

Management of refractory pityriasis rubra pilaris: challenges and solutions

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Abstract: Pityriasis rubra pilaris (PRP) is a rare chronic inflammatory papulosquamous skin disease. Its clinical presentation and evolution is very variable. The most frequent clinical features are follicular papules, progressing to yellow-orange erythroderma with round small areas of normal skin and the well-demarcated palmoplantar keratoderma. Actually, six different types of PRP have been described based on clinical characteristics, age of onset, and prognosis. The pathogenesis is still unknown, and treatment can be challenging. Available treatments are mainly based on case reports or case series of clinical experience because no controlled randomized trials have never been performed because of the rarity of the condition. Traditional systemic treatment consists in retinoids, which are actually considered as first-line therapy, but refractory cases that do not respond or relapse after drug interruption do exist. In recent years, numerous reports have demonstrated the efficacy of new agents such as biological drugs. This article is an overview on available therapeutic options, in particular for refractory forms of PRP.

Keywords: pityriasis rubra pilaris, biologics, retinoids, papulosquamous skin diseases

Introduction

Pityriasis rubra pilaris (PRP) is a rare chronic papulosquamous disorder of keratinization, with an incidence between 1 in 5000 and 1 in 50000 with no gender predilection.¹ The pathogenesis is still unclear: it has been hypothesized that it is induced by an abnormal immune response toward different antigenic stimuli such as infections, trauma, and malignancy.^{2,3} Most of the cases are sporadic, but familial forms of the disease have been described, in particular linked to mutations in the gene CARD.⁴⁻⁶ In PRP, the epidermis is in a hyperkinetic state with an increase in turnover of the follicular keratinocytes. It has been suggested a pathogenetic role of a deficiency or a malfunction of vitamin A⁷ or decreased serum level of retinol-binding protein, which is the carrier of vitamin A,⁸ along with some clinical similarities to phrynodema (a cutaneous manifestation of vitamin A deficiency).⁹

Clinical presentation

Generally, PRP is characterized by small follicular papules ~1 mm in diameter with a central keratotic plug, coalescing scaly yellow pink patches, and by palmoplantar keratoderma. Lesions are symmetrical and diffuse and appear first on the extensor surfaces of the extremities, shoulders, and buttocks, usually spreading caudally with possible development of erythroderma.^{1,7} Differential diagnosis with psoriatic erythroderma can be made if typical roundish areas of normal skin, the island of sparing, can be identified.

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Scaling is frequent and tends to be rather fine and pityriasi-form on the face and scalp and coarser on the lower half of the body. The skin on the palmoplantar regions tends to become thickened and yellow-orange in color, with well-demarcated borders. Sometimes patients complain of fever, chills, itching, and malaise.^{1,7} Nail involvement is also very common with subungueal hyperkeratosis and yellow-brown discolorations.¹⁰ Oral mucosa can also be involved with white spots and lines: erythematous painful lesions with white streaks can appear on the buccal mucosa, gingivae, and tongue, mimicking lichen planus' signs.¹¹ In adults, skin lesions appear first on the face and scalp, spreading in a caudal direction, while in young patients, PRP usually starts on the lower half of the body.¹² However, PRP's clinical presentation and evolution are very variable.

Classification

In 1980, PRP has been classified into the following five types by Griffiths^{13–15} based on clinical features, age of onset, and prognosis: classic adult type I, atypical adult type II, classic juvenile type III, circumscribed juvenile type IV, and atypical juvenile type V. Later, the VI type which is the human immunodeficiency virus (HIV)-related form, has been added.¹⁶ The classic adult type I is the most common with an acute onset and accounts ~50% of patients. Commonly, it begins with the onset of a single erythematous patch on the upper half of the body. Successively, the cutaneous lesions spread caudally within a few weeks or months and can evolve to erythroderma with the typical islands of sparing and palmoplantar yellow-orange hyperkeratosis. The duration of this form is ~3–4 years.^{13–15} The atypical adult type II, developed by 5% of the patients, has a chronic course up to 20 years. It is characterized by ichthyosiform lesions, especially on the legs, in association with alopecia and areas of eczema.^{13–15} The classic juvenile type III is similar to adult-onset type I but affects children (10% of patients) and has a clinical course more favorable than adults, usually going to remission after 1 year.¹² The circumscribed juvenile type IV affects children and young adults (25% of patients) and develops follicular hyperkeratosis and erythema usually only on the knees and elbows with well-demarcated borders. Palmoplantar involvement is also characteristic in this form with keratoderma, or dorsal involvement of hands and feet. It remains localized in most of the cases but can be characterized by remissions and exacerbations.^{12,17,18} The atypical juvenile type V occurs in the first few years of life in up to 5% of patients; it is chronic and characterized by follicular hyperkeratosis and scleroderma-like skin lesions on the hands and feet, whereas erythema is not prominent.^{13–15} The HIV-related form VI is similar to type I, with a symmetrical,

pruritic eruption composed of erythematous and desquamating follicular papules, but it has a more severe course and tends to be refractory to treatment. Prominent follicular plugging with formation of spicules is another common finding in this form; however, other follicular manifestations can be associated to HIV-related PRP, such as acne conglobata, hidradenitis suppurativa, and lichen spinulosus.¹⁶ This classification is not very strict: in fact, it is not always possible to assign every form of PRP to a single type because intermediate forms and transition from one type to another can occur.¹⁵

Diagnosis

The diagnosis is primarily clinical, based on typical above-mentioned findings. However, sometimes, especially when PRP is in the erythroderma state, it is rather difficult to establish a clear-cut clinical diagnosis and it can be misdiagnosed as psoriasis, follicular eczema, follicular ichthyosis, generalized hypersensitivity reaction, T-cell lymphoma, and lichen planopilaris.^{1,7}

In the last few years, dermoscopy has been applied also to evaluate inflammatory cutaneous diseases,¹⁹ and it has been proposed as possible support in the clinical diagnosis, allowing a better distinction of PRP from psoriasis: psoriatic lesions generally show regularly distributed dotted vessels on a light red background while PRP lesions show more irregular linear and dotted vessels and round/oval yellowish areas.^{19–21} Recently, two cases of adult and juvenile PRP have been studied also with reflectance confocal microscopy that might represent an adjunctive tool for improving the diagnostic confidence.²¹ Actually, the clinicopathological correlation remains the “gold standard” for the diagnosis of PRP by excluding other dermatoses especially psoriasis and cutaneous lymphoma. Typical histopathological features of PRP, although not pathognomonic, are alternating orthokeratosis and parakeratosis in both vertical and horizontal directions forming the checkerboard pattern; other frequent findings are hypergranulosis, follicular plugging, broad rete ridges, narrow dermal papillae, and sparse superficial perivascular lymphocytic infiltrate.²²

Therapy

The management of PRP involves topical and systemic therapies, according to extension and severity of disease (Table 1).

Topical treatments

Topical treatment is indicated for localized forms such as PRP type III and is always recommended also in association with systemic therapy for severe forms to reduce cutaneous symptoms such as itching and burning.^{1,23,24}

Table I Topical and systemic treatments of PRP**Topical treatments**Corticosteroids^{23,25}Calcipotriol²⁵Tazarotene^{18,26}Emollients^{23,24} (urea 5–10%, salicylic acid 1–5%)**Systemic treatments**

First-line treatments

Isotretinoin^{27–34}Acitretin^{27–34}

Second-line treatments

Methotrexate^{27,30,34}Acitretin + narrowband-UVB⁴³Acitretin + UVA1⁴⁴Acitretin + PUVA²⁸Cyclosporin^{48–50}

Refractory forms

Anti-TNF- α inhibitors^{55–64} (infliximab, etanercept, and adalimumab)IL-23 and IL-17 inhibitors^{54,65–71} (ustekinumab and sekukinumab^{70,71})PDE4 inhibitor apremilast⁷²

Abbreviations: PDE4, phosphodiesterase 4; PRP, pityriasis rubra pilaris; PUVA, psoralen-ultraviolet A; UVA1, ultraviolet A1.

In localized forms of PRP, topical therapy is the main therapeutic choice,^{23,24} including medium to high potency corticosteroids, keratolytics, emollients, and Vitamin D derived such as calcipotriol,²⁵ tretinoin, and tazarotene.^{18,26}

Topical treatments in association with systemic therapy are helpful to treat hyperkeratosis and palmoplantar keratoderma and to improve skin texture, reducing scaling, erythema, and induration, particularly, keratolytics (5–10% urea or 5% salicylic acid) and emollients.²⁷

Systemic treatments

Systemic treatments are indicated in moderate-to-severe disease. Traditional systemic treatment consists mainly in retinoids, which are actually considered as first-line therapy both in adult and in juvenile forms.^{1,27} Unfortunately, refractory cases that do not respond or relapse after drug interruption do exist. In these instances, treatment is challenging and a standard therapeutic protocol does not yet exist. Treatment is mainly based on case reports or case series of clinical experience because no controlled randomized trials have ever been performed because of the rarity of the condition.²⁷ Nevertheless, in recent years, numerous case reports have demonstrated the efficacy of new therapeutic agents such as biological agents, in particular for refractory forms of PRP.

Retinoids

Systemic retinoids are considered as first-line systemic therapy for adults and children with PRP because most of the case reports and case series demonstrate their efficacy.^{27–39}

Clinical response to retinoids, usually is evident after 3–6 months of therapy, but in some patients, longer treatment is needed. Isotretinoin and acitretin are the most used, but there are some data also about the efficacy of alitretinoin for PRP.^{27–30,35–38} In a retrospective study by Eastham et al,²⁷ all the 12 patients treated with acitretin, eight patients receiving acitretin in monotherapy at dosage of 25–50 mg/day, two patients receiving acitretin in association with methotrexate, and two patients receiving acitretin in combination with cyclosporine, reported partial or significant improvement during treatment. In a prospective study, isotretinoin (2 mg/kg/day) was used in 45 patients with PRP and, after 4 weeks of therapy, 28 (62%) patients showed significant improvement.²⁹ In another retrospective study including 15 patients treated with isotretinoin (primarily 40 mg twice daily), 10 (67%) patients had a complete clearance within an average of 25 weeks (range 16–44 weeks) and only three patients resulted refractory to treatment.³⁰

In clinical practice, the recommended dosage of isotretinoin for adults with PRP is 1 mg/kg/day, while acitretin is used at the dosage of 0.5–0.75 mg/kg/day. However, high dosage of retinoids is not well tolerated because of frequent mucocutaneous side effects.

Most frequent adverse effects of retinoids are dry skin and mucous membranes, hyperlipidemia, transaminase elevations, and visual or bone changes. In children, retinoids could induce hyperostosis and premature epiphyseal closure especially in prepuberal patients treated with high doses. In addition, retinoids should be avoided in women of childbearing potential because of their teratogenic effect: pregnancy must be avoided during and for 3 years after treatment with acitretin and during and for 6 weeks after isotretinoin therapy.

Due to the rarity of the disease and the lack of standardized studies, there are no consistent data about treatment duration, risk of relapse at treatment discontinuation, or need for maintenance treatment.

Phototherapy

Ultraviolet B (UVB) phototherapy and psoralen-ultraviolet A (PUVA) therapy have been proved to be a successful treatment in some patients affected by PRP,^{39,40} although response to light is rather variable. Quite the opposite, exacerbations of PRP have been described in some patients.^{8,41,42} In consideration of reports of photoaggravated PRP, phototesting should be always performed before treatment. A valid alternative treatment in refractory forms to retinoids could be the combination of retinoids and phototherapy. Acitretin has been reported as a combined therapy with narrowband UVB,⁴³

ultraviolet A1 (UVA1),⁴⁴ and PUVA.²⁸ In a recent case report of childhood PRP, phototherapy with narrowband-UVB has been proved to be successful after 2 months of treatment in combination with topical emollients, hydrocortisone cream, and calcipotriene, reaching >90% cutaneous clearance.⁴⁵

Methotrexate

Methotrexate is an alternative therapeutic option for PRP, as second-line treatment.^{27,34} It has been observed in retrospective studies the efficacy of weekly doses of 5–25 mg. Another retrospective study has demonstrated a favorable response in 8/14 patients with type I PRP: the average duration of treatment was 6 months (from 1 to 12 months).³⁰ Another retrospective study has demonstrated the efficacy of methotrexate in association with retinoid, despite the increased risk for hepatotoxicity.³³ In another study including five patients, refractory to retinoids methotrexate has been proved to be effective.³⁴ Gastrointestinal distress is a frequent adverse event reported. Additional serious adverse effects that should be always checked are pancytopenia, hepatotoxicity, and pneumonitis. Moreover, it should be avoided in women of childbearing potential because of its teratogenic effect.

Other immunosuppressants

Other systemic agents such as azathioprine^{46,47} and cyclosporin^{48–50} have been reported as effective in the treatment of PRP in single case report, especially in refractory forms. In particular, cyclosporin could be considered a valid therapy for patients who do not respond to retinoids or methotrexate and could be used both in adult and juvenile forms. Also, fumaric acid esters may be an alternative option.⁵¹

Biological agents

In consideration of clinical and histological similarities between psoriasis and PRP, all the biological agents approved for psoriasis have also been used in the treatment of refractory forms of PRP or in patient resistant or ineligible to conventional systemic treatments.^{27,34} Being the pathogenesis of PRP still not clear, TNF-alpha has been hypothesized to be a key cytokine.⁵² More recently, inhibitors of the IL-23/IL-17 pathway have also been administered successfully in PRP and increased levels of IL-17 have been found in PRP patients, providing a rationale for these new therapies.⁵³ However, clinical experiences about biological agents in the treatment of PRP is limited to case reports and case series and multicenter randomized clinical trials have not been performed because of low incidence of PRP. In contrast, cases of PRP refractory to biological agents are also observed, although

rarely reported as recently described in a case of type IV PRP resistant to anti-TNF-alpha and IL-23 inhibitors.⁵⁴

Anti-TNF-alpha (infliximab, etanercept, and adalimumab)

In the last 10 years, retrospective studies and case reports have shown that anti-TNF-alpha agents are effective in the treatment of PRP both in adult and in juvenile forms.^{53–64} A systematic review of type I PRP, including 15 patients treated with infliximab, etanercept, or adalimumab, have shown a complete response in 12/15 patients and a partial response in 2/15 patients. Just in one case, no improvement has been observed. Six patients received anti-TNF-alpha as monotherapy, whereas nine patients were treated in association with acitretin or methotrexate.⁶³ In the majority of cases, TNF-alpha inhibitors have been used as second-line treatment in refractory PRP to traditional systemic treatment. In a case series of seven patients with refractory adult onset, PRP has proved the efficacy of infliximab (three patients) and etanercept (five patients), 5/7 patients received combination therapy with low-dose acitretin (0.2 mg/kg/day). All the patients experienced significant clearance at week 12, and infliximab was associated with a more rapid response than etanercept. During follow-up, only a patient affected by type II PRP developed recurrence after 2 months from discontinuation.⁵¹ In a recent retrospective study of 40 patients with PRP performed in a third-level center, nine patients have been treated with anti-TNF-alpha agents with a favorable response within 5–7 weeks. Despite this, most of them received initial association therapy with another systemic drug (methotrexate, acitretin, or prednisone).²⁷ In other case reports of refractory PRP treated with adalimumab, rapid and sustained remission was observed after only 4 weeks: no relapses were reported after treatment discontinuation.^{60–62} In patient affected by PRP type I treated with adalimumab and achieving clinical remission after 4 months, increased levels of mRNA of TNF-alpha were found in the lesional and perilesional normal skin. This finding is consistent with the observed clinical remission and supports the use of anti-TNF-alpha for the treatment of PRP.⁶⁴

IL-23 and IL-17 inhibitors (ustekinumab and secukinumab)

Several case reports have described the use of ustekinumab in type I PRP, refractory to conventional systemic therapies, or anti-TNF-alpha agents.^{65–69} Ustekinumab demonstrated striking and rapid efficacy in reducing the signs and symptoms of the disease and also a long-term control of the disease.⁶⁹ In

a recent cases series, lesional skin biopsy sample was taken from three patients affected by refractory PRP and mRNA expression of proinflammatory innate and T-cell-derived cytokines were measured. Gene expression analysis revealed an increase in T-helper (Th) 1 cytokines and in particular Th17 cytokines, such as IL-17A, IL-22, and IL-23. In one patient, levels of IL-17A from lesional skin samples were measured before and after treatment with ustekinumab and reduced after cutaneous improvement. This case report gives evidence of the role of the IL-23/Th17 axis in PRP, providing a rationale for targeting this pathway as a treatment option for refractory PRP.⁵³ Secukinumab has been recently showed to be effective to treat PRP in two case reports.^{70,71} In the first one, it has been used in a patient with type I PRP, refractory to acitretin.⁷⁰ In the second case, it has been proposed as a valid option to treat refractory type II PRP, with improvement of erythema and palmoplantar keratoderma observed after 2 weeks of treatment and no recurrence after a 6-month follow-up.⁷¹

Other treatments

A recent case has proved the efficacy of apremilast in the treatment of refractory PRP: after 4 weeks of therapy, the patient reported significant improvement and, at 6 months of follow-up, he/she showed complete clearance of skin lesions.⁷² Extracorporeal photochemotherapy was also used for the treatment of two patients with erythrodermic PRP type I in combination with systemic retinoids and cyclosporine, with good results.⁷³ In another report, a case of type II adult-onset PRP was successfully treated with intravenous immunoglobulin.⁷⁴

Conclusion

PRP is a rare inflammatory skin disease that can have a severe impact on patients' quality of life, especially in the chronic and refractory forms. Many therapeutic options have been experienced, but we do not have a standard protocol to treat PRP. Treatment of refractory forms remains challenging. Biological agents seem to represent a novel effective treatment for PRP, although multicenter randomized clinical trials should be performed before considering them as first-line option. Further insights into the pathogenesis of the disease will possibly disclose some clinical and phenotypic features in the different forms of PRP as predictive factors allowing a personalized therapeutic choice.

Disclosure

The authors report no conflicts of interest in this work.

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