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JAKi for the treatment of Palmoplantar Pustulosis: A narrative review

Beatriz Mendes e Gomes Henriques dos Santos

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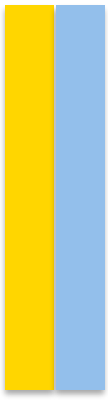

JAKi for the treatment of Palmoplantar Pustulosis: A narrative review

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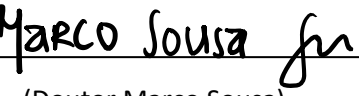

(Doutor Marco Sousa)

Junho 2025

Declaração de Integridade

Eu, Beatriz Mendes e Gomes Henriques dos Santos, estudante do Mestrado Integrado em Medicina, com o número mecanográfico 201908607, declaro assumir toda a responsabilidade pelo conteúdo desta revisão narrativa, intitulada "JAKi for the treatment of Palmoplantar Pustulosis: A narrative review", apresentada ao Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, no âmbito da unidade curricular Dissertação/Projeto/Estágio.

Mais declaro que este documento é um trabalho original e que toda e qualquer informação ou expressão, por mim utilizada, está referenciada na bibliografia, segundo os critérios estabelecidos, salvaguardando sempre os Direitos de Autor, à exceção das minhas opiniões pessoais.

Porto, 2 de junho de 2025

Dedication

I dedicate this thesis to my mother, for her unconditional love, for the strength she has always shown, for being an example, and for never letting me give up, always encouraging me, no matter the circumstances. We did it!

To my family, especially my aunt Sandra, thank you for being a constant source of love and support.

And to my friends: to those who have been with me since the very first day in Aveiro and who will be in my life forever; to those who, even from afar, are always close; and to those who welcomed me into this *mui nobre Invicta* and made it feel like home. Thank you for all the silly conversations, laughter, study sessions, and epic stories throughout this long academic journey.

Each one of you, in your own way, helped me get here, and it was so much better because of that!

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I also thank my co-supervisor, Doctor Marco Sousa, for the valuable suggestions and continuous support.

Resumo

A pustulose palmoplantar é uma doença dermatológica crónica caracterizada pelo aparecimento de pústulas estéreis e pruriginosas sobre uma pele eritematosa e espessada, e que atinge as palmas das mãos e plantas dos pés. Pode originar fissuras dolorosas, comprometendo significativamente a realização de atividades quotidianas e a qualidade de vida dos doentes. O seu tratamento representa um desafio clínico, devido à natureza recorrente da doença e à resposta limitada às terapêuticas convencionais.

Embora a fisiopatologia da pustulose palmoplantar não esteja inteiramente esclarecida, estudos recentes apontam para o papel preponderante das vias Th17, associada à psoríase, e Th2, característica da dermatite atópica. Este conhecimento tem levado a um afastamento da perspetiva tradicional que considera a pustulose palmoplantar como um subtipo de psoríase, e à exploração de terapias com mecanismos de ação mais amplos, como os inibidores da JAK.

Esta revisão bibliográfica teve como objetivo avaliar a evidência científica disponível sobre a eficácia e segurança dos inibidores da JAK no tratamento da pustulose palmoplantar. Foram identificados estudos que analisaram a utilização de fármacos como o tofacitinib, upadacitinib, baricitinib.

Foram observadas melhorias consistentes com a utilização destes fármacos na pustulose palmoplantar, especialmente em casos refratários a outros tratamentos sistémicos. Os dados demonstraram reduções significativas no PPPASI e melhorias na qualidade de vida, juntamente com uma incidência reduzida de efeitos adversos. Adicionalmente, destaca-se o ensaio clínico atualmente em curso com o deucravacitinib, que reforça o interesse emergente nesta classe terapêutica.

Os inibidores da JAK configuram, assim, uma promissora abordagem terapêutica para a pustulose palmoplantar, pela sua capacidade de modular múltiplas vias inflamatórias. Apesar da evidência atual se basear maioritariamente em *case reports* e *case series*, os resultados são encorajadores, sendo fundamental a realização de ensaios clínicos robustos que confirmem a sua eficácia e segurança a longo prazo.

Palavras-Chave: Pustulose Palmoplantar, JAK-STAT, inibidores da JAK, Tofacitinib, Baricitinib, Upadacitinib, Deucravacitinib

Abstract

Palmoplantar pustulosis is a chronic dermatological condition characterized by the presence of sterile, pruritic pustules on erythematous and thickened skin, affecting the palms of the hands and soles of the feet. It may lead to painful fissures, significantly impairing the performance of daily activities and severely impacting patients' quality of life. Treatment poses a clinical challenge due to the recurrent nature of the disease and its limited response to conventional therapies.

Although the pathophysiology of palmoplantar pustulosis is not yet fully understood, recent studies suggest a prominent role of both the Th17 pathway, associated with psoriasis, and the Th2 pathway, characteristic of atopic dermatitis. This emerging understanding has led to a shift away from the traditional view of palmoplantar pustulosis as a psoriasis subtype and towards the exploration of therapies with broader mechanisms of action, such as JAK inhibitors.

This literature review aims to evaluate the current scientific evidence regarding the efficacy and safety of JAK inhibitors in the treatment of palmoplantar pustulosis. Studies investigating the use of drugs such as tofacitinib, upadacitinib, and baricitinib were identified.

Consistent improvements were observed with the use of these drugs in palmoplantar pustulosis, particularly in cases refractory to other systemic treatments. Data demonstrated significant reductions in the PPPASI score and improvements in quality of life, alongside a low incidence of adverse effects. Furthermore, an ongoing clinical trial involving deucravacitinib highlights the growing interest in this therapeutic class.

JAK inhibitors thus represent a promising therapeutic approach for palmoplantar pustulosis due to their ability to modulate multiple inflammatory pathways. Although the current evidence is largely based on case reports and case series, the results are encouraging. Well-designed clinical trials are essential to confirm their long-term efficacy and safety.

Keywords: Palmoplantar Pustulosis, JAK-STAT, JAK inhibitors, Tofacitinib, Baricitinib, Upadacitinib, Deucravacitinib

List of Abbreviations

AD	Atopic Dermatitis
ADA	Adalimumab
CARD14	Caspase Recruitment Domain-containing Protein 14 gene
CCR3	C-C Chemokine Receptor Type 3
CD8	Cluster of Differentiation- 8
CXCR4	C-X-C Chemokine Receptor Type 4
DLQI	Dermatology Life Quality Index
DMARD	Disease-Modifying Antirheumatic Drug
F	Female
HBP	High Blood Pressure
IFN- α	Interferon alfa
IFN- γ	Interferon gama
IL	Interleukin
IL36RN	IL-36 Receptor Antagonist gene
JAK	Janus Kinase
JAKi	Janus Kinase Inhibitor
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription signaling pathway
M	Male
MCP-4	Monocyte Chemoattractant Protein-4
MTX	Methotrexate
NA	Not Available
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PAO	Pustulotic Arthro-Osteitis
PDE4	Phosphodiesterase-4
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
PUVA	Psoralen and Ultraviolet A therapy
QoL	Quality of Life
RA	Rheumatoid Arthritis
SAPHO	Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis
STAT	Signal Transducer and Activator of Transcription
T2DM	Type 2 diabetes *mellitus*
Th1	Type 1 T helper cells
Th2	Type 2 T helper cells
Th17	Type 17 T helper cells
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor inhibitor
TwHF	*Tripterygium wilfordii* Hook F
TYK2	Tyrosine Kinase 2

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Introduction

Palmoplantar pustulosis (PPP) is a chronic inflammatory skin disorder characterized by recurring eruptions of scattered clusters of sterile pustules on the palms and/or soles, often accompanied by erythematous, thickened skin lesions that can crack causing pain and bleeding. In severe cases, the clusters can merge, forming large patches that involve the whole palmoplantar area.[1–3] Additionally, PPP can also be associated with other disorders such as psoriatic arthritis (PsA), pustulotic arthro-osteitis (PAO) and Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis (SAPHO) syndrome.[2,4,5] It can also coexist with psoriatic plaques in other areas of the body, which are present in 14% to 61% of affected individuals.[3,5,6] Nail involvement, particularly onycholysis and crumbling, occurs in 30% -76% of cases, with some correlation between nail changes and disease severity.[3,5–7]

Epidemiologic data is limited and prevalence rates vary across studies, with estimates of 0.050% in Sweden, 0.051% in Korea, 0.091% in Germany and 0.12% in Japan.[3] PPP is more common in women, which make up 58% to 94% of cases, and it typically appears between the fourth and fifth decades of life.[2,3] PPP is also commonly associated with smoking and focal infections, such as tonsilitis.[3]

This disease significantly impacts patients' quality of life (QoL) as the associated pain and bleeding of fissures can impair mobility, limiting the ability to walk and exercise, or even work if the dominant hand is affected. Furthermore, associated complications such as subcutaneous infections (erysipelas and cellulitis) may occur and may require hospitalization.[1,3,5]

This condition has proven to be a therapeutic challenge, as it often exhibits resistance to commonly used treatments for psoriasis. Furthermore, the incomplete understanding of its pathophysiology hinders the development of effective targeted therapeutic strategies.

Although various treatment modalities are currently available, most of them yield insufficient responses, making it difficult to establish a gold-standard therapy. The treatment of mild to moderate cases typically involves high-potency topical corticosteroids, phototherapy, or oral retinoids, such as acitretin. However, these approaches are often insufficient for long-term disease control. Other systemic treatments, such as methotrexate and cyclosporine, have been used with variable success but they are often associated with higher toxicity and more complex adverse effects. More targeted systemic therapies are primarily used in severe and refractory cases. Studies have shown that pustules characteristic of PPP exhibit elevated levels of tumor necrosis factor (TNF), interleukin (IL)-17, IL-22, IL-8, IL-1 and IL-36, making them promising therapeutic targets. Consequently, biologic agents can be utilized, including TNF-α inhibitors (e.g., adalimumab, etanercept, infliximab), IL-23 inhibitors (e.g., guselkumab), IL-17 inhibitors (e.g., secukinumab, ixekizumab, brodalumab, and bimekizumab), and IL-36 inhibitors (e.g., spesolimab and

imsidolimab). Additionally, the small-molecule drug apremilast, a phosphodiesterase-4 (PDE4) inhibitor, is also an available treatment option.[1,2,6,8]

A recent systematic review evaluated the efficacy of current therapeutic approaches for the management of PPP and reported that guselkumab, brodalumab and apremilast demonstrated satisfactory outcomes, with favorable safety profiles; however their long-term efficacy remains limited.[1] The review also highlighted Janus kinase (JAK) inhibitors as a highly promising therapeutic option, given their ability to modulate multiple immune pathways, including the type 2 T helper cells (Th2) pathway, thereby simultaneously inhibiting signaling from various cytokines.[1] For this reason, the focus of this thesis is to elucidate the potential of JAK inibithors (JAKi) as a first-line therapy for this condition.

Objectives

The aim of this literature review is to evaluate the available scientific evidence regarding the efficacy and safety of JAKis as a therapeutic option for PPP. Furthermore, this work seeks to deepen the understanding of the role of the JAK/signal transducers and activators of transcription (STAT) signaling pathway in the pathogenesis of the disease, thereby contextualizing its potential as a therapeutic target.

Methods

A thorough literature search was performed across multiple databases, including Pubmed, ScienceDirect, Google Scholar, Scopus, and ClinicalTrials.gov using the following terms: “Palmoplantar Pustulosis”, “JAK-STAT”, “JAK inhibitors”, “Tofacitinib”, “Baricitinib”, “Upadacitinib”, “Deucravacitinib”. These terms were searched alone or in combination.

The selection criteria included original and review articles, clinical trials, case reports and case series published in English, in the last 10 years, with a particular focus on the application of JAKis for PPP treatment. The references within the selected articles were examined to find additional relevant studies. Twenty articles and a single clinical trial were identified.

Physiopathology

PPP seems to be driven by immune dysregulation, eccrine sweat gland dysfunction, and genetic susceptibility. The acrosyringium (intra-epidermal sweat duct) appears to be the primary site of pustule formation.[2,4] Dysfunction of the eccrine sweat glands and sweat secretion trigger the

development of an initial vesicle at this site, which initially contains cluster of differentiation- 8 (CD8) positive mononuclear cells with minimal neutrophils. As inflammation progresses, the upregulation of multiple pro-inflammatory cytokines, particularly IL-17, IL-36, and IL-8, drives the recruitment of polymorphonuclear cells. Among these, IL-8 plays a key role in attracting neutrophils, which infiltrate the vesicle, leading to pustule formation. As the lesion expands and reaches the granular layer of the epidermis, complement activation occurs, further amplifying neutrophil recruitment. Simultaneously, IL-36 seems to activate dendritic cells, promoting T helper 17 cells (Th17) differentiation and IL-17 production, which in turn amplifies IL-36 expression, creating a self-perpetuating inflammatory loop. The combined effects of IL-8, complement activation, IL-17, IL-23, IL-36, and other inflammatory mediators lead to microabscess formation, epidermal desquamation, and inflammatory infiltration in the dermis.[2,4]

Genetic factors, such as mutations in the IL-36 receptor antagonist gene (IL36RN) and caspase recruitment domain-containing protein 14 gene (CARD14), contribute to disease susceptibility by amplifying inflammatory pathways.[2,9] For example, IL36RN mutations appear to be associated with an earlier onset of the disease.[6,9] Additionally, environmental triggers, particularly smoking, exacerbate the condition by stimulating IL-36 and IL-17 signaling, further increasing disease severity.[2,3,10]

Even though this mechanism was initially considered the keystone of PPP pathophysiology, targeted therapies have not yielded the expected outcomes. This has led to the hypothesis that additional factors may contribute to the disease development.

A study compared genetic signatures in skin biopsies from patients with PPP, atopic dermatitis (AD), and plaque psoriasis.[11] In the skin samples of PPP patients, an upregulation of genes involved in the activation of the Th2 pathway was observed. Notably, there was increased expression of genes encoding the IL-4 receptor and the monocyte chemoattractant protein-4 (MCP-4), which activates the C-C chemokine receptor type 3 (CCR3), expressed on Th2 cells, and C-X-C chemokine receptor type 4 (CXCR4), present on the surface of Th2 cells and eosinophils. Additionally, the genetic signature of PPP biopsies showed a significant overlap with skin samples of AD patients. On the contrary, the Th17 signature, that was previously considered predominant in PPP and a key factor in its classification as a subtype of psoriasis, was less evident than expected.[10,11]

Furthermore, the study revealed a discrepancy between immune patterns observed in tissues and those in circulation: in circulation, Th17 cells predominate, whereas, in the skin, there is an increase in dual-positive Th17/Th2 cells. These findings suggest that upon migration to the skin, Th17 lymphocytes undergo partial conversion into Th2 cells, a process induced by the complex inflammatory environment and the presence of cytokines such as IL-4 and IL-13. This cellular

plasticity may explain the limited efficacy of therapies exclusively targeting the Th17 pathway, as the Th2 pathway also plays a significant role in the pathophysiology of PPP. [11]

The significance of the Th2 pathway in both AD and PPP, along with the overlap in their genetic signatures, suggests the potential applicability of AD therapies for the treatment of PPP.[12,13] Therefore, JAKis present a promising therapeutic approach.

JAK-STAT pathway in PPP

The JAK-STAT pathway is an intracellular signaling cascade responsible for mediating the effects of various cytokines and growth factors. This pathway is orchestrated by a family of non-receptor tyrosine kinases: JAK1, JAK2, JAK3, and Tyrosine Kinase 2 (TYK2). Upon cytokine binding to its receptor, JAKs become activated and phosphorylate STAT proteins, which then dimerize and translocate into the nucleus to regulate gene transcription. Several cytokines, such as IL-6, IL-17, IL-20, IL-22, IL-23, and interferon-γ (IFN-γ), signal through the JAK-STAT pathway.[14,15]

The four JAK subtypes can pair with cytokine receptors to form heterodimers, but only JAK2 forms homodimers. The JAK1/JAK3 heterodimer facilitates signaling through the common γ chain cytokines, including IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, and IL-21, which are crucial for regulating lymphocyte proliferation, differentiation, and homeostasis, as well as B cell class differentiation and immunoglobulin switching. JAK1/JAK2 heterodimers are associated with cytokine receptors for IL-6, IL-10, IL-31, IFN-γ, and interferon- α (IFN-α), playing a role in various inflammatory responses. The JAK1/TYK2 heterodimer participates in innate immune regulation triggered by IFN-α, IL-10, IL-22, and IL-26. In contrast, JAK2/TYK2 heterodimers are involved in the signaling of IL-12 and IL-23, which are key immunomodulatory cytokines that drive the differentiation of type 1 T helper cells (Th1) and Th17 cells, respectively. JAK2 homodimers are vital for controlling erythropoiesis, thrombopoiesis, and myelopoiesis. Overall, these cytokines promote immune cell activation and differentiation, cell proliferation and apoptosis, and humoral immune regulation.[14,15] Dysregulation of this pathway has been associated to the pathogenesis of chronic inflammatory and autoimmune diseases, such as ulcerative colitis, AD and rheumatoid arthritis (RA).[15]

In PPP, both Th17- and Th2-related cytokines, including IL-4, IL-13, IL-17, IL-22, and IL-23, are believed to play significant roles through activation of the JAK-STAT pathway. This activation contributes to keratinocyte dysfunction, recruitment of inflammatory cells, and impairment of the skin barrier.[8,13] Thus, targeting this pathway may offer a more effective therapeutic strategy by simultaneously inhibiting multiple cytokine signaling cascades involved in both Th17 and Th2 responses.

JAK inhibitors

JAKis are small-molecule agents that selectively block the activity of JAK, thereby disrupting cytokine-mediated inflammatory signaling. Several JAKis have been approved for the treatment of various chronic conditions, including RA, PsA, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, AD, and alopecia areata.[14,15] Recent literature has highlighted the use of JAKis as effective therapeutic options for the treatment of PPP.[1,13] Among these, JAKis with established evidence for the management of PPP include tofacitinib, upadacitinib, and baricitinib. Additionally, deucravacitinib, a related selective TYK2 inhibitor, has demonstrated efficacy 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 IFN-γ, 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, as summarized in Table I.

Xu et al. conducted a study involving six cases of PPP refractory to topical treatments and at least one systemic therapy. These patients received tofacitinib at a dosage of 5 mg twice daily over a 12-week period. A significant clinical improvement was observed, with all six patients experiencing at least a 50% reduction in Palmoplantar Pustulosis Area Severity Index **(**PPPASI) within four weeks of treatment, and three of them demonstrating a reduction greater than 80%. By the 12th week, five patients (83.3%) had achieved at least an 80% reduction in PPPASI. Additionally, 5 out of 6 patients (83.3%) achieved a Physician's Global Assessment for PPP (PPGA) score of 0 or 1. No adverse events were reported during the course of treatment.[16]

Mössner et al. reported three cases of PPP resistant to multiple systemic therapies that were successfully managed with 5 mg of tofacitinib twice daily. Two of these patients received concomitant methotrexate. One patient experienced a reduction in PPPASI from 18.6 to 1.8, and another from 15 to 2.3, both after 12 weeks of treatment. A third patient, who had SAPHO syndrome, showed a reduction in the PPGA score from 3 to 1 over the same period. No adverse effects were observed in any of the patients.[17]

Li et al. evaluated the efficacy of tofacitinib in patients with SAPHO syndrome, seven of whom had PPP. After being treated with tofacitinib 5 mg twice daily over a median follow-up of 3.3 months, six patients showed improvement in PPP, with three achieving full resolution. Mild upper respiratory tract infections were the sole adverse events noted, with no hospitalizations required.[18]

Another case report described a patient with SAPHO syndrome and ankylosing spondylitis who experienced significant improvement in cutaneous lesions one month after initiating treatment with tofacitinib, in addition to musculoskeletal benefits. [19]

In the latest case report by Fan et al., a 40-year-old patient with PPP that did not respond to topical corticosteroids and secukinumab showed marked clinical improvement after three months of tofacitinib 5 mg twice daily. The lesions cleared, and pruritus subsided. This improvement was sustained over a six-month follow-up, with no rash recurrence or adverse events.[20]

Koga et al. reported on a 64-year-old Japanese woman with a 15-year history of PPP who started treatment with adalimumab (ADA) for RA. One month after initiating ADA therapy, the patient developed painful pustules with erythema on her heels and soles. ADA was then replaced with tofacitinib 10 mg twice daily, resulting in clinical improvement in both RA and PPP. Flow cytometry analysis revealed a reduction in peripheral effector memory Th1 and Th17-1 cells after 12 weeks of treatment, indicating that tofacitinib modulates T helper cell differentiation and immune response, supporting its potential as a therapeutic agent in PPP.[21]

A case report described a female patient who developed PPP following treatment with ADA for Crohn's disease. Following the discontinuation of ADA, various therapeutic strategies were employed to manage the PPP, although unsuccessfully. Clinical remission of skin lesions was achieved following four injections of ustekinumab, which lasted for approximately nine months. However, the condition later recurred, and none of the subsequent treatments, including ustekinumab, provided sustained disease control. After approximately eight years of ineffective treatments, the patient was started on tofacitinib 5 mg twice daily, which resulted in complete clearance of cutaneous lesions without further flares. After one year of treatment, it was possible to discontinue all other topical and systemic immunosuppressive therapies.[22]

Haynes et al. reported the case of a woman with plaque psoriasis, PsA, and PPP who had been unsuccessfully treated over eight years with multiple topical and systemic therapies. While her plaque psoriasis and arthritis responded to treatment, the PPP remained poorly controlled. Initiation of tofacitinib 5 mg twice daily led to complete resolution of the cutaneous lesions and joint symptoms improvement within two weeks. The patient remained disease-free for three months without any reported adverse effects.[23]

A case report by Zhang et al. described a case involving a 35-year-old woman with PPP who developed alopecia areata during treatment with secukinumab, prompting treatment discontinuation. Although there was mild improvement in PPP and nail lesions with secukinumab, switching to tofacitinib led to significantly better outcomes, achieving near-complete resolution of skin lesions after eight months of therapy.[24]

Finally, a study published by Gleeson et al. reported on two patients in the United Kingdom diagnosed with severe PPP who were treated with tofacitinib. Both individuals had previously undergone multiple systemic and biologic therapies, either without clinical benefit or discontinued due to adverse effects. Following the initiation of tofacitinib, one patient achieved complete resolution of skin lesions while the other experienced near-complete clearance, both within 1 to 2 weeks of treatment. These outcomes support that this JAKi exerts a rapid therapeutic effect with sustained clinical benefit.[13]

Upadacitinib

Upadacitinib is a selective JAK1 inhibitor with minimal activity on other JAK subtypes, potentially resulting in fewer off-target effects. It has been shown to suppress the production of key cytokines, including IL-2, IL-6, IL-17, IL-36, and IFN-γ, thereby modulating T helper cell differentiation and inflammatory cell infiltration.[14]

A total of 8 articles were identified, comprising 42 patients diagnosed with PPP who were treated with upadacitinib (summarized in Table II).

The first reported case was by Mohr et al., describing a 68-year-old female smoker with a seven-year history of PPP. The patient had previously undergone multiple treatments, including topical Psoralen plus Ultraviolet A (PUVA) therapy, guselkumab, and apremilast, all of which were either ineffective or discontinued due to adverse effects. Consequently, oral upadacitinib 15 mg once daily was initiated, as tofacitinib is not recommended for patients over 65 years of age. After 15 weeks of treatment, the patient's PPPASI score dropped from 17.7 to 4.2, her pruritus decreased from 8/10 to 5/10, and her pain went from 7/10 to 0, according to numerical rating scales (NRS). Additionally, the topical therapy with 0.1% mometasone furoate ointment was reduced from twice daily to three times per week. Only mild perioral dermatitis was reported, which was attributed to the use of facial masks rather than systemic therapy.[25]

In a retrospective study conducted in China, 28 patients with PPP were treated with oral upadacitinib (15 mg daily) for 12 weeks. These patients had previously been treated with other systemic therapies, including acitretin, *Tripterygium wilfordii* Hook F (TwHF), cyclosporine, methotrexate, ADA, and secukinumab, with poor response, ineffectiveness, or intolerance. Following treatment, PPPASI scores decreased from 13.86±2.76 to 5.56±1.08, with 18 patients achieving PPPASI90, and 20 patients (71.4%) reaching a Physician Global Assessment (PGA) score of 0/1. Additionally, all patients experienced significant QoL improvements, with Dermatology Life Quality Index (DLQI) scores reducing from 12.55±4.56 to 2.03±1.13. No severe adverse events were reported during the treatment and follow-up periods; only mild acneiform rash, transient

transaminase elevation, and slight increase un creatinine levels were observed, all of which resolved without the need for treatment discontinuation.[26]

The latest case report described a 15-year-old adolescent diagnosed with PPP at the age of six, refractory to topical corticosteroid therapy. Due to joint mobility limitations caused by PPP, the patient experienced difficulties in daily manual activities, such as writing and dressing, resulting in low self-esteem and socialization challenges. Treatment with oral upadacitinib 15 mg once daily was initiated, and after three months, the patient reported a significant improvement in joint mobility, with a reduction in PPPASI from 18.4 to 2.6, no emergence of new pustules, and no adverse events.[27]

A case series by Kooybaran et al. reported five patients with significant improvements under upadacitinib therapy. On average, these patients had failed 5,2 prior systemic therapies, mostly due to inefficacy or adverse events. One of the patients demonstrated a favorable response to tofacitinib therapy, with a reduction in PPPASI from 18.6 to 1.8 after 12 weeks, however treatment was switched to upadacitinib due to concerns about potential side effects, maintaining therapeutic benefits post-transition. Among the remaining four patients, three achieved excellent therapeutic responses, with mean PPPASI scores decreasing from 11.5 ± 7.25 at baseline to 2.13 ± 1.73 after treatment. One patient had a moderate response, with PPPASI reducing from 9.6 to 6.0, and PPGA improving from 3 to 2. Furthermore, associated symptoms or comorbidities, such as PsA, nail psoriasis and urticaria, also improved. Adverse events were limited to two mild infections (bronchitis and cystitis) and headaches.[28]

Another study reported two patients with PPP associated with PsA, initially treated with IL-17 inhibitors (secukinumab or ixekizumab) based on the shared pathogenic pathway hypothesis. Although improvements in joint symptoms were achieved, PPP did not respond. Both patients were subsequently treated with upadacitinib for 20 weeks, resulting in reductions in PPPASI scores from 14.1 to 0.8 and from 21.9 to 0.6, respectively, alongside reduction of DLQI. Additionally, both pruritus and pain resolved under therapy. These findings reinforce that while IL-17 is significant in PPP pathophysiology, it is not the key cytokine, and PPP pathogenesis is more complex, benefiting from broader cytokine inhibition for better disease management.[29]

Gaiani et al. presented three additional cases of PPP refractory to several systemic therapies, all of which achieved excellent responses to upadacitinib, with near-complete resolution of cutaneous lesions and noticeable improvement in pruritus.[30]

Taniguchi et al. 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.[31]

Lastly, Hu et al. reported a patient with PPP and severe pruritus who relapsed after secukinumab therapy and subsequently initiated oral upadacitinib 15 mg daily. After 12 weeks of treatment, the patient's cutaneous lesions had nearly resolved, with significant improvement in pruritus and QoL. Maintenance therapy with alternate-day dosing of upadacitinib was continued, with sustained clinical stability.[32]

Baricitinib

Baricitinib is an oral JAKi with selective activity against JAK1 and JAK2, and moderate inhibitory effects on TYK2, which inhibits downstream production of multiple pro-inflammatory cytokines, including IL-6, IL-12, and IL-23.[1,14]

In the case of baricitinib, 3 articles were identified, comprising a total of 6 patients (summarized in Table III).

A case report by Imafuku et al. described a 64-year-old woman with RA who, after two years of treatment with golimumab (an anti-TNF-α antibody), developed PPP. Golimumab was discontinued, and although therapy with etretinate, topical calcipotriol/betamethasone dipropionate, and 308 nm ultraviolet light was initiated, no significant improvement in the PPP lesions was observed, even after the addition of apremilast. Given the recurrence of RA and the lack of effective control of PPP, baricitinib therapy was initiated. Complete resolution of PPP was achieved four weeks after starting baricitinib.[33]

A case series reported five patients with SAPHO syndrome, four of whom presented with PPP accompanied by nail lesions, treated with 2 mg of oral baricitinib daily for 12 weeks. These patients had previously received treatment with non-steroidal anti-inflammatory drugs, TNF inhibitors, and other therapeutic options; however, the therapeutic outcomes were suboptimal. Although data on the effects of baricitinib on PPP are limited, the authors reported improvements in inflammatory markers, pain, and cutaneous manifestations, without the occurrence of adverse events.[34]

In another case report by Li et al., a 20-year-old man diagnosed with both PPP and AD was treated with 4 mg of oral baricitinib daily. Complete resolution of the cutaneous lesions was observed within the first four weeks of the three-month treatment course. However, a relapse occurred following treatment discontinuation. Baricitinib was subsequently reinitiated at a dose of 4 mg daily for two months, achieving complete remission again. The dose was then tapered to 2 mg daily, and later to 2 mg on alternate days, successfully maintaining disease stability without the emergence of new lesions. This article further reinforced the similarities in the pathophysiology of

AD and PPP, suggesting that an imbalance between Th1 and Th2 immune responses may constitute a common underlying mechanism, which can be effectively targeted using JAKis such as baricitinib. By inhibiting JAK1 and JAK2, baricitinib reduces cytokine production and T helper cell differentiation, thus contributing to disease control.[35]

Deucravacitinib

Deucravacitinib, a selective inhibitor of TYK2, is approved for the treatment of moderate-to-severe plaque psoriasis. It selectively targets cytokines such as IL-12, IL-23, and type I interferons, which are key mediators in the pathogenesis of psoriasis and other immune-mediated disorders. Given its mechanism of action, deucravacitinib represents a promising candidate for targeted therapy in PPP, and its TYK2 selectivity may confer a more favorable 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 subjects will receive 6mg of deucravacitinib daily for 24 weeks, with clinical assessments performed every 4 weeks. The primary outcomes focus on improvements in PPPASI, while secondary endpoints include changes in the DLQI, achievement of PGA score of 1 or 0, as well as pain and pruritus scores. The trial is currently in the recruitment phase, with an estimated enrollment 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 JAKi 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, not yet fully understood pathogenesis. Currently managed with topical corticosteroids, retinoids, phototherapy, and systemic immunosuppressants, PPP often demonstrates suboptimal or transient responses to these treatments. The emergence of biologics and small-molecule therapies has widened the therapeutic options, yet no gold-standard treatment has been established. The growing evidence reviewed in this thesis highlights the therapeutic potential of JAKis in PPP.[1,2]

JAKis offer a multi-targeted approach by modulating several cytokine-driven pathways simultaneously, including the Th17 and Th2 pathways, both implicated in PPP pathophysiology. This broad targeting is especially pertinent considering the recent immunologic and transcriptomic studies that have identified a mixed Th17/Th2 profile in PPP lesions, which may help to explain the limited success of therapies that focus on targeting individual T helper cell populations.[10–12]

Among the JAKis evaluated, tofacitinib, a JAK1/3 inhibitor, has shown consistent clinical benefits on case series and reports, with several patients achieving near-complete or complete remission even after failure of multiple prior therapies. Its ability to attenuate Th17-associated cytokines such as IL-17 and IL-23, as well as Th2-related IL-4 and IL-13, may account for this efficacy.[13,16–24]

Upadacitinib, a selective JAK1 inhibitor, has also demonstrated robust clinical responses across a larger number of patients, with multiple studies reporting significant reductions in PPPASI scores and improvements in QoL. Additionally, it appears to maintain efficacy even in elderly patients and those with longstanding, treatment-resistant disease, and its selective mechanism of action contributes to better tolerability and a lower likelihood of inducing adverse events.[25–32]

Baricitinib (a JAK1/2 inhibitor), although less studied, also shows favorable results, with rapid clinical improvements reported in several cases, particularly among patients with overlapping immune-mediated diseases such as RA or AD.[33–35] Once again, these findings support that PPP involves dysregulation of both the Th17 and Th2 pathways.

Emerging agents like deucravacitinib, a selective TYK2 inhibitor, represent a novel generation of JAKis with potentially enhanced safety profiles, due to their target modulation of IL-12, IL-23, and type I interferons' pathways. Although clinical data on its efficacy in the treatment of PPP remains limited, the initiation of a phase IV clinical trial (NCT05710185) reflects growing interest in its therapeutic potential.[36]

From a mechanistic standpoint, the rationale of JAK inhibition in PPP is compelling. The JAK-STAT pathway mediates the effects of a wide range of pro-inflammatory cytokines implicated in keratinocyte activation, barrier dysfunction, and immune cell recruitment in PPP. By inhibiting this pathway, JAKis can modulate a broad spectrum of immune responses, potentially offering more sustained disease control than agents targeting individual cytokines.

However, while 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 is 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 significant impact on patient QoL and limited response to conventional therapies. The complexity of its pathophysiology, which appears to result from dysregulation of the Th17- and Th2-mediated immune response, poses substantial challenges to the development of effective therapeutic strategies. Ultimately, JAKis appear to represent a paradigm shift in the management of PPP, as they are capable of inhibiting a broad spectrum of cytokines implicated in both inflammatory pathways.

Evidence indicates that JAKis such as tofacitinib, upadacitinib, and baricitinib can achieve substantial clinical improvement, even in patients who have failed multiple systemic therapies. Their favorable efficacy profiles, coupled with the manageable adverse effects reported so far, highlights their potential as valuable therapeutic options. However, the current evidence is derived from low-level studies, underscoring the need for randomized controlled trials to validate these findings and to better define their long-term safety, efficacy, and place in treatment algorithms.

Appendix

Tables

Table I: 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/ 2F4M	Mean: 4,7 years	Obesity, T2DM, Hyperlipidemia, Smoking, AD	Corticosteroids, phototherapy, MTX, cyclosporine, systemic retinoid	5mg twice daily for 12 weeks	83,3% of patients achieved 80% reduction of PPPASI	No
Mössner et al.[17]	3	Mean: 55,7/ 2F1M	Mean: 12,7 years	SAPHO, Psoriasis, PsA, Ulcerative Colitis, smoking	Acitretin, MTX, apremilast, TNFi, ADA, cyclosporine, IL-23 and IL-17 inhibitors	5mg 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	5mg 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	5mg twice daily	Lesions improved after 4 weeks	No
Fan et al.[20]	1	40/M	8 years	Allergic conjuntivitis and rhinitis, Asthma	Corticosteroids, secukinumab	5mg twice daily	Complete resolution after 12 weeks, without recurrence	No
Koga et al.[21]	1	64/F	14 years	RA	None	10mg 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	5mg 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	5mg twice daily	Complete resolution after 2 weeks, without flares	No

Zhang et al.[24]	1	35/F	2 years	Nail lesions	Acitretin, ADA, secukinumab	5mg twice daily	Significant improvment of symptoms	No
Gleeson et al.[13]	2	Mean: 54,5/F	NA	PsA, Ulcerative colitis	NA	One patient did 10mg 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

Abbreviations: AD, atopic dermatitis; ADA, adalimumab; F, female; IL, interleukin; 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, tumor necrosis factor inhibitor; TwHF, Tripterygium wilfordii Hook F.

Table II: 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, Hypercholesteremia, 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/ 18F10M	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

Kooybaran et al.[28]	5	Mean: 61,4/ 4F1M	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	Psoariasis, 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

Abbreviations: ADA, adalimumab; DLQI, Dermatology Life Quality Index; F, female; HBP, high blood pressure; IL, interleukin; 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.

Table III: 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/ 3F1M	NA	SAPHO, Nail lesions	NSAIDs, MTX, TNFi, TwFH	2 mg daily during 12 weeks	Improvement of cutaneous lesions	No
Li et al.[35]	1	20/M	2 years	AD	Corticosteroids, antihistamines	4mg daily for 2 months, then 2mg daily for 2 months and 2mg every other day for another 2 months	Complete resolution after 4 weeks; relapse after discontinuation; effective reintroduction, with complete resolution	NA

Abbreviations: 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, tumor necrosis factor inhibitor; TwHF, Tripterygium wilfordii Hook F.

References

1. Branyiczky MK, Towheed S, Torres T, Vender R. A systematic review of recent randomized controlled trials for palmoplantar pustulosis. J Dermatolog Treat [Internet] 2024; 35(1):2414048. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/39389576/
2. Freitas E, Rodrigues MA, Torres T. Diagnosis, screening and treatment of patients with palmoplantar pustulosis (Ppp): A review of current practices and recommendations. Clin Cosmet Investig Dermatol [Internet] 2020; 13:561–78. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/32884319/
3. Brunasso AMG, Massone C. Recent advances in palmoplantar pustulosis. Fac Rev [Internet] 2021; 10. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/34409425/
4. Murakami M, Terui T. Palmoplantar pustulosis: Current understanding of disease definition and pathomechanism. J Dermatol Sci [Internet] 2020; 98(1):13–9. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/32201085/
5. Brunasso AMG, Puntoni M, Aberer W, Delfino C, Fancelli L, Massone C. Clinical and epidemiological comparison of patients affected by palmoplantar plaque psoriasis and palmoplantar pustulosis: A case series study. British Journal of Dermatology [Internet] 2013; 168(6):1243–51. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/23301847/
6. Misiak-Galazka M, Zozula J, Rudnicka L. Palmoplantar Pustulosis: Recent Advances in Etiopathogenesis and Emerging Treatments. Am J Clin Dermatol [Internet] 2020; 21(3):355–70. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/32008176/
7. Yamamoto T. Extra-palmoplantar lesions associated with palmoplantar pustulosis. Journal of the European Academy of Dermatology and Venereology [Internet] 2009; 23(11):1227–32. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/19453807/
8. Devjani S, Smith B, Javadi SS, Engel P V., Han G, Wu JJ. Palmoplantar Pustulosis: Therapy Update. J Drugs Dermatol [Internet] 2024; 23(8):626–31. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/39093642/
9. Raposo I, Torres T. Palmoplantar Psoriasis and Palmoplantar Pustulosis: Current Treatment and Future Prospects. Am J Clin Dermatol [Internet] 2016; 17(4):349–58. Accessed May 17, 2025. Available from: https://pubmed.ncbi.nlm.nih.gov/27113059/
10. Hernandez-Cordero A, Thomas L, Smail A, et al. A genome-wide meta-analysis of palmoplantar pustulosis implicates TH2 responses and cigarette smoking in disease pathogenesis. Journal of Allergy and Clinical Immunology 2024;154(3):657-665.e9.
11. McCluskey D, Benzian-Olsson N, Mahil SK, et al. Single-cell analysis implicates TH17-to-TH2 cell plasticity in the pathogenesis of palmoplantar pustulosis. Journal of Allergy and Clinical Immunology 2022;150(4):882–93.
12. Zheng YX, Chen XB, Wang ZY, et al. Efficacy of dupilumab in palmoplantar pustulosis treatment highlights the role of Th2 inflammation. Allergy: European Journal of Allergy and Clinical Immunology. 2024;79(5):1361–4.
13. Gleeson D, Barker JNWN, Capon F, et al. Are Janus kinase inhibitors an effective treatment for palmoplantar pustulosis? A critically appraised topic. Br J Dermatol [Internet] 2023; 188:471–3. Accessed May 17, 2025. Available from: https://doi.org/10.1093/bjd/ljac130

14. Samuel C, Cornman H, Kambala A, Kwatra SG. A Review on the Safety of Using JAK Inhibitors in Dermatology: Clinical and Laboratory Monitoring. Dermatol Ther (Heidelb). 2023;13(3):729–49.
15. Taylor PC, Choy E, Baraliakos X, et al. Differential properties of Janus kinase inhibitors in the treatment of immune-mediated inflammatory diseases. Rheumatology (United Kingdom). 2024;63(2):298–308.
16. Xu Q, Wang X, Yang A, Wei G. Refractory Palmoplantar Pustulosis Successfully Treated with JAK Inhibitor Tofacitinib: A Case Series. Infect Drug Resist 2023;16:5165–72.
17. Mössner R, Hoff P, Mohr J, Wilsmann-Theis D. Successful therapy of palmoplantar pustulosis with tofacitinib—Report on three cases. Dermatol Ther 2020;33(4).
18. Li Y, Huo J, Cao Y, et al. Efficacy of tofacitinib in synovitis, acne, pustulosis, hyperostosis and osteitis syndrome: A pilot study with clinical and MRI evaluation. Ann Rheum Dis. 2020;79(9):1255–7.
19. Yuan F, Luo J, Yang Q. SAPHO Syndrome Complicated by Ankylosing Spondylitis Successfully Treated With Tofacitinib: A Case Report. Front Immunol 2022;13.
20. Fan Y, Yin R. Janus kinase inhibitor tofacitinib successfully treated palmoplantar pustulosis after switching from secukinumab: A case report and review of the literature. Int Immunopharmacol 2024;139.
21. Koga T, Sato T, Umeda M, et al. Successful treatment of palmoplantar pustulosis with rheumatoid arthritis, with tofacitinib: Impact of this JAK inhibitor on T-cell differentiation. Clinical Immunology 2016;173:147–8.
22. Wang YA, Rosenbach M. Successful treatment of refractory tumor necrosis factor inhibitor-induced palmoplantar pustulosis with tofacitinib: Report of case. JAAD Case Rep 2020;6(2):115–8.
23. Haynes D, Topham C, Hagstrom E, Greiling T. Tofacitinib for the treatment of recalcitrant palmoplantar pustulosis: A case report. Australasian Journal of Dermatology 2020;61(1):e108–10.
24. Zhang C, Kang T, Qian T, Ma M, Hou X, Li C. Secukinumab-Induced Alopecia Areata Successfully Treated with Tofacitinib in a Patient with Palmoplantar Pustulosis. Clin Cosmet Investig Dermatol 2023;16:2879–83.
25. Mohr J, Rahbar Kooybaran N, Schön MP, Mössner R. Response of palmoplantar pustulosis to upadacitinib. JDDG - Journal of the German Society of Dermatology 2023;21(3):280–2.
26. Du N, Yang J, Zhang Y, Lv X, Cao L, Min W. Successful treatment of refractory palmoplantar pustulosis by upadacitinib: report of 28 patients. Front Med (Lausanne) 2024;11.
27. Gu Q, Zhang C, Song W, Lin Z, Li C, Ying Z. Improvement in Hand Joint Flexibility Following Upadacitinib Treatment of Palmoplantar Pustulosis in Adolescents. Int J Rheum Dis 2025;28(3).
28. Rahbar Kooybaran N, Tsianakas A, Assaf K, Mohr J, Wilsmann-Theis D, Mössner R. Response of palmoplantar pustulosis to upadacitinib: A case series of five patients. JDDG - Journal of the German Society of Dermatology 2023;21(11):1387–92.
29. Zhang Z-Y-O, Mi W-Y, Wang Y-Y, Li W. Palmoplantar pustulosis with psoriatic arthritis ineffective to interleukin-17 inhibitors: two patients successfully treated with upadacitinib. Journal of Dermatological Treatment 2023;34(1).
30. Gaiani FM, Malagoli P, Carrera CG. Palmoplantar pustulosis successfully treated with upadacitinib: Report of three cases. Australasian Journal of Dermatology 2023;64(4):568–70.
31. Taniguchi Y, Yamamoto H. Therapeutic Potential of Janus Kinase Inhibitors for Treating Palmoplantar Pustulosis/Pustulotic Arthro-osteitis. Journal of Clinical Rheumatology 2024;30(6):e157.

32. Hu W, Wang Y, Zhang S, Wu X, Lian C. Treatment of severely itchy scalp psoriasis and palmoplantar pustulosis with unsatisfied response to secukinumab, adalimumab or ustekinumab using upadacitinib: A report of two cases. Journal of Dermatology 2024;51(5):e151–3.
33. Imafuku S, Maeyama A. Remission of anti-tumor necrosis factor-α antibody-induced palmoplantar pustulosis with the Janus kinase inhibitor baricitinib in a patient with rheumatoid arthritis. Journal of Dermatology 2021;48(5):e240–1.
34. Liu S, Yu Y, Liu Y, Ma M, Li C. Efficacy of baricitinib in synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: A case series. Joint Bone Spine. 2023;90(5).
35. Li X, Liu G, Chen S, Liu Y. A case of palmoplantar pustulosis with atopic dermatitis: Baricitinib is a safe and effective treatment. Indian J Dermatol Venereol Leprol 2024;90(5):668–70.
36. ClinicalTrials.gov. Deucravacitinib for the Treatment of Palmoplantar Pustulosis [Internet]. Accessed April 18, 2025. Available from: https://clinicaltrials.gov/study/NCT05710185?cond=Palmoplantar%20Pustulosis&limit=100&page=1&rank=1

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