

Upadacitinib for refractory prurigo nodularis: a two-centre real-world cohort using step-up dosing

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Abstract

Upadacitinib, an oral selective Janus kinase 1 inhibitor, has growing off-label evidence in prurigo nodularis (PN), but real-world data are limited. We evaluated its effectiveness and safety in adults with refractory, biologic-naïve PN without atopic dermatitis and describe a response-guided step-up dosing strategy. We retrospectively reviewed 20 adults with moderate-to-severe PN (≥ 20 nodules) treated at two dermatology centres in Istanbul between January 2024 and December 2025. All patients started upadacitinib 15 mg daily, escalating to 30 mg if the Worst Itch Numeric Rating Scale (WI-NRS) score had not decreased by ≥ 4 points after ≥ 12 weeks. WI-NRS and Peak Pruritus Numerical Rating Scale (PP-NRS) scores were compared between baseline and the last visit. Seventeen patients (85%) were women; mean age was 54.1 years. Eleven (55%) remained on 15 mg and nine (45%) required 30 mg. After a median of 6.6 months (range, 6–18), mean WI-NRS decreased from 9.25 to 0.65 ($p < 0.001$); all patients achieved a ≥ 4 -point reduction and 14 (70%) were itch-free. Mean PP-NRS decreased from 9.05 to 0.95 ($p < 0.001$). Four patients (20%) had non-serious adverse events; none discontinued treatment. In exploratory analyses, patients requiring escalation were older, all had diabetes or cardiovascular disease, and more often had > 100 nodules, whereas baseline itch was similar. Upadacitinib was associated with marked itch improvement in refractory PN, and step-up dosing allowed 55% of patients to remain on 15 mg. It may be a useful oral option when approved biologics are inaccessible; controlled studies with longer follow-up are needed.

Introduction

Prurigo nodularis (PN) is a chronic inflammatory and neuroimmune skin disease marked by intensely pruritic nodules and a persistent itch-scratch cycle. The disease can substantially impair sleep, daily functioning, and quality of life [8, 9, 18].

Dupilumab and nemolizumab became established targeted treatments for moderate-to-severe PN after positive phase 3 trials [11, 19]. Access can still be limited in some health systems. During our study period, approved biologic therapies for PN were not reimbursed for these patients in our setting. Several cytokine pathways involved in PN converge on Janus kinase (JAK) signalling. JAK1 signalling in sensory neurons also contributes to chronic itch [14].

Clinical evidence for upadacitinib in PN has grown in recent years. A prospective cohort of 10 patients treated with 15 mg daily showed a marked reduction in itch over 24 weeks [12]. Later case series and multicentre studies reported similarly high itch response rates [1, 5, 16]. A 2026 Turkish comparative cohort reported a clinically meaningful itch response by month 6 in all eight patients treated with upadacitinib 30 mg [3]. A recent systematic review of 211 patients treated with JAK inhibitors found a consistent effectiveness signal but also highlighted small samples, mainly uncontrolled designs, heterogeneous outcomes, and limited long-term safety data [17]. Similar activity has also been reported with abrocitinib [10].

We therefore evaluated the real-world effectiveness and safety of upadacitinib in adults with refractory, biologic-naïve PN without atopic dermatitis. In routine practice, we used a step-up strategy. All patients started at 15 mg once daily, and the dose was increased to 30 mg only when itch response remained inadequate.

Materials and methods

This retrospective two-centre cohort included adults with PN followed at the dermatology outpatient clinics of University of Health Sciences Türkiye, Istanbul Bağcılar Training and Research Hospital, and Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, between January 2024 and December 2025.

This retrospective study was conducted in accordance with the Declaration of Helsinki. Upon written application in 2025, the Istanbul University-Cerrahpaşa Ethics Committee stated that formal ethics committee approval was not required for this retrospective study, as written informed consent had been obtained from all patients. Institutional permission to access and use patient records was obtained from both participating centres. Written informed consent was obtained from all patients.

PN was diagnosed clinically and/or histologically according to the European Prurigo Project criteria [15]. We included patients aged 18 years or older who had at least 20 nodules, had an inadequate response to at least one conventional treatment, had never received a biologic agent or another JAK inhibitor, and had no past or current atopic dermatitis. Conventional treatments included topical or systemic corticosteroids, intralesional corticosteroids, narrow-band UVB phototherapy, pregabalin, or other systemic treatments. Patients with major gaps in their clinical records or poor treatment adherence were excluded.

Treatment options were discussed individually with each patient. During the study period, targeted biologic therapies were not reimbursed for PN in our setting. Patients who chose upadacitinib obtained the medication at their own expense. Upadacitinib was used off-label for PN.

All patients started upadacitinib 15 mg once daily. The dose was increased to 30 mg once daily if the Worst Itch Numeric Rating Scale (WI-NRS) score had not decreased by at least 4 points after a minimum of 12 weeks on 15 mg. Patients were reviewed monthly during the first 3 months and every 3 months thereafter. Clinical and laboratory safety monitoring was performed at these visits in line with routine practice for oral JAK inhibitors [7].

Itch was assessed at baseline and at the last documented visit using the 0–10 WI-NRS and the 0–10 Peak Pruritus Numerical Rating Scale (PP-NRS). A decrease of at least 4 points in WI-NRS was considered a clinically meaningful itch response. WI-NRS = 0 was considered complete itch resolution. Sleep disturbance was recorded with a 0–10 Sleep-NRS at the last visit. Baseline sleep scores were not consistently available and were therefore not used to estimate change over time.

Baseline nodule burden was grouped as 20–100 nodules or more than 100 nodules. Adverse events and laboratory abnormalities documented during treatment were recorded from the clinical files.

Continuous variables are presented as mean $\pm$ standard deviation unless otherwise stated, and categorical variables as number and percentage. Baseline and last-visit WI-NRS and PP-NRS scores were compared with the Wilcoxon signed-rank test. In an exploratory analysis, baseline characteristics were compared between patients who remained on 15 mg and those who required escalation to 30 mg. The Mann-Whitney U test was used for continuous variables and Fisher's exact test for categorical variables. No multivariable prediction model was fitted because the cohort included only 20 patients and nine dose-escalation events. No adjustment was made for multiple comparisons because these analyses were exploratory. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Twenty patients were included (Table 1). Seventeen (85%) were women. The mean age was 54.1 ± 9.3 years (range, 34–68), and the mean body mass index was 28.4 ± 5.7 kg/m². Mean disease duration was 5.0 ± 3.0 years. Eleven patients (55%) had diabetes mellitus, six (30%) had cardiovascular disease, and 14 (70%) had at least one of these conditions. Half of the cohort had more than 100 nodules at baseline. By design, all patients were biologic-naïve and had no past or current atopic dermatitis. All had previously received topical or systemic corticosteroids. Ten (50%) had received intralesional corticosteroids, eight (40%) phototherapy, four (20%) psychiatric medication, and one (5%) pregabalin.

Table 1
Baseline characteristics and exploratory comparison by dosing pathway

Characteristic	All (n = 20)	Remained on 15 mg (n = 11)	Escalated to 30 mg (n = 9)	p value
Age, years, mean $\pm$ SD	54.1 $\pm$ 9.3	50.2 $\pm$ 9.6	58.9 $\pm$ 6.5	0.044
Age $\geq$ 65 years, n (%)	2 (10)	0	2 (22)	0.189
Female, n (%)	17 (85)	8 (73)	9 (100)	0.218
BMI, kg/m ² , mean $\pm$ SD	28.4 $\pm$ 5.7	26.2 $\pm$ 5.5	31.0 $\pm$ 5.1	0.095
Disease duration, years, mean $\pm$ SD	5.0 $\pm$ 3.0	4.5 $\pm$ 3.3	5.4 $\pm$ 2.7	0.319
Diabetes mellitus, n (%)	11 (55)	4 (36)	7 (78)	0.092
Cardiovascular disease, n (%)	6 (30)	2 (18)	4 (44)	0.336
Diabetes or cardiovascular disease, n (%)	14 (70)	5 (45)	9 (100)	0.014
Chronic viral hepatitis, n (%)	2 (10)	1 (9)	1 (11)	1.000
Nodules 20–100, n (%)	10 (50)	9 (82)	1 (11)	0.005
Nodules > 100, n (%)	10 (50)	2 (18)	8 (89)	0.005
Baseline WI-NRS, mean $\pm$ SD	9.25 $\pm$ 1.02	9.27 $\pm$ 1.10	9.22 $\pm$ 0.97	0.862
Baseline PP-NRS, mean $\pm$ SD	9.05 $\pm$ 1.15	8.91 $\pm$ 1.30	9.22 $\pm$ 0.97	0.624
Prior topical/systemic corticosteroids, n (%)	20 (100)	11 (100)	9 (100)	—
Prior intralesional corticosteroids, n (%)	10 (50)	5 (45)	5 (56)	1.000
Prior phototherapy, n (%)	8 (40)	5 (45)	3 (33)	0.670
Prior psychiatric medication, n (%)	4 (20)	2 (18)	2 (22)	1.000
BMI, body mass index; WI-NRS, Worst Itch Numeric Rating Scale; PP-NRS, Peak Pruritus Numerical Rating Scale; SD, standard deviation. Comparisons between dosing pathways are exploratory. Continuous variables were compared with the Mann-Whitney U test and categorical variables with Fisher's exact test. No adjustment was made for multiple comparisons.				

The median duration of upadacitinib treatment was 6.6 months (range, 6–18), and every patient had at least 6 months of treatment. Mean WI-NRS decreased from 9.25 $\pm$ 1.02 at baseline to 0.65 $\pm$ 1.14 at the last visit (mean reduction, 8.60 $\pm$ 1.70; $p < 0.001$). All 20 patients achieved a WI-NRS reduction of at least

4 points, and 14 (70%) had WI-NRS = 0 at the last visit. Mean PP-NRS decreased from 9.05 ± 1.15 to 0.95 ± 1.19 (mean reduction, 8.10 ± 1.97 ; $p < 0.001$). Nineteen patients (95%) achieved a PP-NRS reduction of at least 4 points, and 10 (50%) had PP-NRS = 0 at the last visit (Table 2).

Table 2
Overall treatment outcomes at the last visit

Outcome	Result	p value
Treatment duration, months, median (range)	6.6 (6–18)	—
WI-NRS, baseline, mean $\pm$ SD	9.25 ± 1.02	—
WI-NRS, last visit, mean $\pm$ SD	0.65 ± 1.14	$< 0.001^a$
WI-NRS reduction, mean $\pm$ SD	8.60 ± 1.70	—
WI-NRS reduction ≥ 4 points, n (%)	20 (100)	—
WI-NRS = 0 at last visit, n (%)	14 (70)	—
PP-NRS, baseline, mean $\pm$ SD	9.05 ± 1.15	—
PP-NRS, last visit, mean $\pm$ SD	0.95 ± 1.19	$< 0.001^a$
PP-NRS reduction, mean $\pm$ SD	8.10 ± 1.97	—
PP-NRS reduction ≥ 4 points, n (%)	19 (95)	—
PP-NRS = 0 at last visit, n (%)	10 (50)	—
Sleep-NRS at last visit, mean $\pm$ SD	1.10 ± 1.77	—
Sleep-NRS = 0 at last visit, n (%)	13 (65)	—
Any adverse event, n (%)	4 (20)	—
Treatment discontinuation due to adverse events, n (%)	0	—
Serious adverse event, n (%)	0	—
^a Wilcoxon signed-rank test comparing baseline with the last visit. Sleep-NRS was recorded only at the last visit.		

At the last visit, mean WI-NRS was 0.82 among patients who remained on 15 mg and 0.44 among those who had required escalation to 30 mg. Seven patients in each dosing pathway were itch-free. Mean Sleep-NRS at the last visit was 1.10 ± 1.77 . Thirteen patients (65%) reported no sleep disturbance. Because baseline sleep scores were unavailable, within-patient sleep improvement was not calculated.

Eleven patients (55%) achieved an adequate itch response while remaining on 15 mg. Nine patients (45%) required escalation to 30 mg because their response was inadequate. Patients who required escalation were older (58.9 ± 6.5 vs. 50.2 ± 9.6 years; $p = 0.044$). All nine had diabetes or cardiovascular

disease, compared with 5 of 11 patients who remained on 15 mg (100% vs. 45%; $p = 0.014$). Baseline nodule burden was also higher in the escalation group: more than 100 nodules were present in 8 of 9 patients (89%) compared with 2 of 11 (18%; $p = 0.005$). Body mass index (31.0 ± 5.1 vs. 26.2 ± 5.5 kg/m²; $p = 0.095$) and diabetes frequency (7/9 [78%] vs. 4/11 [36%]; $p = 0.092$) were numerically higher in the escalation group but did not reach statistical significance. Baseline WI-NRS and PP-NRS were similar between the two dosing pathways (Table 1). These comparisons were exploratory and were not adjusted for confounding.

Four patients (20%) experienced non-serious adverse events, and none discontinued treatment. Three patients developed an acneiform eruption and two reported gastrointestinal intolerance with nausea; one patient had both events. No herpes zoster, serious infection, venous thromboembolism, major cardiovascular event, or malignancy was recorded during the observed treatment period. The cohort was too small and follow-up too short to estimate the risk of uncommon adverse events.

Discussion

In this real-world cohort of adults with refractory PN, upadacitinib was associated with a marked reduction in itch. Every patient achieved at least a 4-point reduction in WI-NRS, and 70% were itch-free at the last assessment. These findings add to the growing evidence that JAK1 inhibition can provide substantial symptom control in PN, including in patients without atopic dermatitis.

Our results are consistent with previous upadacitinib studies. Lee et al. treated 10 patients with refractory PN with upadacitinib 15 mg daily and reported a fall in mean itch NRS from 8.1 at baseline to 0.8 at week 24 [12]. In a 23-centre Italian cohort, 52 of 55 patients (94%) treated with upadacitinib achieved a ≥ 4 -point reduction in PP-NRS at week 16, and the response was maintained at week 24 [1]. A Turkish comparative cohort reported a clinically meaningful itch response by month 6 in all eight patients treated with upadacitinib 30 mg [3]. In the systematic review by Vahabi et al., 139 of 180 patients (77.2%) in clinical studies achieved meaningful improvement with a JAK inhibitor [17]. Together, these studies show a consistent and strong effectiveness signal for JAK inhibition in PN, although the evidence still comes mainly from small or uncontrolled studies.

A practical feature of our cohort was the response-guided step-up strategy. All patients started at 15 mg, and the dose was increased only when WI-NRS had not improved by at least 4 points after 12 weeks. Eleven of 20 patients remained on 15 mg. All nine patients who required escalation met the ≥ 4 -point WI-NRS response criterion by the last visit, and seven were itch-free. Response-guided upadacitinib escalation has prospective support in atopic dermatitis. In the Flex Up study, 48.1% of patients who did not reach a 90% improvement in the Eczema Area and Severity Index (EASI 90) on 15 mg at week 12 achieved EASI 90 after escalation to 30 mg by week 24 [6]. A phase 4 PN study used a similar approach, starting at 15 mg with optional escalation to 30 mg from week 8. That study was terminated after enrolling five participants, and no results have been posted [2]. To our knowledge, published PN cohorts have not reported outcomes of a predefined response-guided 15-to-30 mg step-up strategy. Our data

therefore add practical real-world information, but the two dosing pathways should not be interpreted as independent treatment groups.

Patients who required escalation were older, all had diabetes or cardiovascular disease, and most had more than 100 nodules at baseline. Baseline itch scores were almost identical between the two dosing pathways. This pattern suggests that an inadequate response to 15 mg may relate more to disease extent and comorbidity burden than to baseline itch intensity. However, these findings are exploratory. The sample was small, the variables are interrelated, and no adjusted model was possible. Baseline nodule burden or comorbidity should therefore not be used alone to select a higher dose. They may, however, identify patients who need closer assessment of early response.

Safety deserves particular attention in this population. Class warnings for JAK inhibitors are especially relevant in older patients and in those with cardiovascular risk factors [4, 20]. Our cohort had a high cardiometabolic burden: 55% had diabetes and 30% had cardiovascular disease. No serious adverse event was observed. The recorded events were mild, and none led to treatment discontinuation. This is broadly consistent with the PN literature, in which most reported adverse events have been mild [1, 12, 17]. Still, our study cannot establish long-term safety. This point is especially important because every patient who required 30 mg had diabetes or cardiovascular disease. The decision to escalate the dose should therefore include an individual risk-benefit assessment and appropriate clinical and laboratory monitoring [7].

Part of the published upadacitinib experience comes from patients who had already received biologic therapy. Some patients in the Italian multicentre cohort had previously used dupilumab [1], and successful use of upadacitinib after an inadequate dupilumab response has also been reported [13]. In contrast, all patients in our cohort were biologic-naïve. The high itch response in this setting suggests that upadacitinib may offer a useful oral option when approved biologic therapy is inaccessible or unsuitable. Our study does not compare upadacitinib with biologic therapy and does not establish superiority over approved treatments.

This study has several limitations. It was retrospective and uncontrolled and included only 20 patients from two centres. Outcomes were assessed at the last available visit rather than at a fixed study time point. Although all patients had at least 6 months of treatment, this approach limits direct comparison with clinical trials and may introduce time-window bias. Standardised follow-up lesion scores and nodule counts were not available, and baseline sleep scores were incomplete. Access to treatment depended on the patient's ability to pay for the medication, which may have introduced selection bias. The dose-escalation analysis was exploratory and underpowered for multivariable modelling. These limitations reflect some of the same gaps seen in the wider JAK inhibitor literature, particularly heterogeneity of outcomes and limited long-term safety data [17].

Conclusion

Upadacitinib was associated with marked itch improvement in this small real-world cohort of refractory prurigo nodularis. Starting at 15 mg and escalating to 30 mg only in inadequate responders provided a simple response-guided dosing framework and allowed 55% of patients to remain on the lower dose. Upadacitinib may offer a useful oral option when approved biologic therapy is not accessible, but larger controlled studies with standardised outcomes and longer safety follow-up are needed.

Declarations

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Author contributions Gürbüz Yıldırım and Burhan Engin conceived and designed the study. Bengüsu Yıldız collected the data. Gürbüz Yıldırım and Bengüsu Yıldız drafted the manuscript. Burhan Engin critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval This retrospective study was conducted in accordance with the Declaration of Helsinki. Upon written application in 2025, the Istanbul University-Cerrahpaşa Ethics Committee stated that formal ethics committee approval was not required for this retrospective study, as written informed consent had been obtained from all patients. Institutional permission to access and use patient records was obtained from both participating centres.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent to publish Not applicable; the manuscript contains no identifiable patient information or images.

Data availability De-identified data supporting the findings of this study are available from the corresponding author on reasonable request.

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