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Research Article

Baricitinib for Prurigo Nodularis: A Pilot Study on Efficacy and Safety

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Background. Breaking the itch-scratch cycle and facilitating lesion healing are pivotal in managing prurigo nodularis (PN). This study seeks to assess the efficacy of baricitinib, an oral JAK1/2 inhibitor, for treating PN. *Methods*. In this prospective pilot study, 12 patients with moderate to severe PN were administered oral baricitinib at a dosage of 4 mg/day for 12 weeks. The primary objective was to assess the efficacy of baricitinib in PN patients using the numeric rating scale (NRS) for pruritus, NRS sleep score, a 5-point investigator's global assessment (IGA) scale, dermatology life quality index (DLQI), and nodular lesion count at weeks 0, 1, 2, 4, 8 and 12. In addition, the NRS pruritus and sleep scores were assessed via phone on days 2 and 4 after baricitinib treatment. *Results*. Baricitinib treatment led to a statistically significant improvement in the mean NRS pruritus and sleep scores, evident as early as day 2 (57.7% change from baseline; $P < 0.001$, and 34.7% change from baseline, $P = 0.029$, respectively) and consistently declining thereafter. Evaluation of nodular lesions revealed a significant reduction starting from week 2 (mean difference of 37.08 from baseline; $P < 0.001$). Analysis of other endpoints, including mean DLQI and IGA scores, also demonstrated substantial improvement at all time points (week 1, 2, 4, 8, and 12) compared to baseline. However, it is important to acknowledge the limitation of a small sample size. This constraint warrants consideration when interpreting the results and generalizing the findings. *Conclusion*. This preliminary study underscores baricitinib's potential for PN treatment by providing a rapid clinical response. The larger and longer randomized controlled trials are essential to determine the effectiveness, longevity, and safety of baricitinib in managing PN. This trial is registered with TCTR20230227002.

1. Introduction

Prurigo nodularis (PN), also known as chronic nodular prurigo, is the best-known clinical subtype of chronic prurigo [1]. It is characterized by intensely recalcitrant pruritic hyperkeratotic nodules that interfere with sleep and patients' daily life. A meta-analysis of 13 studies in patients with PN demonstrated a marked reduction in quality of life and higher rates of depression and anxiety than the general population [2, 3].

The exact pathogenesis of PN remains unknown. However, immune and neural dysregulation are implicated in the crucial role of the pathogenesis of PN. Various cytokines and neuropeptides, including interleukin (IL)-4, IL-31, IL-22, and IL-17, substance P, and calcitonin gene-related peptides, show increased expression in PN lesions, resulting in a vicious itch-scratch cycle. These mechanisms are independent of the origin of the pruritus, which can be observed for different underlying etiologies, including dermatologic diseases (e.g., atopic dermatitis), systemic diseases (e.g., uremic pruritus), neurologic diseases, and psychiatric problems. Some may have a combination of the above mentioned conditions, whereas some do not have any known underlying cause [4].

The key treatment goal in treating PN is to break the itch-scratch cycle, thereby allowing the lesions to heal. Treatment of PN is very challenging because most existing treatments, including topical medications (e.g., topical steroids and

topical calcineurin inhibitors), systemic conventional immunomodulators (e.g., methotrexate, cyclosporin, mycophenolate mofetil, and azathioprine), and systemic neuromodulators (e.g., gabapentin, pregabalin, naltrexone, and antidepressants), are off-label with limited effect. Indeed, dupilumab (IL-4/IL-13 inhibitors) is the only approved treatment for PN that received the US Food and Drug Administration and the European Medicines Agency's approval for PN to date [5]. Dupilumab has an excellent safety profile, but it is an injectable drug, which is uncomfortable for some patients. A systematic review and analysis found that only half of patients with PN treated with dupilumab have complete resolution of itch. Furthermore, at least two months of dupilumab are required until the itch relieves, and complete remission of the itch is rarely observed before 4 months of therapy, consistent with a randomized controlled trial [6, 7].

Based on the pathogenesis of PN, a drug class that can regulate multiple cytokines is needed. An oral JAK (Janus kinase) inhibitor would be ideal because the JAK pathway is involved in the intracellular signaling that affects various cytokines. In addition to the role of anti-inflammation, JAK signaling also moderates sensory neurons directly participating in the pathogenesis of itch [8].

Baricitinib is a competitive inhibitor of the JAK family, predominantly the JAK1 and JAK2 subtypes. It received the US-FDA approval for rheumatoid arthritis, atopic dermatitis, and alopecia areata. In clinical trials, treatment with baricitinib demonstrated a rapid and a significant reduction in pruritus among patients with atopic dermatitis, observed as early as one day following the initial dose [9, 10]. Several case reports showed that baricitinib could be a good candidate for treating refractory PN and chronic pruritus, including those who had failed dupilumab [11–14]. To the best of our knowledge, no earlier study has been conducted to investigate the benefit of baricitinib in patients with PN.

The aim of this pilot study was to evaluate the efficacy and safety of baricitinib in patients with moderate to severe PN.

2. Materials and Methods

We conducted this pilot study at Thammasat University Hospital, Thailand. The Human Research Ethics Committee of the Faculty of Medicine, Thammasat University, approved the protocol (reg. no. MTU-EC-IM-1-236/65) and it was registered with the Thai Clinical Trials Registry (ref. ID. TCTR20230227002). Patients were enrolled from June 2023 through November 2023 and participated in a 12-week treatment period. Signed, informed consent was obtained from all participants before their participation in the study.

2.1. Patients. Adults aged 18–75 years who received a clinical diagnosis of moderate to severe PN (moderate is defined as 20 to 100 nodules, while severe is defined as having more than 100 nodules) for at least 6 months were eligible to participate.

The key exclusion criteria were as follows:

(i) Pregnant or lactating women
(ii) Patients with active or serious infections
(iii) Infected with hepatitis B or hepatitis C viruses or HIV.
(iv) Active or latent or inadequately treated infection with mycobacterium tuberculosis
(v) History of lymphoproliferative disease or malignancy
(vi) History of venous thromboembolism or stroke
(vii) History of heart failure or ischemic heart disease
(viii) Uncontrolled/serious medical conditions

Subjects meeting the study criteria underwent a 4-week washout period of systemic therapies that could impact pruritus through the end of the study (including antihistamines, systemic antipruritic therapies, immunosuppressants, neuromodulators, and antidepressants). However, the administration of topical corticosteroids and topical urea 10% was allowed to persist. Since topical corticosteroids and emollients are commonly used as a part of the treatment regimen for PN, maintaining their use as an adjunct therapy reflects real-world clinical practice.

2.2. Treatment. Enrolled patients were treated with baricitinib 4 mg once daily orally for 12 weeks.

2.3. Assessment. The primary endpoint was to evaluate the efficacy of baricitinib in patients with PN using the numeric rating scale (NRS) for pruritus (from 0 = no itch to 10 = worst itch), NRS sleep score (0 = worst sleep to 10 = best sleep), a 5-point investigator's global assessment (IGA) scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe), dermatology life quality index (DLQI) Thai version [15], and number of nodules at weeks 0, 1, 2, 4, 8, and 12. In addition, the NRS pruritus score and NRS sleep score were evaluated by phone on days 2 and 4 after baricitinib treatment.

Safety endpoints, including the incidence of adverse events that emerged during the treatment period and laboratory monitoring, were evaluated. At weeks 0, 4, and 12, the subject had been evaluated for the abnormal laboratory changes by collecting blood samples for complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cr), and creatinine phosphokinase (CPK). The lipid profile was evaluated at baseline and week 12.

2.4. Statistical Analysis. All statistical analyses were conducted using SPSS version 26. Descriptive data were reported as frequencies (%) or mean ± SD. A repeated-measures within-subjects ANOVA was utilized to evaluate the treatment effects over time. The difference was regarded as statistically significant when $P < 0.05$.

3. Results

A total of 12 patients with PN were enrolled in the trial, and all participants completed the trial. Table 1 summarizes the baseline demographic data of patients and disease characteristics. The baseline means that the NRS pruritus score and the number of prurigo nodular lesions were relatively high. All participants had a long standing disease duration of longer than two years, with a mean of 5.75 ± 4.00 years, and had tried multiple treatment modalities including the unsuccessful use of prednisolone, methotrexate, azathioprine, and dapsone.

Treatment with baricitinib 4 mg/day resulted in a statistically significant improvement in the mean NRS pruritus score and NRS sleep score, starting as early as day 2 and continuously decreasing over time. The initial mean NRS pruritus score was 8.67 at baseline, and it reduced to 3.67 at day 2 (57.7% change from baseline; $P < 0.001$) and continued through week 12 with a reduction to 0.33 (96.2% change from baseline; $P < 0.001$) (Figure 1 and Table 2). The mean NRS sleep score also improved significantly, starting at day 2 (34.7% change from baseline, $P = 0.029$) with further improvement at week 12 (56% change from baseline; $P < 0.001$) (Figure 1, Table 2).

Endpoint addressing on skin lesions demonstrated a significant reduction in nodular lesions beginning in week 2 (mean difference of 37.08 from baseline; $P < 0.001$) and continuing to show improvement through week 12 (mean difference of 73.67 from baseline; $P < 0.001$) (Figure 1, Figure 2, and Table 2).

Analysis of other endpoints, including the mean change in DLQI score and IGA score, revealed consistent trends. All outcomes showed significant improvement at all time points (weeks 1, 2, 4, 8, and 12) compared to baseline (Figure 1 and Table 2).

Regarding the safety profile of baricitinib, there were no treatment-emergent serious adverse events, nor were there any instances of treatment discontinuation due to adverse events among all participants. An increase in serum CPK >2.5 times the upper level of normal was observed in only one participant but was not associated with muscle-related symptoms. In addition, three participants experienced mild symptoms of an upper respiratory tract infection, while another exhibited mild symptoms of COVID-19 infection.

Table 1: Baseline patient demographics and disease characteristics ($N = 12$).

Age, mean ± SD, years	53.08 ± 12.35
Female, *n* (%)	7 (58.30%)
Body mass index, mean ± SD	26.70 ± 5.69
Duration since PN diagnosis, mean ± SD, years	5.75 ± 4.00
Number of nodules, mean ± SD	84.12 ± 28.59
Baseline NRS pruritus score	8.67 ± 1.37
Background of atopy, *n* (%)	
(i) Allergic rhinitis	1 (8.33%)
(ii) Asthma	0 (0%)
(iii) Atopic dermatitis	0 (0%)
Previous systemic treatments, *n* (%)	
(i) Prednisolone	6 (50%)
(ii) Methotrexate	2 (16.67%)
(iii) Azathioprine	2 (16.67%)
(iv) Dapsone	2 (16.67%)
(v) Phototherapy	0 (0%)

4. Discussion

Advancements in understanding the pathogenesis of PN, coupled with the emergence of novel therapeutic agents, offer promising opportunities for its treatment. To date, dupilumab represents the only approved systemic treatment for adults with PN. Nonetheless, its efficacy is hindered by the slow onset of action for itch relief and reduction of PN lesions, as well as the requirement for subcutaneous injection [5–7]. A previous retrospective review compared 36 patients receiving dupilumab with 13 patients receiving oral JAK inhibitors (10 patients received baricitinib, and the remaining 3 patients received upadacitinib). This study demonstrated a good clinical response in itch and nodules for both treatments at weeks 12–16. However, those on oral JAK inhibitors showed a significantly faster initial response compared to dupilumab, despite being significantly more likely to have previously used systemic immunosuppressants or even previously used dupilumab [16]. A variety of agents, including biologics (such as nemolizumab, vixarelimab, and barzolvolimab), small molecules (such as ruxolitinib, povorcitinib, and abrocitinib), and opioid modulator (nalbuphine) are presently undergoing investigation, suggesting the potential for the development of more efficacious PN treatments in the near future [17].

The JAK-STAT pathway plays a crucial role in the pathogenesis of itch, especially in chronic pruritic conditions such as prurigo nodularis. Many cytokines that mediate important immunomoduating and neuromodulating pathways in chronic prurigo (e.g., IL-4, IL-13, thymic stromal lymphopoietin, IL-31, IL-17, and IL-23) rely on JAK-STAT pathways. Especially, IL-4, a potent Th2 cytokine, enhances neuronal responsiveness to various pruritogens by directly acting on sensory neurons and promoting itch sensation through binding to its receptor, JAK1, thereby initiating activation of the JAK-STAT pathway. Consequently, JAK inhibitors, particularly those with predominantly selective JAK1 inhibition, hold promise in relieving itch [18].

In this preliminary investigation, treatment with baricitinib in twelve adult patients with long-standing recalcitrant PN yielded highly favorable outcomes. A noteworthy advantage of baricitinib is its prompt and profound reduction of itch, which is a pivotal therapeutic objective in PN management. By effectively interrupting the itch-scratch cycle, subsequent healing of lesions ensued. As evidenced by this study, a significant decrease in PN lesions was observed just two weeks after initiating baricitinib treatment. Beyond lesion improvement, the swift alleviation of itch, noticeable as early as 2 days postinitial dose, translated to amelioration of clinically burdensome symptoms including sleep disturbance and overall quality of life. Baricitinib also demonstrated favorable tolerability and safety profiles across all participants.

The primary limitations of this study include a small sample size and the absence of a comparison control group.

Table 2: Outcomes ($N = 12$).

Outcomes, mean ± SD	Time							
	Baseline	Day 2	Day 4	Week 1	Week 2	Week 4	Week 8	Week 12
Pruritus score	8.67 ± 1.37	3.67 ± 1.83	2.92 ± 2.15	2.42 ± 2.11	1.58 ± 1.17	1.00 ± 0.60	0.50 ± 0.67	0.33 ± 0.49
Sleep score	6.25 ± 1.87	8.42 ± 1.00	8.25 ± 1.49	8.75 ± 1.29	9.00 ± 1.04	9.25 ± 0.62	9.50 ± 1.00	9.75 ± 0.62
No. of nodules	84.12 ± 28.59	NA	NA	76.17 ± 31.60	47.33 ± 31.60	30.67 ± 32.41	13.50 ± 21.22	10.75 ± 21.32
DLQI	13.00 ± 6.41	NA	NA	6.08 ± 3.99	3.17 ± 2.55	2.25 ± 1.69	1.00 ± 1.21	0.92 ± 1.00
IGA	7.17 ± 0.72	NA	NA	5.33 ± 1.16	3.83 ± 1.19	3.25 ± 1.49	2.25 ± 1.66	1.33 ± 1.37

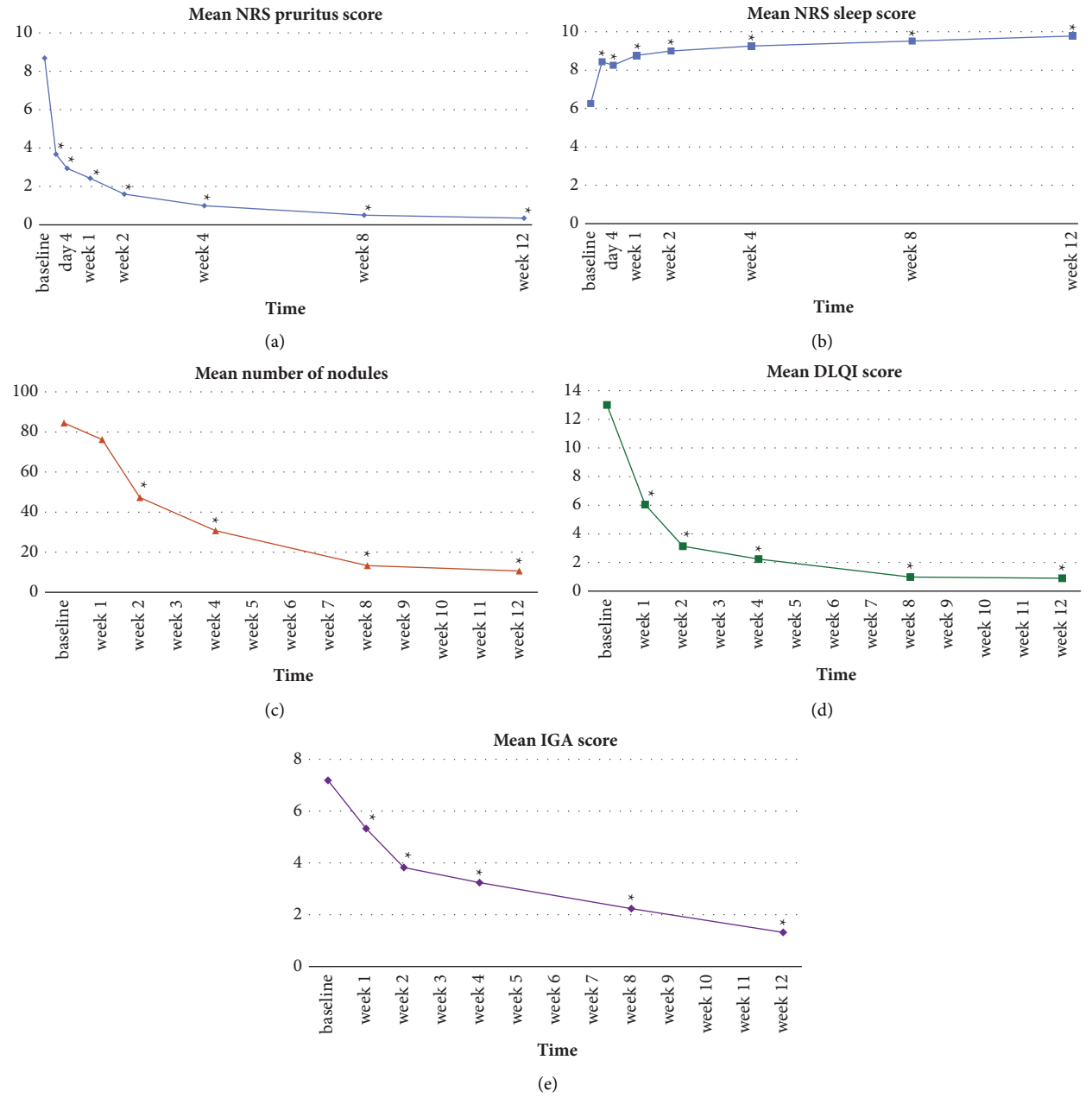

Figure 1: The rapid decrease in mean NRS pruritus and sleep score as early as day 2 of baricitinib treatment. The mean number of nodules significantly decreases starting from week 2 after the administration of baricitinib. The DLQI and IGA scores showed a significant decrease starting from week 1 after receiving baricitinib compared to baseline. $^{*}P < 0.005$. (a) Mean NRS pruritus score. (b) Mean NRS sleep score. (c) Mean number of nodules. (d) Mean DLQI score. (e) Mean IGA score.

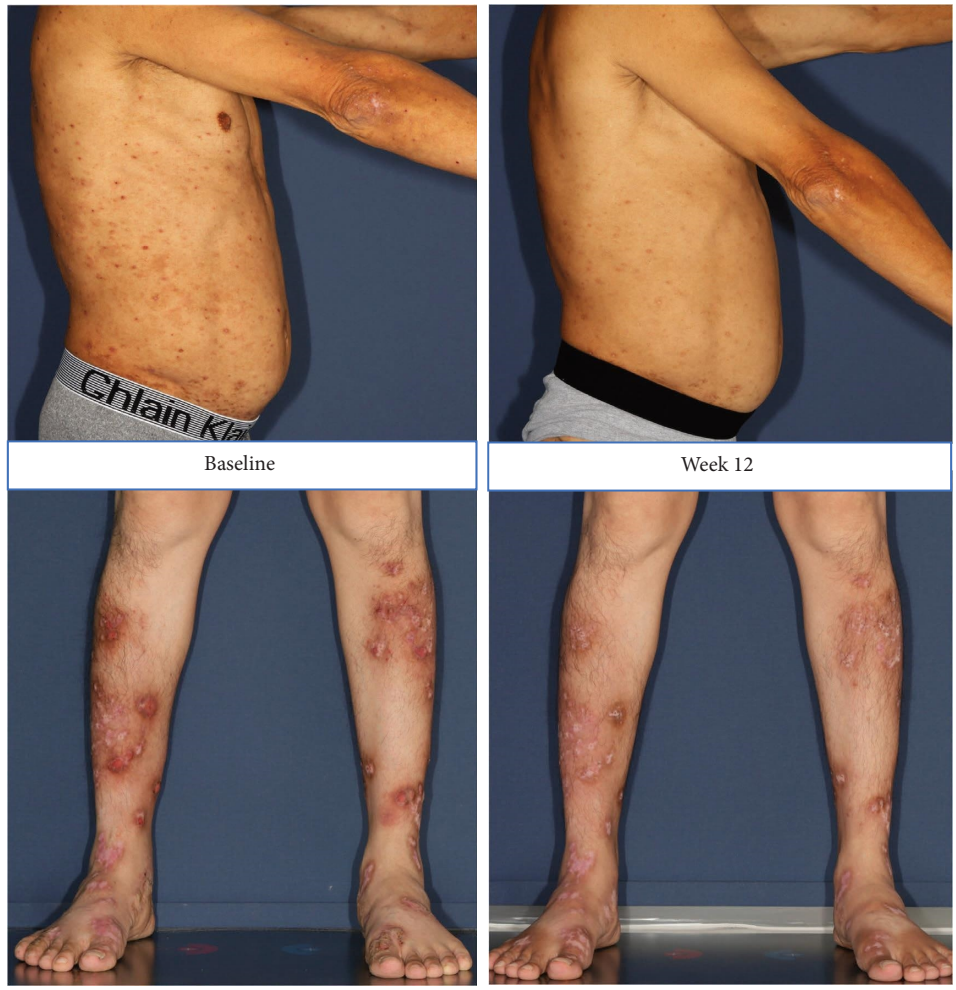

Figure 2: Showed clinical improvement following the administration of baricitinib 4 mg/day orally from baseline to week 12.

Our research comprised volunteers who had not been previously diagnosed with atopic dermatitis, with only one individual exhibiting allergic rhinitis. In contrast, other studies frequently identify atopic dermatitis as a common comorbidity among PN patients. The limited sample size of our study may contribute to the discrepancy, potentially impacting the representation of the general population.

5. Conclusion

Baricitinib is another promising candidate due to its reputation for fast alleviating itch within a few days. This pilot investigation underscores the potential of baricitinib in PN treatment, offering rapid clinical responses. However, larger and longer randomized controlled trials are needed to ascertain the efficacy, durability, and safety of baricitinib in PN treatment.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request. Due to privacy concerns, certain restrictions may apply to accessing or using the data.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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