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Review Article

Management of recalcitrant palmoplantar psoriasis

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ABSTRACT

Management of recalcitrant palmoplantar psoriasis and palmoplantar pustular psoriasis continues to be a challenge. Standardized therapeutic guidelines are not available due to limited data. The recalcitrant nature points to the need for systemic therapy but a trial with topical therapy is needed before planning systemic therapy. Among the topical therapies available topical steroids or combination of topical steroids with calcipotriol are the most effective. Light-based therapies are effective modalities in patients who do not respond to topical therapy. Systemic therapy is indicated in non-responders. Acitretin, methotrexate and cyclosporine are widely used. There are increasing data on the use of biologicals in non-responders to systemic immunomodulators, but the cost is a deterrent. The biologic agents include etanercept, infliximab, adalimumab, ustekinumab, secukinumab, apremilast and others. Traditional therapies such as phototherapy, acitretin or methotrexate are often preferred over newer antitumor necrosis factor (TNF) agents for patients with comorbid conditions due to the immunosuppressive effects of TNF-α inhibitors and concern about paradoxical exacerbation of disease in some patients.

Keywords: Palmoplantar, Pustular, Psoriasis, Recalcitrant, Management

INTRODUCTION

Palmoplantar psoriasis (PPP) is a common condition which may occur alone or at times may alternate with psoriasis in some patients. Palmoplantar pustulosis or palmoplantar pustular psoriasis (PPPP) is regarded as a variant of PPP by some; others consider this to be a separate entity.[1]

The patients suffer from periodic flares induced by seasonal changes, detergents and housework. Itching and painful fissures are the common complaints and this may interfere with their daily activities. They often suffer from poor self-image and the quality of life is affected.

Symmetrically distributed erythematous, hyperkeratotic, scaly and at times fissured plaques are the hallmark of PPP while PPPP begins as a unilateral eruption of tiny sterile pustules which coalesce to form lakes of pus which later develop into erythematous scaly plaques. Lesions of psoriasis may be present at other sites in some patients.

THERAPEUTIC STRATEGY

The therapeutic strategy should be tailored to the age, sex, occupation, patient preference and severity of psoriasis. The presence of comorbid conditions if any, the effect of a particular therapy on the comorbidity, and the available resources are also important considerations. The recalcitrant nature of the disease indicates the need for systemic therapy but a trial with topical agents is warranted before planning specific therapy. There are no standardized guidelines for treatment; evidence-based decisions are not possible due to the paucity of available data.

GENERAL MEASURES

It is important to explain to the patient the nature of the disease, the treatment plan and the need to have realistic expectations of therapy. Emphasis on the need to avoid trauma, particularly in manual laborers and instructions on hand care, is a must. Emollients applied several times a day to maintain the barrier function of the skin, decrease the impact of fissures and the associated disability. Mild soaps and soap substitutes help to prevent painful fissures. Protective gloves are needed during wet work, exposure to chemicals, gardening, manual labor, etc. Improvement in PPPP with cessation of smoking and surgical interventions such as tonsillectomy and intestinal shunt surgeries has been reported.[2-4]

TOPICAL THERAPY

PPP and PPPP are generally resistant to topical therapy, the thick stratum corneum of the palms and soles is a barrier to the penetration of topical agents and hence a decreased efficacy and need for systemic therapy. Topical medications for psoriasis include corticosteroids, Vitamin D analogs, keratolytics, anthralin, coal tar and tazarotene. They may be used individually or in various combinations and may be used under occlusion.

TOPICAL STEROIDS

Conventionally, potent to superpotent steroids with or without occlusion is the recommended first-line topical therapy in published literature. The efficacy depends on the compliance. In spite of repeated emphasis to avoid self-medication and long-term use of topical steroids, it is used with impunity leading to side effects, rebound phenomena and difficulty in weaning them off topical steroids.

VITAMIN D ANALOGUES (CALCIPOTRIOL AND CALCIPOTRIENE)

Calcipotriene is effective in PPP and PPPP and no monitoring is required with doses of <120 g/wk. A regimen alternating calcipotriene and potent topical corticosteroids may be better. In a study of 39 patients with PPP to evaluate the efficacy of twice-weekly occlusive calcipotriol 50 μg/mg ointment versus non-occlusive therapy for 6 weeks, twice-weekly occlusive therapy was as effective as the twice-daily application.[5] Calcipotriene should not be combined with salicylic acid as it deactivates the molecule and if combined with ultraviolet B (UVB), it blocks UVB penetration. The combination of topical calcipotriene with either UVB or PUVA is synergistic.[6] Topical calcipotriene is inactivated by UVA, so it is best not to apply it immediately before PUVA treatment.[7]

TOPICAL STEROIDS AND COMBINATION THERAPIES

Topical corticosteroids frequently used in combination with other agents such as topical Vitamin D analogues or calcineurin inhibitors are more effective than therapy with either agent alone. The combination of topical steroid with calcipotriene is more potent, with fewer side effects and long-term safety than either agent alone and improves adherence.[8,9] The addition of calcipotriene ointment applied on weekdays to a weekend pulse therapy regimen of superpotent corticosteroids can increase the duration of remission. The combination also prevents the rebound effect of steroids. Tazarotene (0.05–0.1%) is also useful in combination with topical steroids.[10,11] Salicylic acid and urea are useful either alone or in combination for fissured hyperkeratotic plaques.

OTHER TOPICAL THERAPIES

1–5% crude coal in petrolatum with salicylic acid 5–10% added as a keratolytic is still a time tested therapy for PPP. Tar is often not acceptable to patients due to its messy application, odor and staining of clothes. Attempts have been made to improve drug delivery through liposomal preparations. Longer duration of use and occlusion increases the efficacy.

Dithranol 1% as short contact therapy followed by sun exposure is effective; it is an irritant and stains the clothes and skin. There are no published randomized controlled trials that demonstrate the efficacy of tar and dithranol. Both coal tar and dithranol cannot be used in PPPP.

Tazarotene is a good alternative for the treatment of palmoplantar psoriasis where hypopigmentation limits the use of clobetasol propionate cream.[10] It also helps in gradual weaning of potent topical steroids and maintaining remission.[11]

Topical methotrexate gel is effective, well-tolerated and no adverse effects were noted but results have been inconsistent due to poor drug penetration into the skin by passive diffusion.[12-14] Iontophoresis may enhance its absorption and efficacy. It is safe and more effective than coal tar ointment in PPP.[15] Tacrolimus is effective in some cases of PPPP.[16] 1% pimecrolimus is reported to be effective in PPPP.[17]

PHOTOTHERAPY

Light-based therapies such as topical PUVA and narrowband (NB)-UVB are other effective modalities of treatment in patients who do not respond to topical treatment. The main drawbacks are the need for repeated hospital visits, the lack of treatment centers in accessible areas and an increased risk of skin cancer.

Soak psoralen plus UVA (PUVA) and oral PUVA with 8-methoxypsoralen (8-MOP) have been successfully used for the treatment of recalcitrant PPP.

Soak PUVA twice- or thrice-weekly with 30-min hand and/or foot soaks in 8-MOP, 2.5 mg/l, followed by UVA irradiation has shown good results.[18] In a comparative study on the efficacy and safety of local NB-UVB phototherapy versus local PUVA paint in patients with PPP unresponsive to conventional therapies in 25 patients

over 9 weeks, the difference in clinical response between the two treatment modalities was statistically significant with the local PUVA faring better than the local NB-UVB.[19]

EXCIMER LIGHT THERAPY AND LASER TREATMENTS

There is a limited clinical evaluation of excimer light as a viable phototherapy option. Some studies have reported it to be an alternative to the PUVA and UVB treatments. It requires a less cumulative dose to relieve the symptoms and fewer treatments; hence a lower risk of adverse effects related to phototoxicity.[20]

PHOTODYNAMIC THERAPY

Mild to marked improvement has been reported in PPPP with PDT, using 20% 5-aminolaevulinic acid and a 630 ± 50 nm light-emitting diode device at a power density of 30 mW/cm^2 and fluence of 15 J/cm^2.[21]

SYSTEMIC THERAPY

Systemic therapy is indicated for patients with severe, disabling recalcitrant disease and those who do not respond to topical therapy and phototherapy. Many of these therapies are immunosuppressive and expose the patient to risk of severe infections; therefore any minor infection must be taken seriously. The risk versus benefit of continuing the drug in the presence of infection must be weighed.

Traditional systemic therapies for psoriasis including retinoids, cyclosporine and methotrexate have shown some benefit. A detailed history, clinical examination and baseline evaluation are necessary to exclude any contraindications and comorbidities before considering systemic therapy. The lack of randomized controlled trials of systemic agents for the treatment of recalcitrant PPP and PPPP is a deterrent to the assessment of efficacy rates.

Acitretin is an effective option in PPP and PPPP but acitretin monotherapy is less effective than other traditional systemic agents and the effect is dose related. Many patients do not tolerate the higher dosages of acitretin to achieve optimal results. In a retrospective study by Adisen *et al*, the charts of 62 patients with PPP and 52 patients with PPPP were reviewed and 17 of 62 patients showed marked improvement to topical corticosteroids (n = 12) or to calcipotriol (n = 5). The remaining patients were treated with systemic therapies. Acitretin (n = 24) was the most common agent used initially while local PUVA (n = 12) and methotrexate (n = 9) were less often prescribed. Marked improvement was seen in 53%, 47%, and 53% of patients treated with acitretin, methotrexate and oral PUVA respectively.[22]

SECOND-LINE SYSTEMIC TREATMENT

Methotrexate remains effective and well-tolerated; a satisfactory response is seen in 3–6 weeks. There is no consensus on the duration of the use of cyclosporin though the US FDA has approved it for 1-year continuous treatment. It can be used intermittently for inducing a clinical response.

COMBINATION THERAPIES

Combination therapy improves efficacy and decreases toxicity of each individual agent. In retinoid plus PUVA therapy, acitretin is given in low doses (0.2–0.5 mg/kg) for 7 days and then PUVA therapy is started 3 times a week. On clearance, acitretin can be withdrawn and maintenance phototherapy with PUVA or, preferably, NB-UVB can be continued.[23]

THIRD-LINE SYSTEMIC AGENTS

Drug intolerance, adverse effects to conventional therapies, or treatment-resistant disease may warrant a trial with third-line drugs. Tetracyclines 250 mg twice daily demonstrated objective improvement over placebo.[23] Azathioprine, mycophenolate mofetil, sulfasalazine, fumaric acid esters, leflunomide, tacrolimus and 6-thioguanine have also been tried. Evidence from randomized controlled trials suggests that colchicine is of limited value.[24] There is limited evidence to suggest that hydroxyurea is ineffective.[23] Oral itraconazole 100 mg/day for 1 month followed by 100 mg on alternate days for another month is reported to be of some benefit.[25]

THERAPY WITH BIOLOGICS[26]

Biologics are reserved for patients who do not respond or cannot complete treatment with topical and/or other systemic medications. There are increasing data on the usefulness of biologicals but the cost is a deterrent to its use. Biosimilar drugs make tumor necrosis factor-α (TNFα) inhibitors accessible to more patients because they are less expensive. Transition from conventional systemic therapy to a biological agent may be done directly or with an overlap if transitioning is needed due to lack of efficacy, or with a treatment-free interval if transitioning is needed for safety reasons. The biologic agents approved by the US FDA for the treatment of psoriasis include etanercept, infliximab, adalimumab, ustekinumab, secukinumab and several others. Etanercept showed a statistically significant reduction in PPPASI in a dose of 50 mg twice weekly for 24 weeks of therapy. Infliximab 5 mg/kg at weeks 0, 2, and 6 and then, every 8 weeks showed a 50% reduction in the mean surface area of the palms and soles. Adalimumab 40 mg subcutaneously (SC) every 2 weeks for a total of 3 months improved quality of life in clinical studies. Ustekinumab an interleukin (IL)-12 and IL-23 inhibitor in a dose of 45 mg (<100 kg body weight) or 90 mg SC (when body weight is 100 kg or more) every 3 months resulted in complete clearance in 35% of patients at 16 weeks. Secukinumab an IL-17A inhibitor 300 mg (90 kg or more) or 150 mg SC (<90 kg) every week from baseline to week 3, then every 4 weeks thereafter demonstrated that 33% and 22.1% of patients were clear or almost clear at week 16 with 300 mg and 150 mg respectively.

A *post hoc* analysis of data pooled from Phase IIb (PSOR-005) and Phase III (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1 and 2) showed apremilast to be a useful oral treatment option for patients with moderate-to-severe palmoplantar plaque psoriasis. This *post hoc* analysis was limited to 16 weeks and did not assess palmoplantar pustulosis.[27] Haebich and Kalavala reported successful treatment of refractory palmoplantar pustulosis with apremilast.[28] Combination therapy with biologics in refractory PPPP with adalimumab and ustekinumab and successful clearance of severe recalcitrant PPP using a novel combination of acitretin and apremilast has been reported.[29,30] Guidelines on the use of biologics in PPP are needed in view of reports of paradoxical induction of PPPP and plaque psoriasis in a significant number of patients treated with biologics, mostly with infliximab followed by etanercept and adalimumab.[31] Primary or secondary treatment failure may occur in patients on anti-TNF monotherapy, adjusting the dose or switching to another therapy or combination therapy may be needed.

THERAPY IN PREGNANCY

Topical therapies have a low absorption through the skin so the risk is low. Topical PUVA is considered to be of very low risk. Phototherapy with broadband UVB and narrowband UVB is safe. Psoralens are effective partly because it damages cellular DNA; hence it is better to avoid oral PUVA during pregnancy. Acitretin and methotrexate are contraindicated in pregnancy while cyclosporine can be used with caution (pregnancy category C). If a woman of childbearing potential requires oral retinoid therapy, a course of isotretinoin is preferred to acitretin though both drugs are potent teratogens, pregnancy can be safely initiated 1 month after discontinuing isotretinoin. It is necessary to avoid pregnancy for at least 3 months with methotrexate and 6 weeks with biologics. Biologics (Category B) are better avoided in pregnancy and breastfeeding as the risk is unknown at present.

COMORBIDITIES AND RECALCITRANT PPP

Comorbid conditions such as chronic liver disease, chronic renal failure, congestive cardiac failure, multiple sclerosis, malignancy and HIV infection predispose a patient to develop side effects from medications. Careful consideration and evaluation are needed before starting systemic treatment in such patients.

Traditional therapies such as phototherapy, acitretin or methotrexate have often been preferred over newer anti-TNF agents for psoriasis patients with comorbid conditions in view of the immunosuppressive effects of TNF inhibitors and concern about exacerbation of disease.

There are not many controlled clinical trials on the treatment of PPP and PPPP in literature. A systematic literature search from Embase, Medline and Cochrane Library databases for English or French articles published after 1980 to February 2013 reporting trials in patients with PPPP assessing therapeutic interventions, other than biologics was analyzed. The authors concluded that oral retinoid therapy (acitretin), photochemotherapy or combination of both, low dose of cyclosporin, or topical corticosteroids under occlusion appear to be helpful in relieving symptoms of PPPP.[31] A Cochrane review in 2006 on interventions for chronic PPP supported the use of systemic retinoids and oral PUVA as being better than the individual treatments and concluded that the ideal treatment for PPP remains elusive. The standards of study design and reporting need to be improved to assess the relative merits of the available treatments. At present the treatment of palmoplantar pustulosis continues to be a challenge.

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Conflicts of interest

There are no conflicts of interest.

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