CASE SERIES

Abrocitinib Monotherapy for Refractory Prurigo Nodularis: Report of Two Successful Cases

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Abstract: Prurigo nodularis (PN) is a debilitating chronic neuroimmunologic skin condition due to the intense pruritus and difficult to treat. The pruritogenic cytokines, particularly IL-4, IL-13, IL-22, IL-31, and oncostatin M (OSM), play a crucial role in the pathogenesis of PN, potentially involving the JAK1-STAT pathway. An oral JAK1 inhibitor, abrocitinib, is presently undergoing Phase 2 trials for the treatment of PN. We evaluated the efficacy of abrocitinib at a daily dosage of 100 mg in treating two patients with PN affecting both lower limbs: a 50-year-old male with a 16-year disease history and a 38-year-old female with over three years of disease history, both of whom had failed to respond to multiple conventional treatments. Both patients responded rapidly after one week of treatment and exhibited a marked improvement. Following eight weeks of therapy, near-complete resolution of both pruritus and lesions was achieved, and no adverse effects were reported. Additionally, there were no reported side effects during the initial four months of continued treatment. Abrocitinib is an effective targeted therapy for PN, offering a promising new option for refractory patients.

Keywords: prurigo nodularis, abrocitinib, pruritus

Introduction

Prurigo nodularis (PN) is a debilitating chronic neuroimmunologic skin disorder, characterized by intensely pruritic, multiple excoriated/crusted hyperkeratotic nodules that are typically distributed symmetrically on the limbs.[1] Patients with PN have a higher burden of associated disease compared to those with other inflammatory skin disorders (such as atopic dermatitis and psoriasis), primarily attributed to the severe itch-scratch cycle and the lack of sufficiently effective and safe therapies.[2] The interaction between immunological and neural dysregulation is thought to play a crucial role in sustaining the itch-scratch cycle.[3] The upregulation of inflammatory cells (including Th2 cells, mast cells, and eosinophilic granulocytes), as well as cytokines (such as IL-4, IL-13, and IL-31) has been observed in PN lesions and is strongly associated with severe itching.[3] Elevated levels of IL-4 and IL-31 facilitate the crosstalk between inflammatory cells and sensory nerve fibers, mediated by their respective receptors expressed on sensory neurons in the dorsal root ganglia.[4] The dysregulation of neuropeptides, specially substance P (SP) and calcitonin gene-related peptide (CGRP) in dermal PN skin, are implicated in the neural inflammatory reaction manifested as plasma extravasation, vasodilatation, and degranulation of mast cells.[3] Currently, immunotherapies targeting key molecules or immune checkpoint pathways are revolutionizing the management of PN. In September 2022, dupilumab, a dual inhibitor of interleukin-4 (IL-4) and IL-13 signaling, was approved by the US Food and Drug Administration (FDA) as the first and only therapy specifically indicated for patients with PN. In a real-life observational study, 87.5% of patients with PN exhibited a favorable response to dupilumab, while 12.5% had a poor response.[5] These findings are similar to the outcomes reported by Calugareanu et al.[6] Nemolizumab, an anti-IL-31 receptor alpha inhibitor, has recently completed Phase 3 trials (NCT04501679), exhibiting positive outcomes.[1] Furthermore, abrocitinib, an oral once-daily JAK1 inhibitor, for the

treatment of PN is currently in phase 2 trials (NCT05038982). Herein, we present two PN patients who were refractory to conventional therapies but responded very favorably to abrocitinib monotherapy.

Case Reports

Patient 1 A 50-year-old male patient presented with a 16-year history of recurrent, intensely pruritic, raised skin lesions accompanied by black dried blood spots, affecting both lower limbs. The patient had been diagnosed with PN through pathological biopsy and had undergone various therapies, including glucocorticoids, hydroxychloroquine, thalidomide, doxycycline, ciclosporin, and vitamin C, across multiple hospitals. However, these treatments had lost their efficacy over time. Clinical examination revealed numerous hyperpigmented hyperkeratotic nodules with central erosions and crusts in different sizes from 1 to 3 cm, exclusively present on bilateral lower extremities (Figure 1A). No lesions were observed on other body areas. The patient reported his pruritic intensity, disease-associated sleep impact, and dermatology life quality index (DLQI) as 8/10, 9/10, and 22/30, respectively, using the numerical rating scale (NRS), with higher scores indicating worse outcomes. Given the absence of response to traditional therapies, we initiated treatment with oral abrocitinib at a dosage of 100 mg once daily. Rapid improvement was observed within just one week of treatment, with a significant reduction in pruritus and inflammation (Figure 1B). After 8 weeks, the nodules had been significantly reduced in size and flattened, accompanied by the presence of scars. Additionally, there was a marked improvement in
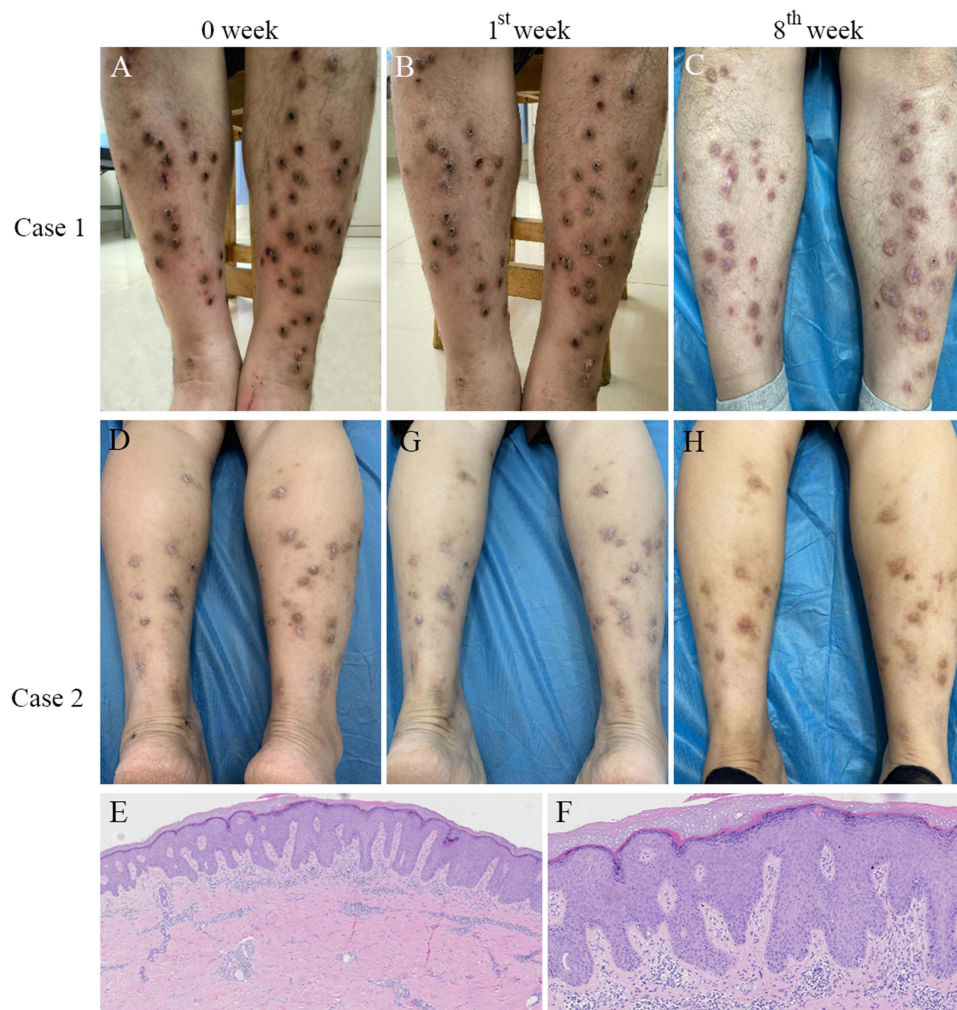

Figure 1 Case 1 presented with recurrent pruritic PN affecting both lower limbs before abrocitinib treatment (**A**). Gradual and significant improvement was observed in Case 1 at week 1 (**B**) and week 8 (**C**). Case 2 presented with refractory PN on both lower extremities before abrocitinib treatment (**D**). The histopathology of a nodular lesion from Case 2 is shown in (**E**, ×40; **F**, ×100). Following the initiation of abrocitinib treatment, Case 2 also exhibited significant improvement at week 1 (**G**) and week 8 (**H**).

the NRS scores for pruritus (from 8 to 0), sleep (from 9 to 2), and DLQI (from 22 to 4) (Figure 1C). The patient's dosage was adjusted to 100 mg twice daily for the next two months, during which further improvement was observed, with no occurrence of active rash or adverse effects. However, he subsequently lost to follow-up.

Patient 2 A 38-year-old woman was referred to our hospital due to recurrent, symmetrical pruritic, pigmented, dome-shaped plaques and nodules on her lower limbs for over three years. Previously, the patient had been prescribed a range of treatments, including topical steroids, phototherapy such as NB-UVB, oral antihistamines, prednisone 20 mg, cyclosporine 200 mg, thalidomide 100 mg once daily, and methotrexate 12.5 mg once weekly. However, her symptoms were unsuccessfully controlled, and multiple plaques and nodules recurrently appeared in the same area (Figure 1D). Moreover, the patient rated her pruritic intensity as 7/10 according to the NRS, which had significantly impacted her quality of life. To rule out secondary causes of PN, a series of examinations were conducted, including complete blood count, liver and kidney function tests, fasting sugar levels, thyroid function tests, erythrocyte sedimentation rate, stool occult blood examination, and serum IgE levels. All the reports were found within normal limit. The pathological report demonstrated thick compact hyperkeratosis, irregular epidermal hyperplasia, parakeratosis, hypergranulosis, and a superficial infiltrate of mainly lymphocytes with papillary dermal fibrosis (Figure 1E and F). After obtaining informed consent from the patient, monotherapy with abrocitinib was administered at a dose of 100 mg orally daily. After 1 week, the patient experienced a notable improvement in both the itching sensation and the lesions (Figure 1G). By the end of 8 weeks, the symptoms, particularly the itching (NRS scores decreasing from 7 to 0), had nearly resolved, leaving only residual pigmentation (Figure 1H). The patient has maintained a stable condition for over two months and remains under ongoing monitoring, exhibiting no adverse effects.

Discussion

Numerous studies have revealed that inflammatory cytokines, specifically IL-4, IL-13, IL-17, IL-22, IL-31, and oncostatin M (OSM), along with their respective receptors, exhibit significant upregulation in PN lesional skin. Concurrently, there is a marked elevation in the number of Th2, Th17, and Th22 cells.[7,8] Th2 cytokines IL-4 and IL-13 can directly activate sensory neurons through IL-4Rα and upregulate the expression of IL-31R to interact with IL-31, together resulting in the sensation of itch.[7] Similarly, IL-31, another Th2 cytokine, plays a pivotal role in eliciting pruritus and stimulating release of cytokines (such as IL-4, IL-6, and IL-13) from keratinocyte to exacerbate inflammatory, via its interaction with the heterodimeric receptor (IL-31Rα and OSMRβ).[8] IL-17A can induce the expression of pruritogenic endothelin-1 (ET-1) in keratinocytes, and both the levels of IL-17A and ET-1 are increased in the lesional skin and serum of patients with PN.[9] IL-22 directly increased the expression of Th2 cytokines (thymic stromal lymphopoietin (TSLP) and IL-33), as well as pruritogenic gastrin-releasing peptides (GRP) and its receptors in keratinocytes.[10] TSLP is known to be associated with itch-scratch cycle.[11] OSM can sensitize sensory neurons in inflammatory pruritus by enhancing neural responses to pruritogens and neural excitability.[12] Also, it can upregulate the expression of receptors associated with IL-4 and IL-13 in the dorsal root ganglion (DRG).[13] In addition to causing pruritus, these cytokines also mediate pathological proliferation and differentiation of epidermal keratinocytes and fibroblasts.[7,8] More notably, these cytokines exert their actions exclusively through the specific JAK-STAT signaling pathway, including IL-4 and IL-13 through JAK1-3 and TYK2; IL-22 through JAK1 and TYK2; IL-31, TSLP, and OSM through JAK1 and JAK2.[7] Therefore, JAK inhibitors have the potential to effectively disrupt the signal transduction cascade of these cytokines, offering a promising therapeutic approach for PN treatment. Currently, the oral abrocitinib and povorcitinib (JAK1 inhibitors) are undergoing in phase 2 trials and the topic ruxolitinib (JAK1/2 inhibitor) is in phase 3 trials. Several case reports have demonstrated very favorable outcomes in treating refractory PN with JAK inhibitors, including tofacitinib (JAK1/3 inhibitor), baricitinib (JAK1/2 inhibitor), and upadacitinib (JAK1 inhibitor).[14–16] More recently, one case report described a 62-year-old female patient with severe PN refractory to dupilumab who experienced rapid and complete improvement with abrocitinib combined with ruxolitinib 1.5% cream.[17] This finding is similar to our two cases, who failed to respond to conventional therapies but responded well to abrocitinib monotherapy.

The most frequently reported short-term adverse effects of abrocitinib include nausea, headache, upper respiratory tract infection, acne, dizziness, vomiting, and herpes zoster, often manifesting mild-to-moderate severity and being self-limiting.[18] Nevertheless, long-term/high-dose usage of abrocitinib is associated with a black box warning due to its

potential to increase the risk of serious infections, thrombosis, malignancy, and mortality.[18] Therefore, abrocitinib should be administered with caution to patients with older age, obesity, deep venous thrombosis (DVT)/pulmonary embolism (PE) history, prothrombotic disorders, or undergoing major surgery/prolonged immobilization, who have high risk of developing DVT/PE.[19] In patients with moderate or severe renal impairment, the abrocitinib dose should be reduced to 100 mg or 50 mg, respectively, from the original 200-mg or 100-mg once-daily dose.[20] Furthermore, abrocitinib is contraindicated in patients with active serious systemic infections, such as tuberculosis, severe hepatic impairment, as well as in pregnant and breastfeeding women.[19]

In summary, abrocitinib exhibits great promise as a potential treatment for PN due to its ability to selectively block the JAK1 signaling pathway of multiple crucial cytokines, although its long-term efficacy and safety should be evaluated through further real-world studies.

Consent Statement

The institutional ethics committee has granted ethical approval for this study to publish case details (No. gzsp202429), and consent for the publication of images and information was obtained from all participating individuals.

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Disclosure

The authors report no conflicts of interest in this work.

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