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REVIEW

JAK inhibitors for the treatment of palmoplantar pustulosis: a narrative review

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Abstract

Background: Palmoplantar pustulosis (PPP) is a chronic, relapsing skin condition characterized by sterile, pruritic pustules on erythematous, thickened skin of the palms and soles. It often causes painful fissures, leading to functional impairment and reduced quality of life. Due to its limited response to conventional therapies and biologic therapies, PPP remains a therapeutic challenge. Recent findings implicate both T helper 17 (T_H17)-mediated and T_H2-mediated inflammation, prompting interest in broader immunomodulatory treatments such as Janus kinase (JAK) inhibitors.

Methods: This narrative review evaluates current evidence on the efficacy and safety of JAK inhibitors in the treatment of PPP. Published studies involving tofacitinib, upadacitinib and baricitinib were identified and reviewed.

Results: Clinical improvements with JAK inhibitors have been reported, particularly in cases refractory to conventional systemic therapy. Findings include reductions in the Palmoplantar Pustulosis Area and Severity Index (PPPASI) and improvements in patient-reported quality of life, with a low incidence of adverse effects. An ongoing trial investigating deucravacitinib reflects growing interest in this drug class.

Conclusion: JAK inhibitors show promise as a novel therapeutic option for PPP, given their ability to modulate multiple inflammatory pathways. Although current evidence is limited to case series and reports, results are encouraging and warrant confirmation through well-designed clinical trials.

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Introduction

Palmoplantar pustulosis (PPP) is a chronic inflammatory skin disease characterized by recurrent eruptions of sterile pustules on erythematous, thickened skin of the palms and/or soles. These lesions frequently fissure, causing pain, bleeding and functional impairment. In severe cases, pustules may coalesce into extensive plaques affecting the entire palmoplantar surface, significantly compromising mobility and quality of life.[1–3] PPP may coexist with conditions such as psoriatic arthritis (PsA), pustulotic arthro-osteitis (PAO), and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome[2,4,5] as well as with psoriatic plaques in other body regions (14–61% of cases).[3,5,6] Nail changes, including onycholysis and crumbling, are reported in 30–76% of cases and may correlate with disease severity.[3,5–7] The disease predominantly affects middle-aged women and has been linked to smoking and chronic focal infections such as tonsillitis.[2,3]

PPP remains a therapeutic challenge as it often responds poorly to conventional psoriasis treatments and even biologic therapies. Topical corticosteroids, phototherapy and oral retinoids are commonly used for mild to moderate cases, though with limited long-term efficacy. Systemic agents, such as methotrexate and cyclosporine,

offer variable results and are frequently restricted by adverse effects. In more severe or refractory cases, targeted systemic therapies are considered. Histopathological studies have revealed elevated levels of tumour necrosis factor (TNF), IL-17, IL-22, IL-8, IL-1 and IL-36 in PPP pustules, identifying these cytokines as promising therapeutic targets. As a result, biologic agents, including TNF inhibitors (e.g. adalimumab, etanercept, infliximab), IL-23 inhibitors (e.g. guselkumab) and IL-17 inhibitors (e.g. secukinumab, ixekizumab, brodalumab, bimekizumab), have been used showing limited or variable benefit, with high rates of partial responses or non-response. Similarly, IL-36 inhibitors, such as spesolimab and imsidolimab, have been investigated, but neither met their primary endpoints in clinical trials.[1,2,6,8]

A recent systematic review highlighted guselkumab, brodalumab and apremilast (a phosphodiesterase 4 (PDE4) inhibitor) as treatment options with favourable short-term outcomes, though concerns persist regarding the durability of response. The review also highlighted Janus kinase (JAK) inhibitors (JAKis) as a promising therapeutic class given their capacity to modulate multiple immune pathways, including the T helper 2 (T_H2) axis, through simultaneous inhibition of various cytokine signals.[1]

This narrative review aims to assess current evidence on the efficacy and safety of JAKis in the treatment of PPP and to explore the role of the JAK–STAT signalling pathway in disease pathogenesis, supporting its potential as a novel therapeutic target.

Review

Pathogenesis of PPP

PPP results from a multi-factorial interplay between immune dysregulation, eccrine sweat gland dysfunction and genetic susceptibility. The acrosyringium, the intraepidermal portion of the sweat duct, appears to be the initial site of vesicle and pustule formation.[2,4] Early lesions are infiltrated by $CD8^+$ T cells, with neutrophilic recruitment later driven by upregulated cytokines such as IL-8, IL-17 and IL-36. IL-8 mediates neutrophil chemotaxis, whilst IL-36 promotes T_H17 differentiation and further IL-17 production, establishing a self-amplifying inflammatory loop. Complement activation enhances this process, ultimately leading to pustule formation and dermoepidermal inflammation.[2,4]

Genetic mutations, notably in *IL36RN* and *CARD14*, contribute to enhanced inflammatory signalling and earlier disease onset.[2,6,9] Smoking is a known environmental trigger, amplifying IL-36 and IL-17 pathways and increasing disease severity.[2,3,10] Although these mechanisms were initially considered central to PPP pathogenesis, therapeutic targeting of the T_H17–IL-36 axis has produced limited clinical responses, prompting the search for alternative or complementary immunological pathways.

Recent transcriptomic analyses comparing skin biopsies from patients with PPP, atopic dermatitis (AD) or psoriasis revealed a surprising upregulation of T_H2-related genes in PPP lesions.[11] Overall, the gene expression profile of PPP showed greater similarity to AD than to psoriasis. In contrast, T_H17 signatures, previously considered dominant in PPP, were less prominent than expected.[10,11]

Interestingly, a discrepancy was observed between systemic and local immune patterns: whilst T_H17 cells predominate in circulation, lesional skin revealed an increase in dual-positive T_H17/T_H2 cells. This suggests a possible conversion of T_H17 cells into T_H2 phenotypes upon skin migration, likely mediated by local cytokines such as IL-4 and IL-13.[11] This immune plasticity may underlie the limited efficacy of T_H17-specific therapies and highlights the significant contribution of the T_H2 pathway in PPP pathogenesis.[12,13]

The JAK–STAT pathway is a key intracellular signalling mechanism activated by various cytokines involved in PPP pathogenesis. It involves four JAK isoforms (JAK1, JAK2, JAK3 and TYK2), which, upon cytokine receptor engagement, phosphorylate STAT proteins that modulate gene expression.[14,15] Each JAK isoform pairs with specific cytokine receptors, forming heterodimers, or in the case of JAK2, homodimers, to mediate distinct immunological functions. JAK1/JAK3 regulates γ-chain cytokines (e.g. IL-2, IL-4, IL-13), supporting lymphocyte development and B cell function. JAK1/JAK2 and JAK1/TYK2 modulate pro-inflammatory and innate responses, whilst JAK2/TYK2 governs IL-12–IL-23 signalling, key to T_H1 and T_H17 differentiation. Dysregulation of this pathway has been linked to inflammatory and autoimmune diseases such as ulcerative colitis, atopic dermatitis and rheumatoid arthritis (RA).[14,15]

In PPP, both T_H17-associated and T_H2-associated cytokines, namely IL-4, IL-13, IL-17, IL-22 and IL-23, are thought to contribute to disease pathogenesis via activation of the JAK–STAT signalling cascade. This activation promotes keratinocyte dysfunction, recruitment of inflammatory cells and disruption of the skin barrier.[8,13] Consequently, therapeutic strategies targeting the JAK–STAT pathway may provide a more effective approach by concurrently inhibiting multiple cytokine signalling pathways implicated in both T_H17 and T_H2 immune responses.

These findings, along with shared immunological features between PPP and AD, support the rationale for exploring therapies effective in AD for use in PPP. JAKis, which simultaneously target multiple cytokine pathways, including T_H17-related and T_H2-related signalling, have emerged as particularly promising candidates.[12,13]

Current evidence on the use of JAK inhibitors in PPP

JAKis are small-molecule agents that selectively inhibit the activity of JAK enzymes, thereby disrupting cytokine-mediated inflammatory signalling pathways. Several JAKis have been approved for the treatment of chronic inflammatory and autoimmune conditions, including psoriasis, PsA, RA, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, AD and alopecia areata.[14,15] Emerging evidence has highlighted the therapeutic potential of JAKis in the management of PPP.[1,13] Amongst the agents with reported efficacy in PPP are tofacitinib, upadacitinib and baricitinib. Furthermore, deucravacitinib — a selective tyrosine kinase 2 (TYK2) inhibitor — has also demonstrated clinical benefit in this condition.

Tofacitinib

Tofacitinib is an oral JAKi that primarily targets JAK1 and JAK3, leading to the downregulation of multiple pro-inflammatory cytokines, particularly IFNγ, IL-6, IL-17A and IL-23, all of which are implicated in the pathogenesis of PPP.[1,14] Tofacitinib was the first JAKi to be used off-label for the treatment of PPP. Across the 10 identified articles, a total of 24 patients diagnosed with PPP were treated with tofacitinib (Table 1).

Xu et al.[16] reported a case series involving six patients with PPP refractory to topical agents and at least one systemic therapy. Participants received tofacitinib 5 mg twice daily for 12 weeks. Marked clinical improvement was observed: all patients achieved at least a 50% reduction in the Palmoplantar Pustulosis Area Severity Index (PPPASI) within 4 weeks, and three patients reached a reduction greater than 80%. By week 12, five individuals (83.3%) exhibited ≥80% improvement in PPPASI, and five achieved a Physician's Global Assessment for PPP (PPGA) score of 0 or 1. No adverse events were reported during treatment.

Similarly, Mössner et al.[17] described three cases of PPP resistant to multiple systemic therapies, successfully managed with tofacitinib 5 mg twice daily. Two patients received concomitant methotrexate. One patient's PPPASI decreased from 18.6 to 1.8 and another's from 15 to 2.3 after 12 weeks. A third patient with comorbid SAPHO syndrome demonstrated PPGA improvement from 3 to 1. No adverse events were reported.

Li et al.[18] assessed the therapeutic effect of tofacitinib in patients with SAPHO syndrome, including seven individuals with concomitant PPP. Following treatment with tofacitinib 5 mg twice daily for a median duration of 3.3 months, six patients exhibited clinical improvement in PPP, with three achieving complete resolution. Mild upper respiratory tract infections were the only adverse events reported, and none required hospitalization. Additionally, a separate case report described a patient with SAPHO syndrome and ankylosing spondylitis who experienced marked improvement in cutaneous manifestations within 1 month of initiating tofacitinib, alongside musculoskeletal symptom relief.[19]

In a recent case report by Fan et al.,[20] a 40-year-old patient with PPP refractory to topical corticosteroids and secukinumab exhibited substantial clinical improvement following 3 months of treatment with tofacitinib 5 mg twice daily. Complete clearance of lesions and resolution of pruritus were observed. This response was maintained throughout a 6-month follow-up period, without recurrence or adverse events.

Koga et al.[21] described the case of a 64-year-old Japanese woman with a 15-year history of PPP who initiated adalimumab for RA. One month after adalimumab initiation, the patient developed painful pustular lesions with erythema on the palms and soles. Adalimumab was discontinued and replaced by tofacitinib 10 mg twice daily, resulting in significant clinical improvement in both RA and PPP. Flow cytometry demonstrated a reduction in peripheral effector memory T_H1 and T_H17 cells after 12 weeks of therapy, suggesting that tofacitinib modulates T helper cell differentiation and supports its potential utility in PPP management.[21]

A case report described a female patient who developed PPP following the administration of adalimumab for Crohn's disease. After adalimumab discontinuation, multiple therapeutic strategies were attempted without success. Clinical remission of PPP was achieved after four doses of ustekinumab, though the response was not sustained beyond 9 months. Subsequent treatments, including reintroduction of ustekinumab, failed to maintain disease control. After approximately 8 years of refractory disease, initiation of tofacitinib 5 mg twice daily resulted in complete resolution of skin lesions, with no further flares. After 1 year of therapy, all other topical and systemic immunosuppressive treatments were successfully discontinued.[22]

Haynes et al.[23] reported a case of a woman with concomitant plaque psoriasis, PsA and PPP, who had experienced inadequate control of PPP despite multiple topical and systemic therapies over an 8-year period. Whilst her plaque

Table 1. Case reports and case series of tofacitinib in the treatment of PPP.

Author	Cases	Age/ Sex	Duration of PPP	Comorbidities	Previous treatments	Intervention	Therapeutic efficacy	Adverse reactions
Xu et al.[16]	6	Mean: 49.8/2F, 4M	Mean: 4.7 years	Obesity, T2DM, hyperlipidaemia, smoking, AD	Corticosteroids, phototherapy, MTX, cyclosporine, systemic retinoid	5 mg twice daily for 12 weeks	83.3% of patients achieved 80% reduction of PPPASI	No
Mössner et al.[17]	3	Mean: 55.7/2F, 1M	Mean: 12.7 years	SAPHO, psoriasis, PsA, ulcerative colitis, smoking	Acitretin, MTX, apremilast, TNFi, ADA, cyclosporine, IL-23 and IL-17 inhibitors	5 mg twice daily for 12 weeks	PPPASI reduction from 18.6 to 1.8 and from 15 to 2.3; PPGA reduction from 3 to 1	No
Li et al.[18]	7	Mean: 36.6/F	Mean: 4.9 years	SAPHO	MTX, TNFi and TwHF	5 mg twice daily during a mean follow up of 13 weeks	85.7% had improvement of cutaneous lesions (42.9% with complete resolution)	Upper respiratory tract infection
Yuan et al.[19]	1	36/M	3 months	SAPHO, ankylosing spondylitis	MTX, ADA	5 mg twice daily	Lesions improved after 4 weeks	No
Fan et al.[20]	1	40/M	8 years	Allergic conjunctivitis and rhinitis, asthma	Corticosteroids, secukinumab	5 mg twice daily	Complete resolution after 12 weeks, without recurrence	No
Koga et al.[21]	1	64/F	14 years	RA	None	10 mg twice daily	Lesions improved after 12 weeks	NA
Wang et al.[22]	1	47/F	10 years	Crohn's disease	Corticosteroids, cyclosporine, phototherapy, apremilast, tocilizumab, ustekinumab, MTX, guselkumab	5 mg twice daily	Complete resolution without flares	NA
Haynes et al.[23]	1	45/F	14 years	Obesity, psoriasis, PsA and smoking	MTX, phototherapy, corticosteroids, acitretin, ADA, cyclosporine, ustekinumab, guselkumab, secukinumab, apremilast	5 mg twice daily	Complete resolution after 2 weeks, without flares	No
Zhang et al.[24]	1	35/F	2 years	Nail lesions	Acitretin, ADA, secukinumab	5 mg twice daily	Significant improvement of symptoms	No
Gleeson et al.[13]	2	Mean: 54.5/F	NA	PsA, ulcerative colitis	NA	One patient did 10 mg twice daily, then 10 mg daily; the other did 10 mg daily	One patient achieved complete resolution of cutaneous lesions; the other achieved almost clear resolution of the lesions	NA

AD, atopic dermatitis; ADA, adalimumab; F, female; M, male; MTX, methotrexate; NA, not available; PPGA, Physician's Global Assessment for PPP; PPP, palmoplantar pustulosis; PPPASI, Palmoplantar Pustulosis Area and Severity Index; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SAPHO, synovitis, acne, pustulosis, hyperostosis and osteitis; T2DM, type 2 diabetes mellitus; TNFi, tumour necrosis factor inhibitor; TwHF, *Tripterygium wilfordii* Hook F.

psoriasis and arthritis had shown improvement, the palmoplantar component remained refractory. Treatment with tofacitinib 5 mg twice daily led to complete clearance of PPP lesions and amelioration of joint symptoms within 2 weeks. The patient maintained remission for at least 3 months, without any reported adverse events.

Zhang et al.[24] reported the case of a 35-year-old woman with PPP who developed alopecia areata during treatment with secukinumab, leading to discontinuation of the biologic. Although secukinumab had resulted in mild improvement of both PPP and associated nail changes, the switch to tofacitinib yielded markedly superior outcomes, with near-complete resolution of cutaneous lesions after 8 months of treatment.[24]

In a case series by Gleeson et al.,[13] two patients with severe, treatment-refractory PPP were successfully managed with tofacitinib. Both had previously received multiple systemic and biologic agents, either without clinical efficacy or with limiting adverse events. Initiation of tofacitinib resulted in a rapid clinical response, with one patient achieving complete clearance and the other near-complete resolution of lesions within 1–2 weeks. These findings highlight the rapid onset and sustained efficacy of this JAKi in PPP management.[13]

Upadacitinib

Upadacitinib is a selective JAK1 inhibitor that exhibits minimal activity on other JAK isoforms, potentially reducing off-target effects. It has been shown to inhibit the production of key pro-inflammatory cytokines, including IL-2, IL-6, IL-17, IL-36 and IFNγ, thereby modulating T helper cell differentiation and limiting inflammatory cell infiltration.[14] A total of eight articles discussing the use of upadacitinib to treat 42 patients diagnosed with PPP were identified (Table 2).

Mohr et al.[25] described the first reported case involving a 68-year-old female smoker with a 7-year history of PPP. The patient had previously been treated with topical therapies, psoralen with ultraviolet A, guselkumab and apremilast, all of which proved ineffective or were discontinued due to adverse effects. Consequently, oral upadacitinib 15 mg once daily was initiated, considering age-related safety concerns with tofacitinib in patients over 65 years. After 15 weeks of therapy, the patient exhibited a marked clinical response: her PPPASI score decreased from 17.7 to 4.2, pruritus intensity declined from 8/10 to 5/10, and pain resolved completely (from 7/10 to 0), based on numerical rating scales. Additionally, topical mometasone furoate 0.1% ointment was tapered from twice daily to three times weekly. The only reported adverse event was mild perioral dermatitis, attributed to facial mask usage rather than the systemic agent.

A retrospective study conducted in China evaluated the efficacy and safety of oral upadacitinib (15 mg once daily) in 28 patients with PPP over a 12-week period. All patients had previously failed or were intolerant to other systemic therapies, including acitretin, *Tripterygium wilfordii* Hook F, cyclosporine, methotrexate, adalimumab and secukinumab. Treatment with upadacitinib resulted in a significant reduction in disease severity, with mean PPPASI scores decreasing from 13.86±2.76 to 5.56±1.08. Notably, 18 patients achieved PPPASI90, and 20 patients (71.4%) reached a PGA score of 0 or 1. Furthermore, substantial improvements in quality of life were observed, with DLQI scores decreasing from 12.55±4.56 to 2.03±1.13. The treatment was well tolerated; no serious adverse events occurred. Mild adverse effects included acneiform rash, transient elevations in liver transaminases and slight increases in serum creatinine, all of which resolved without treatment discontinuation.[26]

The most recent case report described a 15-year-old female adolescent diagnosed with PPP at the age of six, who was refractory to topical corticosteroids. The severity of PPP led to joint mobility limitations that interfered with routine activities such as writing and dressing, negatively impacting the patient's self-esteem and social interactions. Oral upadacitinib (15 mg once daily) was initiated, and after 3 months of treatment, the patient exhibited marked clinical improvement, with a reduction in PPPASI score from 18.4 to 2.6, restoration of joint mobility, absence of new pustules, and no adverse events reported.[27]

A case series by Rahbar Kooybaran et al.[28] described five patients with PPP who exhibited substantial clinical improvement following treatment with upadacitinib. These patients had previously failed an average of 5.2 systemic therapies, primarily due to lack of efficacy or adverse events. One patient initially responded well to tofacitinib, achieving a PPPASI reduction from 18.6 to 1.8 over 12 weeks, but was switched to upadacitinib out of concern for potential side-effects, with clinical benefit maintained. Amongst the remaining four patients, three experienced marked responses, with mean PPPASI scores decreasing from 11.5±7.25 to 2.13±1.73. The fourth patient had a moderate response, with a PPPASI reduction from 9.6 to 6.0 and a PPGA improvement from 3 to 2. In addition, comorbidities such as PsA, nail psoriasis and urticaria showed concurrent improvement. Adverse events were limited to two mild infections (bronchitis and cystitis) and transient headaches.

Another study reported two patients with PPP associated with PsA who were initially treated with IL-17 inhibitors (secukinumab or ixekizumab) based on the hypothesis of shared immunopathogenic pathways. Whilst joint symp-

Table 2. Case reports and case series of upadacitinib the treatment of PPP.

Author	Cases	Age/Sex	Duration of PPP	Comorbidities	Previous treatments	Intervention	Therapeutic efficacy	Adverse reactions
Mohr et al.[25]	1	68/F	7 years	Psoriasis, hypothyroidism, hypercholesterolaemia, depression, smoking	Phototherapy, MTX, acitretin, alitretinoin, guselkumab, apremilast	15 mg daily	PPPASI reduction from 17.7 to 4.2; improvement of pruritus and pain	No
Du et al.[26]	28	Mean: 36.3/18F, 10M	5 months to 6 years	SAPHO, smoking	Acitretin, TwHF, cyclosporine, MTX, ADA, secukinumab	15 mg daily for 12 weeks	PPPASI reduction (from 13.86±2.76 to 5.56±1.08); 71.4% achieved PGA 0/1; DLQI reduction (from 12.55±4.56 to 2.03±1.13)	Acneiform rash, transient increase of transaminases and creatinine
Gu et al.[27]	1	15/M	11 years	NA	Topical corticosteroids	15 mg daily	PPPASI reduction from 18.4 to 2.6	No
Rahbar Kooybaran et al.[28]	5	Mean: 61.4/4F, 1M	Mean: 9.9 years	Psoriasis, PsA, T2DM, HBP, hyperthyroidism, alopecia areata smoking	MTX, acitretin, apremilast, guselkumab, tofacitinib	15 mg daily	PPPASI and PPGA reduction; sustained response post-switch from tofacitinib	Mild infections (bronchitis, cystitis), headaches
Zhang et al.[29]	2	Mean: 50.5/F	Mean: 1.3 years	PsA, hyperthyroidism, smoking, anxiety	Corticosteroids, secukinumab, ixekizumab	15 mg once daily for 20 weeks	PPPASI reduction from 14.1 to 0.8 and from 21.9 to 0.6; DLQI reduction; complete relief of pruritus and pain	No
Gaiani et al.[30]	3	Mean: 49.7/F	Mean: 19 years	Psoriasis, PsA, osteopenia, Hashimoto's thyroiditis, vitiligo, smoking	Corticosteroids, acitretin, cyclosporine, MTX, apremilast, secukinumab, ustekinumab, ixekizumab, brodalumab	15 mg once daily	Excellent response with near-complete resolution (PPGA 0/1); improvement of pruritus	NA
Taniguchi et al.[31]	1	58/F	10 years	PAO	IL-23 inhibitor	NA	Significant improvement of skin and musculoskeletal symptoms	NA
Hu et al.[32]	1	55/M	1 year	Severe pruritus	Secukinumab	15 mg daily for 12 weeks, then 15 mg every other day for maintenance	Near complete resolution of skin lesions; improved pruritus and QoL	No

ADA, adalimumab; DLQI, Dermatology Life Quality Index; F, female; HBP, high blood pressure; M, male; MTX, methotrexate; NA, not available; PAO, pustulotic arthro-osteitis; PGA, Physician's Global Assessment; PPGA, Physician's Global Assessment for PPP; PPP, palmoplantar pustulosis; PPPASI, Palmoplantar Pustulosis Area and Severity Index; PsA, psoriatic arthritis; QoL, quality of life; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; T2DM, type 2 diabetes mellitus; TwHF, *Tripterygium wilfordii* Hook F.

toms improved, the cutaneous manifestations of PPP remained unresponsive. Subsequent treatment with upadacitinib for 20 weeks resulted in substantial improvement, with PPPASI scores decreasing from 14.1 to 0.8 and from 21.9 to 0.6, respectively. Both patients also reported resolution of pruritus and pain, as well as improved quality of life, as reflected by reduced DLQI scores. These findings suggest that, though IL-17 plays a role in PPP, broader cytokine blockade may yield superior therapeutic outcomes.[29] In a separate report, Gaiani et al.[30] described three additional cases of PPP refractory to multiple systemic therapies, all of which demonstrated excellent clinical responses to upadacitinib, characterized by near-complete clearance of skin lesions and significant relief of pruritus.

Taniguchi et al.[31] described a 58-year-old female patient with a history of PPP and PAO, who had previously been treated with an IL-23 inhibitor. During a clinical flare, she was initiated on upadacitinib therapy. Given the significant improvement in both cutaneous and musculoskeletal symptoms, the authors emphasized the potential utility of JAKis in the management of both PPP and PAO.

Similarly, Hu et al.[32] described a patient with PPP and severe pruritus who relapsed following secukinumab treatment. The patient was subsequently started on oral upadacitinib 15 mg daily. After 12 weeks, near-complete resolution of cutaneous lesions and significant relief from pruritus were observed, accompanied by improved quality of life. Maintenance therapy with alternate-day dosing of upadacitinib sustained clinical stability without relapse.

Baricitinib

Baricitinib is an oral JAK inhibitor that selectively targets JAK1 and JAK2, whilst also exerting moderate inhibitory activity against TYK2. This results in the suppression of downstream signalling of multiple pro-inflammatory cytokines, including IL-6, IL-12 and IL-23.[1,14] Regarding its use in PPP, three published articles were identified, encompassing a total of six patients treated with baricitinib (Table 3).

A case report by Imafuku et al.[33] described a 64-year-old female patient with RA who developed PPP following 2 years of treatment with golimumab, an anti TNF monoclonal antibody. Upon discontinuation of golimumab, the patient was treated with etretinate, topical calcipotriol/betamethasone dipropionate, and 308-nm ultraviolet light, but no significant clinical improvement was observed. The addition of apremilast also failed to yield satisfactory outcomes. Due to the recurrence of RA symptoms and persistent PPP, baricitinib therapy was initiated, resulting in complete clearance of PPP lesions within 4 weeks of treatment initiation.[33]

A case series involving five patients with SAPHO syndrome, four of whom presented with concomitant PPP and nail involvement, reported clinical outcomes following treatment with oral baricitinib at 2 mg daily for 12 weeks. These individuals had previously received non-steroidal anti-inflammatory drugs, TNF inhibitors and other systemic therapies, with limited efficacy. Following baricitinib administration, improvements were noted in cutaneous lesions, inflammatory markers and pain severity, with no adverse events reported.[34]

In another case report by Li et al.,[35] a 20-year-old male patient with concomitant PPP and AD was treated with oral baricitinib at a dose of 4 mg daily. Complete clearance of cutaneous lesions was achieved within the first 4 weeks of the 3-month treatment course. However, relapse occurred upon treatment discontinuation. Baricitinib was subsequently reinitiated at the same dose for an additional 2 months, leading to complete remission once again. The dose was then gradually tapered to 2 mg daily and later to 2 mg on alternate days, successfully maintaining disease control without recurrence of lesions. This report supports a shared immunopathogenic mechanism between AD and PPP, possibly involving a dysregulated T_H1/T_H2 balance. By inhibiting JAK1 and JAK2, baricitinib downregulates cytokine production and modulates T helper cell differentiation, contributing to clinical improvement in both conditions.[35]

Deucravacitinib

Deucravacitinib is an oral, selective TYK2 inhibitor approved for the treatment of moderate-to-severe plaque psoriasis. It exerts its therapeutic effects by selectively inhibiting TYK2-mediated signalling downstream of cytokines such as IL-12, IL-23 and type I interferons, key drivers in the pathogenesis of psoriasis and various other immune-mediated disorders. Owing to its targeted mechanism of action and TYK2 specificity, deucravacitinib holds promise as a potential therapeutic option in PPP, with the added advantage of a potentially more favourable safety profile compared to broader JAKis.[1,14]

A prospective, single-arm, open-label, phase IV clinical trial (NCT05710185) is currently being conducted to evaluate the efficacy and safety of deucravacitinib in patients with moderate to severe PPP, as defined by a PPPASI score exceeding 12. Eligible participants are those who have shown an inadequate response to topical therapy and are candidates for systemic treatment or phototherapy. All enrolled participants will receive 6 mg of deucravacitinib daily for 24 weeks, with clinical assessments performed every 4 weeks. The primary outcomes focus on improvements in PPPASI, whilst secondary endpoints include changes in the Dermatology Life Quality Index (DLQI), achievement of PGA score of 1 or 0, as well

Table 3. Case reports and case series of baricitinib in the treatment of PPP.

Author	Cases	Age/ Sex	Duration of PPP	Comorbidities	Previous treatments	Intervention	Therapeutic efficacy	Adverse reactions
Imafuku et al.[33]	1	64/F	NA	RA	Corticosteroids, phototherapy, apremilast	NA	Complete resolution after 4 weeks	NA
Liu et al.[34]	4	Mean: 49.8/3F, 1M	NA	SAPHO, nail lesions	NSAIDs, MTX, TNFi, TwFH	2 mg daily for 12 weeks	Improvement of cutaneous lesions	No
Li et al.[35]	1	20/M	2 years	AD	Corticosteroids, antihistamines	4 mg daily for 2 months, then 2 mg daily for 2 months and 2 mg every other day for another 2 months	Complete resolution after 4 weeks; relapse after discontinuation; effective reintroduction, with complete resolution	NA

AD, atopic dermatitis; F, female; M, male; MTX, methotrexate; NA, not available; NSAIDs, non-steroidal anti-inflammatory drugs; PPP, palmoplantar pustulosis; RA, rheumatoid arthritis; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; TNFi, tumour necrosis factor inhibitor; TwHF, *Tripterygium wilfordii* Hook F.

as pain and pruritus scores. The trial is currently in the recruitment phase, with an estimated enrolment of 18 participants. It commenced in July 2023, with the estimated primary completion date set for December 2025.[36]

Despite the absence of published case reports specifically involving deucravacitinib, the launch of a phase IV trial reflects growing scientific interest in JAKis as a potential therapeutic strategy for PPP.

Discussion

PPP presents a significant therapeutic challenge due to its chronic nature, frequent resistance to standard treatments, and the complex yet not fully understood pathogenesis. Current therapeutic strategies, comprising topical corticosteroids, retinoids, phototherapy and systemic immunosuppressants, often yield sub-optimal or short-lived responses. Whilst the advent of biologic agents and small-molecule therapies has expanded the therapeutic arsenal, no universally accepted standard of care has yet been established. The growing body of literature reviewed in this article underscores the promising role of JAKis in the treatment of PPP.[1,2]

JAKis offer a multi-targeted approach by modulating several cytokine-driven pathways simultaneously, including the T_H17 and T_H2 pathways, both implicated in PPP pathophysiology. This broad targeting is especially pertinent considering the recent immunological and transcriptomic studies that have identified a mixed T_H17/T_H2 profile in PPP lesions. Such findings may help to explain the sub-optimal efficacy of therapeutic approaches that target individual T helper cell pathways in isolation.[10–12]

Amongst the JAKis reviewed, tofacitinib — a JAK1/JAK3 inhibitor — has demonstrated consistent clinical efficacy across multiple case series and reports, with several patients achieving near-complete or complete remission despite prior treatment failures. Its ability to suppress both T_H17-associated cytokines, such as IL-17 and IL-23, and T_H2-related cytokines, including IL-4 and IL-13, may underlie its therapeutic potential.[13,16–24]

Upadacitinib, a selective JAK1 inhibitor, has also shown promising clinical outcomes across a broader patient population, with several studies documenting marked reductions in PPPASI scores and notable improvements in quality of life. Its sustained efficacy in elderly individuals and those with longstanding, treatment-refractory disease highlights its therapeutic potential. Moreover, its JAK1 selectivity may contribute to a more favourable safety profile, with fewer off-target effects and a reduced incidence of adverse events.[25–32]

Baricitinib, a JAK1/JAK2 inhibitor, though less extensively studied, has also yielded favourable outcomes, with several case reports describing rapid clinical improvement, particularly in patients with coexisting immune-mediated

conditions such as RA or AD.[33–35] These findings further support the hypothesis that PPP pathogenesis involves dysregulation of both T_H17-mediated and T_H2-mediated immune pathways.

Finally, deucravacitinib, a selective TYK2 inhibitor currently being investigated in clinical trials for PPP, has not yet published any results. Unlike JAKis that broadly modulate multiple cytokine pathways, deucravacitinib exerts its effect primarily by selectively inhibiting TYK2 -mediated signalling, which is central to the activity of IL-23, IL-12 and type I interferons. Whilst this mechanism aligns well with the T_H17-driven component of PPP pathophysiology, TYK2 inhibition does not directly suppress T_H2 cytokines such as IL-4 and IL-13. Given that recent transcriptomic analyses suggest a mixed T_H17/T_H2 immune profile in PPP lesions, it will be particularly interesting to assess whether deucravacitinib can achieve comparable clinical efficacy to JAKis with broader immunomodulatory activity.

From a mechanistic perspective, the rationale for JAK inhibition in PPP is compelling. The JAK–STAT signalling pathway transduces the effects of multiple pro-inflammatory cytokines involved in keratinocyte hyperactivation, epidermal barrier disruption and immune cell recruitment — hallmarks of PPP pathophysiology. By targeting this pathway, JAKis exert broad immunomodulatory effects, potentially offering more durable disease control than therapies that selectively block individual cytokines.

However, whilst initial results are promising, important limitations must be acknowledged. Most of the current evidence comes from case reports and small retrospective series, lacking the precision of randomized controlled clinical trials. Additionally, long-term safety data in this specific patient population are limited. Given the immunosuppressive potential of JAKis, concerns regarding risk of infections, thromboembolic events and malignancy remain relevant, particularly with long-term use. Therefore, further prospective studies with larger sample sizes and longer follow-up periods are needed to better characterize the long-term efficacy and safety profile of JAKis in PPP.

Conclusion

PPP is a chronic and refractory skin disorder with a significant impact on patient's quality of life and limited response to conventional therapies. Its complex pathogenesis, involving a dysregulated interplay between T_H17 and T_H2 immune responses, presents substantial challenges to therapeutic management. JAKis offer a novel and promising therapeutic avenue by targeting multiple pro-inflammatory cytokines implicated in both immune axes.

Accumulating evidence suggests that JAKis, such as tofacitinib, upadacitinib and baricitinib, can induce meaningful clinical responses, even in refractory cases where conventional and biologic therapies have failed. Their broad immunomodulatory effects, together with the overall favourable safety profile observed in the available literature, support their potential as valuable additions to the therapeutic armamentarium for PPP. Nevertheless, most data are derived from case reports and small-scale studies, highlighting the urgent need for randomized controlled trials to confirm efficacy, assess long-term safety and determine their optimal positioning within existing treatment algorithms.

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