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Long-term Management of Psoriasis: Flexible Therapeutic Regimens Providing Safe and Effective Outcomes

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Introduction

Psoriasis is a chronic, inflammatory skin condition prone to periods of skin flaring. As with any chronic disease, it requires long-term patient adherence with prescribed management to ensure optimal clinical benefits. There are many safe and effective topical treatment options that provide control of mild-to-moderate psoriatic disease. As our understanding of the etiology of psoriasis becomes clearer, the treatment regimes can be better tailored to control the disease and address psychological fears of patients, thus, resulting in greater clinical outcomes and patient satisfaction.

Etiology of Psoriatic Inflammation

- In the past few decades, much progress has been made in both the understanding and the treatment of psoriasis.
- In general, psoriasis is characterized by four skin abnormalities: redness or erythema, inflammation, hyperproliferation of the keratinocytic layer, and altered epidermal differentiation.[1]
- Psoriasis is no longer regarded as a chronic primary dysregulation of keratinocyte proliferation as was originally thought, but now, is attributed to a combination of genetic (numerous loci have been isolated) and environmental factors (such as streptococcal infections, stress, or drugs including beta-blockers and lithium) that promote a systemic T cell-mediated autoimmune response in the skin with innate immune responses playing an important role.[2]
- The hypothesis for the pathogenesis of psoriasis proposes that a pro-inflammatory stimulus leads to the development of 'immunological synapses' between dendritic and T cells with subsequent antigen-specific T cell activation.[2]
- The subsequent release of cytokines and growth factors initiates the proliferation and altered differentiation of keratinocytes, which further promotes the activation of T cells and antigen-presenting cells (mainly dendritic cells) within the psoriatic plaque.
- The clinical success of anti-TNF therapy in the treatment of psoriasis has further validated the role of these cytokines in psoriasis pathogenesis.[3]

General Treatment Paradigms

- The main goal of treatment in psoriasis is to gain rapid control of the disease and reduce its signs and symptoms.
- This can be achieved by decreasing erythema, scaling, and induration of plaques; reducing the frequency and intensity of psoriatic flare-ups; reducing the extent of body surface area (BSA) disease involvement; and effectively managing side-effects.
- Tailoring treatment to a format that is acceptable to the patient is important.

ALSO IN THIS ISSUE: **Optimizing Topical Acne Therapy** *(page 4)* &
Update on the Management of Chronic Hand Dermatitis *(page 7)*

- These needs vary depending on body location, characteristics of the psoriasis being treated, including lesion thickness, degree of erythema, and amount of scaling, as well as patient preferences.

Topical Treatment Options

Corticosteroids

- High-potency corticosteroids have been a mainstay in the topical treatment of psoriasis for decades. Their efficacy can be attributed to multiple mechanisms of action, including their anti-inflammatory, immunosuppressive, and antiproliferative effects.[3] Corticosteroids are formulated in a variety of vehicles (e.g., cream, lotion, ointment, gel, shampoo, and spray) to address the possible combinations of treatment conditions. Appropriate selection can promote adherence and improve outcomes.
- The disease severity, location being treated, ease of use, cosmetic acceptability, and patient age and preferences should be taken into consideration when choosing a suitable potency of corticosteroid treatment.[4]

Coal Tar

- Coal tar has been used since ancient times to treat various skin diseases and for approximately 100 years in the treatment of psoriasis.[4]
- Although the mechanism of action of coal tar is not well understood, it is known to suppress DNA synthesis by lessening the mitotic labeling index of keratinocytes.[4]
- Often, coal tar products are not well tolerated by patients due to cosmetic inelegance, including staining of clothes and a potent tar odour that is present in almost all products to some degree.
- Other potential adverse effects include irritant contact dermatitis, folliculitis, and photosensitivity to UVA.

Retinoids

- Retinoids are a unique class within the armamentarium of antipsoriatic treatments, which are largely dominated by immunomodulatory therapies.
- The mechanism of action of retinoids in psoriasis may include direct suppression of inflammation, as well as inhibition of proliferation and normalization of differentiation in the epidermal layer.[3]
- The topical retinoid approved for psoriasis is tazarotene gel and cream and is available in 0.05% and 0.1% formulations. Due to the common side-effect of irritation, they are not frequently used.

Calcineurin Inhibitors

- There are two topical preparations of calcineurin inhibitors: tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream (1.0%).
- The initial trials indicated treatment efficacy in patients with psoriasis when used under occlusion. Hence, it led to the belief that the penetration of topical calcineurin inhibitors into thick psoriatic plaques was limited.
- Consequently, tacrolimus and pimecrolimus have been used in areas of skin where greater topical penetration is improved, such as on flexural or facial skin.[5]
- Side-effects for calcineurin inhibitors include a burning sensation and pruritus with initial treatments in some patients; however, this discomfort is generally reduced with ongoing use.[5]

Justification for Long-term Treatment Options

Long-term topical treatment options are necessary as psoriasis is a chronic disease requiring ongoing patient adherence to better maintain optimal clinical outcomes. Early intervention can limit flares and minimize progression to more severe disease. As well, over time, psoriasis can become recalcitrant to treatment, requiring more potent medicines that expose the patient to greater risk for adverse side-effects.

Corticosteroids

- Several potencies of corticosteroid treatment are available, ranging from Class 1 (highest potency) to Class 7 (lowest potency).
- Superpotent steroids are suitable for intermittent/pulse therapy or as a component of sequential therapy. Chronic recalcitrant plaques, control of flares, or thickened lesions (i.e., palms and soles) generally require treatment with the higher potency corticosteroids (i.e., Classes 1 and 2). Available data demonstrate safety and efficacy of Class 1 topical steroids when used short-term (2 to 4 weeks); however, the risk of both cutaneous and systemic adverse effects increases if they are used continuously for longer periods of time.[4]
- The ability to vary strength and administration method gives steroids the versatility to mildly treat sensitive and thin-skinned areas, such as the face and body folds, and the option to provide stronger treatment to more resistant areas of the body, such as extensor surfaces and the palmoplantar areas.[6]
- Fear of side-effects is a key reason patients use steroids less often than prescribed, leading to decreased efficacy. Counseling patients on proper usage (e.g., dosing, application, and duration) and the therapeutic objectives can promote treatment adherence.
- Local side-effects to look for include skin atrophy, telangiectasia, striae distensae, folliculitis, acne, and purpura. Systemic side-effects of corticosteroids include hypertension, osteoporosis, Cushing's syndrome, cataracts, glaucoma, diabetes, and avascular necrosis of the hip.[5]

Steroid-sparing Options: Vitamin D3 Derivatives

- Vitamin D analogs are known to play an important role in the treatment of chronic plaque psoriasis, as they have shown to provide good clinical efficacy without the side-effects typically seen with long-term corticosteroid use.
- Vitamin D analogs work through the stimulation of cellular differentiation, inhibition of proliferation, and immunomodulation.[5]
- Their discovery was prompted by the realization that oral vitamin D had a therapeutic effect on psoriatic plaques.
- However, parent vitamin D3 might not be suitable for treating psoriasis owing to the potential for hypercalcemia.[6] Hence, several vitamin D3 analogues have been developed for the treatment of psoriasis.
- Vitamin D analogues, such as calcipotriol and calcitriol, inhibit corneocyte proliferation and stimulate corneocyte differentiation *in vitro*.[5] In addition, these analogues

have only minimal effects on calcium levels and calcium excretion.
- Vitamin D analogs are also valuable and clinically effective in combination therapy, especially with topical corticosteroids, thus allowing for a steroid-sparing effect.[7]
- Newer topical treatments that contain vitamin D analogs and have shown good clinical efficacy and safety profiles include:
  - Calcitriol ointment (Silkis™) - a naturally occurring derivative of vitamin D
  - Calcipotriol + betamethasone dipropionate gel (Xamiol®) - a two-compound scalp formulation containing a synthetic vitamin D3 with a potent topical steroid

Calcitriol Ointment

- Calcitriol 3µg/g ointment is a naturally occurring active form of Vitamin D3 demonstrated to be as effective as other vitamin D analogs, but calcitriol has the advantage of increased tolerability in sensitive areas such as the face, hairline, and postauricular and flexural areas.[8]
- The use of a tolerable vitamin D3 analog in sensitive areas may minimize corticosteroid use in these skin regions, allowing for better individualization of a psoriasis regimen.
- It is indicated to treat mild-to-moderate plaque-type psoriasis in adults ≥18 years of age with up to 35% body surface area involvement and is suitable for long-term therapy.
- Calcitriol ointment has been extensively evaluated for the treatment of chronic plaque-type psoriasis and has been shown to be effective, safe, and well-tolerated in a number of short-term and long-term clinical trials.[9]
- In a 52-week uncontrolled, open label study of 324 patients, efficacy did not appear to diminish over time.[10]
- Recommended dosing is twice-daily (morning and evening) to affected areas. The maximum weekly dose should not exceed 200g and improvement may be seen as early as 2 weeks after initiating therapy.
- Pharmacokinetic studies in patients with psoriasis and healthy control subjects have demonstrated that topical calcitriol ointment produces little systemic absorption of calcitriol and does not result in systemic hypercalcemia even when applied to approximately one-third of the body surface area.[9]

Calcipotriol + Betamethasone Dipropionate Gel

- This once-daily lipophilic gel is specially formulated for the scalp and contains the active ingredients calcipotriol 0.005% and betamethasone dipropionate 0.05%.[11] Studies have shown that the two agents in combination have a more rapid onset of action and greater efficacy than monotherapy with either agent.[12,13]
- A study investigating the combination of betamethasone dipropionate 0.5mg/g plus calcipotriol 50µg/g in a new gel formulation showed that 92% of patients achieved marked improvement to clearance of their scalp psoriasis following once-daily use for up to 8 weeks.[14]
- The gel vehicle improves cosmetic acceptability, minimizes irritation, facilitates ease of use, is odourless, and may encourage patient adherence with a once-daily regimen.
- To avoid the potential effects of calcium metabolism, usage should be limited to 15g daily, or 100g weekly.

Improving Long-term Quality of Life

- Topical corticosteroids are a useful intermittent therapy for managing stable disease affecting relatively small areas of the body, leading to an improved quality of life over a long-term period.
- In general, a gradual reduction in the frequency of corticosteroid use following clinical response is recommended.[4]
- Therapy should be monitored by physicians to limit the risk of cutaneous or systemic side-effects, especially if it is to be used for a prolonged duration.
- Controlling these adverse side-effects will improve patient adherence and outcomes. Hence, the addition of newer vitamin D analogs to the topical armamentarium for psoriasis will no doubt widen therapeutic options and improve adherence.
- Additionally, in quality of life questionnaires administered to psoriatic patients, psychological distress appears to be a self-reported trigger for flare periods in up to 60% of patients.[15]
- Psychological interpersonal difficulties can impinge on all aspects of the patient's daily life. As such, it is important to assess how the patient's life is affected by the psoriasis, what the patient perceives as the most bothersome aspects of their psoriasis, and what their hopes and expectations of treatment are.[16]
- It should also remain a priority to provide treatment that addresses these psychological fears and concerns of patients.
- In order for the treatment to be successful, appropriate therapeutic regimes for patients should take into consideration long-term self-reported assessments for quality of life improvements.

Conclusion

Establishing an effective therapeutic regimen is crucial in managing not only the psoriasis, but also patient adherence to treatment and satisfaction with outcomes. Understanding both patient-specific needs and the available topical therapies are essential in order to successfully treat the majority of psoriatic patients. However, primary care physicians should continually review with patients the therapeutic options and elicit their feedback to optimize long-term management of this chronic condition.

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