

# Palmoplantar Pustulosis: A Systematic Review of Risk Factors and Therapies

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**Abstract:** Palmoplantar pustulosis (PPP) is a chronic, relapsing, inflammatory disease that can occur alone or in association with arthritis. There is still controversy about whether it should be separated from psoriasis or classified as pustular psoriasis. Furthermore, drug-induced paradoxical PPP is a special variant of PPP that differs from classic PPP in several ways. Treatment of PPP is still challenging, and there are a number of treatment-resistant cases. This review summarizes the risk factors for the development of PPP and the currently available treatment modalities. Female sex, smokers or ex-smokers, obesity, thyroid dysfunction, and treatment with a tumor necrosis factor (TNF)- $\alpha$  inhibitor have been identified as risk factors for the disease's development, severity, and course. Topical treatments and phototherapy are effective for some patients and are used as a first-line or adjuvant treatment modality. Conventional treatments including retinoids and fumaric acid show good effects and can increase the efficacy of treatment with psoralen + ultraviolet light therapy (PUVA). Ciclosporin is fast acting, but relapse mostly occurs immediately after cessation. TNF- $\alpha$  inhibitors are efficient, and an even better response can be achieved with IL-17 and IL-23 blockers as well as apremilast. The effect of Janus kinase inhibitors seems to be promising according to case reports, but further investigations with larger cohorts are needed.

**Keywords:** palmoplantar, pustulosis, psoriasis, treatment, risk factors

## Introduction

Palmoplantar pustulosis (PPP) is a chronic, recurrent, inflammatory skin disease that has a significant impact on quality of life.<sup>1,2</sup> It is characterized by sterile pustules on an erythematous scaly base on the palms and soles, and hyperkeratotic plaques and fissures can appear as well. Pustules can disappear within days and leave brown scabs.<sup>1,3</sup> Nail involvement occurs in 30–76% of cases and mainly includes onycholysis, pitting, onychodystrophy, subungual hyperkeratosis or pustulation, ridging, thickening, discoloration, and splinter hemorrhage.<sup>4</sup>

The prevalence of PPP is estimated as 0.005 to 0.12% and is clearly higher in Japan than in Western countries.<sup>1,4–6</sup> There is a prominent female predominance, the mean age of patients is 40–58 years, and earlier onset occurs in patients with a positive family history of psoriasis.<sup>4,7</sup> PPP can appear isolated, but in up to 10–30% of cases, it occurs in association with pustulotic arthro-osteitis (Sonozaki-Syndrome), which has mainly been reported in Japan, as well as syndromes such as SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome.<sup>1,8</sup> There is still debate in the literature about whether PPP should be considered as a variant of pustular psoriasis, as stated in a consensus by the European Rare and Severe Psoriasis Expert Network, or whether it is a different entity that has to be separated from even palmoplantar pustular psoriasis.<sup>3,7</sup> Palmoplantar pustular psoriasis has been suggested for patients with palmoplantar pustulosis and concomitant psoriasis, psoriasis arthritis, or a positive family history of psoriasis.<sup>2</sup> This discordance could also lead to variations in results regarding triggers and associated diseases, as well as treatment response.

Psoriasis and PPP share some genetic and pathogenetic similarities. Although PPP is not associated with the *PSORS1* locus as in the case of psoriasis vulgaris (PV), mutations in the *CARD14*, *APIS3*, and *ATG16 L1* genes have been found in PPP, PV, and generalized pustular psoriasis (GPP). Interestingly, a mutation in the *IL36RN* gene is only found in 2% of

PPP patients, and its relationship is controversial.<sup>1,3</sup> This gene codes for the IL-36 receptor antagonist, which is frequently involved in other phenotypes of pustular psoriasis, such as GPP and acrodermatitis continua of Hallopeau.

The exact pathogenesis of PPP is still not fully understood. Besides genetic factors, several environmental factors and immune dysregulation are hypothesized. Bacteria and antimicrobial peptides (ie, LL-37) contribute to the pathogenesis of PPP by induction of inflammation.<sup>2,9</sup> IL-36 and IL-8 are a chemoattractant and activator of neutrophils and have recently been suggested to be important for pustule formation in the acrosyringium.<sup>4,9,10</sup> The IL23-Th17 axis and IL-36 participate in the exacerbation of the disease by inducing positive feedback,<sup>9</sup> which has motivated the development and use of targeted therapies.

The severity of PPP is usually evaluated using adapted variants of the Psoriasis Area and Severity Index (PASI) and the Palmoplantar Pustulosis Area and Severity Index (PPPASI). The calculations are based on a subjective scoring of the severity of erythema (0–4), desquamation (0–4), infiltration and pustules (0–4), and the percentage of the affected area (0–6).<sup>11</sup> The modified PPPASI considers each of these variables separately for the palms and soles.<sup>12</sup> The evaluations also include subjective global assessment scores such as the Physician Global Assessment (PGA) with a grading of severity of the disease (0–5).<sup>13</sup>

Topical therapies including corticosteroids and vitamin D derivatives remain first-line therapies for PPP. Furthermore, UV therapies such as UVA and UVB therapies, excimer laser, and psoralen and UVA (PUVA) treatment are widely recommended.<sup>5</sup> In the early 1980s, retinoid etretinate showed good efficacy in PPP. Nowadays, etretinate is no longer licensed in most Western countries, but the next-generation systemic retinoid acitretin is still one of the most frequently applied systemic therapies.<sup>5</sup> The introduction of new biologics and optimized treatment protocols has been a significant development in the treatment of plaque psoriasis.<sup>14,15</sup> However, although these medications are also used for PPP, breakthrough therapies are still limited. Several comorbidities, lifestyle habits, and medications have been described as triggers, associated factors, or risk factors for disease onset or aggravation. This review summarizes possible risk factors for the development and severity of PPP or its progression, as well as available treatment modalities.

## Methods

### Literature Search Strategy

This systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Articles published until February 2023 were included. The literature search was conducted on the 15th of February using the MEDLINE, EMBASE, and Cochrane databases. The search terms included “palmoplantar pustulosis” AND “treatment”, as well as “palmoplantar pustulosis” AND “risk factor”.

### Inclusion and Exclusion Criteria

All reports in English or German language were included in the analysis. Case reports (<5 patients), articles in other languages, and articles not matching the topic were excluded. Studies that did not distinguish between palmoplantar pustulosis and palmoplantar psoriasis without pustular eruption were excluded after review of the article, while studies on palmoplantar pustular psoriasis were retained. Studies involving etretinate and acitretin were not included as the medications are no longer available in the US or Europe. Furthermore, studies were excluded if they had a design examining associated factors but not risk factors and non-clinical factors such as genetics.

### Data Extraction, Analysis, and Quality Assessment

Review of the abstracts and data extraction were performed by two independent dermatologists (KH, MML). The data extracted for risk factors included the author, year of publication, study design, risk factor, number of patients, characteristics of population, outcome, and NIH study rating. The data extracted for treatment included the author, year, study type, drug/therapy, treatment duration, number of patients, scoring tool, outcome, adverse effects (AEs), and study rating. Any disagreements among the reviewers regarding study selection and quality were resolved by consensus (KH, MML). Duplicates and articles including results from the same patients were removed. Nondetailed data, such as aggregated data, were not considered. Studies were rated according to the NIH rating scale.

## Results

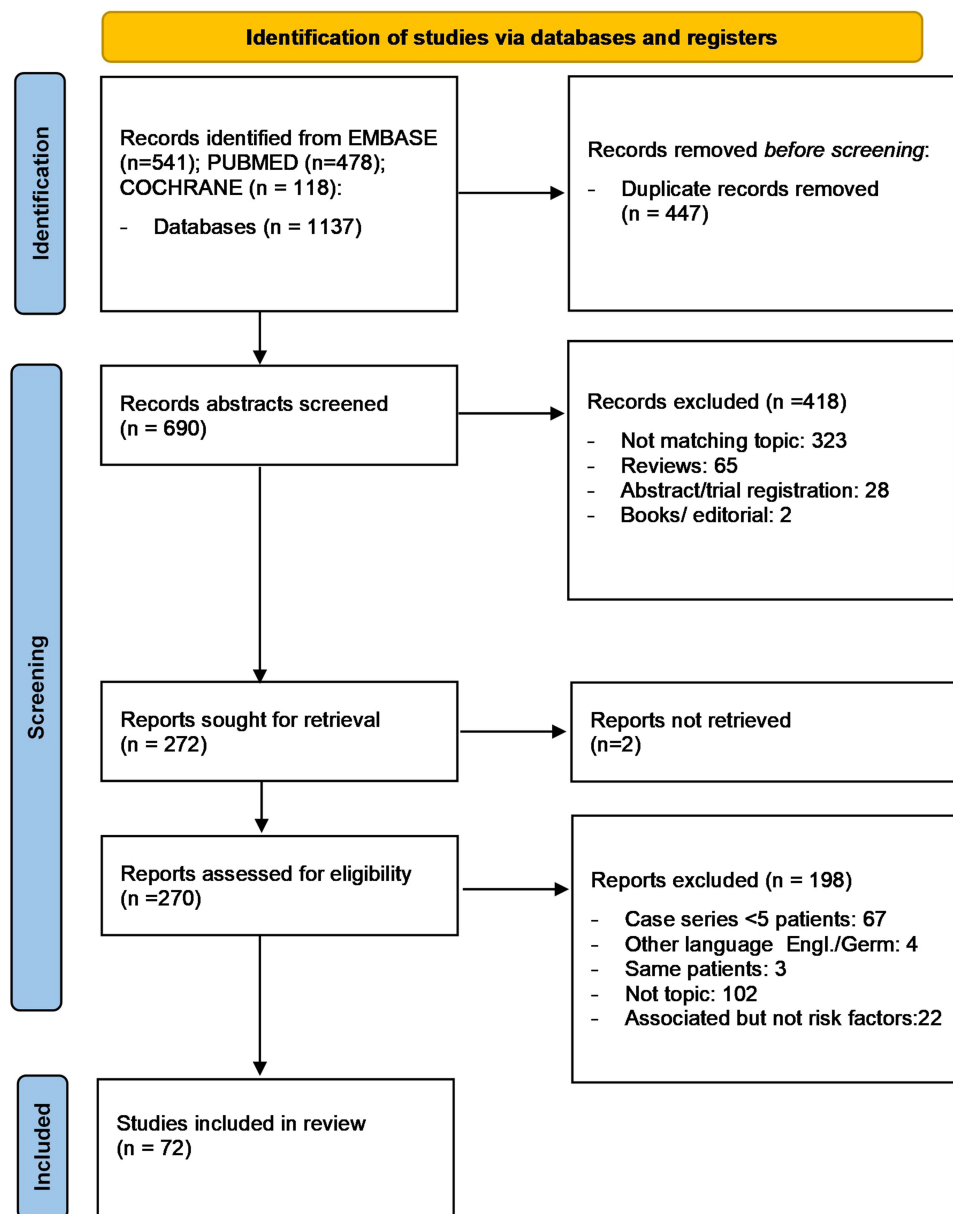
### Screening results

The preliminary search identified 1137 studies, and 447 duplicates were removed. After abstract screening, 418 articles were excluded, and after reading the full text, 195 articles were removed (Figure 1). Finally, 72 studies were included in the review (63 treatment studies and 9 studies about risk factors).

### Risk Factors

#### Study Description

There were 12 studies on clinical risk factors of PPP, including 4 case control studies, 2 cross-sectional studies, and 4 cohort studies. There were 3 studies on genetic risk factors and 19 studies describing associated factors, which were excluded. Major risk factors were female sex, smoking, obesity, and thyroid dysfunction (Table 1).



**Figure 1** Identification of studies via databases.

**Table 1** Risk Factors for Development of PPP and Disease Severity

Author, Year	Study Type	Level of Evidence	Risk Factor	Number of Patients	Characteristics of Population	Outcome	Rating of Study (NIH)
Ataş H, 2017 <sup>16</sup>	Case-control study	3	Sex, smoking, thyroid pathologies, thyroid autoantibodies, insulin resistance	33 patients with PPP and 27 age and gender-matched controls	1 female, 2 male	Predictive risk factors: female sex (8.8-fold increased risk; OR = 141.7, $p < 0.0001$ ); tobacco use: smokers (32.7-fold increased risk (OR = 147.6, $p = 0.006$ ); anti-TPO level > 35 U/mL (OR = 4.2, $p = 0.025$ ) and thyroid dysfunction (OR = 5.4, $p = 0.004$ ) risk factors in univariate, but not multivariate analysis insulin resistance: no correlation ( $p > 0.05$ )	Medium
Serizawa N, 2021 <sup>17</sup>	Case-control study	2	Dietary habits	72	72 cases and 72 controls (each 25 men and 47 women), Japanese patients	PPP was associated with high BMI (OR 1.21; 95% confidence interval 1.08–1.35; $p = 0.000879$ ), high intake of pulses (OR 1.18; 95% confidence interval 1.02–1.36; $p = 0.0225$ ), and low intake of vitamin A (OR 0.998; 95% confidence interval 0.996–0.999; $p = 0.0482$ ). PPPASI was predicted by BMI ( $\beta = 0.4405$ , $t = 2.048$ , $p = 0.0444$ ) and sodium (Na) intake ( $\beta = 2.6959$ , $t = 2.013$ , $p = 0.0480$ )	Medium
Kim DH, 2022 <sup>18</sup>	Cross-sectional analysis	3	Comorbidities	37,399	37,399 patients with PPP, 332,279 patients with psoriasis vulgaris, 365,415 patients with pompholyx extracted from Korean National Health Insurance database	51.7% female, significantly higher risk of AS ( $p < 0.001$ ) and thyroid disorder ( $p < 0.001$ ) compared to PsV patients. Risk of PsA was significantly higher in patients with PsV ( $p < 0.001$ ). History of smoking in 49.0%, 38.7% were overweight or obese. 22.5% had PsV. Those with PsV had older age ( $p < 0.001$ ) with fewer women ( $p < 0.001$ ). Current smokers ( $p < 0.001$ ) and obese patients ( $p = 0.001$ ) had a higher risk of developing PPP than Pso. Heavy drinkers had lower risk for PPP than PsV ( $p < 0.001$ ). Smoking and obesity are significant risk factors for development of PPP	High

Misiak-Galazka M 2018 <sup>7</sup>	Case-control study	3	Comorbidities, compared to Pso	63	63 patients with PPP (92.06% female; mean age 58.51 years), 37 controls with PsV sex/age matched	Significantly more smokers 95.23% ( $p=0.001$ ) with significantly higher py and longer period of smoking, higher rate of thyroid disease 31.75% ( $p=0.0421$ ); higher intensity of pain in PPP ( $p=0.0001$ ); infections, high BMI, prevalence of arthralgias (57.14%), psychiatric disorders and stress not higher than in PsV, menopause and pregnancy do not influence PPP; pos FA for PPP in 4.76% and for PsV in 22.22%; 44.44% had hypertension, 11.11% had diabetes mellitus, 30.16% had metabolic syndrome, no difference to control. 30.77% had positive patch test, most frequently nickel, chlorides, and fragrances; significantly higher than PsV ( $p<0.05$ ). No higher frequency of atopic diseases. No differences in calcium and mg levels; none had increased level of anti-endomysial IgG/IgA; 25–30% had PsV features	High
Mazloom SE, 2014 <sup>19</sup>	Retrospective cohort study	3	TNF- $\alpha$ inhibitor	102	102 patients with TNF- $\alpha$ inhibitor-induced psoriasis; 41/102 developed PPP	41% of TNF- $\alpha$ inhibitor-induced psoriasis was PPP; INX (18/41), ADA (14/41), ETA (9/41); 43% smokers, smoking was significantly associated with risk of PPP but not other types of psoriasis	Medium
López-Robles A, 2012 <sup>20</sup>	Retrospective cohort study	3	TNF- $\alpha$ inhibitor	450	450 rheumatic patients exposed to TNF- $\alpha$ inhibitor in a tertiary care center in Spain	1.56% developed psoriasiform lesion within 4–38 months (mean 9); 3/7 (71,3%) were PPP, 2 ADA, 1 INX	High
Bae JM, 2018 <sup>21</sup>	Case control	3	TNF- $\alpha$ inhibitor agents in patients with IBD	5428 patients treated with anti-TNF > 6 months and 10,856 matched controls	50,502 IBD patients from the Korea National Health Insurance Claims database from January 2007 to December 2016	Highly increased risk of palmoplantar pustulosis in males with TNF- $\alpha$ inhibitor compared to control (HR 19.682, 95% CI 3.867–100.169), but not females (HR 1.181, 95% CI 0.101–13.783). Increased risk predominant in younger patients (HR 14.318, 95% CI 2.915–70.315). Infliximab but not adalimumab showed significant associations with risk of PPP: HR 9.504, 95% CI 2.767–32.648	High

(Continued)

**Table I** (Continued).

Author, Year	Study Type	Level of Evidence	Risk Factor	Number of Patients	Character-istics of Population	Outcome	Rating of Study (NIH)
Thein D, 2022 <sup>22</sup>	Cohort study	3	TNF- $\alpha$ inhibitor	109,085	108,024 patients received conventional therapy and 20,910 received TNF- $\alpha$ inhibitor, 62% female, median age 50 (34–64) years with TNF- $\alpha$ inhibitor for IBD or RA	0.12% development of new PPP. TNF- $\alpha$ inhibitor-associated Pso: Non-pustular Pso is more prevalent but pustular Pso has the highest relative risk (HR of developing a pustular type of psoriasis 6.50 (95% CI, 4.60–9.23; P < 0.001))	High
Kim M, 2021 <sup>23</sup>	Retrospective cohort study	3	Nail involvement	116	116 patients with PPP from Seoul University Hospital, 59.9% female, 14.7% had concomitant Pso and 8.6% had concomitant PsA, 66.3% had Involvement	NAPSI is correlated with PPPASI (p=0.01) and involvement area (p=0.04); Crumbling was associated with higher PPPASI (p = 0.01) and onycholysis was associated with lower PPPASI (P = 0.03). Risk factors for nail involvement: female sex (p < 0.001), younger age at diagnosis (p = 0.01), and higherPPPASI (p = 0.01).	High

**Abbreviations:** OR, odds ratio; PsV, psoriasis vulgaris; AS, Acrodermatitis suppurativa Hallopeau.

## Sex and Lifestyle

Female sex is a predictive risk factor with an 8.8-fold higher risk for PPP (OR 141.7,  $p < 0.0001$ ).<sup>16,18</sup> Smoking is another risk factor with a 32.7-fold increased risk for the development of PPP (OR 147.6,  $p = 0.006$ ).<sup>7,16,18,19</sup> Smokers were 43–95.23% of the cohorts, and higher package-years and a longer period of smoking were associated with higher risk.<sup>7,16,18,19</sup> Smokers were significantly more prevalent in the PPP cohort than the PV cohort.<sup>18</sup>

Obesity/high body mass index (BMI) is another risk factor for PPP (OR 1.21,  $p = 0.0009$ ).<sup>16,17,24</sup> However, it is unclear whether obese people have a higher risk for the development of PPP than PV, with higher risk reported in a cross-sectional study but not in a case-control study.<sup>7,24</sup> Disease severity (PPPASI) is predicted by BMI ( $p = 0.0444$ ).<sup>17</sup> Other alimentary risk factors are listed in Table 1.<sup>17</sup> Insulin resistance was not a risk factor.<sup>16</sup> Heavy drinkers had a lower risk for the development of PPP than PV.<sup>18</sup> Menopause and pregnancy did not influence PPP.<sup>7</sup>

## Medication and Comorbidities

The use of tumor necrosis factor (TNF)- $\alpha$  inhibitors, including infliximab, adalimumab, and etanercept, is a risk factor for the development of psoriasiform lesions (mainly PPP).<sup>19–22</sup> In cohort studies, 1.56% of patients developed psoriasiform lesions, and 0.12% developed PPP.<sup>20,22</sup> In the cohort of patients with TNF- $\alpha$ -induced psoriasiform lesions, 41–71.3% of the lesions were PPP.<sup>19,20</sup> TNF- $\alpha$ -induced non-pustular psoriasis had a higher risk of occurring than PPP, but PPP had a higher relative risk (HR 6.5,  $p < 0.001$ ).<sup>22</sup> In contrast to PPP occurring independently of TNF- $\alpha$  inhibitors, TNF- $\alpha$ -induced PPP was more common in men (HR 19.682) and younger patients (HR 14.318).<sup>21</sup>

Thyroid dysfunction and elevated anti-TPO levels are also possible risk factors (OR 5.4,  $p = 0.004$  and OR 4.2,  $p = 0.025$ ) compared to control patients and patients with PV.<sup>7,16,18</sup> A positive patch test, especially for nickel, chlorides, and fragrances, is significantly more common in patients with PPP than those with PV.<sup>7</sup> Kim et al described nail involvement as a risk factor for higher PPP severity.<sup>18</sup>

## Treatment

### Study Description

Of the 63 studies analyzed, 21 were randomized controlled trials (RCTs), 12 were retrospective cohort studies, 15 were clinical trials (not controlled), and 5 were case series ( $\geq 5$  patients).

### Topical and Intralesional Therapies

Topical clobetasol propionate led to complete clearance of PPP in 1–7 weeks in 18/19 patients in an older study.<sup>25</sup> Maxacalcitol ointment showed highly and significantly better improvement compared to a placebo.<sup>26</sup> The combination of maxacalcitol and betamethasone butyrate (BBP) ointment led to a significant improvement of PPP and a significantly better improvement of pustules than MBBP alone.<sup>27</sup> Triamcinolone acetonide led to complete or near complete clearance of lesions in 5/5 patients after intralesional injection<sup>28</sup> and in 63% of patients after topical application under hydrocolloid dressing. A significantly higher rate of clearance was achieved compared to clobetasol propionate.<sup>29</sup> An oral rinse with ozone nanobubble water over 6 months led to complete clearance of PPP in 6/7 patients in a case series.<sup>30</sup> Adjuvant treatment with jumihaidokuto significantly decreased disease activity.<sup>31</sup>

### Light, Laser, and Radiation Therapies

Two RCTs, three clinical trials, and a retrospective study have reported controversial results about the efficacy of PUVA in PPP. While one RCT demonstrated no significant difference from a placebo, another reported clearance in 12/22 patients after PUVA, whereas no clearance occurred in the placebo group.<sup>32,33</sup> Partial or complete response and good or excellent improvement occurred in 46.7% and 10–80% of patients, respectively.<sup>34–36</sup> Another clinical trial showed better response on the palms compared to the soles (complete clearance occurred in 31/36 palms but only in 5/34 soles).<sup>37</sup>

UVA1 has shown good efficacy for PPP with PPASI 75 occurring in 72.6% of patients<sup>38</sup> and significant superiority to UVB,<sup>39</sup> but it was significantly inferior to PUVA.<sup>40</sup> However, after nbUVB treatment, 40% of patients achieved PPASI 75 in another trial.<sup>41</sup> The efficacy of excimer laser and light treatment was demonstrated in 3 clinical trials, which achieved PPPASI 50 in 60% of patients and PPPASI 75 in 6/34 patients, respectively. Success regarding PPPASI was dose dependent and ranged from 8.3 to 95%, with 95% being achieved using 6



times the minimal erythema dose (MED).<sup>42–44</sup> A retrospective study with Grenz rays showed marked improvement in 9/9 patients,<sup>45</sup> but an RCT with superficial X-ray therapy showed only little or no effect on PPP<sup>46</sup> (Table 2).

### Tonsillectomy, Dental Fillings, and Dental Infection Control

The effect of tonsillectomy, dental infection control, and removal of dental fillings was examined in 2 retrospective studies. Tonsillectomy led to complete clearance in 78% of patients after 2 years,<sup>47</sup> and PPPASI 75 was reached by 84% of patients.<sup>48</sup> Removal of dental fillings and control of dental infection led to PPPASI 75 in 11% and 63% of patients, respectively<sup>48</sup> (Table 2).

### Conventional Therapies

Oral acitretin at 25–55 mg/d has demonstrated a clinical improvement and reduction of pustule count within 3–6 months in two clinical trials, and better results occurred with higher dosage.<sup>52,53</sup> In a clinical trial, acitretin at 25–50 mg/d was combined with PUVA and achieved 87% improvement of mPASI, but after cessation of acitretin, all patients relapsed within 2 weeks while continuing PUVA.<sup>54</sup> In another clinical trial, this combination therapy led to PPPASI 90 in 90% of patients.<sup>55</sup>

Alitretinoin at 30 mg/d was not significantly superior to a placebo over 24 weeks in an RCT.<sup>56</sup> But in a retrospective study, it was reported to result in a PGA of “almost clear” or “clear” in 4/10 patients, and better results occurred for hyperkeratotic lesions.<sup>57</sup> Two RCTs described a significant reduction of pustules compared to a placebo ( $p < 0.001$  and  $p = 0.001$ , respectively) after 4 and 18 weeks of cyclosporine treatment at 2.5 or 1–4 mg/kg.<sup>58,59</sup> Two other clinical trials showed clinical improvement and PPPASI 60 in 45.8% of patients after 15 days to 6 months of treatment with cyclosporin at 3 mg/kg.<sup>60,61</sup> Colchicine led to no significant improvement of PPP in 2 RCTs over 6 weeks and 3 months.<sup>62,63</sup> Dimethylfumarate combined with PUVA resulted in PPPASI 90 in 81.8% of patients at week 38 in one clinical trial, and there was no significant difference from treatment using acitretin + PUVA.<sup>55</sup> (Table 3).

### Further Systemic Therapies

Liarozole improved PPPASI significantly over 12 weeks in an RCT.<sup>51</sup> Itraconazole was demonstrated to lead to a complete clearance of pustules in 3/6 patients over 8 weeks, but relapse occurred quickly after cessation.<sup>49</sup> The antibiotic clomocycline had a significantly higher number of responders compared to a placebo over 3 months in an RCT.<sup>50</sup>

### Biologics and Small Molecules

The effect of the IL23 inhibitors guselkumab, risankizumab, and tildrakizumab was investigated in a retrospective study, which led to PPPASI 75 in 25% of patients after 12 weeks and in 43.8% of patients after one year of treatment.<sup>65</sup> In 3 RCTs, guselkumab showed good efficacy with PPPASI 50 achieved by 60% of patients and PPPASI 75 achieved by 11.5–20.4% of patients at week 16. At weeks 52 and 84, PPPASI 75 was achieved by 55.6–59.6% and 71.4% of patients, respectively.<sup>66–68</sup> The response to a 200-mg dose of guselkumab was no better than that of a 100-mg dose at week 16.<sup>67,68</sup>

The long-term effect of the IL-17 antagonist secukinumab has been demonstrated in an RCT, and PPPASI 75 occurred in 26.6% of patients at week 16, 41.8% (300 mg) and 35.0% (150 mg) of patients at week 52, and 75–100% of patients at week 148.<sup>69,70</sup> In a retrospective cohort study, 47% of patients were responders at 32 months, and 100% of patients were responders after 18 and 24 months.<sup>71</sup> The effect of the IL-12/23-antagonist ustekinumab is controversial and showed no significant difference in the rate of PPPASI 50 achieved at week 16 in an RCT.<sup>72</sup> But clearance occurred in 5/9 patients and 5/5 patients, complete or partial response occurred in 45% of patients, and PPPASI 75 occurred in 4/9 patients in 2 retrospective cohort studies and 2 case series.<sup>73–76</sup>

Etanercept led to a significantly higher PPPASI reduction compared to the control group in an RCT.<sup>77</sup> In another RCT, 2 different doses of the IL-36 inhibitor spesolimab were not significantly more effective than a placebo. Other retrospective studies examining different biologics and conventional therapies are listed in Table 4.<sup>78,79</sup>

Alefacept at 15–30 mg/week led to PSI 50 in 10/14 patients, PPPASI 50 in 53.3% of patients, and PPPASI 75 in 26.7% of patients in two clinical trials.<sup>13,82</sup> Anakinra was not superior to a placebo in an RCT.<sup>88</sup> The phosphodiesterase 4 inhibitor apremilast showed PPPASI 50 in 61.9% and PPPASI 75 in 14.3% of patients after 20 weeks in a clinical trial,<sup>84</sup>



**Table 2** Laser-and Light Therapies, Topical Treatments, Surgical Interventions, and Other Systemic Therapies

Author, Year	Study Type	Therapy (Drug/ Intervention, Dosage)	Treatment Duration	Number of Patients	Scoring Tool	Outcome	Adverse Events	Rating of Study (NIH)
Layton AL, 1990 <sup>32</sup>	RCT	PUVA vs placebo	8 weeks	27	Clinical score	No significant difference btw groups	PUVA group (blistering, erythema, pruritus)	Medium
Murray D, 1979 <sup>33</sup>	RCT	PUVA vs control (4x/week)	8 weeks (30 treatments)	22	Clinical score	Total clearance in PUVA (12/22); control (0/22)	4 burn in topical psoralen, in oral psoralen: 1 burn, 4 ankle swelling, 4 nausea, 6 conjunctivitis	High
Paul R, 1983 <sup>35</sup>	Clinical trial	PUVA	5–20 treatment sessions	9	4-point clinical score	4/5 completed treatment with good or excellent improvement	Nausea (1/9)	Low
Jansen CT, 1981 <sup>34</sup>	Clinical trial	PUVA	NA	10	Clinical evaluation	1/10 good improvement, 2/10 moderate improvement, 5/10 unchanged and 2/10 exacerbation of disease	Disease exacerbation, burning sensation, erythema	Low
Riad K, 2006 <sup>36</sup>	Retrospective cohort study	PUVA; 3x/week	1–42 weeks	11	Clinical evaluation	46.7% complete or partial response	Superficial burn of the skin, hyperpigmentation	Low
Agren-Jonsson S, 1985 <sup>37</sup>	Clinical trial	PUVA, 1–3x/week	Max 2–3 months	40	Clinical evaluation	Complete clearance 31/36 palmar lesions, 5/34 patients plantar lesions	Nausea (24/40), subungual petechiae (1/40)	Low
Su LN, 2017 <sup>39</sup>	RCT	UVA1 vs UVBnb; 3x/week	10 weeks	64	PPPASI	Significant reduction in both groups ( $P < 0.05$ ). Significantly greater in the UVA1 group ( $p < 0.05$ )	UVA1: burning sensation and hyperpigmentation; UVBnb: xerosis	High
Su LN, 2016 <sup>38</sup>	Clinical trial	UVA1 (80 J/cm <sup>2</sup> ), 3x/week	10 weeks, 3 months follow up	62	PPPASI	PPPASI 50 (90.3%), PPPASI 75 (72.6%)	Burning sensation, pruritus, hyperpigmentation	Medium

(Continued)

Table 2 (Continued).

Author, Year	Study Type	Therapy (Drug/ Intervention, Dosage)	Treatment Duration	Number of Patients	Scoring Tool	Outcome	Adverse Events	Rating of Study (NIH)
Engin B, 2005 <sup>40</sup>	Left-right comparison clinical trial	PUVA vs UVA	6 weeks	5	Severity index	Significantly better reduction after PUVA ( $P<0.05$ ).	Localized phototoxicity (1/5)	Medium
Peng C, 2021 <sup>44</sup>	RCT	308-nm Excimer laser 2 MED vs 4 MED vs 6 MED, 3x/week	12 weeks	73	PPPASI, DLQI	PPPASI 75 at week 12: 8.3% (low dose), 29.17% (medium dose), 95% (high dose)	Erythema, blistering, erosions, pain (more frequent at high dose)	High
Fumimori T, 2013 <sup>42</sup>	Clinical trial	Excimer Light, 2x/week	2x/week	34	PPPASI	PPPASI 50 (19/34), PPPASI 75 (6/34)	NA	Medium
Furuhashi T, 2011 <sup>43</sup>	Clinical trial	Excimer light (308 nm); 1x/week	30 weeks	15	PPPASI	PPASI 50 (60%), PPPASI 90 (20%)	NA	Medium
Kawada A, 2013 <sup>41</sup>	Clinical trial	nbUVB	Max 12 week	15	mPPPASI	mPPPASI 75 (40.0%); mPPPPSI 50 (73.3%)	Slight pain (1)	Medium
Fairris GM, 1984 <sup>46</sup>	RCT	Superficial X-ray therapy (100 rad; 1 Gy; 50 kV) vs placebo; 3 treatment	63 d (intervals of 21 days)	9	Clinical evaluation	X-ray therapy has little or no therapeutic effect	NA	Low
Fenton L, 2016 <sup>45</sup>	Retrospective cohort study	Grenz rays weekly, 5 Gy per treatment, 9 total courses	NA	9	Clinical evaluation	Marked improvement after three courses in 100%	NA	Low
Umezawa Y, 2016 <sup>26</sup>	RCT	Maxacalcitol ointment vs placebo, 2x/d	8 weeks	188	Clinical score	Significant medication group compared placebo group ( $P < 0.0001$ )	Comparable to placebo (irritation, swelling)	High
Muro M, 2014 <sup>27</sup>	RCT	1) Maxacalcitol ointment+ betamethasone butyrate propionate ointment (MBBP) vs 2) betamethasone butyrate propionate ointment (BBP) 1x/d	8 weeks	21	mPPPASI	Significant improvement both groups ( $p<0.01$ ); significantly higher improvement of pustules and erythema ( $p<0.05$ )	No AEs	High
Volden G, 1992 <sup>25</sup>	Clinical trial	Clobetasol propionate occlusive, 1x/ week	1–7 weeks (mean 2.2 weeks)	19	Clinical evaluation	Complete resolution in 18/ 19	NA	Low

Kragballe K, 1991 <sup>29</sup>	RCT	1) Triamcinolone acetonide 0.1% cream+ hydrocolloid dressing 3x/week vs 2) clobetasol propionate 0.05% 2x/d	4 weeks	19	5-point severity score	Complete clearance 1) 63%, 2) 21% w (p=0.001)	No AEs	Medium
Goette D, 1982 <sup>28</sup>	Case series	Triamcinolone acetonide; 3.3–5.0 mg/mL (local injection)	Single treatment	5	Clinical evaluation	5/5 clear or near clear within 3 weeks	Hypopigmentation, atrophy, tinea pedis	Low
Horiuchi Y, 2020 <sup>30</sup>	Case series	Ozone nanobubble water oral rinse; 10–20 mL rinse 1x/d	6 months	7	Clinical scale (5 point)	6/7 complete clearance	NA	Low
Mizawa M, 2016 <sup>31</sup>	Clinical trial	Jumihaidokuto (EKT-6) 6.0 g/d as adjuvant therapy	4–8 weeks	10	PPPASI	Significant reduction (p < 0.01)	No AEs	Medium
Takahara M, 2018 <sup>47</sup>	Retrospective cohort study	Tonsillectomy	Single treatment, 24 months follow-up	138	PPPASI, Skin severity score (SSS)	12/24 months after tonsillectomy: PPPASI 100 in 44%/78%	NA	Medium
Kouno M, 2017 <sup>48</sup>	Retrospective cohort study	Dental infection control, tonsillectomy, dental filling removal	Single treatment	85 (70 dental infection control; 9 dental filling removal; 6 tonsillectomy)	PPPASI	PPPASI 75 reached by 63% after dental infection control, 11% after dental metal removal and 84% after tonsillectomy	NA	Medium
V'Lckova-Laskoska MT, 2009 <sup>49</sup>	Clinical trial	Itraconazole, 100 mg/d for 4 weeks, then 100 mg 1x/2d for 4 weeks	8 weeks	6	Clinical evaluation	3/6 complete clearance of pustules, 100% relapse within 1 months after therapy	None	Low
Ward J, 1976 <sup>50</sup>	RCT	Clomocycline, 170 mg po 3x/d	3 months treatment, 3 months placebo	40	Clinical score	Significantly higher rate of responders to clomocycline (p=0.003)	Nausea and vomiting (6), vaginal thrush (1), constipation (1), heartburn (1), miscellaneous symptoms (4)	High
Bhushan M, 2001 <sup>51</sup>	RCT	Liarozole, 75 mg po, 2x/d	12 weeks	15	PPPASI	Significant improvement (P = 0.02) in treatment group	Pruritus, cheilitis, xerosis	High

**Abbreviations:** RCT, randomized controlled trial; PPPASI, palmoplantar pustulosis area and severity index; mPPPASI, modified palmoplantar pustulosis area and severity index; MED, minimal erythema dose.

**Table 3** Conventional Therapies for the Treatment of PPP

Author, Year	Study Type	Therapy (Drug/ Intervention, Dosage)	Treatment Duration	Number of Patients	Scoring Tool	Outcome	Adverse evenTs	Rating of Study (NIH)
Ettler K, 2001 <sup>64</sup>	Clinical trial	Acitretin 25–50 mg/d po, followed by PUVA	3 months	10	mPASI	Average PASI reduction 87%; significant improvement. Relapses within 2 weeks despite PUVA in all patients	Exanthema, cheilitis, dry mucosa, hyperlipidemia	Low
Lassus A, 1988 <sup>52</sup>	Clinical trial	Acitretin 30 mg/d po	12 weeks	30	Pustule count	Decrease of mean number of pustules from 57.8 ( $\pm 8.6$ ) to 3.9 ( $\pm 1.6$ )	Cheilitis, scaling, hair loss	
van de Kerskhov PCM, 1988 <sup>53</sup>	Clinical trial	Acitretin 25–55 mg/d po	6 months	6	Clinical score 0–4 for erythema, scaling, pustules	Prompt improvement, better at higher dosage, relapse within 2 weeks after cessation	Dry skin, dry lips, hair loss, pruritus, transient increase in triglycerides and transaminases	Low
Reich K, 2016 <sup>56</sup>	RCT	Alitretinoin 30 mg/d po	24 weeks	33 (24 alitretinoin, 9 placebo)	PPPASI, mPASI, number of pustules, NAPSI	No significant difference between alitretinoin and placebo	1 SAE (dizziness), 4 AE leading to dose interruption (dizziness, headache, loss of appetite)	High
Lee SJ, 2019 <sup>57</sup>	Retrospective cohort study	Alitretinoin 30 mg/d po	NA	10	PGA	PGA clear/almost clear (4/10), higher response rate in hyperkeratotic PPP ( $p=0.033$ )	NA	Medium
Erkko P, 1998 <sup>58</sup>	RCT	Ciclosporin 1–4 mg/kg/d po	18 weeks, 12 months	58 (CyA 27, placebo 31)	Number of fresh pustules	Significant reduction of number of fresh pustules ( $p < 0.001$ )	Increased serum creatinine levels (2), hypertension (7), hypertrichosis (6)	High
Reitamo S., 1993 <sup>59</sup>	RCT	Ciclosporin 2.5 mg/kg/d po	4 weeks	38 (19 CyA and 19 control)	Number of pustules	Significant reduction of pustules in CyA but not placebo ( $p=0.001$ ).	Headache, cold feet, common cold, nausea, diarrhea, dryness of mouth, weakness/stiffness, arthralgia, paronychia, sinusitis, hypertension, hypertrichosis, vaginitis, paresthesia, secretion of the eyes, dizziness, sweating, abdominal pain	Medium

Jin XH, 2019 <sup>60</sup>	Clinical trial	Ciclosporin, 3 mg/kg / d po	15 days-6 months	48	PPPASI	PPPASI 90 (16.7%), PPPASI 60 (45.8%)	Hypertension 6/48, frequent urination and enuresis nocturna 6/48, gastrointestinal reactions 6/48, hypertrichosis 3/48, increased creatinine 1/48	Medium
Remitz A, 1996 <sup>61</sup>	Controlled clinical trial	Ciclosporin 2.5 mg/kg/ d po Vs placebo	4 weeks	14 vs 14	Clinical evaluation	Clinical improvement only in CyA group	NA	Medium
Mann RJ, 1982 <sup>63</sup>	RCT	Colchicine, 0.5 mg po, 2x/d	6 weeks	12	Clinical evaluation	No significant improvement with colchicine	Neck pain, headache, diarrhea, nausea	Medium
English JSC, 1983 <sup>62</sup>	RCT	Colchicine 0.5 mg po, 2x/d vs placebo	3 months	10	Number of pustules	No significant difference between colchicine and placebo.	The only side-effect reported was diarrhea for 1 week in one patient on colchicine but this settled spontaneously. No hematological abnormality was found throughout the trial period.	Low
Aichelburg MC, 2021 <sup>55</sup>	RCT	1) Dimethylfumarate, max 720 mg po/d +PUVA vs 2) acitretin (50 mg/day) +PUVA	38 weeks	21	PPPASI	PPPASI 90 1) 81.8%, 2) 90% (P = 0.593)	Nausea (1)	Medium

**Abbreviations:** RCT, randomized controlled trial; PPPASI, palmoplantar pustulosis area and severity index; mPPPASI, modified palmoplantar pustulosis area and severity index; PGA, physician global assessment; CyA, ciclosporin A; SAE, severe adverse event.

**Table 4** Biologics and Small Molecules for the Treatment of PPP

Author, year	Study Type	Therapy (Drug/ Intervention, Dosage)	Treatment Duration	Number of Patients	Scoring Tool	Outcome	Adverse Events	Rating of Study (NIH)
Poortinga S, 2021 <sup>65</sup>	Retrospective cohort study	IL-23p19 antibodies	Median 12.5 months	16 (12 Gus, 3 ris, 1 til)	PPPASI	Week 12: PPPASI 50 56.3%, PPASI 75 25.0%; 1 year; PPPASI 50 62.5% PPPASI 75 43.8%	No relevant AE	High
Terui T, 2018 <sup>67</sup>	RCT	Guselkumab 200 mg sc; week 0 and 4	24 weeks	41	PPSI, PPPASI, PGA	Week 16: PPPASI 50 60%, significantly higher than placebo (0.009)	No severe AE, frequency of treatment-emerged AE (75%) comparable to placebo	High
Terui T, 2019 <sup>68</sup>	RCT	Guselkumab 200 mg vs 100 mg sc vs placebo (week 0, 4, 12, then every 8 weeks)	52 weeks	159	PPPASI, PPSI, PGA, DLQI	Week 16: PPPASI 75 (compared to placebo) GUS100 (20.4%; p = 0.01) GUS 200 mg (11.5%, p = 0.12). Week 52: PPPASI 75 GUS 100 (55.6%) and GUS 200 (59.6%)	TAES Gus100 mg < than placebo and Gus200	High
Okubo Y, 2021 <sup>66</sup>	RCT	Guselkumab 100 mg vs 200 mg vs placebo (week 0, 4, 12, then every 8 weeks)	60 weeks (24 weeks follow up)	133 with 4 groups; 1) 45 GUS 100 mg, 2) 43 GUS 200 mg, 3) 21 placebo switch to GUS 100 mg at weeks 16, 4) 24 placebo switch to GUS 200 mg at weeks 16	PPPASI, PPSI, PGA, patients reported outcomes	Week 16: significantly higher number of PPPASI 50 responders with GUS 100 mg (p=0.02) but not GUS 200 mg compared to placebo. At week 84 PPPASI 75: 1) 61.9%, 2) 66.7%, 3) 68.9%, 4) 81.4% (all groups 71.4%)	SAE 7.6%, most frequent TEAE: nasopharyngitis, oral herpes, eczema, urticaria, dental caries, injection site swelling/ pruritus/erythema, hyperlipidemia, AE of special interest: severe infection 1.3%	High
Mrowietz U, 2019 <sup>69</sup>	RCT	Secukinumab standard dose (phase 1: 300 mg vs 150 mg vs placebo; Phase 2: non-responders to placebo randomized to secu 300 or 150)	Phase 1: 16 weeks; phase 2: 52 weeks	1) 237 (sec 300 mg: 79, sec 150: 80, placebo: 78); 2) 184 (sec 300: 92 and sec 150: 92)	PPPASI, DLQI	Week 16: PPPASI 50 52.2% by SEC 300 vs 32.9 by placebo (p= 0.0159); PPPASI 75 26.6% by SEC 300 mg vs 14.1% in placebo (p = 0.0411) and 17.5% by SEC 150 mg (P = 0.5722); At week 52, PPPASI 75 in 41.8% with SEC 300 mg vs in 35.0% with SEC 150 mg	Most frequent AEs: nasopharyngitis, upper respiratory tract infections; no new or unexpected safety event	High

Mrowietz U, 2020 <sup>70</sup>	RCT	Secukinumab initiation, 1x/4w 1) 300 mg 2) 150 mg sc 3) placebo switch secu 300 mg 4) placebo switch secu 150 mg after 16 weeks	148 weeks	94 1) 36 2) 31 3) 17 4) 10)	PPPASI	PPPASI 75: 4) 75%, 3) 77.8%, 1) 78.3% and 2) 100%	No new or unexpected AE	High
Reolid A, 2022 <sup>80</sup>	Retrospective cohort study	Secukinumab (standard dose)	Mean 13.4 months	17	pppIGA, responders defined if achieving PPPIGA 0/1 or reduction of at least 2 points on scale	3 months: 47% responders, 18 and 24 months: 100% responders (52.9% in last observation carried forward analysis)	No severe adverse events	Medium
Bissonnette R, 2014 <sup>72</sup>	RCT	1) Ustekinumab 45 mg –90 mg, weeks 0, 4, 16, followed by placebo at weeks 20; 2) Placebo weeks 0 and 4, Ustekinumab weeks 16 and 20	16 weeks	20	PPPASI	No statistically significant difference in achieving PPPASI-50 at week 16 (P = 1.000)	Cellulitis (1), pneumonia (1)	Medium
Hegazy S, 2018 <sup>76</sup>	Retrospective cohort study	Ustekinumab 45 mg-90 mg sc, weeks 0 and 4 then every 12 weeks	6–17 months	9	Clinical response	Week 16: clearance in 5/9	1 urinary tract infection	Low
Buder V, 2016 <sup>73</sup>	Case Series	Ustekinumab 45 mg-90 mg sc, weeks 0, 4, 12, and 24	24–60 months	9	PPPASI	PPPASI 100 (2/9), PPPASI 75 (4/9)	Local injection site reactions (1)	Medium

(Continued)



**Table 4** (Continued).

Author, year	Study Type	Therapy (Drug/ Intervention, Dosage)	Treatment Duration	Number of Patients	Scoring Tool	Outcome	Adverse Events	Rating of Study (NIH)
Bertelsen T, 2014 <sup>75</sup>	Retrospective cohort study	Ustekinumab 45 mg sc at weeks 0 and 4 then 12-weeks intervals	1 month-5 years	11	Clinical evaluation	Complete or partial response in 45%	Flu-like symptoms, headache, fatigue (2)	Low
Morales- Múnera C, 2013 <sup>74</sup>	Case series	Ustekinumab 45 mg sc, weeks 0 and 4 then every 12 weeks	11–23 months	5	PPPASI, DLQI, PASI	Response after 2–3 weeks, PPPASI 100 after 16 weeks in all patients. No relapse	No AEs	Medium
Bissonnette R, 2008 <sup>77</sup>	RCT	Etanercept 50 mg sc 2x/week vs placebo (2:1)	3 months	15	PPPASI	Week 24: significant reduction of PPPASI in ETA (p = 0.038) but not control		
Husson B, 2020 <sup>78</sup>	Retrospective cohort study	Etanercept, Adalimumab, Infliximab, Ustekinumab	Mean 5 months (range 1–72)	82	Clinical evaluation	Complete clearance ETA (13.3%), ADA (17.6%), UST (37.9%), INX 19.0%). No significant difference in complete clearance rates between biologics	Paradoxical psoriasis (ADA, UST, ETA), injection site reaction (ADA/ETA), tuberculosis (ADA), alopecia areata (ADA), pneumonia (UST), angioedema (ETA, INX), Hypersensitivity reaction/ gain of weight/ Schoenlein-Henoch purpura/ influenza-like illness/headache/ nausea (INX)	High
Mrowietz U, 2021 <sup>81</sup>	RCT	Spesolimab 300 mg vs 900 mg iv; weeks 0, 4, 8, 12, and 16	16 weeks treatment, 16 weeks follow-up	59 (19: 300 mg, 19: 900 mg, 21: placebo); 47 completed weeks 16	PPPASI	No significant differences between spesolimab and placebo	Comparable to placebo; 1 SAE non treatment related, 1 SAE treatment related (syncope), mild/moderate AEs: nasopharyngitis, headache, PPP, arthralgia, cough	High

Kromer C., 2018 <sup>79</sup>	Retrospective cohort study	Conventional therapies, biologics, small molecules	NA	347	PPPASI	PPPASI 75 reached by CyA (51.4%; 36/70), APR (31.4%; 11/35), ALI (22.6%; 12/53), ACI (19.5%; 40/205), FAE (17.7%; 17/96), MTX (16.8%; 7/220), CER 62.5% of (5/8), GOL (41.7%; 5/12), INX (40.6%; 13/32), ADA (33.3%; 23/69), UST (31%; 13/42), SEC (29%; 9/31), and ETA (19.4%; 12/62);	AEs were the reason for discontinuation (if discontinued) in ACI 59.6%, MTX 41.1%, FAE 68.8%, CyA 46.7%, ALI 28.2%, APR: 28.6%, ADA 38.3%, ETA 21.2%, INX 45.0%, GOL 16.7%, CER 100%, UST 14.3%, SEC 11.1%	Medium
Carr D, 2008 <sup>13</sup>	Clinical trial	Alefacept 15 mg im/week for 8 weeks, then 30 mg im/week	16 week	15	PSI, PGA	Week 28: significant reduction of mean PSI (p<0.0001). PSI 50 (10/14)	Pneumonia, upper respiratory tract infections, sinus infection, bronchitis, cellulitis of bilateral ring fingers, an inguinal abscess, and perianal cyst	Medium
Guenther LC, 2007 <sup>82</sup>	Clinical trial	Alefacept 15 mg im, 1x/week	16 weeks	15	PPPAS, PGA	PPPASI reduction of 49.6%; PPPASI 50 (53.3%) PPPASI 75 (26.7%)	Injection-site reactions, mild headaches, severe-moderate dermatitis, infections, upper respiratory tract infection	Medium
Cro S, 2021 <sup>79</sup>	RCT	Anakinra, 100 mg/0.67 mL sc, 1x/d	8 weeks	64 (31 anakinra, 33 placebo)	PPPASI	No superiority of anakinra vs placebo	No severe events, injection site reactions (19)	High
Wolk, 2023 <sup>83</sup>	Clinical trial	Apremilast	20 weeks	21	IL-19 level	Significant reduction in IL-19 mRNA level in skin at week 20 and IL-19 level in serum at weeks 4 and 20	NA	Medium
Wilsmann-Theis D, 2021 <sup>84</sup>	Clinical trial	Apremilast	20 weeks	21	PPPASI, pustule count, DLQI	PPASI 50 (61.9%), PPPASI 75 (14.3%); median reduction 76.3%	TEAE nausea (6), diarrhea (5), headache (5), nasopharyngitis (5)	Medium

(Continued)

**Table 4** (Continued).

Author, year	Study Type	Therapy (Drug/ Intervention, Dosage)	Treatment Duration	Number of Patients	Scoring Tool	Outcome	Adverse Events	Rating of Study (NIH)
Kato N, 2021 <sup>85</sup>	Retrospective cohort study	Apremilast 30 mg po, 2x/d (after induction)	2 weeks (min)	10	PPPASI	Significant decrease of PPPASI compared to baseline after 2 weeks (p=0.013)	Frequent bowel movements (8/10), diarrhea (6/10), weight loss (3/10), headache (1/10), palpitation (1/10), nausea (1/10)	Medium
Ständer S, 2020 <sup>86</sup>	Case series	Apremilast 30 mg po, 2x/d	18 months	6	PGA	PGA reduction from 4 to 1 (2/6), from 3 to 1 (3/6)	Mild nausea, diarrhea	Low
Soufila KT, 2021 <sup>87</sup>	Case series	Apremilast 30 mg po 2x/d (after initiation dose)	4–24 weeks	5	PPPASI	PPPASI 100 in 2/5, PPPASI 50 in 4/5	2/4 had AE (nausea, vomiting, epigastric pain, and diarrhea)	Medium

**Abbreviations:** RCT, randomized controlled trial; PPPASI, palmoplantar pustulosis area and severity index; PGA, physician global assessment; PPPSI, PPP severity index; GUS, guselkumab; SEC, secukinumab; UST, ustekinumab; ETA, etanercept; ADA, adalimumab; INX, infliximab; GOL, golimumab; CER, certolizumab; APR, apremilast; FAE, fumaric acid esters; ACI, acitretin; ALI, alitretinoin; CyA, ciclosporin A; MTX, methotrexate; SAE, severe adverse event.

as well as a significant PPPASI reduction after 2 weeks in a retrospective study.<sup>85</sup> Furthermore, a case series and a clinical trial showed a reduction in PGA after 18 months<sup>86</sup> and a reduction in serum levels of IL-19 after 20 weeks.<sup>83</sup>

## Discussion

PPP is still a very challenging chronic inflammatory disease. Its pathogenesis is not fully understood yet, and knowledge of proven predictive risk factors is limited. Although the therapies for psoriasis have shown impressive improvements, there has been no breakthrough treatment option for PPP. Several genetic alterations have been found, such as mutations in the *CARD14*, *APIS3*, and *ATG16 L1* genes, as well as the *IL36RN* gene (2–14.3%), although the latter is controversial.<sup>1,3</sup> Furthermore, variations of genes in the IL-19 subfamily of cytokines and TNF $\beta$ 2 have been hypothesized to influence susceptibility to PPP, and 2 bins with 5 different genes (*LOC 100129540*, *MIR599*, *MIR875*, *RASGRF1*, and *VPS13B*) have been suggested to be associated with higher risk for the development of PPP under TNF- $\alpha$  inhibitor therapy.<sup>71,89–91</sup>

Many conditions and drugs have been associated with PPP. These include increased IgA antibodies against gliadin, moderate to severe anxiety ( $p < 0.001$ ), dysbiosis of the oral biota, infections of the oral cavity (mainly the tonsils), thyroid disease, metabolic syndrome, arthritis (such as pustulotic arthro-osteitis or psoriatic arthritis), and PV.<sup>18,84,92–101</sup> PPP has also been identified as a predictor for the development of psoriatic arthritis in patients with psoriasis.<sup>102</sup> However, some authors separate palmoplantar pustular psoriasis from palmoplantar pustulosis in cases of psoriatic features such as plaques, generalized pustules, psoriatic arthritis, or a positive family history of psoriasis. Thus, the association of PPP with psoriasis features is difficult to describe.<sup>3,4</sup> In our review, we focused on risk factors instead of associated factors.

Women have an 8.8-fold higher risk for the development of PPP, but hormonal changes such as menopause and pregnancy do not influence the risk.<sup>7</sup> Interestingly, in the case of TNF- $\alpha$ -inhibitor-induced PPP, there is a predominance of males.<sup>21</sup> The most relevant lifestyle factor is smoking. Smokers have a 32.7-fold increased risk for the development of PPP, and ex-smokers also have increased risk. The duration and amount of smoking influence the risk and disease severity.<sup>7,16,101,103</sup> Quitting smoking leads to a clinical improvement of PPP ( $p = 0.007$ ) and improves treatment efficacy.<sup>9,104</sup>

The pathomechanism regarding smoking is not fully understood, but the following factors have been considered. Nicotine accumulates in the sweat glands of smokers and stimulates neutrophils to produce IL-8.<sup>105</sup> Furthermore, PPP lesions of smokers have shown alterations in keratinocyte nicotinic acetylcholine receptors, and 42% of patients with PPP were found to have elevated serum levels of nicotinic acetylcholine receptor antibodies.<sup>105,106</sup> The effects of cigarette smoke on the IL-17/IL-36 axis could also be involved in the pathogenesis of PPP.<sup>107</sup> Kobayashi et al demonstrated that cigarette smoke can enhance the expression of IL-17A-induced cytokines, including IL-8 and IL-36 in the tonsillar epithelium.<sup>103,107</sup>

The second lifestyle factors influencing the risk of development of PPP are high BMI and obesity. Obese patients have a higher risk for the development and higher severity of PPP, but there is controversy about whether the risk is higher for PPP than other variants of psoriasis.<sup>16,17,24</sup> Thyroid dysfunction seems to be associated with an increased risk for PPP.<sup>16,24</sup> In contrast, the suspected association with increased IgA antibodies against gliadin is controversial.<sup>7,94</sup> A positive patch test (mainly for nickel chloride and fragrances) has been found in 30.77% of patients in a cohort with PPP.<sup>7</sup> Nakamura et al described an exacerbation of pustules and increased levels of leukotriene B4 in pustules and serum, as well as at 48 h after a metal patch test in 7 PPP patients with a positive patch test for certain metals.<sup>108</sup> This could indicate that metal allergies increase the risk of flare-up of PPP.

Under treatment with TNF- $\alpha$  inhibitors, paradoxical psoriasiform lesions occur in 1.56% of treated patients or 2–5% according to a recently published review about biological-induced PPP.<sup>109</sup> Although non-pustular variants are the most frequent paradoxical reaction, the relative risk of development of PPP is the highest.<sup>22</sup> In cohorts of patients treated with TNF- $\alpha$  inhibitors, PPP appeared in 0.12–0.66% of patients with a mean onset after 6 months of treatment.<sup>22,110</sup> After treatment, 80% had a relapse with a second TNF- $\alpha$  inhibitor.<sup>110</sup>

One possible explanation is that TNF- $\alpha$  inhibition leads to specific patients having a higher expression of INF- $\alpha$ , resulting in T-cell activation and higher release of TNF- $\alpha$ .<sup>109</sup> Others have hypothesized that an overexpression of CXCR3 occurs with recruitment of auto-reactive T cells and increased release of INF- $\alpha$ .<sup>109</sup> Adalimumab and infliximab followed

by etanercept are the most frequently reported causative TNF- $\alpha$  inhibitors.<sup>19</sup> However, there are also reports about certolizumab and other biologics, including secukinumab, brodalumab, ustekinumab, rituximab, atezolizumab, and tocilizumab, as well as the JAK inhibitors tofacitinib and baricitinib.<sup>111–117</sup> Smoking is a risk factor for the development of paradoxical PPP, but interestingly, it is not a risk factor for other paradoxical psoriasiform lesions.<sup>19</sup> Paradoxical PPP differs from classic PPP in some ways. The risk is higher among men and younger patients, and DLQI is higher than in classic PPP.<sup>21,118</sup>

The efficacy of therapies for PPP is difficult to compare as the endpoints and cohort selection of different studies vary in treatment duration, disease severity, and previous treatment. Topical steroids such as clobetasol propionate ointment, betamethasone butyrate propionate ointment, and triamcinolone acetonide applied intralesionally or under occlusion have shown good efficacy, leading to complete clearance in 21–100% of patients.<sup>25,27–29</sup> Maxacalcitol ointment can improve lesions significantly and enhance the effect of betamethasone butyrate propionate ointment.<sup>26,27</sup>

Phototherapy has an advantage of lacking systemic side effects and has been used for decades for the treatment of PPP. Among phototherapies, PUVA is the most efficient treatment.<sup>35,38–40,119</sup> Although one RCT showed no better improvement compared to a placebo, several other trials showed moderate to excellent response in the majority of patients.<sup>32,35,38–40,119</sup> PUVA is superior to UVA1 and UVBnb and is more efficient on the palms than the soles.<sup>35,37–40,119</sup> Excimer laser can improve PPP, especially with higher dose regimes.<sup>44</sup>

Among systemic therapies, retinoids are the most commonly used, especially acitretin in recent decades. Acitretin has shown good efficacy in several clinical trials, especially at higher doses, but relapse occurs after cessation. It may also increase the efficacy of PUVA.<sup>53,54</sup> The effect of alitretinoin has to be investigated more precisely as the results are controversial. It seems to mainly affect hyperkeratotic lesions.<sup>56,57</sup> Ciclosporin A seems to have good and fast efficacy for the treatment of PPP, but relapse can occur after cessation, and due to side effects, long-term treatments are not always optimal.<sup>58,59</sup>

In a retrospective study, Kromer et al demonstrated the response of PPP to conventional therapies with the best efficacy. PPPASI 75 was achieved in 51.4% of patients with ciclosporin, 22.6% with alitretinoin, 19.5% with acitretin, 17.7% with fumaric acid, and 16.8% with methotrexate.<sup>79</sup> In this analysis, ciclosporin reached PPASI 75 at comparable rates to those of apremilast (31.4%), infliximab (40.6%), adalimumab (33.3%), certolizumab (62.5), golimumab (41.7%), secukinumab (29%), and ustekinumab (31%).<sup>79</sup> The oral selective phosphodiesterase 4 inhibitor apremilast has been shown to be fast (2 weeks) and to have long-term efficacy (18 months) in case series.<sup>85,86</sup> However, a clinical trial showed the achievement of PPPASI 50 in 61.9% and PPPASI 75 in 14.3% of patients after 20 weeks of treatment, which do not seem to be superior to the results of conventional therapies described thus far.<sup>84</sup> Nevertheless, apremilast had the longest drug survival among non-biologic agents in a retrospective analysis by Kromer et al.<sup>79</sup>

In a very recent phase-2 RCT that was published after the literature screening for this review, apremilast showed improved results with achievement of PPPASI 50 in 78.3% of patients at week 16, which was significantly higher compared to the results of a placebo ( $P = 0.0003$ ). PPPASI 75 was achieved by 43.5% of patients.<sup>120</sup> These findings are comparable with the results of biologics. Among biologics, a recombinant interleukin (IL)-1 receptor antagonist, anakinra, has demonstrated good effectiveness in neutrophilic dermatosis by blocking the activity of IL-1 $\alpha$  and IL-1 $\beta$ . These two cytokines have been repeatedly linked to neutrophil activation and extravasation. However, anakinra has failed to show effectiveness in PPP.<sup>88</sup>

Among small molecules, Janus kinase (JAK) inhibitors are being examined for the treatment of various inflammatory skin diseases. Due to a lack of clinical trials, we did not include them in the result section, but tofacitinib (a JAK 1/2 inhibitor) has shown impressive improvement of PPP in 5 cases, and baricitinib (a JAK 1/3 inhibitor) has been used in 1 case of PPP and in cases of resistance to biologics and paradoxical PPP.<sup>121–124</sup> In a review, Gleeson et al suggested that tofacitinib may be beneficial for PPP and could be considered for patients with an acceptable comorbidity indication. However, routine use cannot be recommended due to the limited evidence and uncertain safety profile of JAK inhibitors.<sup>125</sup>

Despite the observed side effects of paradoxical PPP, TNF- $\alpha$  inhibitors have been successfully used for the treatment of PPP.<sup>78,126</sup> In a retrospective analysis, Husson et al found no difference in the percentage of complete clearance between TNF- $\alpha$  inhibitors, with 13.3% clearance achieved using etanercept, 17.6% achieved using adalimumab, and

19.0% achieved using infliximab.<sup>78</sup> In the case of TNF- $\alpha$ -induced PPP, a review by Li et al suggested that possible considerations include a treat-through strategy (resolution in 26–41% of cases), switching to another TNF- $\alpha$  inhibitor, or switching to another conventional or biologic therapy.<sup>127</sup>

The therapeutic effects of IL-17 and IL-23 blockers have been investigated due to findings supporting the importance of the IL23-TH17 axis in the pathogenesis of PPP. Patients with PPP have shown an increased level of IL-17A in the acrosyngium of the palms and soles, increased IL-17 serum levels, and increased mRNA encoding IL-17, IL-22, IL-23, and IL-8 in the lesional skin of PPP patients.<sup>2,70,128</sup> Among biologic agents, the anti-IL-23 antibody guselkumab is the first to be approved for the treatment of PPP in Japan.<sup>2</sup> In 3 RCTs, guselkumab was significantly superior to a placebo at week 16, at which it achieved PPPASI 50 in 60% of cases and PPASI 75 in 11.5–20.4% of cases. The efficacy increased over time, with PPASI 75 occurring in 55.6–59.6% of cases at week 52 and 61.9–81.4% of cases at week 84.<sup>66–68</sup> Patients who received prior phototherapy or non-biologic therapies had a tendency toward worse response, and non-smokers tended to sustain efficacy for a longer time.<sup>66</sup> An RCT evaluating the efficacy of risankizumab, another IL-23 inhibitor, is under way.<sup>129</sup>

Ustekinumab at 45 mg was not superior to placebo at week 16 in an RCT.<sup>72</sup> However, retrospective studies and case series with longer observation periods showed complete or partial clearance in 44–100% of patients, suggesting a need for further long-term trials. Secukinumab has demonstrated a fast response (16 weeks) and long-term effect (148 weeks) in 2 RCTs.<sup>69,70</sup> The effect of brodalumab, another IL-17 inhibitor, is still under investigation. The IL-1 inhibitor anakinra does not seem to be efficient for the treatment of PPP.<sup>130</sup>

Regarding IL-36 inhibitors, spesolimab showed no significant superiority to a placebo in an RCT, and imsidolimab did not induce any relevant improvement in a single case.<sup>81,131</sup> In case reports, the effectiveness of dupilumab, brodalumab, and vedolizumab has been suggested, but there is a lack of evidence in the literature.<sup>132–134</sup> Recently, RIST 4721, a CXC chemokine receptor type 2 (CXCR2) inhibitor, was investigated for the treatment of PPP in a phase-2A study. RIST 4721 is hypothesized to prevent neutrophil migration by blocking CXCR2 ligands including IL-8, but it was not significantly superior to a placebo.<sup>135</sup> Another trial is under way. Its potential efficacy could not be excluded in a subgroup analysis.<sup>135</sup> New therapies such as the TYK2 inhibitor deucravacitinib are being examined.<sup>136</sup>

## Conclusion

Compared to the large list of known factors associated with PPP, little is known about real risk factors for the development of PPP and its severity. Smoking remains the most obvious risk factor, and the fact that PPP improves after cessation should motivate patients to stop smoking. The second lifestyle factor influencing not only the risk of development but also disease severity of PPP is obesity. Therefore, patients should be motivated to achieve a normal BMI. Regarding therapies, topical therapies and phototherapies can result in good improvement in some cases and remain as the first-line therapy. As a second step, retinoids can be prescribed. In cases of side-effects or non-response, conventional therapies such as ciclosporin can show good efficacy, but they are limited by long-term side-effects and immediate relapse after cessation. In these cases, biologics (namely TNF- $\alpha$ -inhibitors, IL-17 and IL-23 blockers, and apremilast) can show good effectiveness in some patients. Due to the lack of comparative trials, however, it is difficult to name a preferable biologic. IL-17 inhibitors and IL-23 inhibitors have shown good results, but they are used off-label in most countries. An advantage for the IL-23-inhibitor guselkumab could be that it is licensed for PPP in Japan. In general, treatments with biologics should be continued over 1 year in cases of partial response as the efficacy increases with the duration of treatment, and the response is rather slow compared to that of PV. Recent case reports about JAK inhibitors show promising results, but clinical trials and comparative trials with well-established treatments are needed.

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