Review paper

Biologics as a novel treatment option for palmoplantar pustulosis: a comprehensive review

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Abstract

Introduction: Palmoplantar pustulosis (PPP) is a complex inflammatory skin disease. Currently, no standardized treatments exist, and traditional systemic therapies often display limited effectiveness and substantial adverse effects. Biologics, however, have shown potential for enhanced clinical outcomes in psoriasis patients, thereby prompting this investigation into their applicability in PPP treatment.

Aim: This study constitutes the first comprehensive review to assess the effectiveness and underlying mechanisms of biologics for PPP.

Material and methods: We conducted a PubMed search to identify studies on biologics for PPP from 1992 onward. The review focused on assessing the efficacy of biologics targeting cytokines like IL-1, IL-8, IL-17, IL-12/23, IL-36, and TNF-α.

Results: Biologics for PPP are generally less effective than for psoriasis. Secukinumab and guselkumab, IL-17 and IL-23 inhibitors respectively, have shown better results compared to other biologics in trials. However, the effectiveness of other biologics remains uncertain due to limited data.

Conclusions: More research is needed to find effective treatments for PPP, and selecting the right biologic for each patient is challenging.

Key words: palmoplantar pustulosis, biologics, treatments.

Introduction

Palmoplantar pustulosis (PPP) is an inflammatory skin condition characterized by persistent, sterile pustules on palms and soles. Recent genetic research indicates that PPP may not even be related to psoriasis [1]. PPP remains poorly understood, with its exact mechanisms yet unexplored and no standard treatment guidelines available to address its symptoms. Traditional therapies tend to have limited benefits while potentially having adverse side effects. Biologics, however, have already shown superior efficacy for psoriasis. In this paper we aim to review the efficacy and mechanisms of biologics for PPP treatment.

Anti-IL-1

Anakinra

The Interleukin-1 family comprises eleven members, divided into 7 agonists (IL-1α, IL-1β, IL-18, IL-33 and IL-36α/β/γ) and 4 antagonists (IL-1Ra/IL-36Ra, IL-37/38) [2].

Anakinra acts as an antagonist to IL-1 receptor (IL-1Ra), blocking both pro-inflammatory cytokines IL-1α and IL-1β from functioning properly. Both these cytokines have pro-inflammatory effects; IL-1α can stimulate T-cell-driven inflammation in skin tissues [3] while IL-1β induces keratinocytes to produce inflammatory chemokines [4]. Studies have noted increased levels of IL-1-related chemokines within PPP lesions [5]. Therefore, therapeutic strategies targeting IL-1 such as anakinra maybe helpful for PPP.

Previous phase II open-label dose-escalation trials demonstrating the efficacy of anakinra treatment on pustular psoriasis support this claim, with > 50% TBSAI reduction for half of 14 patients after 12 weeks of treatments [6]. Nonetheless, the randomised controlled trial (RCT) "APRICOT" demonstrated that anakinra showed limited effectiveness in treating PPP. In this trial, 31 PPP patients received anakinra for 8 weeks; however, there was no significant difference in the number of responders achieving palmoplantar pustulosis Psoriasis Area and Severity Index (ppPASI-50/75) compared to the placebo

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group [7]. The lack of significant results may be attributed to the brief duration of the follow-up period.

Moreover, there are few case reports indicating that anakinra is effective in treating diseases related to PPP such as SAPHO syndrome and generalized pustular psoriasis (GPP) [8–11]. At present, the efficacy of anakinra in treating PPP is not fully understood, and need further studies.

Canakinumab

Unlike anakinra, canakinumab is an inhibitor that specifically targets IL-1β. There has been a case report of a PPP patient experiencing good results when using canakinumab in conjunction with cyclosporine, but the effectiveness of canakinumab alone in treatment was not satisfactory [12].

Anti-IL-8

HuMab 10F8

HuMab 10F8 is a novel fully human monoclonal antibody that effectively neutralizes IL-8. IL-8 is an inflammatory chemokine related to neutrophil activation, and previous studies have confirmed that levels of IL-8 are elevated in the lesions of PPP patients [13, 14]. Previous research also confirmed that levels of IL-8 in the epidermis and sweat glands of PPP patient lesions are increased [15], making IL-8 inhibitors a potential option for PPP treatment. A previous open-label, multicentre study showed that the number of pustules of PPP patients treated with HuMab 10F8 were significantly decreased, with most patients experiencing significant symptom relief [16]. However, due to the limited amount of research related to IL-8 biologics, the true efficacy of IL-8 inhibitors in improving PPP symptoms cannot be fully confirmed.

Anti-IL-17

Secukinumab

IL-17 is associated with psoriasis [17]. The IL-17 family cytokine comprises six subcomponents – A, B, C, D, E and F – with A and F being the main components. Both IL-17A/F are produced by Th17 cells and play an essential part in epithelial defence processes [18].

RCTs have proven the efficacy of secukinumab, a humanized monoclonal antibody targeting IL-17A, for treating psoriasis [19–26]. Furthermore, recent investigations have uncovered significant elevation of IL-17A expression in lesions from PPP patients [27]. IL-17A is implicated in the abnormal proliferation and differentiation of keratinocytes [28]. It also amplifies inflammation by boosting pro-inflammatory cytokines and chemokines [29, 30].

While the efficacy of secukinumab in treating psoriasis is well established, its effectiveness in treating PPP remains less thoroughly researched. Nevertheless, a phase 3b RCT focused on PPP patients demonstrated promising results for secukinumab. Notably, at week 16, 52.2% of patients receiving 300 mg of secukinumab achieved a ppPASI-50 score compared to 32.9% in the placebo group ($p = 0.0159$). Additionally, 26.6% of the same secukinumab group reached ppPASI-75, outperforming both the 150 mg secukinumab group (17.5%, $p = 0.0411$) and the placebo group (14.1%, $p = 0.05722$) (Figure 1). These results support the hypothesis that IL-17A is a key factor in the pathogenesis of PPP and suggest that secukinumab holds substantial therapeutic promise for this condition [31].

Furthermore, the efficacy of secukinumab in addressing conditions closely aligned with PPP, such as GPP and palmoplantar psoriasis, has been reported to be superior [32, 33]. This observation, drawn from current literature and empirical evidence, underscores Secukinumab's es-

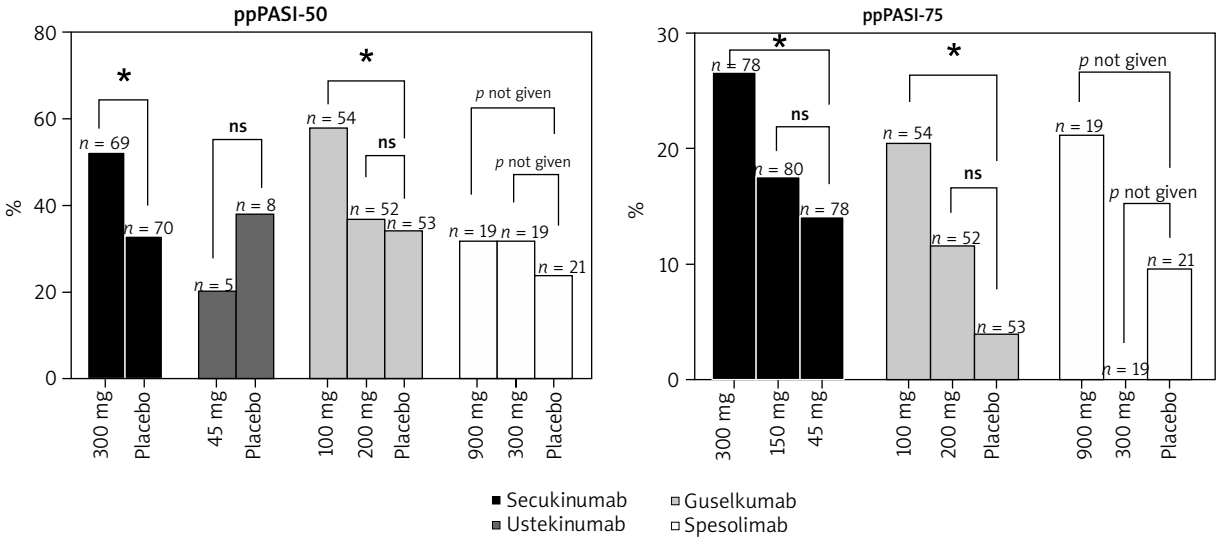

Figure 1. Four published RCTs included in this paper

tablished effectiveness in psoriasis treatment and suggests its potential applicability in managing PPP.

Ixekizumab

Ixekizumab, like secukinumab, is a humanized monoclonal antibody targeting IL-17A. A phase 3 RCT with 351 psoriasis patients found that ixekizumab administration every 2 weeks resulted in 50% of patients achieving ppPASI-75 at week 4. Effectiveness of treatment progressively increased, with 90% of patients reaching ppPASI-75 by week 12 [34]. This emphasizes ixekizumab's significant therapeutic efficacy for treating psoriasis while suggesting its potential use against similar skin conditions.

Brodalumab

Brodalumab, a human IgG2 monoclonal antibody, has shown significant effectiveness for managing both psoriasis and psoriatic arthritis in multiple RCTs [35–41]. Brodalumab stands apart from secukinumab and ixekizumab as it targets multiple subtypes of IL-17 including IL-17A, IL-17A/F, and IL-17F [42]. IL-17A/F could act on keratinocytes to produce neutrophil-attracting chemokines [43]. PPP lesions exhibit higher expression levels for IL-17A/C/D/F than normal palmar skin, and elevated serum IL-17 levels in PPP patients have also been observed [44]. Despite the theoretical advantage, a case series involving four PPP patients revealed minimal or no improvement after brodalumab treatment [45].

Anti-IL-12/23

Ustekinumab

IL-12 and IL-23, both secreted by myeloid cells, are crucial for the development of Th1 cells and the activity of Th17 cells, respectively [46]. Research has demonstrated that mRNA levels of IL-12/23p40 in psoriasis lesions exceed those in healthy skin [47], with associated cytokines also elevated due to IL-12 and IL-23 stimulation [48]. Ustekinumab, which specifically targets the p40 subunit shared by both IL-12 and IL-23, effectively reduces IL-17A and IL-17F production from Th17 cells [49]. Previous RCTs have shown that ustekinumab not only improves the symptoms and overall quality of life for psoriasis patients but also ameliorates symptoms of depression and anxiety [50]. However, a smaller RCT involving 13 PPP patients showed that 45 mg of ustekinumab failed to offer significant benefits over placebo at 16 weeks, with response rates of 10% and 20% for ppPASI-50, respectively (p = 1.000) (Figure 1). This suggests that IL-17 may play a more crucial role in PPP pathogenesis than IL-12/23, as evidenced by a 190-fold increase in IL-17 gene expression in PPP patients versus healthy individuals, with no significant changes in IL-12/23 subunits p19 and p40 expression levels [27]. Despite these findings, various case reports have documented mixed results [51–53].

In another study focused on the effectiveness of biologics for PPP, participants were treated with specific biologics for over 12 weeks. Results indicated that among 30 patients in the ustekinumab group, 37.9% achieved complete clearance, with a clinical symptom improvement rate of 70%, and the lowest rate of adverse reactions among the biologics evaluated [54]. These findings are in stark contrast to earlier results [27]. Furthermore, research indicates that 90 mg of ustekinumab significantly alleviates symptoms in patients with palmoplantar psoriasis. Of the nine patients administered 90 mg, 67% achieved complete lesion clearance, compared to only 9% of the 11 patients treated with 45 mg [55].

Guselkumab

Compared to ustekinumab, the IL-23 inhibitor guselkumab exhibits more significant therapeutic effects in treating PPP. Previous RCT reports demonstrate that PPP patients treated with guselkumab experienced significant improvements as early as week 2, with further improvements at weeks 16 and 52 [56, 57] (Figure 1). At week 16, the 100 mg group, the 200 mg group, and the placebo group had ppPASI-50 responders at 57.4%, 36.5%, and 34.0%, respectively; ppPASI-75 responders at 20.4%, 11.5%, and 3.8%, respectively. Guselkumab, identified as a fully human IgG1λ monoclonal antibody, acts by inhibiting the production of related cytokines through blocking the binding of IL-23 to its p19 subunit [58], suggesting that guselkumab represents a safe and effective option for PPP treatment.

Risankizumab

Risankizumab, a humanized IgG1 monoclonal antibody, targets the p19 subunit of IL-23. Numerous RCTs have documented its effectiveness in managing psoriasis [59–66]. Furthermore, risankizumab has demonstrated remarkable results in treating palmoplantar psoriasis, with the ppPASI90 response rate improving from 18.7% at week 4 to 81.2% by week 52 [67]. These findings suggest that risankizumab may be an option for diseases related to PPP, such as psoriasis and palmoplantar psoriasis. However, high quality evidence confirming its efficacy for PPP remains lacking.

Tildrakizumab

Tildrakizumab is also an antibody targeting the p19 subunit of IL-23. Currently, there is only one case report concerning the treatment of PPP with tildrakizumab [68]. Moreover, RCTs have shown superior results of tildrakizumab in treating psoriasis [69].

TNF-α inhibitors

Infliximab

TNF-α serves as a pro-inflammatory mediator, facilitating T cell infiltration and modulating the antigen-

presenting function of dendritic cells [70]. Inhibitors of TNF-α operate by modulating the IL-23/Th-17 pathway; specifically, they reduce IL-23 concentrations and decrease the levels of Th17 effector molecules such as IL-17 and IL-22, thereby exerting their therapeutic effects [71].

Infliximab, a chimeric monoclonal antibody, exhibits a specific binding affinity to TNF-α [72]. Extensive research from numerous RCTs highlights infliximab's robust effectiveness in managing both psoriasis and psoriatic arthritis [73–79]. Additionally, further RCTs confirm its success in treating palmoplantar psoriasis [80]. A multicentre retrospective study, which included 347 patients with PPP, revealed that infliximab provided the longest maintenance of efficacy, averaging 26 months. This was compared to ustekinumab at 21 months, adalimumab at 18 months, and etanercept at 8 months. Moreover, infliximab achieved the highest treatment success rate, with 40.6% of patients experiencing more than 75% improvement in symptoms. This is significantly better than the outcomes with ustekinumab (31%), adalimumab (33.3%), and etanercept (19.4%) [81].

Concurring with this perspective, a German study involving 92 patients compared infliximab with ustekinumab, adalimumab, and etanercept, revealed that up to 77.3% of PPP patients achieved symptom improvement, exceeding the improvement rates of other biologics. However, infliximab did not demonstrate superiority in the complete clearance rate (CC) compared to other biologics [54]. These results indicate that infliximab may be a viable option for PPP treatment. However, numerous reports highlight adverse reactions associated with infliximab [82–84].

Adalimumab

Adalimumab is a fully human monoclonal antibody that blocks the interaction between TNF-α and its receptors, the p55 and p75 subunits [85]. Similarly, numerous RCTs have confirmed adalimumab's significant efficacy in treating psoriasis [86–91]. A multicentre, retrospective study demonstrated that 50% of 50 PPP patients treated with adalimumab experienced improvements in disease severity, and 17.6% achieved complete lesion clearance (CC) [54]. Case reports also suggest adalimumab's effectiveness in treating PPP [932,93], although it can sometimes induce PPP [94,95].

Etanercept

Etanercept is a recombinant human TNF receptor p75 Fc fusion protein [96]. Previous studies have demonstrated significant effectiveness of etanercept in treating plaque psoriasis [97]. In PPP patients, several case reports document rapid symptom improvement following etanercept use [98, 99]. However, in a prior RCT involving PPP patients, 15 patients treated with etanercept for 12 weeks exhibited no superior outcomes compared to placebo [100]. Given the conflicting reports on etanercept's efficacy in treating PPP, there is a need for further high-level clinical evidence to corroborate its effectiveness.

It is crucial to acknowledge that TNF-α inhibitor treatment does not universally benefit all forms of pustular psoriasis, and may, in some instances, exacerbate the condition [101, 102]. The underlying mechanisms of this paradoxical exacerbation remain incompletely understood. Some researchers postulate that this phenomenon could be linked to the activation of plasmacytoid dendritic cells. Under anti-TNF-α therapy, these cells may commence overproduction of IFN-γ, subsequently activating T cells and prompting an increased production of TNF-α [103].

Anti-IL-36

Spesolimab

The IL-36 family comprises three agonists (IL-36α/β/γ) and one antagonist (IL-36Ra) [104]. Studies have demonstrated that Th17 cytokines can influence IL-36 levels, and conversely, IL-36 can affect the expression of Th17 cytokines [105]. A robust link between Th17 cytokines and psoriasis has been well established [106,107]. The involvement of IL-36α/β/γ in psoriatic development is posited to occur through the IL23/IL-17A pathway [108].

Spesolimab, a humanized monoclonal IgG1 antibody, has been shown to be effective in blocking IL-36R signalling [109]. Elevated IL-36 levels have been observed in the lesions of patients with PPP compared to normal levels [110]. RCTs have demonstrated that spesolimab significantly improves symptoms in patients with generalized pustular psoriasis (GPP) [111–112]. Given the substantial overlap between GPP and PPP, spesolimab is considered a potential treatment for PPP. However, in a phase 2a, multicentre, double-blind, randomised pilot study including 59 patients, neither 900 mg nor 300 mg doses of spesolimab demonstrated significant efficacy over placebo in treating PPP. At 16 weeks, 31.6% of participants in both the 900 mg and 300 mg spesolimab groups, and 23.8% in the placebo group, achieved ppPASI-50; corresponding figures for ppPASI-75 were 21.1%, 0%, and 9.5% [113]. Another multicentre, double-blind, phase 2b RCT corroborated these findings as it also failed to meet efficacy endpoints with no significant differences in ppPASI scores observed between the spesolimab and placebo groups at 16 weeks [114]. Given these outcomes, spesolimab may not be an effective treatment option for PPP, although further phase 3 trials are required to confirm this assessment.

Conclusions

Currently, the effectiveness of biologic therapies in treating palmoplantar pustulosis (PPP) appears to be inferior to their performance against plaque psoriasis.

Among biologics proven effective in randomised controlled trials, the IL-17 inhibitor, secukinumab, and the IL-23 inhibitor, guselkumab, have exhibited relatively higher effectiveness compared to others. Nonetheless, the efficacy of several other biologics, including IL-17 inhibitors like ixekizumab and brodalumab, and IL-23 inhibitors such as risankizumab, as well as various TNF inhibitors, remains uncertain due to the lack of robust clinical efficacy data. Extensive clinical research is essential to identify more effective biologic treatments for PPP. The response of PPP to biologics varies significantly, necessitating additional investigation and clinical trials to pinpoint the most beneficial treatments. While biologics hold considerable promise for alleviating symptoms in PPP patients, selecting the most suitable biologic for an individual patient at the optimal time remains a significant challenge (Supplementary).

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Conflict of interest

The authors declare no conflict of interest.

References

1. Mrowietz U, van de Kerkhof PC. Management of palmoplantar pustulosis: do we need to change? Br J Dermatol 2011; 164: 942-6.
2. Palomo J, Dietrich D, Martin P, et al. The interleukin (IL)-1 cytokine family--balance between agonists and antagonists in inflammatory diseases. Cytokine 2015; 76: 25-37.
3. Di Paolo NC, Shayakhmetov DM. Interleukin 1 and the inflammatory process. Nat Immunol 2016; 17: 906-13.
4. Renne J, Schäfer V, Werfel T, Wittmann M. Interleukin-1 from epithelial cells fosters T cell-dependent skin inflammation. Br J Dermatol 2010; 162: 1198-205.
5. Cai Y, Xue F, Quan C, et al. A critical role of the IL-1 -IL-1R signaling pathway in skin inflammation and psoriasis pathogenesis. J Investig Dermatol 2019; 139: 146-56.
6. Naik HB, Pichard DC, Schwartz DM, et al. Anakinra for refractory pustular psoriasis: a phase II, open-label, dose-escalation trial. J Am Acad Dermatol 2022; 87: 1380-3.
7. Cro S, Cornelius VR, Pink AE, et al.; APRICOT Study Group. Anakinra for palmoplantar pustulosis: results from a randomized, double-blind, multicentre, two-staged, adaptive placebo-controlled trial (APRICOT). Br J Dermatol 2021; 186: 245-56.
8. Wendling D, Prati C, Aubin F. Anakinra treatment of SAPHO syndrome: short-term results of an open study. Ann Rheum Dis 2012; 71: 1098-100.
9. Hüffmeier U, Wätzold M, Mohr J, et al. Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations. Br J Dermatol 2014; 170: 202-4.
10. Hüffmeier U, Wätzold M, Mohr J, et al. Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations. Br J Dermatol 2014; 170: 202-4.
11. Viguier M, Guigue P, Pagès C, et al. Successful treatment of generalized pustular psoriasis with the interleukin-1-receptor antagonist Anakinra: lack of correlation with IL1RN mutations. Ann Inter Med 2010; 153: 66-7.
12. Mansouri B, Kivelevitch D, Campa M, Menter A. Palmoplantar pustular psoriasis unresponsive to the interleukin-1 antagonist canakinumab. Clin Exp Dermatol 2016; 41: 324-6.
13. Skov L, Beurskens FJ, Zachariae CO, et al. IL-8 as antibody therapeutic target in inflammatory diseases: reduction of clinical activity in palmoplantar pustulosis. J Immunol 2008; 181: 669-79.
14. Murakami M, Hagforsen E, Morhenn V, et al. Patients with palmoplantar pustulosis have increased IL-17 and IL-22 levels both in the lesion and serum. Exp Dermatol 2011; 20: 845-7.
15. Anttila HS, Reitamo S, Erkko P, et al. Interleukin-8 immunoreactivity in the skin of healthy subjects and patients with palmoplantar pustulosis and psoriasis. J Investig Dermatol 1992; 98: 96-101.
16. Skov L, Beurskens FJ, Zachariae CO, et al. IL-8 as antibody therapeutic target in inflammatory diseases: reduction of clinical activity in palmoplantar pustulosis. J Immunol 2008; 181: 669-79.
17. Balato A, Scala E, Balato N, et al. Biologics that inhibit the Th17 pathway and related cytokines to treat inflammatory disorders. Expert Opin Biol Ther 2017; 17: 1363-74.
18. Miossec P, Kolls JK. Targeting IL-17 and Th17 cells in chronic inflammation. Nature reviews. Drug Discov 2012; 11: 763-76.
19. Thaçi D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol 2015; 73: 400-9.
20. Langley RG, Sofen H, Dei-Cas I, et al. Secukinumab long-term efficacy and safety in psoriasis through to year 5 of treatment: results of a randomized extension of the phase III ERASURE and FIXTURE trials. Br J Dermatol 2023; 188: 198-207.
21. Bodemer C, Kaszuba A, Kingo K, et al. Secukinumab demonstrates high efficacy and a favourable safety profile in paediatric patients with severe chronic plaque psoriasis: 52-week results from a Phase 3 double-blind randomized, controlled trial. J Eur Acad Dermatol Venereol 2021; 35: 938-47.
22. Iversen L, Conrad C, Eidsmo L, et al. Secukinumab demonstrates superiority over narrow-band ultraviolet B phototherapy in new-onset moderate to severe plaque psoriasis patients: week 52 results from the STEPIn study. J Eur Acad Dermatol Venereol 2023; 37: 1004-16.
23. Bissonnette R, Luger T, Thaçi D, et al. Secukinumab demonstrates high sustained efficacy and a favourable safety profile in patients with moderate-to-severe psoriasis through 5 years of treatment (SCULPTURE Extension Study). J Eur Acad Dermatol Venereol 2018; 32: 1507-14.
24. Magnolo N, Kingo K, Laquer V, et al. Efficacy of secukinumab across subgroups and overall safety in pediatric patients with moderate to severe plaque psoriasis: week 52 results from a phase III randomized study. Paediatr Drugs 2022; 24: 377-87.

25. Puig L, Augustin M, Blauvelt A, et al. Effect of secukinumab on quality of life and psoriasis-related symptoms: a comparative analysis versus ustekinumab from the CLEAR 52-week study. J Am Acad Dermatol 2018; 78: 741-8.
26. Bissonnette R, Luger T, Thaçi D, et al. Secukinumab sustains good efficacy and favourable safety in moderate-to-severe psoriasis after up to 3 years of treatment: results from a double-blind extension study. Br J Dermatol 2017; 177: 1033-42.
27. Bissonnette R, Nigen S, Langley RG, et al. Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar(PP) pustular psoriasis or PP pustulosis; results from a randomised controlled trial. J Eur Acad Dermatol Venereol 2014; 28: 1298-305.
28. Lai Y, Li D, Li C, et al. The antimicrobial protein REG3A regulates keratinocyte proliferation and differentiation after skin injury. Immunity 2012; 37: 74-84.
29. Nograles KE, Zaba LC, Guttman-Yassky E, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol 2008; 159: 1092-102.
30. Liang SC, Tan XY, Luxenberg DP, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. J Exp Med 2006; 203: 2271-9.
31. 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: 1344-52.
32. Gottlieb A, Sullivan J, van Doorn M, et al. Secukinumab shows significant efficacy in palmoplantar psoriasis: results from GESTURE, a randomized controlled trial. J Am Acad Dermatol 2017; 76: 70-80.
33. Imafuku S, Honma M, Okubo Y, et al. Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: a 52-week analysis from phase III open-label multicenter Japanese study. J Dermatol 2016; 43: 1011-7.
34. Griffiths CE, Reich K, Lebwohl M, et al.; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet 2015; 386: 541-51.
35. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. N Engl J Med 2012; 366: 1181-9.
36. Puig L, Lebwohl M, Bachelez H, et al. Long-term efficacy and safety of brodalumab in the treatment of psoriasis: 120-week results from the randomized, double-blind, placebo- and active comparator-controlled phase 3 AMAGINE-2 trial. J Am Acad Dermatol 2020; 82: 352-9.
37. Gordon KB, Kimball AB, Chau D, et al. Impact of brodalumab treatment on psoriasis symptoms and health-related quality of life: use of a novel patient-reported outcome measure, the Psoriasis Symptom Inventory. Br J Dermatol 2014; 170: 705-15.
38. Gottlieb AB, Gordon K, Hsu S, et al. Improvement in itch and other psoriasis symptoms with brodalumab in phase 3 randomized controlled trials. J Eur Acad Dermatol Venereol 2018; 32: 1305-13.
39. Nakagawa H, Niiro H, Ootaki K; Japanese brodalumab study group. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: efficacy and safety results from a phase II randomized controlled study. J Dermatol Sci 2016; 81: 44-52.
40. Mease PJ, Genovese MC, Greenwald MW, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. N Engl J Med 2014; 370: 2295-306.
41. Mease PJ, Helliwell PS, Hjuler KF, et al. Brodalumab in psoriatic arthritis: results from the randomised phase III AMVISION-1 and AMVISION-2 trials. Ann Rheum Dis 2021; 80: 185-93.
42. Papp KA, Reid C, Foley P, et al. Anti-IL-17 receptor antibody AMG 827 leads to rapid clinical response in subjects with moderate to severe psoriasis: results from a phase I, randomized, placebo-controlled trial. J Investig Dermatol 2012; 132: 2466-9.
43. Martin DA, Towne JE, Kricorian G, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. J Investig Dermatol 2013; 133: 17-26.
44. Murakami M, Hagforsen E, Morhenn V, et al. Patients with palmoplantar pustulosis have increased IL-17 and IL-22 levels both in the lesion and serum. Exp Dermatol 2011; 20: 845-7.
45. Pinter A, Wilsmann-Theis D, Peitsch WK, Mössner R. Interleukin-17 receptor A blockade with brodalumab in palmoplantar pustular psoriasis: report on four cases. J Dermatol 2019; 46: 426-30.
46. Teng MW, Bowman EP, McElwee JJ, et al. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med 2015; 21: 719-29.
47. Lee E, Trepicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med 2004; 199: 125-30.
48. Chan JR, Blumenschein W, Murphy E, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. J Exp Med 2006; 203: 2577-87.
49. Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Investig Dermatol 2009; 129: 1339-50.
50. Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: results from a randomized, double-blind, placebo-controlled phase III trial. J Am Acad Dermatol 2010; 63: 457-65.
51. Gerdes S, Franke J, Domm S, Mrowiet, U. Ustekinumab in the treatment of palmoplantar pustulosis. Br J Dermatol 2010; 163: 1116-8.
52. Hegazy S, Konstantinou MP, Bulai Livideanu C, et al. Efficacy of ustekinumab in palmoplantar pustulosis. J Eur Acad Dermatol Venereol 2018; 32: e204e206.
53. Bertelsen T, Kragballe K, Johansen C, Iversen L. Efficacy of ustekinumab in palmoplantar pustulosis and palmoplantar pustular psoriasis. Int J Dermatol 2014; 53: e464-6. 1
54. Husson B, Barbe C, Hegazy S, et al.; « Groupe de Recherche sur le Psoriasis » de la Société Française de Dermatologie. Efficacy and safety of TNF blockers and of ustekinumab in palmoplantar pustulosis and in acrodermatitis continua of Hallopeau. J Eur Acad Dermatol Venereol 2020; 34: 2330-8.
55. Au SC, Goldminz AM, Kim N, et al. Investigator-initiated, open-label trial of ustekinumab for the treatment of moderate-to-severe palmoplantar psoriasis. J Dermatol Treat 2013; 24: 179-87.
56. 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: 309-16.
57. Terui T, Kobayashi S, Okubo Y, et al. Efficacy and safety of guselkumab in japanese patients with palmoplantar pustulosis: a phase 3 randomized clinical trial. JAMA Dermatol 2019; 155: 1153-61.
58. Mease PJ, Rahman P, Gottlieb AB, et al.; DISCOVER-2 Study Group. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020; 395: 1126-36.
59. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet 2018; 392: 650-61.
60. Reich K, Gooderham M, Thaçi D, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet 2019; 394: 576-86.
61. Blauvelt A, Leonardi CL, Gooderham M, et al. Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: a phase 3 randomized clinical trial. JAMA Dermatol 2020; 156: 649-58.
62. Stein Gold LF, Bagel J, Tyring SK, et al. Comparison of risankizumab and apremilast for the treatment of adults with moderate plaque psoriasis eligible for systemic therapy: results from a randomized, open-label, assessor-blinded phase IV study (IMMpulse). Br J Dermatol 2023; 189: 540-52.
63. Papp KA, Blauvelt A, Puig L, et al. Long-term safety and efficacy of risankizumab for the treatment of moderate-to-severe plaque psoriasis: interim analysis of the LIMMitless open-label extension trial up to 5 years of follow-up. J Am Acad Dermatol 2023; 89: 1149-58.
64. Gooderham M, Pinter A, Ferris LK, et al. Long-term, durable, absolute Psoriasis Area and Severity Index and health-related quality of life improvements with risankizumab treatment: a post hoc integrated analysis of patients with moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol 2022; 36: 855-65.
65. Al-Janabi A, Jabbar-Lopez ZK, Griffiths CEM, Yiu ZZN. Risankizumab vs. ustekinumab for plaque psoriasis: a critical appraisal. Br J Dermatol 2019; 180: 1348-51.
66. Ohtsuki M, Fujita H, Watanabe M, et al. Efficacy and safety of risankizumab in Japanese patients with moderate to severe plaque psoriasis: results from the SustaIMM phase 2/3 trial. J Dermatol 2019; 46; 686-94.
67. Caldarola G, Zangrilli A, Palmisano G, et al. Effectiveness of risankizumab in the treatment of palmoplantar psoriasis: a 52-week Italian real-life experience. Drugs Context 2023; 12: 2023-1-8.
68. Del Campo DC. Successful use of tildrakizumab for treatment of palmoplantar pustulosis: a case report. J Drugs Dermatol 2021; 20: 1117-9.
69. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet 2017; 390: 276-88.
70. Goldminz AM, Au SC, Kim N, et al. NF-κB: an essential transcription factor in psoriasis. J Dermatol Sci 2013; 69: 89-94.
71. Deng Y, Chang C, Lu Q. The inflammatory response in psoriasis: a comprehensive review. Clin Rev Allergy Immunol 2016; 50: 377-89.
72. Gottlieb AB, Chaudhari U, Mulcahy LD, et al. Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis. J Am Acad Dermatol 2003; 48: 829-35.
73. Chaudhari U, Romano P, Mulcahy LD, et al. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet 2001; 357: 1842-7.
74. Antoni C, Krueger GG, de Vlam K, et al.; IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005; 64: 1150-7.
75. Gottlieb AB, Evans R, Li S, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004; 51: 534-42.
76. Reich K, Nestle FO, Wu Y, et al. Infliximab treatment improves productivity among patients with moderate-to-severe psoriasis. Eur J Dermatol 2007; 17: 381-6.
77. Yang HZ, Wang K, Jin HZ, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. Chinese Med J 2012; 125: 1845-51.
78. Torii H, Nakagawa H; Japanese Infliximab Study investigators. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci 2010; 59: 40-9.
79. Torii H, Nakagawa H; Japanese Infliximab Study investigators. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci 2010; 9: 40-9.
80. Bissonnette R, Poulin Y, Guenther L, et al. Treatment of palmoplantar psoriasis with infliximab: a randomized, double-blind placebo-controlled study. J Eur Acad Dermatol Venereol 2011; 25: 1402-8.
81. Kromer C, Wilsmann-Theis D, Gerdes S, et al. Drug survival and reasons for drug discontinuation in palmoplantar pustulosis: a retrospective multicenter study. J Dtsch Dermatol Ges 2019; 17: 503-16.
82. Sladden MJ, Clarke PJ, Wettenhall J. Infliximab-induced palmoplantar pustulosis in a patient with Crohn disease. Arch Dermatol 2007; 143: 1449.
83. Hiremath G, Duffy L, Leibowitz I. Infliximab-induced psoriasis in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutrition 2011; 52: 230-2.
84. Cemil BC, Atas H, Canpolat F, et al. Infliximab-induced discoid lupus erythematosus. Lupus 2013; 22: 515-8.
85. Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006; 55: 598-606.
86. McInnes IB, Behrens F, Mease PJ, et al.; EXCEED Study Group. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet 2020; 395: 1496-505.
87. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol 2008; 58: 106-15.
88. Menter A, Gordon KB, Leonardi CL, et al. Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis. J Am Acad Dermatol 2010; 63: 448-56.

89. Papp K, Thaçi D, Marcoux D, et al. Efficacy and safety of adalimumab every other week versus methotrexate once weekly in children and adolescents with severe chronic plaque psoriasis: a randomised, double-blind, phase 3 trial. Lancet 2017; 390: 40-9.
90. Cai L, Gu J, Zheng J, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. J Eur Acad Dermatol 2017; 31: 89-95.
91. Gordon K, Papp K, Poulin Y, et al. Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL. J Am Acad Dermatol 2012; 66: 241-51.
92. Yawalkar N, Hunger RE. Successful treatment of recalcitrant palmoplantar pustular psoriasis with sequential use of infliximab and adalimumab. Dermatology 2009; 218: 79-83.
93. Yang Q, Xiang T, Wu Y, et al. SAPHO syndrome with palmoplantar pustulosis as the first manifestation successfully treated with adalimumab. Clin Cosmet Investig Dermatol 2022; 15: 2547-54.
94. Ibis N, Hocaoglu S, Cebicci MA, et al. Palmoplantar pustular psoriasis induced by adalimumab: a case report and literature review. Immunotherapy 2015; 7: 717-20.
95. Gkalpakiotis S, Fridman M, Tivadar S. Adalimumab biosimilar-induced severe paradoxical palmoplantar pustulosis in a patient with psoriasis and psoriatic arthritis successfully treated with ixekizumab. Dermatol Ther 2022; 12: 605-9.
96. Weinberg JM, Ritu Saini BA. Biologic therapy for psoriasis: the tumor necrosis factor inhibitors infliximab and etanercept. Cutis 2003; 71: 25-9.
97. Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003; 139: 1627-32.
98. Kasche A, Pfab F, Hein R, et al. Severe psoriasis pustulosa palmaris et plantaris (Barber-Königsbeck) treated successfully with soluble tumour necrosis factor receptor fusion protein (etanercept). J Eur Acad Dermatol Venereol 2007; 21: 255-7.
99. Antoniou C, Nicolaidou E, Moustou AE, et al. Palmoplantar pustulosis with arthro-osteitis: successful treatment with etanercept and acitretin. J Eur Acad Dermatol Venereol 2009; 23: 854-5.
100. Bissonnette R, Poulin Y, Bolduc C, et al. Etanercept in the treatment of palmoplantar pustulosis. J Drugs Dermatol 2008; 7: 940-6.
101. Michaelsson G, Kajermo U, Michaelsson A, Hagforsen E. Infliximab can precipitate as well as worsen palmoplantar pustulosis: possible linkage to the expression of tumour necrosis factor-alpha in the normal palmar eccrine sweat duct? Br J Dermatol 2005; 153: 1243-4.
102. Seol JE, Park IH, Lee W, et al. Palmoplantar pustulosis induced by both adalimumab and golimumab for treatment of ankylosing spondylitis. Ann Dermatol 2016; 28: 522-3.
103. Wendling D, Prati C. Paradoxical effects of anti-TNF-α agents in inflammatory diseases. Exp Rev Clin Immunol 2014; 10: 159-69.
104. Elias M, Zhao S, Le HT, et al. IL-36 in chronic inflammation and fibrosis – bridging the gap? J Clin Investig 2021; 131: e144336.
105. Carrier Y, Ma HL, Ramon HE, et al. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications in psoriasis pathogenesis. J Investig Dermatol 2011; 131: 2428-37.
106. Wilson NJ, Boniface K, Chan JR, et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. Nat Immunol 2007; 8: 950-7.
107. Pène J, Chevalier S, Preisser L, et al. Chronically inflamed human tissues are infiltrated by highly differentiated Th17 lymphocytes. J Immunol; 180: 7423-30.
108. Kavanaugh A, McInnes IB, Mease P, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). Ann Rheum Dis 2014; 73: 1689-94.
109. Ganesan R, Raymond EL, Mennerich D, et al. Generation and functional characterization of anti-human and anti-mouse IL-36R antagonist monoclonal antibodies. mAbs 2017; 9: 1143-54.
110. Johnston A, Xing X, Wolterink L, et al. IL-1 and IL-36 are the dominant cytokines in Palmar Plantar Pustulosis. J Dermatol Sci 2016; 84: E99.
111. Bachelez H, Choon SE, Marrakchi S, et al.; Effisayil 1 Trial Investigators. Trial of spesolimab for generalized pustular psoriasis. N Engl J Med 2021; 85: 2431-40.
112. Morita A, Strober B, Burden AD, et al. Efficacy and safety of subcutaneous spesolimab for the prevention of generalised pustular psoriasis flares (Effisayil 2): an international, multicentre, randomised, placebo-controlled trial. Lancet 2023; 402: 1541-51.
113. 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 2021; 11: 571-85.
114. Burden AD, Bissonnette R, Navarini AA, et al. Spesolimab efficacy and safety in patients with moderate-to-severe palmoplantar pustulosis: a multicentre, double-blind, randomised, placebo-controlled, phase iib, dose-finding study. Dermatol Ther 2023; 13: 2279-97.