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THE SPECTRUM OF MANAGEMENT FOR PSORIASIS: FROM THE KNOWN TO NEW ALTERNATIVES

Introduction

Psoriasis is a chronic, immune-mediated systemic condition characterized by inflammatory changes that may involve the skin and joints.[1] It is relatively common, with a prevalence rate of 2–4% in North America, and a global prevalence rate of up to 11.4%.[2-4] Years ago, affected patients may have ranged in age from 18–39 to 50–69 due to bimodal distribution.[5] While initially thought to be a dermatologic disease, it is now a recognized multisystem condition with a genetic predisposition.[5] The complex pathophysiology is thought to originate from dysregulation between the innate and adaptive immune systems.[2] T-lymphocytes, dendritic cells, cytokines such as interleukin (IL) 23, IL-17, and tumor necrosis factor (TNF) have all been implicated in and contribute to the inflammatory sequelae.[2,6] The chronicity and pathogenesis of disease may predispose patients to significant functional impairments, associated comorbidities such as metabolic syndrome and cardiovascular disease, and diminished quality of life.[2,7] This has prompted novel approaches to management with the introduction of biologics and small molecule therapies that address the underlying immune dysregulation.[8]

There are multiple clinical manifestations including plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis.[5,6] Among the most common is plaque psoriasis which typically presents as symmetrically distributed, well demarcated, erythematous, scaly plaques or patches that may be pruritic.[5,6] Common sites of involvement include the extensor surfaces of the elbows, knees, the trunk, gluteal cleft, and scalp. Guttate psoriasis is typically preceded by upper respiratory infections and represents approximately 2% of all cases of psoriasis. It involves several small (<1 cm) confetti-like papules

and plaques.[5] A severe, although uncommon form is erythrodermic psoriasis which results in widely distributed erythema, scales and exfoliation of a large surface area of the skin. Due to the widespread loss of the epidermal, dermal barrier and associated risk of fluid loss, electrolyte disturbances and infection, it is considered a dermatologic emergency. Pustular psoriasis is also an uncommon, potentially severe, clinical variant, with possible complications secondary to acute widespread erythema and development of multiple pustules.[5,6]

Psoriasis at other sites such as the intertriginous regions, nails, palms, and soles may present differently.[6] For example, intertriginous also known as inverse psoriasis, involves smooth, shiny plaques that generally lack scale and appear in skin folds such as the inguinal, genital, and inframammary regions. Nail psoriasis can present alone or concurrently with psoriasis or psoriatic arthritis. Features include pitting of the nail matrix, leukonychia, crumbling of the nail, and oil spots or tan brown discoloration of the nail bed.[5,6]

Differential Diagnosis

The differential diagnosis varies depending on the clinical presentation and variant of psoriasis. Given plaque psoriasis is the most common form, it is important to recognize other conditions such as, lichen simplex chronicus, seborrheic dermatitis, atopic dermatitis, nummular eczema, and superficial fungal infections which can present similarly.

Assessing Disease Severity

Clinical disease burden is generally quantified by extent of body surface involvement.[9] In terms of disease severity, several validated scoring scales have been used primarily in clinical trials. They may also serve a role in clinical practice. The Psoriasis Area and Severity Index (PASI) score is most often used. The Dermatology Life Quality Index (DLQI) may be used to assess impact on quality of life.[9,10]

There are several comorbidities associated with psoriasis, consideration of which may influence treatment choice.[1,9] The most implicated is psoriatic arthritis, affecting as many as one-third of patients with psoriasis.[2,5] Psoriatic arthritis can present as joint swelling, stiffness and pain of the small and large joints, or the axial skeleton.[5,11] Many of the current treatments for psoriasis, particularly biologics, can also effectively manage psoriatic arthritis.[11] Furthermore, cardiometabolic disease disproportionately affects patients with psoriasis compared to the general population. Psoriasis, in particular severe disease, is a risk factor for myocardial infarction, obesity, metabolic syndrome, and atherosclerosis.[2,5] However, the recent literature suggests that the risk of major adverse cardiovascular events such as myocardial infarction, stroke, heart failure, and cardiovascular death in fact decreases with ongoing treatment for psoriasis.[1] There is also an increased risk of inflammatory bowel disease such as Crohn's disease.[2,5] Lastly, the incidence of psychological illnesses such as depression and anxiety has been well documented and they play a role in overall quality of life for patients living with psoriasis. This highlights the importance of screening patients with concomitant mood symptoms while promptly and effectively managing the dermatologic manifestations, which has been shown to correlate with improvement in psychiatric symptoms.[1,5]

Indications for Referral

To prevent morbidity, primary care providers should consider early referral to dermatology for patients with extensive body surface area (BSA) involvement, disease refractory to first-line topical treatments, potentially severe variants including erythrodermic and pustular psoriasis, and if the diagnosis is uncertain. In addition, primary care providers play an important role in informing patients about the association between psoriasis and other conditions, and recognizing systemic findings, particularly musculoskeletal complaints, which necessitates prompt referral to rheumatology.

Management

Psoriasis is a chronic, relapsing condition which, while incurable, can be actively managed with an array of treatments. These include novel treatments such as biologics and small molecule therapies. Management is generally directed by the severity of disease activity and any associated comorbidities.[1,11]

In general, patients should be advised to maintain a healthy BMI and quit smoking due to the interplay between disease activity and cardiovascular risk. Additionally, for patients beginning systemic immunosuppressive therapy it is imperative to assess immunization history and update routine vaccinations prior to treatment. (**Box 1**)[12]

Baseline:
CBC with differential
Complete Metabolic Profile
TB test +/- Chest xray
Hep B and C serology
HIV serology based on risk factors
Ongoing:
Infectious work up, if indicated
Skin cancer screening
Case by case testing for latent TB
CBC with differential, CMP including liver function tests in patients on infliximab at the discretion of treating physician

Box 1. General monitoring parameters; *adapted from Menter, A et al., 2019.*

Mild Disease

Mild disease is classified as involving less than 3% of total BSA, where the size of the hand is approximately 1% BSA.[11] Topical corticosteroids play a critical role in management, particularly in patients with well localized disease.[9,11,13] Due to their anti-inflammatory, antiproliferative, vasoconstrictive, and immune suppressing mechanism of action, they serve as a cornerstone of therapy.[5] The vehicle used and potency of the corticosteroid in congruence with the disease location, severity, and patient preference are key considerations. Overall, potent and super potent corticosteroids have been shown to be the most effective agents compared to mild or moderately potent corticosteroids with efficacy rates ranging from 58–92%.[13] Intralesional corticosteroids such as triamcinolone may be utilized in regions with thick plaques or lesions.[13]

Ultimately, topical corticosteroids carry a risk of skin atrophy, folliculitis, telangiectasia, and striae, therefore combination therapy with steroid-sparing agents such as Vitamin D analogues (calcipotriol) or keratolytics (salicylic acid, tazarotene) may be used. Topical Vitamin D analogies block keratinocyte proliferation by binding to receptor sites on T cells with the potential to cause mild irritant dermatitis and rarely hypercalcemia.[5,11] Tazarotene is a topical retinoid that regulates keratinocyte proliferation, thus addressing hyperkeratosis. It has been shown to be more effective in combination with a topical corticosteroid compared to tazarotene monotherapy.[13] Side effects include pruritus, erythema, and burning. Calcineurin inhibitors such as pimecrolimus and tacrolimus block the activation of T cells and therefore propagation of proinflammatory cytokines, and have off-label use in psoriasis, with data derived from established efficacy in atopic dermatitis.[13] Coal tar is a traditional treatment option for psoriasis; however, the associated odour, staining, risk of local irritation, contact dermatitis, and phototoxicity limit its use in practice.[13] In 2023, roflumilast, a phosphodiesterase Type 4 inhibitor (PDE4), became approved in Canada as a topical alternative for plaque psoriasis. Through inhibition of PDE4 and thus cyclic adenosine monophosphate (cAMP), it results in downstream inhibition of proinflammatory cytokines which are propagated in patients with psoriasis.[14] Studies have demonstrated comparable side effects to placebo; commonly reported side effects include diarrhea, headache, and insomnia. While it offers a promising alternative to topical corticosteroids, as it was recently introduced to the market, it remains a costly alternative.

Phototherapy may be used for mild-to-severe psoriasis.[5,11,13] Among the various forms of phototherapy, narrowband UVB (NB-UVB) is typically used. A 2013 review found that a 75% improvement in PASI (PASI 75) was seen in an average of 62% of individuals after 14 to 34 treatments.[15] Although NB-UVB is less effective than psoralen and UVA (PUVA), its demonstrated efficacy combined with negligible risk of skin malignancy makes it a more favourable option.[5,11,13] It is usually administered 2–3 times per week, although it may be inaccessible for patients depending on their geographic location.

Moderate-to-Severe Disease

Approximately 20–30% of patients have moderate-to-severe psoriasis.[8] Moderate disease is classified as involving 3–10% BSA, while severe disease typically involves >10% BSA and is not expected to resolve with topical therapy, resulting in significant impact on quality of life.[9,11]

While biologic treatments have rapidly improved the management of moderate-to-severe psoriasis in the past decade, oral systemic therapies have long been used as treatment. These oral therapies are generally integrated as the first- or second-line treatments in stepwise reimbursement programs. As a result, the cost prohibitive nature of biologics means they are considered third-line therapies despite their superior efficacy compared to both conventional systemic therapies and small molecule agents.[8]

Methotrexate is considered a first-line systemic agent.[9] One RCT found that methotrexate's PASI 75 after 16 weeks was 35.5%.[16] Methotrexate exerts its action as an antimetabolite by inhibiting nucleic acid synthesis via folate antagonism. This decreases proliferation of lymphocytes, which drive the inflammatory process in psoriasis.[11,17,18] Methotrexate has been used in combination with etanercept and NB UVB phototherapy, and has shown benefit in psoriatic arthritis. Adverse effects include nausea, stomatitis and hepatotoxicity.[9,11,17]

Cyclosporine is a calcineurin inhibitor that blocks signalling of proinflammatory cytokines.[17] At a moderate dose it has been shown to achieve a PASI 75 in 50–70% of patients.[19] It can be utilized for its rapid onset of action which is particularly useful in an acute flare of disease; however, the cumulative risk of hypertension and nephrotoxicity preclude its long-term use.[17,18]

Acitretin is an oral retinoid, a derivative of Vitamin A that has increased benefit with combination phototherapy.[17] Acitretin exhibits immunomodulatory properties by affecting epidermal cell growth. Interestingly, it does not have immunosuppressive effects and thus may be used in patients with concurrent immunodeficiency states.[17] The efficacy ranges depending on the duration of therapy, although it is less efficacious overall in comparison with other systemic therapies. Due to its long half-life and risk of teratogenicity, there is a 3-year washout period required for patients intending to conceive.[12]

Class	Name of Biologic Generic (Brand Name)	Other Indications[13,19]	Relative Contraindications[19]	Dosing Frequency[13]	Adverse Events [13]	Efficacy in Clinical Trials[14,19]
TNFi	Adalimumab (Humira)	PsA, IBD	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection, NYHA class III or IV heart failure, MS	Every 2 weeks (SC)	Injection site reactions, serious infections, malignancies	PASI 75 at 16 weeks – 71%
TNFi	Certolizumab	PsA, Crohn's disease	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection, NYHA class III or IV heart failure, MS	Every 2 weeks (SC)	Headache, autoimmune phenomenon	PASI 75 at 12 weeks – 75–83%
TNFi	Etanercept (Enbrel, Brenzys, Erelzi)	PsA, RA, AS	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection, NYHA class III or IV heart failure, MS or demyelinating disease	Twice weekly x 3 months, then weekly thereafter (SC)	Injection site reactions, worsening heart failure, autoimmune phenomenon	PASI 75 at 12 weeks – 48%
TNFi	Infliximab (Remicade)	PsA, IBD	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection, NYHA class III or IV heart failure, MS or demyelinating disease	Dose at 0, 2, and 6 weeks then every 8 weeks thereafter (IV)	Infusion reactions, infections, allergic reactions, demyelinating disorders	PASI 75 at 10 weeks – 70–89%
IL-12/IL-23 inhibitor	Ustekinumab (Stelara)	PsA, Crohn's disease	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection	Dose at 0, and 4 weeks, then every 12 weeks thereafter (SC)	Nasopharyngitis, URTI, headache, infections, malignancy	PASI 75 at 12 weeks – 67%
IL-17 inhibitor	Brodalumab (Siliq)	PsA	History of IBD, recent suicidal behaviour or history of suicidal ideation	Weekly for 3 weeks then every 2 weeks thereafter (SC)	Injection site reactions, URTI	PASI 75 at 12 weeks – 67–-86%
IL-17 inhibitor	Bimekizumab (Bimzelx)	Undergoing investigation for PsA	Hypersensitivity to the medication or any of the excipients	Every 4 weeks for the first 16 weeks, then every 8 weeks thereafter (SC)	nasopharyngitis, oral candidiasis, URTI	PASI 90 at week 16 –85-86%
IL-17 inhibitor	Ixekizumab (Talz)	PsA	Hypersensitivity to the medication or any of the excipients	Dose at 0, 2, 4, 6, 8, 10 and 12 weeks then every 4 weeks thereafter (SC)	Injection site reactions, URTI	PASI 75 at 12 weeks – 81–84%
IL-17 inhibitor	Secukinumab (Cosentyx)	PsA, AS	History of IBD	Dose at 0,1, 2, 3 weeks then every 4 weeks thereafter (SC)	Nasopharyngitis, URTI, rhinitis, oral herpes, diarrhea	PASI 75 at 12 weeks – 81.6%
IL-23 inhibitor	Guselkumab (Tremfya)	PsA	Active infection, hypersensitivity to the medication or any of the excipients	Dose at 0, 4 weeks then every 8 weeks thereafter (SC)	Injection site reactions, URTI	PASI 90 at 16 weeks –70%
IL-23 inhibitor	Risankizumab (Skyrizi)	PsA, Crohn's disease	Active infection, Hypersensitivity to the medication or any of the excipients	Dose at 0, 4 weeks then every 12 weeks thereafter (SC)	URTI, headache	PASI 90 at 16 weeks – 70%
IL-23 inhibitor	Tildrakizumab (Ilumya)	/	Active infection, Hypersensitivity to the medication or any of the excipients	Dose at 0, 4 weeks then every 12 weeks thereafter (SC)	Nasopharyngitis, URTI, injection site reactions, headache	PASI 75 at 12 weeks – 64%

Table 1. Summary of biologic agents indicated for psoriasis; *courtesy of Jaggi Rao, MD, FRCPC.*

Abbreviations: PsA: psoriatic arthritis, **IBD:** inflammatory bowel disease (Crohn's and Ulcerative colitis), **NYHA:** New York Heart Association, **MS:** multiple sclerosis, **RA:** rheumatoid arthritis, **AS:** ankylosing spondylitis, **URTI:** upper respiratory tract infection, **IL:** interleukin, **TNFi:** tunour necrosis factor inhibitor, **SC:** subcutaneous, **IV:** intravenous

Small Molecules

Tofacitinib may be used off-label for psoriasis and has demonstrated utility in rheumatoid arthritis, ulcerative colitis and psoriatic arthritis (PsA). It is an oral Janus kinase inhibitor that interferes with signalling pathways of proinflammatory cytokines.[17] In clinical trials, at the low end of the dosing range, tofacitinib was more effective than placebo (PASI 75 of 46% vs 6.2%). Nevertheless, the FDA has issued black box warnings regarding the risk of thrombosis associated with tofacitinib. In 2022, Health Canada released a safety alert about the association between increased cardiovascular concerns and malignancy, in addition to the risk of thrombosis.[17,20]

Deucravacitinib is an oral tyrosine kinase 2 inhibitor. It exerts its mechanism of action through halting downstream proinflammatory cytokine signalling. In clinical trials the PASI 75 at 16 weeks ranged from 53–58%. Upper respiratory tract infections and nasopharyngitis were the most commonly observed side effects.

Apremilast is another non biologic therapy, specifically, an oral PDE4 inhibitor that is least frequently used.

Biologic agents have consistently shown to be significantly more efficacious in comparison to oral systemic agents and tofacitinib. **Table 1** provides a summary of the biologic agents.

A recent meta-analysis demonstrated that biologics, namely infliximab, ixekizumab, bimekizumab, and risankizumab resulted in a 90% improvement in PASI score and therefore were the most effective in treating psoriasis compared to non-biologics. Various combinations of biologics, topical therapies, such as topical corticosteroids, Vitamin D analogues, phototherapy, and oral systemic agents have also been studied in the literature.[9,19] The choice of initial biologic therapy requires consideration of a patient's psoriasis variant, their comorbidities, particularly PsA and other inflammatory conditions, desire to conceive, and access to insurance coverage, as well as response to previous treatment.

Conclusion

Psoriasis is a genetically linked, lifelong, widespread immune mediated condition with potentially severe medical and psychosocial implications.[11] The impact on a patient's quality of life can be detrimental, and patients are also at increased risk of several diseases including cardiac disease, metabolic syndrome, inflammatory bowel disease, and depression.[1,11,18] Due to the unremitting and relapsing nature of the condition, prompt and effective treatment is an essential aspect of management.

The immune activation and dysregulation via various cytokines play a central role in the pathogenesis of psoriasis, therefore novel biologic treatments aim to target the implicated mediators of disease. Biologics have revolutionized the landscape of moderate-severe psoriasis management and are highly effective at controlling and remitting disease. Despite this, cost and accessibility continue to be barriers to widespread use in clinical practice. Further insight into the disease process continues to shape the evolving treatment options and offers promising results for patients.

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