the importance of assessing pruritus intensity, and disease burden, and comorbid medical disorders. Elmariah et al emphasize that treatment goals should address first and foremost the resolution of itch followed by improvement in nodules.[9] Elmariah et al describe the exciting recent phase 3 studies of targeted treatments for Type 2 cytokines including dupilumab and nemolizumab, as well as other phase 2 studies including vixarelimab.[9,11] Elmariah et al also cover the landscape of drugs targeting the neural pathways, such as nalbuphine and non-specific drugs with nerve pain medications such as GABAergic drugs and Serotonin and norepinephrine reuptake inhibitors (SNRIs).[9]

In conclusion, PN patients are facing a new era where their disease is effectively treatable with current targeted treatments as well as new options on the horizon.

DISCLOSURE

Gil Yosipovitch has served as an advisory board member for Abbvie, Arcutis, Escient Health, Eli Lilly, Galderma, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals Inc., Sanofi, Vifor, GSK, and Kamari; received grants/research funding from Eli Lilly, LEO Pharma, Novartis, Pfizer, Galderma, Escient, Sanofi Regeneron, and Celldex; and as an investigator for Regeneron Pharmaceuticals Inc., and Sanofi.

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