

Treatment of psoriasis

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Abstract

Psoriasis is a prevalent chronic inflammatory disease. Beyond skin and joint manifestations, psoriasis has numerous associated comorbidities, including metabolic and cardiovascular disease. There are many treatment options available, from topical treatment for mild psoriasis, phototherapy for moderate disease, to systemic therapy or biological agents for severe disease. This article aims to focus on the treatment for the majority of patients where topical agents alone are generally appropriate.

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Psoriasis is a chronic, immune-mediated genetic disorder affecting approximately 2% of the world's population.¹ Genome-wide association studies show the majority of the genes implicated are immune-related genes which emphasise dysregulated interactions of the innate and adaptive immune systems in the pathogenesis of psoriasis.² There are relatively few genes that encode for skin-specific proteins. Several environmental triggering factors are known to elicit psoriasis in genetically predisposed individuals, including stress, infections, trauma and some medications.

There are five main types of psoriasis: plaque; guttate; inverse; pustular (either generalised or of the palms and soles) and erythrodermic psoriasis. The characteristic lesion, as seen in plaque-type psoriasis is that of sharply demarcated erythematous plaques covered by silvery lamellar scales.

Psoriasis varies in severity with the clinical classification ranging from mild disease with less than 5% body surface area (BSA), moderate disease (5–10%) and severe disease, where there is greater than 10% body surface area involved.³ Around 80% of patients with psoriasis have mild to moderate disease, which can be treated with topical agents. Management of psoriasis should begin by assessing disease severity and the presence of comorbid conditions.

Non-pharmacological treatment

Psoriasis is increasingly being recognised as a systemic inflammatory disease.⁴ Comprehensive care of patients with psoriasis requires focus not only on the cutaneous manifestations but additionally on the comorbidities that may occur more often in psoriasis than in the general population. Comorbid diseases include psoriatic arthritis, Crohn's disease, malignancies, diabetes, obesity, fatty liver disease, hypertension and metabolic syndrome, amongst others. General practitioners are in an excellent position to investigate and manage these comorbidities and to provide counsel on lifestyle modifications. It is recommended that blood pressure, body mass index, waist circumference, smoking, alcohol consumption, serum lipids, and fasting glucose should be regularly assessed in patients with psoriasis, particularly in those with severe disease.⁵

Topical treatments

Topical agents can be initiated at primary healthcare level. These treatments are used as first-line therapy in mild disease or as adjunctive treatment for patients on systemic treatments or phototherapy. Several topical therapies are available and factors to consider when selecting a therapy include efficacy, body location and patient preferences regarding characteristics such as frequency of application and the texture of formulation. The main therapies are corticosteroids, vitamin D₃ analogues, retinoids, dithranol, calcineurin inhibitors and coal tar. Each of these agents has been shown to be significantly more effective than placebo.

Corticosteroids

Topical corticosteroids are a mainstay of therapy for mild-moderate psoriasis. They are available in numerous strengths and formulations ranging from weaker preparations such as 1% hydrocortisone to superpotent preparations like clobetasol propionate. They are well established in efficacy due to their mechanism of action having anti-inflammatory, antiproliferative, vasoconstrictive and immunosuppressive effects. In a systematic review very potent and potent topical steroids were shown to be more efficacious for psoriasis compared to mild and moderate potency agents.⁶

The selection of the class of corticosteroids must be guided by the specific skin area to be treated. Low to mid-potency steroids are preferred for the areas on the face, intertriginous zones and in children. More potent steroids can be used on thick chronic plaques and on the scalp. The duration of use of high potency steroids is usually limited to 2–4 weeks. In clinical practice, however under appropriate monitoring, longer durations are frequently used. Care should be taken to monitor for adverse effects. The long-term use of topical steroids is well known and includes cutaneous atrophy, telangiectasia, striae distensae, acne, folliculitis and purpura.⁷ Systemic side-effects, although uncommon, are tachyphylaxis and hypothalamic-pituitary-adrenal axis suppression. Several regimens have been used to minimise complications, such as use on weekends only with three consecutive doses of corticosteroids applied at 12-hour intervals, following successful initial therapeutic response to daily potent topical corticosteroids.⁸

Vitamin D analogues

Calcipotriene (calcipotriol) and other vitamin D₃ analogues are an alternative first-line therapy for psoriasis. Three topical vitamin D₃ compounds are available: calcitriol (the active metabolite of vitamin D) and its synthetic analogues, tacalcitol and calcipotriol. Psoriasis is characterised by a hyperproliferative epidermis. Vitamin D₃ acts by binding to vitamin D receptors and normalises epidermal keratinocyte proliferation and differentiation. Calcipotriol ointment 50 µg/g twice daily was shown to be significantly more effective than placebo in two randomised, double-blind studies.^{9,10} A Cochrane meta-analysis of fourteen trials compared vitamin-D analogues directly with potent corticosteroids (3 542 patients) and found no significant difference between the two groups of drugs.¹¹ Vitamin D analogues can potentially cause adverse effects relating to lesional and perilesional irritation, erythema, pruritus and oedema as short-term side-effects. Systemic side-effects such as hypercalcaemia and parathyroid hormone suppression are quite rare unless patients are applying more than the recommended dosage of 100 g/week, have underlying renal disease or impaired calcium metabolism.¹²

Combination therapy

Combination topical therapies for psoriasis may increase compliance and are convenient to use. Several clinical trials have shown that a combination of calcipotriol and betamethasone dipropionate corticosteroid was more effective than monotherapy alone. A systematic review of six randomised controlled trials (RCTs) of 6 050 patients showed after four weeks of treatment the mean reduction in the Psoriasis Area and Severity Index (PASI) ranged from 65% to 74% with the two-compound product applied once or twice daily, as opposed to 46% to 59% with calcipotriol alone and from 57% to 63% with betamethasone dipropionate alone.¹³

Topical retinoids

Tazarotene is a third-generation retinoid (vitamin A derivative) that is FDA approved for the treatment of stable plaque psoriasis. Topical retinoids function by normalising abnormal keratinocyte differentiation, diminishing hyperproliferation, and decreasing expression of inflammatory markers. They are available in cream or gel formulations and are predominantly used in combination with Vitamin D₃ analogues or moderate to potent topical corticosteroids. Tazarotene efficacy was evaluated in four RCTs. About 50% of patients treated with tazarotene experienced a 50% or higher improvement in severity score.¹⁴ Adverse effects are common and include burning, pruritus, erythema and photosensitivity.¹¹ Tazarotene is teratogenic being pregnancy category X and should be avoided in pregnancy.

Calcineurin inhibitors

The calcineurin inhibitors, tacrolimus and pimecrolimus, block the synthesis of numerous inflammatory cytokines that play an essential role in the pathogenesis of psoriasis. Calcineurin inhibitors are recommended for the use on facial and flexural psoriasis.¹⁵ Topical calcineurin inhibitors offer the potential for anti-inflammatory effect without the atrophy or local side-effects associated with the use of topical corticosteroids.

Dithranol

Dithranol has been used for the treatment of mild-to-moderate disease, typically in an inpatient setting. Its use has been declining in clinical practice due to more cosmetically acceptable treatment options. The most common adverse effects are skin irritation and staining of the skin.¹⁶

Coal tar

Coal tar has historically been used for approximately a century in the treatment of psoriasis but its use has decreased over time. The

Table I: Established systemic drugs for psoriasis

Drug	Mechanism of action	Dosage	Toxicity
Methotrexate	Dihydrofolate reductase (DHFR) inhibitor. MTX inhibits DNA synthesis thereby decreasing epidermal hyperproliferation. Decreases inflammation.	Once-weekly dose of up to 30 mg. Starting weekly at 5 to 7.5 mg a week and gradually increased by 2.5 to 5 mg every 2–4 weeks. Folate supplementation: 1–5 mg/d given daily except the day of methotrexate.	Nausea, anorexia, stomatitis, fatigue, myelosuppression, hepatotoxicity, pulmonary fibrosis, photosensitive reactions.
Cyclosporine	Cyclosporine binds to cyclophilin. This complex blocks the dephosphorylation of NFAT _c preventing the production of IL-2 and IL-2 receptors. This leads to a decreased number of CD4 ⁺ and CD8 ⁺ (cytotoxic) T cells in the epidermis. ⁷	Used on a short-term basis (< 6–12 months) Therapy should be initiated at 2.5 mg/kg/day and increased by 0.5 to 1 mg/kg/day every other week until clinical improvement or a maximum dose of 4–5 mg/kg/day.	Nephrotoxicity, hypertension, elevated triglyceride levels, gingival hyperplasia, hyperkalaemia, malignancies including cutaneous squamous cell carcinomas and lymphoma.
Acitretin	Antiproliferative and immunomodulatory properties.	0.5 mg/kg/day as the initial dose which can be increased depending upon the clinical response and side-effects.	Mucocutaneous dryness, arthralgia, gastrointestinal upset, photosensitivity, teratogenicity, transaminitis hyperlipidaemia.
Aprimelast	Phosphodiesterase 4 inhibitor, decreases PDE4-mediated degradation of cyclic adenosine monophosphate, a secondary messenger that promotes anti-inflammatory processes.	Gradual increasing to 30 mg twice daily.	Nausea, diarrhoea, nasopharyngitis, headache.

tar odour and staining of clothes can make this form of treatment poorly tolerated by patients. In addition it can potentially cause folliculitis, photosensitivity and irritant contact dermatitis.¹⁷

Phototherapy

Phototherapy is a treatment modality in patients with moderate to severe psoriasis. UV light therapy decreases keratinocyte proliferation. Phototherapy can be delivered as broadband or narrowband UVB, and photochemotherapy using UVA and a topical application or oral ingestion of psoralens (PUVA). Narrowband-UVB (311–313 nm) is often considered as first-line treatment owing to its safety and efficacy in multiple RCTs.¹⁸ The risk of skin cancer is significantly increased with PUVA, and there is a theoretical risk with NB-UVB.¹⁵ The need for frequent sessions (three times a week for at least three months or longer) and the distance to centres that offer the treatment is a limiting factor for some patients.

Systemic treatment

According to South African guidelines, referral of patients to a dermatologist for systemic therapy initiation is advised.³ Indications for systemic therapy include high BSA involvement (more than 10%) or psoriatic arthritis. Patients should be asked about the presence of joint pain, regardless of the extent of psoriasis severity to identify psoriatic arthritis and to avoid inappropriate treatment with topical therapy only. Established systemic drugs for psoriasis are listed in Table 1.

Biologics

Biological agents are now well established and a highly effective treatment option for patients with moderate to severe psoriasis and psoriatic arthritis. There are several guidelines which restrict their use to patients for whom systemic treatment has led to insufficient improvement or are contraindicated. The current biological agents for psoriasis or psoriatic arthritis target the systemic inflammatory cytokine tumour necrosis factor alpha (infliximab, etanercept, adalimumab, golimumab, and certolizumab), interleukin IL-12 and IL-23 (ustekinumab), IL-17 (secukinumab, ixekizumab), the IL-17 receptor (brodalumab), and IL-23 (guselkumab).¹⁹ A recent meta-analysis found that brodalumab, guselkumab, ixekizumab, and risankizumab were associated with the highest PASI response rates in both short-term and long-term therapy.²⁰

Conclusion

Psoriasis is a multisystem inflammatory disease and managing all aspects of the patient's care, including comorbidities, is imperative. The majority of patients with psoriasis have mild disease, and thus,

it is important to understand how to optimise topical treatments. Patients with severe disease or for whom topical therapy fails may require further evaluation by a dermatologist for systemic therapy.

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