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REVIEW ARTICLE

A Review on Pityriasis Rubra Pilaris

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Abstract Pityriasis rubra pilaris (PRP) is an idiopathic, papulosquamous inflammatory dermatosis. It is characterized by hyperkeratotic follicular papules coalescing into orange-red scaly plaques, islands of sparing, and palmoplantar keratoderma. PRP can be subdivided into six clinical subtypes according to Griffiths' classification, based on age of onset, disease extent, prognosis, and other associated features. The sixth subtype of PRP occurs in individuals affected by HIV infection, and retroviral screening in all de novo cases of PRP is advised. Other reported associations include various infections, autoimmunity, drugs, and malignancies, although the true significance of these is still unclear. The genetic basis for familial cases, most commonly categorized under the fifth subtype, has been mapped to gain of function mutations in the caspase recruitment domain family, member 14 (*CARD14*) gene. Treatment of PRP remains a challenge to this day due to a paucity of high-quality evidence. Therapeutic regimens have been guided mostly by case reports and case series, with the mainstay of treatment being oral retinoids. Recently, biologics have emerged as a promising treatment for PRP. We present a review of the clinicopathologic features, pathogenesis, associated disorders, and treatment of PRP, with an emphasis and critical appraisal of the existing literature on the latter.

Key Points

Pityriasis rubra pilaris (PRP) is subdivided into five subtypes based on age of onset, disease extent, and associated ichthyosiform or sclerodermoid features. The classic forms have a tendency towards spontaneous remission. A sixth type is seen in patients with HIV and individual lesions may show prominent follicular spicules.

Gain-of-function mutations in the caspase recruitment domain family, member 14 (*CARD14*) gene have been identified as the genetic basis in familial cases of PRP. Such mutations result in activation of nuclear factor (NF)-κB, which in turn promotes cutaneous inflammation.

Currently, there is paucity of high-quality evidence on the treatment of PRP. Oral retinoids represent first-line systemic treatment as the evidence is greatest for their use, including the only prospective, single-arm, non-blinded study performed in PRP patients to date. Methotrexate is an alternative agent, although the efficacy demonstrated in later retrospective studies contrasts with results from earlier ones. Biologics appear to be beneficial based on multiple case reports, especially in recalcitrant cases, although more prospective clinical data are needed to fully establish this. Topical treatment alone can be considered in pediatric patients or those with limited disease.

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1 Introduction

Pityriasis rubra pilaris (PRP) was first described by Claudius Tarral in 1835 as a variant of psoriasis [1]. The term 'pityriasis pilaris' was later coined by Alphonse Devergie in 1856, which led to PRP bearing the eponymous name 'Devergie's disease' [2].

PRP is a rare dermatosis, and its exact incidence is not well-documented. In Great Britain, it is diagnosed in about 1 in 5000 new patients presenting with skin disease [3]; in India, this is approximately 1 in 50,000 patients [4]. Within the pediatric group, a higher incidence of 1 in 500 new patients presenting with dermatologic disease has been reported [5]. PRP affects all races and both sexes equally. The disorder has a bimodal distribution, peaking in the first and fifth decades of life [3].

In this article, we present a descriptive review of the clinical features, pathogenesis, histological features, and treatment of PRP. Publications, pertaining particularly to the treatment of PRP, were identified via a search of PubMed, EMBASE, and MEDLINE databases using the term "Pityriasis Rubra Pilaris" within the articles' title. Only articles published from 1 January 1990 to 30 September 2017 inclusive, and in the English language, were included; conference abstracts were excluded. A total of 286 articles were identified and reviewed. Select publications prior to 1990 have also been included for their significance to this review.

2 Clinical Manifestations

There are several classification systems for PRP but Griffiths' classification is the most commonly used. In 1980, Griffiths classified PRP into five subtypes based on age of onset, morphology, clinical course, and prognosis [3]. Miralles et al. [6] proposed a type VI subtype of HIV-infected individuals with PRP.

2.1 Type I: Classical Adult

The type I (classical adult) subtype is the most common form of PRP, accounting for up to 55% of all cases [3]. The onset is usually acute and starts with the upper half of the body, usually the face and neck. Over weeks or months, the lesions spread caudally, affecting the trunk, arms, and legs. Classical features include red-orange keratotic follicular papules coalescing into plaques with characteristic islands of sparing (Fig. 1). Erythroderma and a waxy palmoplantar keratoderma may ensue (Fig. 2). Fine powdery scales may be seen on the face and scalp while scales on the lower half of the body are coarser [3]. Nail changes may also be present, with patients developing rough, thickened nails, yellow–brown discoloration of the nail plate, subungual hyperkeratosis, and longitudinal ridging [3, 7]. Ectropion may develop in those with prolonged facial involvement. Other findings include lymphadenopathy and associated

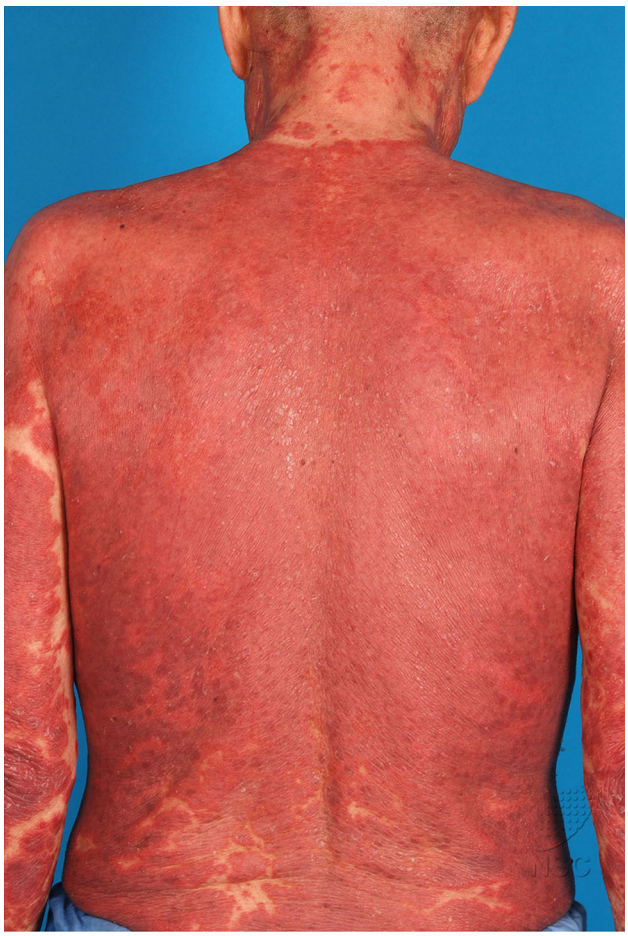

Fig. 1 Red–orange confluent, scaly plaques over the back. Well-demarcated, conspicuous islands of sparing are seen over the pre-sacral areas

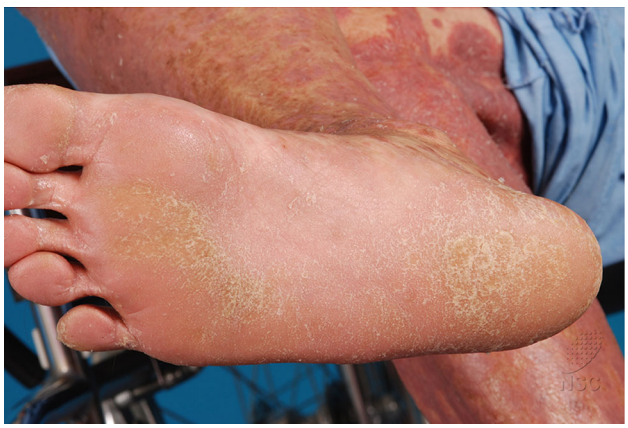

Fig. 2 Diffuse keratotic thickening of the sole with an orange hue

arthropathy [7, 8]. Type I PRP has the best prognosis, with up to 80% experiencing spontaneous remission within 3 years [7].

2.2 Type II: Atypical Adult

The type II (atypical adult) subtype accounts for approximately 5% of all PRP cases [3]. It does not follow the cephalocaudal progression seen in type I. It is typified by ichthyosiform dermatitis with a predilection for the lower extremities. Palmoplantar hyperkeratosis is coarse with lamellated scales. There may also be associated sparseness of hair and alopecia. This subtype is usually chronic, running a course of more than 20 years, with less than 20% experiencing clinical resolution within 3 years [3, 9].

2.3 Type III: Classic Juvenile

The type III (classical juvenile) form of PRP accounts for 10% of all cases [3]. Clinical presentation is similar to type I, with the exception of onset in childhood, usually around 5–10 years of age. The prognosis is good, with most lesions spontaneously resolving within 1 year [7].

2.4 Type IV: Circumscribed Juvenile

The type IV (circumscribed juvenile) form of PRP accounts for about 25% of all cases [3]. This subtype affects prepubertal children and presents with sharply demarcated areas of follicular hyperkeratosis and erythema over the elbows and knees. Transient scaly erythematous macules over other parts of the body and hyperkeratosis over bony prominences may be seen. Prognosis is less favorable than classical juvenile PRP, with only a third of patients achieving remission within 3 years.

2.5 Type V: Atypical Juvenile

Type V (atypical juvenile) PRP represents about 5% of cases [3]. Most cases of familial PRP fall under this subtype. This disease has an early onset and runs a protracted course. Patients present with follicular hyperkeratosis and ichthyosiform features. Some patients display sclerodermatous changes of their hands and feet.

2.6 Type VI: HIV-Associated

Occurrences of PRP in HIV patients have been classified into a separate subtype as these patients may have additional unique features such as follicular occlusion, acne conglobata, hidradenitis suppurativa, and lichen spinulosus-like lesions [6, 10–12]. Most patients start developing erythematous desquamating follicular papules and prominent follicular plugging with formation of spicules. There is inconsistent involvement of the nails, palms, and soles. Erythroderma with islands of sparing is a frequent complication [7].

3 Pathogenesis

The etiology and pathogenesis of PRP remains unclear. Several possible mechanisms have been postulated.

3.1 Genetics

Most cases of PRP are sporadic; however, familial forms have been described. This is most commonly seen in type V PRP. Familial PRP typically demonstrates autosomal dominant inheritance and variable penetrance, although inheritance in an autosomal recessive fashion has also been observed [13–15]. Autosomal dominant PRP has been linked to gain-of-function mutations in the caspase recruitment domain family, member 14 (*CARD14*) gene on chromosome 17q25 [14]. *CARD14* encodes a 1004 amino acid protein that activates nuclear factor κ-light-chain enhancer in activated B cells (NF-κB), which in turn regulates the activity of genes involved in immune and inflammatory reactions. The *CARD14* gene corresponds to the psoriasis susceptibility locus 2 (PSORS2), mutations of which have also been described in familial psoriasis vulgaris [16]. While *CARD14* mutations have been detected in both familial and sporadic type V PRP [17], a case series did not detect any mutation in *CARD14* in 61 patients with sporadic PRP [18].

3.2 Vitamin A Metabolism Abnormalities

Similarities between the cutaneous manifestations of phrynoderma and PRP amongst Chinese patients and Ugandan prisoners led to early theories of vitamin A deficiency causing PRP [19–21]. However, serum vitamin A levels in PRP patients are often normal [22, 23]. Although serum retinol binding protein (RBP), a carrier protein for vitamin A, was observed to be low in 11 PRP patients and their relatives [24], most other studies have shown normal RBP levels in PRP patients [25–27]. Moreover, administration of high doses of vitamin A has not always led to remission of PRP [26]. These findings have led to the postulation of aberrant vitamin A metabolism, rather than a true deficiency, underlying PRP. One possibility is an abnormal immune response to certain antigens interfering with epidermal retinoid signaling pathways and disrupting keratinocyte differentiation [28]. However, the exact role of vitamin A deficiency and/or metabolism abnormalities still remains unclear currently.

3.3 Infections

The role of viral and bacterial infections in the development of PRP has been documented most convincingly in HIV infections. In some cases, PRP skin lesions may be the initial manifestation of underlying HIV disease [6, 12]. Infections due to *Staphylococcus aureus* and *Streptococcus pyogenes* have been found in patients with juvenile PRP, and resolution of skin lesions following appropriate antibiotics has been described [29, 30]. This has given rise to the theory of bacterial superantigens triggering PRP; however, there have been no conclusive studies to date. Moreover, the apparent therapeutic response to antibiotics observed may be confounded by juvenile PRP's propensity for spontaneous resolution. Other infectious triggers that have been reported include cytomegalovirus, Epstein-Barr virus, hepatitis A virus, and varicella zoster virus [31–34].

3.4 Other Factors

There have been case series and case reports of koebnerization or trauma preceding the onset of PRP in children [35, 36]. However, a large case series over 10 years failed to demonstrate Koebner phenomenon in PRP [37]. Photoaggravated PRP has been described in both children and adults [38–44]. Multiple drugs have been reported to trigger PRP-like eruptions, but these have largely been confined to isolated case reports. The two classes of drugs with a greater number of reports are kinase inhibitors [45–47] and modern antivirals for hepatitis C [48, 49]. Dermatologic treatments such as imiquimod [50–52] and photodynamic therapy [53] have also been reported to incite PRP.

4 Associated Conditions

PRP has been associated with infections, autoimmune diseases, and malignancies. With the exception of HIV infection, the relationship between PRP and these disorders is unclear, hence routine screening is not always performed.

There are case reports of PRP being associated with autoimmune diseases such as myasthenia gravis [54], autoimmune thyroiditis [55–57], celiac disease [58], and vitiligo [59]. PRP has also been associated with malignancies, with 12 case reports published in the English-language literature. All were solid-organ malignancies [60–70] except for a single case of leukemia [71]. Although a marked improvement following oncologic treatment was reported in seven of the patients [61–66, 69], the relationship between PRP and malignancy may be more fortuitous than a truly paraneoplastic one given that only one case of malignancy was detected in an earlier case series of 168 PRP patients [70].

5 Diagnosis

The diagnosis of PRP is based on the aforementioned constellation of clinical signs and histopathological features.

5.1 Histological Findings

Characteristic histological findings in PRP include the following:

1. Alternating orthokeratosis and parakeratosis in both vertical and horizontal directions ('checkerboard' pattern).
2. Focal or confluent hypergranulosis.
3. Irregular acanthosis in the form of short and broad rete ridges.
4. Thick supra-papillary plates.
5. Sparse superficial perivascular lymphohistiocytic infiltrate in the dermis.
6. Follicular plugging with parakeratosis at the edges of follicular orifice ('shoulder parakeratosis').

Various non-classical histological features have also been described, including those discussed in Sects. 5.1.1–5.1.3.

5.1.1 Lichenoid Infiltrate

A lichenoid inflammatory infiltrate was observed in 16–38% of PRP cases from two small retrospective studies [28, 72]. There is also a single case report of the infiltrate resembling that of lichen nitidus [73].

5.1.2 Dermal Eosinophilia

The presence of eosinophils within the dermal inflammatory infiltrate has been observed in 22–63% of PRP cases from three small retrospective studies, and such a finding should not necessarily exclude the diagnosis of PRP [28, 72, 74].

5.1.3 Acantholysis

Acantholysis has been identified in 5.8–72% of PRP biopsies across four small retrospective studies [28, 72, 74, 75]. Some of these patients did have erosions clinically or carried a pre-biopsy diagnosis of pemphigus or Grover's disease. Ko et al. [72] have even proposed that acantholytic changes within the biopsy of patients

presenting with a papulosquamous eruption may warrant the diagnosis of PRP.

6 Differential Diagnosis

Erythrodermic PRP presents as a diagnostic conundrum with an array of differential diagnoses such as atopic eczema, psoriasis, seborrheic dermatitis, cutaneous T cell lymphoma, erythroderma progressiva symmetrica, erythrokeratoderma variabilis, follicular eczema, follicular ichthyosis, generalized hypersensitivity reactions, and lichen planopilaris [7, 76, 77]. The rare 'Wong' variant of dermatomyositis may also present with a PRP-like eruption.

There have been several case reports of PRP evolving into an erythema gyratum repens-like morphology during treatment, especially with systemic retinoids [78–80]. No underlying malignancy has been found in any of these cases [78].

Types I and III PRP may be confused with psoriasis. Distinguishing features of PRP include palmoplantar keratoderma, characteristic islands of sparing, and hyperkeratotic scalp scaling. Conversely, coarser silvery scales, sharply demarcated salmon pink plaques, and characteristic nail changes are more typical of psoriasis. Types II and V PRP may present with ichthyosiform changes. These may appear similar to lesions seen in other ichthyotic disorders such as follicular ichthyosis and erythrokeratodermas.

Type IV PRP, which presents with focal lesions, may be misdiagnosed as lichen spinulosus, keratosis pilaris, Darier's disease, pemphigus foliaceus, and epidermal nevus [28, 81]. Another differential would be follicular psoriasis, but histological examination reveals an absence of Munro's microabscesses in PRP [82].

7 Treatment

Evaluating treatment efficacy in PRP is confounded by its rarity, as well as its natural tendency towards spontaneous resolution. As a result, there have been no large-scale trials conducted on the treatment of PRP, and the bulk of evidence comes primarily from small retrospective case series and isolated case reports.

Although no consensus on the treatment of PRP exists, we recommend the treatment algorithm given in Table 1. A more indepth discussion on each class of therapy can be found in Sects. 7.1–7.7.

7.1 Topical Treatment

Various topical treatments have been employed in the treatment of PRP, with the mainstay being topical corticosteroids. The response to topical treatment appears to be more favorable amongst pediatric patients or those with limited disease (e.g., type IV PRP). Two retrospective studies of juvenile PRP showed a moderate to excellent response to topical treatment alone in 73.7% [38] and 78.6% [83] of patients with type IV disease. The review by Marrouche et al. [74] of 32 Lebanese patients showed an excellent response to topical steroids in 40% (6 of 15) of juvenile patients compared to just 12.5% (2 of 16) of adult patients. Practitioners should always be mindful of the risks of cutaneous atrophy, or even systemic absorption, especially when used in children.

Other topical agents that have been tried include topical retinoids [81, 84], calcipotriol [85, 86], and calcineurin inhibitors [87]. Topical keratolytics can be considered in the presence of hyperkeratosis and palmoplantar keratoderma. Emollients and oral antihistamines may also ameliorate any associated pruritus.

7.2 Systemic Retinoids

Oral retinoids are now considered a first-line systemic treatment based on several case series. They have antiproliferative, immunomodulatory, and anti-inflammatory effects that are mediated by intranuclear retinoic acid receptors (RARs). The most commonly used retinoids are acitretin, isotretinoin, and etretinate.

In one of the largest, prospective studies of retinoids in PRP, 28 of 45 patients (62%) treated with isotretinoin (mean dose 2.13 mg/kg/day) had marked improvement within 4 weeks, and all 34 patients who returned for follow-up after 12–16 weeks of treatment had marked improvement [88]. Subsequent smaller retrospective studies have demonstrated a 55–66% rate of clinical remission with isotretinoin or etretinate after a mean treatment duration of between 5 and 13 months [89–91].

With regards to acitretin, a good response was observed in all five patients with type I PRP (including two patients who had concurrent psoralen and ultraviolet [UV] A [PUVA] therapy), with improvements seen as early as 2–3 weeks [92]. Eastham et al. [93] treated ten type I PRP patients with acitretin monotherapy (dose range 25–50 mg/day): five (50%) achieved $\geq$ 75% improvement from baseline, three patients had $<$ 75% improvement, and two patients progressed to biologic treatment [93].

Alitretinoin, a newer retinoid, has been successfully used in PRP (types I–IV) across five case reports and one case series [94–99]. In the case series, four of five adults with type I PRP had a 71% mean reduction in disease

Table 1 Treatment options for pityriasis rubra pilaris, including level of evidence

Treatment	Indication	Level of evidence[a]
Topical corticosteroids	May be sufficient to induce remission in *limited disease* (e.g.. type IV PRP)	4
	Alternative topical medications: calcipotriol, calcineurin inhibitors, retinoids	
Oral retinoids	*First-line systemic agents* for the treatment of PRP	4
	Can be combined with phototherapy	
	Typical doses for adults:	
	Isotretinoin: up to 1 mg/kg/day (avoid conception 1 month post-cessation)	
	Acitretin: up to 0.5 mg/kg/day (avoid conception 3 years post-cessation)	
Methotrexate	*Alternative systemic agent* if contraindicated or refractory to retinoid therapy	4
	Can also be used concurrently with oral retinoids (monitor for hepatotoxicity)	
	Typical dosing in adults: 5–25 mg/week	
	Very limited data for use in juvenile PRP	
Biologics	Majority used in *recalcitrant* PRP, but *few cases of use as first-line therapy*	4
	Infliximab has largest body of evidence supporting its use	
	Treatment failure with one agent does not preclude secondary response to other agents within the same class	
	Can be combined with methotrexate or retinoids	
	Dosing as for psoriasis:	
	(a) IV infliximab 5 mg/kg at weeks 0, 2, 6, and then every 8 weekly	
	(b) SC etanercept 50 mg weekly	
	(c) SC adalimumab 80 mg at day 0, 40 mg at day 7, then fortnightly	
	(d) SC ustekinumab	
	Body weight $\leq$ 100 kg: 45 mg at weeks 0 and 4 and then every 12 weeks	
	Body weight $>$ 100 kg: 90 mg at weeks 0 and 4 and then every 12 weeks	
	(e) SC secukinumab 150 or 300 mg at weeks 0, 1, 2, 3, and 4, followed by every 4 weeks	
Phototherapy	May be used in widespread disease if systemic agents have been declined by patient or are contraindicated	5
	Consider *pre-treatment phototesting* to exclude photoaggravated PRP	
	NBUVB and PUVA have been used standalone or with systemic agents. UVA1 has been used with systemic retinoids	
	In *photoaggravated PRP*, treatment with the *non-offending spectra* has been reported to be effective	
Miscellaneous	Consider *HAART for type VI PRP*	5
	Cyclosporine: weak and inconsistent evidence for efficacy	4
	Azathioprine: successfully used in earlier case series of between 3 and 8 patients; no reports of successful use since 1990	4
	Extracorporeal photopheresis: 3 patients successfully treated	
	Penicillins: 2 patients successfully treated	
	Fumarates, apremilast, mycophenolate, IVIg: reported successful in 1 patient for each	

HAART highly active antiretroviral therapy, *IV* intravenous, *IVIg* intravenous immunoglobulin, *NBUVB* narrowband ultraviolet B light, *PRP* pityriasis rubra pilaris, *PUVA* psoralen and ultraviolet A light, *SC* subcutaneous, *UVA1* ultraviolet A1 light

[a]Based on *The Oxford 2011 Levels of Evidence* [182]: Level 1: *N*-of-1 randomized trials OR systematic reviews of randomized trials, Level 2: Randomized trial OR observational study with dramatic effect, Level 3: Non-randomized controlled cohort/follow-up study, Level 4: Case-series OR case-control study OR historically controlled study, and Level 5: Mechanism-based reasoning

severity after 4–8 weeks of alitretinoin 30 mg/day [99]. Notably, four of the case reports involved patients who had previously failed to respond to acitretin; the ability of alitretinoin to bind to retinoid X receptors, in addition to conventional retinoic acid receptors, has been proposed as the mechanism for its relative efficacy [94, 95, 97, 98].

Juvenile PRP has also been treated with oral retinoids. Allison et al. [36] achieved a 90–100% improvement in five of six patients with type III PRP within 6 months of

treatment with isotretinoin (dose range 0.75–1.5 mg/kg/day), with the remaining patient being lost to follow-up. Two further retrospective studies from Taiwan, however, showed slightly less impressive results. In the first study involving a series of 18 patients with juvenile PRP, all five patients that required oral retinoids (acitretin) achieved a 30–90% improvement in their condition. This comprised two patients with type III and three patients with type IV PRP. The initial dose of acitretin was 0.5–1 mg/kg/day; treatment duration ranged from 1 to 12 weeks [83]. In the study by Yang et al. [38], six patients of a sample of 23 histologically confirmed cases of juvenile PRP had required oral retinoids. Five patients received acitretin (dose range 10–25 mg/day) over a mean duration of 15.4 weeks, with only one patient with type IV disease achieving 90–100% improvement. Two patients each with type III and IV disease had 30–90% improvement. The sixth patient, who had type IV PRP, experienced 90–100% improvement with a 1-week course of etretinate 10 mg/day [38].

In children, an important adverse effect of retinoid therapy is that of bony changes, especially premature epiphyseal closure. Based on data on the use of oral retinoids for other pediatric dermatoses, its short-term use appears to be safe and well-tolerated. However, the risk of skeletal toxicities increases with prolonged treatment at higher doses [100].

Teratogenicity is another significant complication of retinoid therapy, and child-bearing potential may be regarded as a relative contraindication. Pregnancy should strictly be avoided via the use of two reliable forms of contraception before, during, and after treatment. This should commence 1 month before initiation of isotretinoin therapy and continue during treatment and 1 month after the last dose [101]. After completion of acitretin, pregnancy should be delayed for another 3 years [102].

Other potential adverse effects include dry skin and mucous membranes, dyslipidemias, transaminase elevations, corneal opacities, and decreased dark adaptation.

7.3 Methotrexate

Although early literature demonstrated only a 39% response rate (17 of 44 patients) [3], subsequent studies have yielded more favorable outcomes with methotrexate, both as an alternative and adjunct to systemic retinoid therapy.

A retrospective study showed significant improvement in all eight patients with type I PRP treated with methotrexate (dose range 10–25 mg/week) over an average treatment duration of 6 months; this included three patients who were refractory to isotretinoin previously [91]. Another retrospective study evaluated five adult patients, including two non-responders to acitretin, who all showed improvement with methotrexate over a mean treatment duration of 12 months [103]. Van Dooren-Greebe and van de Kerkhof [104] also reported marked response to methotrexate 15 mg/week in a 33-year-old male with type III PRP who had developed extraspinal hyperostosis following successful long-term retinoid therapy.

Combining methotrexate with oral retinoids may be considered in recalcitrant cases, albeit with a greater risk of hepatotoxicity [105, 106]. Clayton et al. [37] evaluated 11 adult patients who received combination therapy for disabling or resistant disease, and found that 91% (10 of 11) eventually achieved $\geq$ 95% clearance; this compared favorably with the eight of 11 adult patients (73%) treated with retinoid monotherapy who achieved $\geq$ 95% clearance [37].

Adverse effects vary by route of methotrexate administration and dosage. Common adverse effects include alopecia and gastrointestinal disturbances. More serious adverse effects include hepatotoxicity, myelosuppression, and pneumonitis. Methotrexate is teratogenic and can also cause defective spermatogenesis.

There are currently limited data on the use of methotrexate in children with PRP.

7.4 Phototherapy

The response of PRP to UV light is variable, with reports of successful treatment with phototherapy (i.e., PUVA, narrowband UVB [NBUVB], UVA1) as well as paradoxic photoaggravation. Photoaggravated PRP is rare, but has been reported following exposure to either UVA or UVB [39–44].

Earlier studies involving the use of UVB phototherapy, including the Goeckerman regimen, were largely unsuccessful [91, 107]. A retrospective series involving 12 children treated with the Goeckerman regimen also showed that the majority (58%; 7 of 12) had a poor response of $<$ 30% improvement [36]. Khoo et al. [108] published the first case report of treating PRP with NBUVB, achieving a partial therapeutic response [108]. Further case reports of the successful use of NBUVB in both adults and children have since been published [51, 74, 109, 110]. PUVA therapy was shown to be ineffective in all five patients in a retrospective series [103]; however, it was used successfully to treat a patient with photoaggravated PRP that was provoked by the UVB spectrum [44].

Combining phototherapy and oral retinoids has also been tried with some success. Acitretin combined with PUVA, NBUVB, or UVA1 has been reported efficacious in case series and several case reports [31, 92, 93, 111–114].

Due to the potential risk of photoaggravation, phototesting may be considered prior to initiation of phototherapy [41, 42, 115].

7.5 Biologic Agents

Biologics are increasingly being used in the treatment of PRP. Although their use has predominantly been in treatment-resistant PRP, there have been a few case reports of biologics as first-line therapy, including where other systemic agents have been contraindicated [116–121]. Tumor necrosis factor-α inhibitors (TNFi), ustekinumab, and, more recently, secukinumab have all been used in PRP, either as monotherapy or in combination with methotrexate or retinoids.

7.5.1 Tumor Necrosis Factor-α Inhibitors

TNFi have been the most widely reported class of biologics used in PRP; the evidence for their efficacy comes largely from case reports and a few case series. Although the tendency for PRP to undergo spontaneous resolution and the possibility of reporting bias towards positive outcomes may overestimate the efficacy of TNFi, a 2013 systematic review of 15 patients treated with TNFi found that the response in 83% of the 12 patients achieving complete remission could be directly attributable to TNFi therapy [122]. This was further corroborated by a subsequent retrospective series that demonstrated partial or marked improvement after a mean of 5.7 weeks in all nine patients treated with TNFi [93].

Our literature search revealed that infliximab is the most commonly reported agent used to date. A total of 39 patients have been treated with infliximab [53, 92, 93, 119, 121–134] (31 with type I, one with type II, and two with type III PRP; unspecified in five patients), including a single case of treatment failure [135]. The majority of cases demonstrated clinical response within 1–6 weeks. Two separate case series involving a total of seven patients showed no cases of relapse following cessation of therapy [119, 132]. Two patients were transitioned to etanercept [53] or adalimumab [134], with maintenance of clinical response. Paradoxically, a PRP-like eruption following infliximab therapy for Takayasu's arteritis has been described [136].

The next most common agent used is etanercept. A total of 15 patients have been reported in the literature (ten with type I, two with type II, one with type III, and one with type V PRP; unspecified in one patient) [93, 116, 132, 134, 137–140], including two cases of treatment resistance [132, 141]. The majority of patients who demonstrated clinical response did so within 6–8 weeks. There were three documented cases of relapse, occurring 1–6 months following treatment cessation [116, 132, 137].

Adalimumab has been reported in the treatment of 13 patients (ten with type I, one with type II, and one with type III PRP; unspecified in one patient) [93, 117, 118, 142–149], including two cases of treatment failure [74, 97]. Amongst responders, clinical improvement was observed within 1–6 weeks. There were insufficient data from the individual reports on the risk of relapse with treatment cessation.

Interestingly, treatment failure with a single TNFi does not preclude a secondary response to other agents within the same class. Kim et al. [148] and Chiu et al. [145] each reported one patient who subsequently responded to adalimumab despite previous treatment failure with etanercept.

7.5.2 Ustekinumab and Secukinumab

Ustekinumab is a human monoclonal antibody directed against the p40 subunit shared by interleukin (IL)-12 and IL-23. Secukinumab is a recombinant, high-affinity, fully human IgGκ monoclonal antibody that directly binds to and neutralizes IL-17A. The efficacy of these agents relates to the postulated pathogenic role of the IL-23/T helper 17 (Th17) axis in PRP.

Activation of the NF-κB pathway, which occurs as a result of the *CARD14* gene mutation described in familial (and, rarely, sporadic) PRP, has been shown to positively regulate Th17 differentiation [150]. Moreover, Feldmeyer et al. [151] identified over-expression of messenger RNA (mRNA) levels of cytokines of the IL-23/Th17 axis in the lesional skin of three patients with PRP, comparable with patients with psoriasis. Furthermore, clinical and histopathologic improvements paralleled the expression levels of Th17 cytokines in a single patient treated with ustekinumab [151].

To date, 11 patients treated with ustekinumab have been reported in the English-language literature. Lernia et al. [152] reported treatment failure in a 29-year-old female who presented with a relapse of type IV PRP that was also unresponsive to adalimumab, etanercept and infliximab [152]. Of the remaining ten patients who responded to ustekinumab, three had type V PRP, including a mother and son kindred, all of whom harbored *CARD14* mutations [153, 154]; seven patients had type I disease [120, 151, 155–159]. Three patients had failed to respond to prior treatment with other biologics (infliximab or its biosimilar, adalimumab, etanercept) [154–156]. Clinical response was evident within 8 weeks, but data on long-term efficacy is lacking given that the longest treatment duration was only 64 weeks. The HLA-cw6 allele, which predicts a superior response to ustekinumab in patients

with psoriasis [160], was detected in one patient [155] but was negative in the mother and son kindred [153].

Secukinumab has been successfully used in two patients so far. In the first, a patient with type I PRP received subcutaneous secukinumab 300 mg administered weekly for 5 weeks then monthly. Improvements were observed within 3 weeks and near complete resolution within 6 months [161]. There were no adverse effects noted. The second patient had a 9-year history of type II PRP refractory to multiple therapies, including ustekinumab and infliximab, which improved significantly within 4 weeks of initiating secukinumab, in conjunction with prednisone and cyclosporine (ciclosporin), at an identical dosing regimen. She was negative for *CARD14* gene mutations. The patient tolerated the treatment well except for oral and esophageal candidiasis which was treated with fluconazole [162]. Other biologics targeting the IL-17 pathway, such as brodalumab and ixekizumab, have not been used in PRP so far.

7.6 Other Therapies

Vitamin A therapy has largely been supplanted by systemic retinoids, and, given its inconsistent therapeutic results, should no longer be regarded as standard practice [7, 91]. Systemic corticosteroids have not been shown to be useful in PRP either [82].

Successful treatment with azathioprine (dose range 50–200 mg/day) has been previously reported in a few case series involving three to eight patients [3, 163, 164]; however, no similar reports since 1990 were identified in our literature search.

The evidence for cyclosporine is mixed. Usuki et al. [165] reviewed 13 published cases of PRP treated with cyclosporine and found a good to excellent response in five patients, including three of their own. Seven patients had no clinical response, and one patient only had a minimal response [165]. Within another series of 38 biopsy-proven cases of PRP, three patients with type I disease received cyclosporine, with two achieving a partial response and the remaining patient progressing on to TNFi therapy [93]. Even fewer data exist on the use of cyclosporine in juvenile PRP, with only one successful case report identified. Wetzig and Sticherling [166] treated a 4-year-old male with type III PRP with cyclosporine starting at 3 mg/kg/day over a 23-week period. A clinical response was evident at 5 weeks, and the patient remained in remission over an 8-month therapy-free period [166].

Various miscellaneous therapies have also been described in the literature, but these are limited to isolated reports involving no more than three patients. These include apremilast [167], mycophenolate [93], intravenous immunoglobulin [168], penicillins [169, 170], fumarates [171], and extracorporeal photopheresis [172, 173].

7.7 Treatment of Type VI Pityriasis Rubra Pilaris

Data on the treatment of type VI PRP are rare and limited to case reports. Within the English-language literature, there have been 13 published articles involving 16 type IV PRP patients [6, 10, 11, 90, 174–181]. Various treatments have been used with inconsistent results, with the commonest being systemic retinoids, antiretroviral therapy (ART), or both. Of the six patients who received combination therapy, four had at least moderate improvement and one each had slight or no improvement. The most recent case report described disease resolution and sustained remission using combined ART with stavudine/lamivuidine/efavirenz [178]. Menni et al. [181] also reported spontaneous resolution in a 4-year-old male with HIV-associated PRP.

8 Conclusion

PRP is a rare inflammatory dermatosis affecting both children and adults. Although its exact pathogenesis remains obscure, the *CARD14* mutations identified in familial cases may provide an insight into the inflammatory pathway derangements that underpin this disorder. The diagnosis of PRP can occasionally be difficult in the atypical subtypes or early phases of the disease, until the characteristic islands of sparing or waxy keratoderma ensue. Clinicopathologic correlation is essential in confirming the diagnosis, although one must be aware of atypical histological findings, such as acantholysis, that have increasingly been described.

The treatment of PRP is challenging due to a lack of good-quality evidence, and no consensus currently exists. Although spontaneous disease resolution is recognized, the possible widespread and distressing nature of PRP may necessitate prompt initiation of treatment. Systemic retinoids, methotrexate, cyclosporine, phototherapy, and, more recently, biologics have all been reported to be efficacious in the literature. However, more studies are needed to further validate the efficacy and safety of current treatment modalities.

Compliance with Ethical Standards

Funding No funding support has been received for this study.

Conflict of interest Dr. Hazel H. Oon is a clinical investigator for Janssen, Novartis, and Pfizer, and an advisory board member for AbbVie. Dr. Oon has also served as a speaker, advisory board member, and researcher for Galderma. Drs. V. C. L. Chong, D.

Y. Wang, and W.S. Chong do not have any conflicts of interest to declare.

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