NEWS, VIEWS, AND REVIEWS

Precision, Research, Progress: Updates in the Management of Pityriasis Rubra Pilaris

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INTRODUCTION

Pityriasis rubra pilaris (PRP) is a rare, papulosquamous skin disease that is notoriously challenging to treat. There are six different subtypes of PRP that vary based on age of onset, distribution of lesions, and prognosis, though they all share the characteristic clinical features of hyperkeratotic follicular papules coalescing into orange-red plaques and palmoplantar keratoderma.[1] A variety of etiologic factors for PRP have been proposed, including impaired vitamin A metabolism, dysregulated immune response to superantigens, and genetic factors, though there is still no consensus regarding PRP's pathogenesis.[2] This, combined with the absence of standardized treatment guidelines, makes PRP a difficult condition to manage. While topical therapies such as topical corticosteroids, calcineurin inhibitors, vitamin D analogs, and retinoids may be sufficient for treating localized disease, the majority of PRP cases require systemic therapy.[1] This review will explore both conventional systemic therapies as well as emerging off-label treatment strategies for PRP.

Conventional Therapies

Oral retinoids, methotrexate, and phototherapy have long comprised the most widely utilized treatments for PRP. Systemic retinoids, most commonly acitretin and isotretinoin, are regarded as first-line therapy for PRP. In a systematic review of 475 patients with PRP, isotretinoin (n=140) elicited an excellent response, defined as >75% reduction in disease severity, in 61.1% of patients at a mean dose of 1.55 mg/kg/day, while only 24.7% of patients on acitretin (n=90) experienced an excellent response.[3] Alitretinoin, a relatively newer retinoid that has been employed to treat PRP, demonstrated the highest success rate among retinoids in the systematic review, with 72.7% of treated participants experiencing an excellent response at a mean dose of 0.42 mg/kg/day, though this was among a sample size of only 10 patients.[3] Typically, PRP responds to oral retinoids within 3-6 months of treatment.[2]

For patients who exhibit an inadequate response to oral retinoids, methotrexate is typically the standard second-line therapy. In a study of 116 patients with PRP treated with methotrexate at a mean dose of 15 to 25 mg weekly, 65.5% demonstrated improvement, with 23.3% experiencing complete clearance and 17.2% experiencing 'excellent' improvement.[4] Improvement was observed within 3-12 weeks in the majority of cases, though patients generally required treatment for several months. Fifteen patients experienced adverse effects, the majority of which were mild; however, five patients discontinued therapy due to more severe drug reactions, most commonly gastrointestinal intolerance.[4]

Finally, although phototherapy has historically been utilized in PRP management, the evidence supporting its efficacy is limited. The most common types of phototherapy employed in PRP management include narrowband ultraviolet B and psoralen plus ultraviolet A; however, most studies demonstrate variable responses. Another concern that has been associated with phototherapy is disease worsening due to photo-exacerbation.[5] Ultimately, while conventional therapies, particularly oral retinoids and methotrexate, are effective and well-tolerated in some patients, a significant proportion of patients do not respond, highlighting the need for alternative therapies.

Emerging Therapies

Tumor Necrosis Factor-α Inhibitors (TNFis)

In patients who don't respond to conventional systemic agents, biologics have shown promising results. TNFis were among the first biologics to be successfully utilized in patients with PRP. In one review of biologic therapies for PRP, 37 patients treated with infliximab, 22 patients treated with etanercept, and 20 patients treated with adalimumab were identified. Among these patients, 84% of those treated with infliximab (5 mg/kg at varying intervals), 86.4% treated with etanercept (50 mg 1-2 times per week), and 75% treated with adalimumab (40 mg every two weeks) achieved a marked-to-complete (>75% clearing) or partial response (50-75% clearing).[6] Notably, however, approximately 50% of these patients were on concomitant therapies, most often acitretin, methotrexate, systemic steroids, or topical steroids, making it challenging to elucidate the individual role of TNFis. The side effect rate ranged from 4.7% for etanercept to 16.7% for infliximab, and included renal insufficiency, skin infections, and arthritis exacerbation, among others.[6] Additionally, two patients developed small cell lymphocytic leukemia and follicular non-Hodgkin lymphoma after infliximab and adalimumab, respectively, which may be drug-related or sporadic. Although TNFis are viable treatment options, their side effect profile should be carefully considered.

Interleukin (IL)-17A Inhibitors

IL-17A inhibitors comprise another class of biologics that are gaining traction in the management of PRP. A recent systematic review evaluated 77 cases of PRP treated with IL-17A inhibitors. 63% of patients were treated with secukinumab and 37% were treated with ixekizumab (both administered at standard plaque psoriasis dosing).[7] Almost 90% of patients with PRP, spanning types I-IV, who were treated with secukinumab, experienced complete improvement in disease. Of the 15 patients with PRP types I-IV treated with

ixekizumab, all achieved a complete response; however, there were an additional 13 patients with an unknown PRP subtype treated with ixekizumab, and only 18% of these patients achieved a complete response.[7] A limitation of this review is the absence of an assessment of adverse effects. While higher-powered studies are critical to fully understanding the efficacy and safety of IL-17A inhibitors, based on these findings, the authors recommend considering these biologics as third-line therapies after oral retinoids and methotrexate.

Interleukin (IL)-23 Inhibitors

IL-23 inhibitors are among the newest biologic classes to be explored for the management of PRP. A recent review identified 11 patients with PRP treated with risankizumab and 5 patients treated with guselkumab, both at standard plaque psoriasis dosing.[8] Of those treated with risankizumab, 9 experienced disease improvement, 1 experienced initial worsening followed by improvement, and 1 experienced continuous disease progression. All 5 patients treated with guselkumab improved; 3 patients completely cleared, while 2 exhibited near-complete responses. Most patients experienced symptom improvement after the induction dose, and no adverse effects were experienced by patients on either medication. Furthermore, ustekinumab, a dual IL-23/IL-12 inhibitor, has also shown efficacy in treating PRP. In a case series of five patients treated with ustekinumab 45 mg at weeks 0, 4, and 16, all patients experienced improvement starting four weeks after the initial dose, 4 patients showed complete clearance within 4-8 weeks, and 1 showed partial improvement.[6] Although there are fewer reported cases of IL-23 inhibitors and IL-12/23 inhibitors compared to TNFis and IL-17A inhibitors, the high response rate and favorable safety profile among existing reports are promising and warrant further evaluation.

Janus Kinase Inhibitors (JAKis)

While biologics have been the primary focus in emerging PRP therapies, JAKis have also started to gain attention in the past two years. A recent systematic review of small-molecule drugs in PRP management identified 12 cases managed with JAKis: abrocitinib (n=5), upadacitinib (n=5), and tofacitinib (n=2).9 The majority of patients were administered abrocitinib, upadacitinib, and tofacitinib at doses of 100 mg daily, 15 mg daily, and 5 mg twice daily, respectively. All 12 patients experienced complete alleviation of symptoms within 3-6 months of treatment initiation. Additionally, the only adverse effects reported by two patients were acne and headache, which resolved without intervention.

Phosphodiesterase-4 Inhibitors (PDE4is)

Lastly, PDE4is comprise another new therapeutic option for PRP. There are currently 4 case reports of patients experiencing complete responses to apremilast when dosed at 30 mg once daily to twice daily for a duration of 2-6 months.[9] Two patients experienced mild adverse effects, headaches and gastrointestinal discomfort, which self-resolved. These reports suggest that apremilast may serve as a safe and effective treatment option for PRP, though larger studies are needed to validate these findings.

CONCLUSION

Although oral retinoids and methotrexate remain mainstays in the PRP treatment toolbox, the landscape of PRP management is evolving, with a range of emerging therapies showing significant promise. Biologics, specifically, TNFis and IL-17A inhibitors, have demonstrated success in the greatest number of patients thus far; however, this may merely be due to their longer history of use in treating PRP. Additionally, while the number of cases managed with JAKis and PDE4is is currently limited, the achievement of complete patient responses among all reported cases, combined with minimal side effects, is highly compelling. Moving forward, to optimize PRP management, randomized controlled head-to-head trials, including both emerging and conventional therapies, will be crucial for establishing the relative efficacy and safety of these therapies.

DISCLOSURE

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