doi:10.36849/JDD.7612R1

 ORIGINAL ARTICLE

Palmoplantar Pustulosis: Therapy Update

Shivali Devjani MS,[a] Brandon Smith BA,[b] Sogol Stephanie Javadi BS,[c] Priya V Engel MPH,[d] George Han MD PhD,[e] Jashin J. Wu MD[f]

[a]SUNY Downstate College of Medicine, Brooklyn, NY
[b]Drexel University College of Medicine, Philadelphia, PA
[c]David Geffen School of Medicine, University of California, Los Angeles, CA
[d]California University of Science and Medicine, Colton, CA
[e]Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY
[f]University of Miami Miller School of Medicine, Miami, FL

ABSTRACT

Palmoplantar pustulosis is a variant of psoriasis and a chronic skin disorder in which pruritic pustular eruptions appear on the palms and soles. It is thought to arise from a variety of genetic and environmental factors, is limited in prevalence, and has proven quite difficult to treat. The symptoms it inflicts on those affected are quite debilitating and the treatment landscape is constantly evolving, thus emphasizing the need for updates of the literature as time passes. Current treatments include topical agents, oral therapies, and phototherapy, amongst other treatments. In this systemic review, we explore newer literature from 2015 to 2022 on various treatment regimens for palmoplantar pustulosis.

J Drugs Dermatol. 2024;23(8):626-631. doi:10.36849/JDD.doi:10.36849/JDD.7612R1

INTRODUCTION

Palmoplantar pustulosis (PPP), also known as palmoplantar pustular psoriasis, is a chronic skin disorder in which pruritic pustular eruptions appear on the palms and soles. It is thought to be a variant of psoriasis.[1] Despite its localized involvement, PPP is chronic and has been shown to reduce quality of life. The disorder affects all ages, with females more likely to be affected than males.[2]

Although its exact cause is unknown, PPP is thought to be multifactorial and caused by a combination of genetic and environmental factors. Although the PSORS1 locus that is associated with psoriasis vulgaris is not associated with PPP, variations of IL-19, IL-20, and IL-24 genes may be associated with both psoriasis and PPP. Human leukocyte antigen (HLA) Cw6, CARD14, and ATG16L1 genes have also been associated with the conditions. Additionally, environmental triggers, such as smoking, stress, drugs, infection, sweating, repetitive trauma, and irritants play a role in the pathophysiology.[3] The underlying immunologic mechanism is hypothesized to involve inflammation that destroys the acrosyringium, the primary site of sterile pustule formation. Mast cells, lymphocytes, neutrophils, and eosinophils contribute to this process. Furthermore, chemotactic factors such as IL-8 and IL-17 related cytokines, tumor necrosis factor alpha, interferon-gamma, and complement pathway activation are also thought to be involved. Genetic factors and environmental triggers spur an immune cascade, leading to immune cell proliferation and the formation of lesions on the skin.[4]

PPP lesions often induce itching, pain, and breakdown of the skin barrier that can be exacerbated in flares of disease. On examination, the skin contains thick, hyperkeratotic plaques and/or sterile pustules that can be symmetric, erythematous, and scaly. Although most patients only exhibit lesions on the palms and soles, nail changes, including pitting and ridging, can be observed in approximately 60% of cases. More extensive nail changes are found in Acrodermatitis continua of Hallopeau, a relatively rare subset of pustular psoriasis that classically affects the nail apparatus, giving rise to its clinical description as "nails floating away on a lake of pus." This condition can coexist with PPP and is important to recognize because it can lead to anonychia or osteolysis of the distal phalanges if left untreated. A subset of patients with PPP may also have arthritic symptoms. Associated disorders include pustulotic arthro-osteitis (PAO) and Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis syndrome (SAPHO).[5] The presentation of PPP may mimic numerous other conditions such as dyshidrotic eczema, contact dermatitis, pityriasis rubra pilaris, and tinea pedis and manuum. As a result, a thorough history and physical examination are warranted, though additional workup is also

necessary. A potassium hydroxide preparation and bacterial culture are often performed to rule out fungal and bacterial infections. While biopsies on acral surfaces are challenging, they can help diagnose PPP where biopsies will show histologic findings consistent with epidermal changes, spongiosis, and accumulations of various cell types, such as lymphocytes, eosinophils, mast cells, and neutrophils.[6]

PPP is limited in prevalence and has proven to be quite difficult to treat. The condition is chronic and stems from an interplay of genetic and environmental factors. Furthermore, high-quality data on the treatment of PPP is sparse. Nonetheless, the research landscape is constantly evolving, thus emphasizing the need for an updated review of the literature.

Aim

In this comprehensive review, we discuss the evaluation of PPP and the mechanism of action, efficacy, and safety profiles of existing, alternative, and upcoming therapeutics for this debilitating condition.

MATERIALS AND METHODS

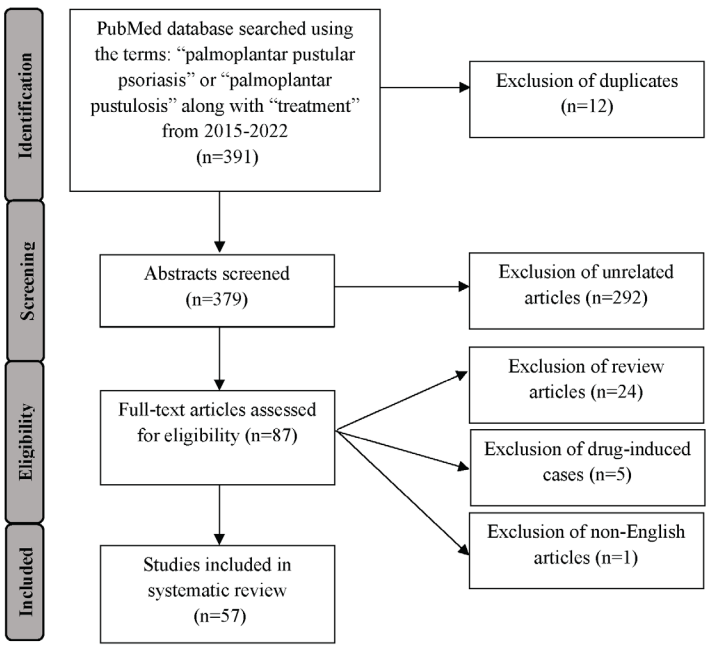
Published articles assessing the efficacy and safety of therapeutic agents for the treatment of PPP were identified through the healthcare journal database, Pubmed. The keywords "palmoplantar pustular psoriasis" or "palmoplantar pustulosis" and "treatment" were queried from 2015 to 2022. Initially, articles were screened by their titles and abstracts. Those that appeared to meet the inclusion criteria were assessed further, by full text, and were included in the analysis if subjects were diagnosed with PPP based on the assessment by the authors of each publication and if subjects were being treated for their condition with medication or alternative therapy. Incorporation of efficacy and safety of the attempted treatment were required for the inclusion criteria. Articles that were duplicates of others, review articles, or drug-induced cases of PPP were excluded.

Efficacy outcomes were analyzed by a reduction in the PPP Area and Severity Index (PPPASI), the PPP Physician Global Assessment (PPPGA), the Dermatology Life Quality Index score (DLQI), or another standardized criterion of characterizing symptom reduction.

RESULTS

An initial search on Pubmed for the keywords PPPASI, PPPGA, and DLQI, identified 391 published articles. After excluding duplicates, 379 articles were screened by title and abstract, leaving 87 articles for full-text review. Following a full-text review, 57 articles were ultimately included in our analysis (Figure 1). Ten articles evaluated apremilast, a phosphodiesterase 4 inhibitor (PDE-4i), eighteen articles studied biologics, four examined Janus kinase inhibitors (JAKi), five studied retinoids, four evaluated disease-modifying antirheumatic drugs (DMARDs), 1 examined topical agents, 3 studied alternative treatments, and 5 assessed phototherapies.

FIGURE 1. Flow chart illustrating the literature search using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMA) guidelines.



Topical Agents

Topical corticosteroids have historically been considered first-line therapeutic options for PPP with limited cutaneous involvement. Their minimal side effect profile and easy application make them a viable option. A 2016 randomized left-right comparison study evaluated the efficacy of combination therapy, maxacalcitol ointment (vitamin D derivate), and betamethasone butyrate propionate (BBP) ointment, versus monotherapy with BBP in 27 PPP patients for 8 weeks. Patients treated with combination therapy had a significantly greater improvement (P<0.05) in symptoms than those treated with monotherapy, demonstrating the efficacy of combination corticosteroids and vitamin D treatment in PPP.[7]

Biologics

Multiple biologics have been used to treat PPP with varying degrees of success. However, it is important to note that notwithstanding various publications citing treatment success, the development of PPP in patients being treated with biologics (with the majority of TNF-alpha inhibitors) for other indications has regularly been reported.[8] This, combined with the fact that various case reports show differing efficacy of various biologics, makes the data sometimes difficult to interpret. There are several larger studies, including randomized controlled trials, that have studied the use of biologics for PPP and have somewhat helped to elucidate the confusion.

IL-36 Receptor Blockers

Spesolimab functions by blocking interleukin-36 (IL-36), which is thought to play a role in the pathogenesis of PPP in some patients. A 2022 cohort study comparing blood and skin samples from patients with PPP showed that spesolimab was able to modulate dysregulated molecular pathways common to PPP.[9] In a 2021 multicenter randomized control trial, 31.6% of patients treated with 300 mg or 900 mg of spesolimab achieved PPPASI50 vs 23.8% treated with placebo. Although these results were below the primary endpoint, individuals treated with spesolimab improved at a faster rate.[10] Given current evidence, further studies on subsets of PPP patients who may respond better to spesolimab may be warranted given the clear pathophysiologic link between IL-36 and forms of PPP.

IL-17 Inhibitors

IL-17 inhibitors have become a mainstay of treatment of psoriasis over the past several years, as IL-17 is the effector cytokine that leads to hyperproliferation of keratinocytes seen in psoriasis. These medications have shown efficacy in both skin and joint disease in psoriasis and have proven to be important therapies for patients with psoriasis and PPP, specifically.

Dramatic improvement of psoriatic lesions was noted within 2 weeks of administering brodalumab after failure of adalimumab and secukinumab in a case report in 2019.[11] Another case series showed no improvement or moderate improvement in four patients with severe PPP.[12]

Ixekizumab has also shown some efficacy in patients with PPP. A case report in 2022 showed successful treatment of PPP with ixekizumab after the patient had failed numerous other therapies, suggesting that ixzekizumab can be a potential treatment option for recalcitrant PPP.[13]

The only prespecified trial on PPP among the IL-17 inhibitors is one that was performed with secukinumab. A 2019 phase 3b multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared treatment with 300 mg secukinumab to 150 mg secukinumab and placebo in subjects with moderate-to-severe PPP over 1 year. The primary endpoint of achieving a 75% reduction in PPPASI at week 16 was not met, the significance level was set at 2.5%, but patients treated with secukinumab 300 mg still showed benefit in PPPASI 75 responses (numerically higher than placebo; 26.6% for secukinumab vs 14.1% for placebo, P=0.0411) as well as improved quality of life.[14]

Interestingly, a prospective cohort study of both palmoplantar psoriasis and PPP showed reasonable efficacy for secukinumab, with over half of the patients in the PPP cohort achieving a PPPGA of clear or almost clear.[15] These results were similar across the palmoplantar psoriasis and PPP groups, though it should be noted that there was a relatively small number of patients with PPP (n=17) and a relatively high attrition rate. Notwithstanding, this study highlighted some interesting findings, such as the need to treat for longer periods of time to achieve treatment success, which may help guide our understanding of further trial data in PPP. Multiple case reports showed improvement of PPP symptoms with minimal side effects in patients with refractory disease treated with 300 mg secukinumab.[16-17]

IL-23 Inhibitors

Various studies have identified the IL-23/IL-17 axis as the primary signaling pathway leading to the abnormal growth of keratinocytes and the production of psoriatic skin.[18] As a result, interleukin-23 (IL-23) inhibitors are efficacious in the treatment of psoriasis and its subtypes. They generally require less frequent dosing than IL-17 inhibitors and have demonstrated a favorable side effect profile without carrying a risk of exacerbating inflammatory bowel disease (IBD). Guselkumab, tildrakizumab, and risankizumab all operate by similar mechanisms.

Tildrakizumab is a humanized IgG1 kappa monoclonal antibody that targets the p19 subunit of IL-23. It is approved for plaque psoriasis, but little evidence exists for its use in difficult-to-treat areas such as palmoplantar surfaces. A 2021 case report showed efficacy with tildrakizumab in a patient with PPP refractory to other therapies.[19]

Another IL-23 inhibitor targeting the p19 subunit of IL-23 is risankizumab. A case report in 2021 showed significant improvement in recalcitrant PPP and concomitant ichthyosis vulgaris in a 60-year-old female patient after 16 weeks of therapy.[20]

Guselkumab also binds the p19 subunit of IL-23 and is effective in treating psoriasis and its subtypes. There is more data available for guselkumab in treating PPP as compared to other IL-23 inhibitors. A 24-week randomized clinical trial in 2018, including 49 patients with PPP treated with either 200 mg subcutaneous guselkumab or placebo, found significant improvements in the experimental group at both week 16 and week 24. No safety concerns were identified and improvements in skin-related outcomes were visible as early as after the second dose, or four weeks into treatment.[21] Another randomized phase 3 study echoed these results, with roughly 79% sustained improvement in PPPASI scores from baseline to week 84 in those treated with guselkumab vs placebo.[22] A 2020 case report describing a patient with PPP refractory to both cyclosporine and apremilast demonstrated complete clearance of symptoms with guselkumab.[23]

IL-12/23 Inhibitor

Ustekinumab binds to the p40 subunit of IL-12 and IL-23 to prevent its interaction with its receptor. A 2016 case series of nine patients with PPP treated with ustekinumab demonstrated an average of 71.6% improvement in the PPPASI in 24 weeks. No adverse effects were observed aside from local injection site reactions and mild infections.[24] A similar response was cited in another article in 2018.[25] Additionally, 1 case described a patient with PPP who initially failed treatment with a standard dose of ustekinumab, but achieved a response with the use of higher doses following a new diagnosis of inflammatory bowel disease.2[6]

Apremilast

Apremilast is a low-molecular-weight oral phosphodiesterase 4 (PDE-4) inhibitor that has been used to treat psoriasis and various psoriasis subtypes. By blocking PDE-4, apremilast upregulates intracellular cyclic adenosine monophosphate (cAMP) and subsequently suppresses interleukin-8 (IL-8), which is thought to be involved in the pathogenesis of PPP. As a result, pustule formation is decreased, reducing symptoms and disease burden.[27] Several case reports and cohort studies of up to 300 patients support the role of apremilast in treating PPP with limited adverse effects.[28-33] A number of these studies demonstrated PPPASI reductions of greater than 50%. Two case reports even showed the efficacy of using apremilast in cases of PPP refractory to topical steroids, UVA, and multiple systemic therapies.[34-35] One larger open-label trial (APLANTUS) of 21 patients, reported that palmoplantar pustulosis PASI decreased by a median of 57.1% and pustule lesion counts decreased significantly as well, with over three-quarters of patients exceeding 50% decrease in pustule counts by week 20. DLQI scores decreased substantially, from a median of 8.5 at baseline to 2.0 at week 20.[36] Notable side effects of apremilast include GI side effects, namely diarrhea, headache, and photosensitivity.

JAK Inhibitors

Janus kinase (JAK) inhibitors have been approved for a variety of immune-mediated chronic conditions. By blocking a wider array of proinflammatory cytokines, the mixed inflammatory picture of PPP can be more effectively treated. Tofacitinib inhibits JAK1, JAK2, and JAK3, thus blocking a cascade of cytokines (eg, IL-23, IL-22, and IFN-gamma) involved in the pathogenesis of the disease. A case report in 2019 demonstrated the efficacy of tofacitinib in treating PPP and recalcitrant PPP within a 6-month period.[37] Many of the patients studied also had a history of psoriatic arthritis.[38] Another study found that tofacitinib was beneficial in spurring T-cell differentiation in a patient with PPP and concomitant rheumatoid arthritis.[39] A single-arm, prospective pilot study in 2021 studied the efficacy of tofacitinib in the treatment of PPP in 13 female Asian patients with SAPHO. Significant improvements in both PPASI (P<0.001) and DLQI scores (P<0.001) were observed at week 12 and no serious adverse events were reported.[40]

DMARDs

Disease-modifying antirheumatic drugs (DMARDs) are a group of medications commonly used to treat types of inflammatory arthritis via the suppression of the body's overactive immune response. There are a variety of DMARDs with various mechanisms. Anakinra is a biologic medication originally derived from *E. coli* and acts as an interleukin-1 (IL-1) receptor antagonist that binds to and blocks the effects of IL-1. A randomized, double-blind, multicenter, two-staged, adaptive placebo-controlled trial was performed in 2020. Despite postulations that anakinra would deliver therapeutic benefit in PPP, no evidence of the superiority of anakinra over placebo was found. The mean difference in PPASI was greater in the anakinra subgroup, but this difference was not significant.[41-43]

Methotrexate is a folate antagonist that interferes with DNA synthesis and repair, thus inhibiting the formation of major cell lineages involved in the inflammatory cascade of immune disease. One case report of beta-blocker-induced PPP was treated successfully with low-dose methotrexate (2.5 mg weekly) after failure of acitretin. It should be noted that despite beta-blocker discontinuation, the patient's PPP improved minimally, therefore treatment with other systemics was attempted and the natural history of PPP in this case could not be ascertained.[44]

Retinoids

Alitretinoin is an orally administered systemic retinoid often used for acne and occasionally for recalcitrant eczema. It is

a retinoid X receptor and retinoid A receptor agonist that is thought to inhibit sebaceous gland function and keratinization. A double-blind, placebo-controlled trial was performed to evaluate alitretinoin 30 mg daily vs placebo for treatment-resistant PPP using PPPASI after 24 weeks. No significant differences were found between both groups, which differed from other case studies and series conducted in the past that found significant efficacy of isotretinoin for PPP. The authors attribute these differences to differences in study design.[45-46] Another retinoid, acitretin, was not tolerated well in a case series of 2 patients with PPP refractory to topical treatments. However, isotretinoin monotherapy worked remarkably in 1 of the 2 patients.[47] It should be noted that, while out of the scope of the present systematic review, previous studies have proven the efficacy of acitretin in treating PPP.[48-49]

Phototherapy

Phototherapy has emerged as a safe and effective therapeutic agent for various dermatologic conditions. Targeted modalities, such as topical psoralen-ultraviolet phototherapy (tPUVA), paint psoralen-ultraviolet phototherapy (pPUVA), ultraviolet A1 (UVA1), and narrowband ultraviolet B (UVB), have proven to be efficacious forms of phototherapy. Various case studies, cohort studies, and randomized prospective studies have demonstrated the efficacy of narrowband UVB for PPP with minimal side effects. These studies largely demonstrated the delivery of UVB at a 308 nm wavelength using an XeCl excimer laser.[50-52] UVA1 was also successful in reducing PPPASI scores in a pilot prospective study in 2016 with minimal adverse effects including burning, pruritus, and hyperpigmentation.[53] When compared with one another, UVA1 was found to be more effective than narrowband UVB, with a greater reduction in the PPPASI score (P<0.05).[54]

Alternative Treatment

Given the difficult treatment landscape of PPP, alternative treatments have been devised over the years to help patients with recalcitrant disease and shorten the course to remission. A few case studies have described the use of radiation therapy for PPP. A 2019 study with 2 patients demonstrated significant improvement in PPP within 3 to 4 treatments of radiation, with 1 patient experiencing recurrence after cessation of radiation.[55] Brachytherapy, or radiation therapy in which radiation is placed inside or next to the area requiring treatment, was also shown to be efficacious in a case of treatment-resistant PPP.[56]

Six patients with PPP treated with an oral rinse containing ozone nanobubble water were found to achieve complete remission within 3 to 4 months of continuous use. The rinse's mechanism of action involves the destruction of oral bacteria that are thought to be involved in the formation of PPP lesions.[57]

CONCLUSION

While no medications are FDA-approved for PPP, a variety of therapeutic options have shown promise. Topical medications are often useful for patients with limited disease involvement, but they may not sustain their response long-term. Systemic treatments, including biologics, JAK inhibitors, DMARDs, and retinoids can be effective in achieving PPP clearance, but not without side effects. Phototherapy, while efficacious, may pose other challenges of accessibility and cost.

The multifactorial origin and often chronic nature of PPP makes it challenging to treat. Despite hundreds of studies and trials, a treatment schematic for PPP has yet to be established. While the efficacy of these treatments has been studied in clinical trials, some studies are limited by small sample sizes, varying methodologies and endpoints, and short follow-up periods. Direct comparisons between different treatment options are often not found, further complicating the ability of clinicians to choose the appropriate treatment for their patients. Additional large, double-blinded, placebo-controlled randomized trials and studies with direct comparisons between treatments will be helpful for healthcare providers and patients in making informed decisions about PPP treatments.

DISCLOSURES

Dr Wu is or has been an investigator, consultant, or speaker for AbbVie, Almirall, Amgen, Arcutis, Aristea Therapeutics, Bausch Health, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, DermTech, Dr. Reddy's Laboratories, Eli Lilly, EPI Health, Galderma, Janssen, LEO Pharma, Mindera, Novartis, Pfizer, Regeneron, Samsung Bioepis, Sanofi Genzyme, Solius, Sun Pharmaceutical, UCB, and Zerigo Health. Dr Han is or has been an investigator, consultant/advisor, or speaker for AbbVie, Athenex, Boehringer Ingelheim, Bond Avillion, Bristol-Myers Squibb, Celgene Corporation, Dermavant, Eli Lilly, Janssen, LEO Pharma, MC2, Novartis, Ortho Dermatologics, PellePharm, Pfizer, Regeneron, Sanofi/Genzyme, SUN Pharmaceutical, and UCB. Authors Devjani, Smith, and Collier have no conflicts of interest to declare.

REFERENCES

1. Murakami M, Terui T. Palmoplantar pustulosis: Current understanding of disease definition and pathomechanism. *J Dermatol Sci.* 2020;98(1):13-19. doi: 10.1016/j.jdermsci.2020.03.003.
2. Benzian-Olsson N, Dand N, Chaloner C, et al. Association of clinical and demographic factors with the severity of palmoplantar pustulosis. *JAMA Dermatol.* 2020 Nov 1;156(11):1216-1222. doi: 10.1001/jamadermatol.2020.3275.
3. Asumalahti K, Ameen M, Suomela S, et al. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. *J Invest Dermatol.* 2003;120(4):627-32.
4. Hagforsen E, Hedstrand H, Nyberg F, et al. Novel findings of Langerhans cells and interleukin-17 expression in relation to the acrosyringium and pustule in palmoplantar pustulosis. *Br J Dermatol.* 2010;163(3):572-9. doi: 10.1111/j.1365-2133.2010.09819.x.
5. Brunasso AM, Puntoni M, Aberer W, et al. Clinical and epidemiological comparison of patients affected by palmoplantar plaque psoriasis and palmoplantar pustulosis: a case series study. *Br J Dermatol.* 2013;168(6):1243-51. doi: 10.1111/bjd.12223.
6. 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.* 2020;13:561-578.

7. Muro M, Kawakami H, Matsumoto Y, et al. Topical combination therapy with vitamin D3 and corticosteroid ointment for palmoplantar pustulosis: A prospective, randomized, left-right comparison study. *J Dermatolog Treat.* 2016;27(1):51-3. doi: 10.3109/09546634.2015.1052036.
8. Baum P, Visvanathan S, Garcet S, et al. Pustular psoriasis: Molecular pathways and effects of spesolimab in generalized pustular psoriasis. *J Allergy Clin Immunol.* 2022;149(4):1402-1412. doi: 10.1016/j.jaci.2021.09.035.
9. Mrowietz U, Burden AD, Pinter A, et al. Spesolimab, an anti-interleukin-36 receptor antibody, in patients with palmoplantar pustulosis: results of a phase IIa, multicenter, double-blind, randomized, placebo-controlled pilot study. *Dermatol Ther (Heidelb).* 2021;11(2):571-585. doi: 10.1007/s13555-021-00504-0.
10. Nakao M, Asano Y, Kamata M, et al. Successful treatment of palmoplantar pustular psoriasis with brodalumab. *Eur J Dermatol.* 2018;28(4):538-539. doi: 10.1684/ejd.2018.3325.
11. Pinter A, Wilsmann-Theis D, Peitsch WK, et al. Interleukin-17 receptor A blockade with brodalumab in palmoplantar pustular psoriasis: Report on four cases. *J Dermatol.* 2019;46(5):426-430. doi: 10.1111/1346-8138.14815.
12. Menter A, Warren RB, Langley RG, et al. Efficacy of ixekizumab compared to etanercept and placebo in patients with moderate-to-severe plaque psoriasis and non-pustular palmoplantar involvement: results from three phase 3 trials (UNCOVER-1, UNCOVER-2 and UNCOVER-3). *J Eur Acad Dermatol Venereol.* 2017;31(10):1686-1692. doi: 10.1111/jdv.14237.
13. He F, Long F, Yin Z, et al. Local injection of low dose ixekizumab for the treatment of palmoplantar pustular psoriasis. *Int J Dermatol.* 2022;61(6):742-743. doi: 10.1111/ijd.16185.
14. Mrowietz U, Bachelez H, Burden AD, et al. Secukinumab for moderate-to-severe palmoplantar pustular psoriasis: Results of the 2PRECISE study. *J Am Acad Dermatol.* 2019;80(5):1344-1352. doi: 10.1016/j.jaad.2019.01.066.
15. Li QY, Wang G. Successful treatment of adalimumab-resistant palmoplantar pustulosis with secukinumab: a case report. *Chin Med J (Engl).* 2020;133(24):3013-3014. doi: 10.1097/CM9.0000000000001246.
16. Reymundo A, Vilarrasa E, Baniandrés O, et al. Effectiveness and safety profile of secukinumab for the treatment of patients with generalized pustular psoriasis in daily practice. *J Eur Acad Dermatol Venereol.* 2022;36(10):e849-e851. doi: 10.1111/jdv.18317.
17. Platsidaki E, Kostopoulos N, Marnelakis I, et al. Secukinumab shows significant efficacy in two patients with difficult-to-treat areas of psoriasis: a Greek experience. *Dermatol Online J.* 2018;24(3):13030/qt9w02w406.
18. Chan TC, Hawkes JE, Krueger JG. Interleukin 23 in the skin: role in psoriasis pathogenesis and selective interleukin 23 blockade as treatment. *Ther Adv Chronic Dis.* 2018;9(5):111-119. doi: 10.1177/2040622318759282.
19. Del Campo DC. Successful use of tildrakizumab for treatment of palmoplantar pustulosis: a case report. *J Drugs Dermatol.* 2021;20(10):1117-1119. doi: 10.36849/JDD.6031.
20. Hugo J, Arenbergerova M, Arenberger P, et al. Coexistence of palmoplantar pustulosis and ichthyosis vulgaris treated by risankizumab. *Br J Dermatol.* 2021;184(6):e195. doi: 10.1111/bjd.19835.
21. Terui T, Kobayashi S, Okubo Y, et al. Efficacy and safety of guselkumab, an anti-interleukin 23 monoclonal antibody, for palmoplantar pustulosis: a randomized clinical trial. *JAMA Dermatol.* 2018;154(3):309-316. doi: 10.1001/jamadermatol.2017.5937.
22. Okubo Y, Morishima H, Zheng R, et al. Sustained efficacy and safety of guselkumab in patients with palmoplantar pustulosis through 1.5 years in a randomized phase 3 study. *J Dermatol.* 2021;48(12):1838-1853. doi: 10.1111/1346-8138.16132.
23. Duderstadt S, Raap U, Patsinakidis N. Rapid therapeutic response of palmoplantar pustulosis under biologic treatment with guselkumab. *Dermatol Ther.* 2021;34(2):e14792. doi: 10.1111/dth.14792.
24. Buder V, Herberger K, Jacobi A, et al. Ustekinumab in the treatment of palmoplantar pustular psoriasis - a case series of nine patients. *J Dtsch Dermatol Ges.* 2016;14(11):1108-1113. doi: 10.1111/ddg.12825.
25. Hegazy S, Konstantinou MP, Bulai Livideanu C, et al. Efficacy of ustekinumab in palmoplantar pustulosis. *J Eur Acad Dermatol Venereol.* 2018;32(5):e204-e206. doi: 10.1111/jdv.14718.
26. Bohdanowicz M, Sajic D. Refractory palmoplantar pustular psoriasis treated with high-dose ustekinumab after initial failure. *J Cutan Med Surg.* 2019;23(1):102-104. doi: 10.1177/1203475418795823.
27. Dorgham N, Crasto D, Skopit S. Successful treatment of palmoplantar pustulosis with apremilast. *J Drugs Dermatol.* 2021;20(11):1255-1256. doi: 10.36849/jdd.6098.
28. Del Alcázar E, Suárez-Pérez JA, Armesto S, et al. Real-world effectiveness and safety of apremilast in psoriasis at 52 weeks: a retrospective, observational, multicentre study by the Spanish Psoriasis Group. *J Eur Acad Dermatol Venereol.* 2020;34(12):2821-2829. doi: 10.1111/jdv.16439.
29. Eto A, Nakao M, Furue M. Three cases of palmoplantar pustulosis successfully treated with apremilast. *J Dermatol.* 2019;46(1):e29-e30. doi: 10.1111/1346-8138.14516.
30. Pavia G, Gargiulo L, Cortese A, et al. Apremilast for the treatment of palmo-plantar non-pustular psoriasis: A real-life single-center retrospective study. *Dermatol Ther.* 2022;35(2):e15253. doi: 10.1111/dth.15253.
31. Marovt M, Marko PB. Apremilast monotherapy for palmoplantar pustulosis: Report of three cases. *SAGE Open Med Case Rep.* 2021;9:2050313X211034926. doi: 10.1177/2050313X211034926.
32. Kt S, Thakur V, Narang T, et al. Apremilast in treatment of palmoplantar pustulosis - a case series. *Int J Dermatol.* 2021;60(6):e247-e248. doi: 10.1111/ijd.15398.
33. Kato N, Takama H, Ando Y, et al. Immediate response to apremilast in patients with palmoplantar pustulosis: a retrospective pilot study. *Int J Dermatol.* 2021;60(5):570-578. doi: 10.1111/ijd.15382.
34. Ständer S, Syring F, Ludwig RJ, et al. Successful treatment of refractory palmoplantar pustular psoriasis with apremilast: a case series. *Front Med (Lausanne).* 2020;7:543944. doi: 10.3389/fmed.2020.543944.
35. Carrascosa de Lome R, Conde Montero E, de la Cueva Dobao P. Refractory palmoplantar pustulosis succesfully treated with apremilast. *Dermatol Ther.* 2020;33(2):e13230. doi: 10.1111/dth.13230.
36. Wilsmann-Theis D, Kromer C, Gerdes S, et al. A multicentre open-label study of apremilast in palmoplantar pustulosis (APLANTUS). *J Eur Acad Dermatol Venereol.* 2021;35(10):2045-2050. doi: 10.1111/jdv.17441.
37. Haynes D, Topham C, Hagstrom E, et al. Tofacitinib for the treatment of recalcitrant palmoplantar pustulosis: A case report. *Australas J Dermatol.* 2020;61(1):e108-e110. doi: 10.1111/ajd.13117. PMID: 31318041.
38. Mössner R, Hoff P, Mohr J, et al. Successful therapy of palmoplantar pustulosis with tofacitinib-Report on three cases. *Dermatol Ther.* 2020;33(4):e13753. doi: 10.1111/dth.13753.
39. 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. *Clin Immunol.* 2016;173:147-148. doi: 10.1016/j.clim.2016.10.003.
40. Li C, Li Z, Cao Y, et al. Tofacitinib for the treatment of nail lesions and palmoplantar pustulosis in synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome. *JAMA Dermatol.* 2021;157(1):74-78. doi: 10.1001/jamadermatol.2020.3095.
41. Cro S, Smith C, Wilson R, et al. Treatment of pustular psoriasis with anakinra: a statistical analysis plan for stage 1 of an adaptive two-staged randomised placebo-controlled trial. *Trials.* 2018;19(1):534. doi: 10.1186/s13063-018-2914-y.
42. Cro S, Patel P, Barker J, et al. A randomised placebo-controlled trial of anakinra for treating pustular psoriasis: statistical analysis plan for stage two of the APRICOT trial. *Trials.* 2020;21(1):158. doi: 10.1186/s13063-020-4103-z.
43. Cro S, Cornelius VR, Pink AE, et al. Anakinra for palmoplantar pustulosis: results from a randomized, double-blind, multicentre, two-staged, adaptive placebo-controlled trial (APRICOT). *Br J Dermatol.* 2021;186(2):245–56. doi: 10.1111/bjd.20653.
44. Stanford CW, Kollipara R, Melookaran AM, et al. Palmoplantar pustular psoriasis following initiation of a beta-blocker: disease control with low-dose methotrexate. *Cutis.* 2014;94(3):153-5.
45. Reich K, Graff O, Mehta N. Oral alitretinoin treatment in patients with palmoplantar pustulosis inadequately responding to standard topical treatment: a randomized phase II study. *Br J Dermatol.* 2016;174(6):1277-81. doi: 10.1111/bjd.14401.
46. Brunasso AMG, Massone C. Alitretinoin therapy for palmoplantar pustulosis. *Br J Dermatol.* 2017;177(2):578-579. doi: 10.1111/bjd.15605. Epub 2017 Jun 14.
47. Wilken R, Sharma A, Patel F, et al. Successful treatment of palmoplantar pustulosis with isotretinoin. *Dermatol Online J.* 2015;21(8):13030/qt4b4776gb.
48. Lassus A, Geiger JM. Acitretin and etretinate in the treatment of palmoplantar pustulosis: a double-blind comparative trial. *Br J Dermatol.* 1988;119(6):755-9. doi: 10.1111/j.1365-2133.1988.tb03499.x.
49. Adişen E, Tekin O, Gülekon et al. A retrospective analysis of treatment responses of palmoplantar psoriasis in 114 patients. *J Eur Acad Dermatol Venereol.* 2009;23(7):814-9. doi: 10.1111/j.1468-3083.2009.03197.x.
50. Gianfaldoni S, Tchernev G, Wollina U, et al. Pustular palmoplantar psoriasis successfully treated with Nb-UVB monochromatic excimer light: a case-report. *Open Access Maced J Med Sci.* 2017;5(4):462-466. doi: 10.3889/oamjms.2017.080.
51. Esen Salman K, Kıvanç Altunay İ, Salman A. The efficacy and safety of targeted narrowband UVB therapy: a retrospective cohort study. *Turk J Med Sci.* 2019;49(2):595-603. doi: 10.3906/sag-1810-110.
52. Peng C, Hu Y, Chen W, et al. A randomized prospective study of different dose regimens using the 308-nm excimer laser in the treatment of palmoplantar pustulosis. *Dermatol Ther.* 2021;34(5):e15079. doi: 10.1111/dth.15079.
53. Su LN, Xu X, Tang L, et al. UVA1 phototherapy in the treatment of palmoplantar pustulosis: a pilot prospective study. *Lasers Med Sci.* 2016;31(8):1641-1643. doi: 10.1007/s10103-016-2031-7.
54. Su LN, Ren J, Cheng SM, et al. UVA1 vs. narrowband UVB phototherapy in the treatment of palmoplantar pustulosis: a pilot randomized controlled study. *Lasers Med Sci.* 2017;32(8):1819-1823. doi: 10.1007/s10103-017-2280-0.
55. King BJ, Langeveld AP, Davis MDP, et al. Skin-directed radiation therapy for palmoplantar pustulosis. *JAAD Case Rep.* 2019;5(6):478-480. doi: 10.1016/j.jdcr.2019.01.010.
56. Timerman D, Devlin PM, Nambudiri VE, et al. Novel application of high-dose rate brachytherapy for severe, recalcitrant palmoplantar pustulosis. *Clin Exp Dermatol.* 2016;41(5):498-501. doi: 10.1111/ced.12803.
57. Horiuchi Y. Palmoplantar pustulosis treated with oral rinse using ozone nanobubble water: a case series. *Dermatol Ther.* 2020;33(6):e13924. doi: 10.1111/dth.13924.

AUTHOR CORRESPONDENCE

Jashin J. Wu MD

E-mail:..... jashinwu@gmail.com