ONTARIO PHARMACISTS ASSOCIATION
Drug Information & Resource Centre

PHARMACISTS MANITOBA

Therapeutic Options

FOCUS ON PLAQUE PSORIASIS

BACKGROUND

Psoriasis is a chronic, inflammatory, skin disorder characterized by erythematous plaques and papules, often with a silver scale[1]. An estimated 1-3% of Canadians are affected[2], with a worldwide prevalence as high as 8.5%[3].

Although most cases are not severe and can be managed in an outpatient setting, psoriasis can significantly impact quality of life. Patients with highly visible plaques can be exposed to stigmatization, high stress levels, and poor self-esteem[4].

This summary reviews the main treatment options for psoriasis, with a focus on plaque psoriasis. Recommendations are based on both Canadian and American guidelines[4-8].

ETIOLOGY & PATHOPHYSIOLOGY

Psoriatic plaques are characterized by keratinocyte hyperproliferation, dilated blood vessels in the dermis, and an inflammatory infiltrate comprised of T-cells, neutrophils and macrophages producing the characteristic thick, scale-like lesions, silver in appearance[4].

A critical mechanism of psoriasis is dysregulation of the immune system. Dendritic cells in the skin are activated by an antigenic stimulus in susceptible patients[1]. These cells secrete a number of pro-inflammatory cytokines including interferon (IFN-alpha) and interleukins (IL-23 and IL-12), leading to activation and development of CD4+ helper T cells, and production of additional cytokines including IL-1, IL-6, TNF-alpha, IL-22[1]. Targeting these pathways is central to current psoriasis therapies.

RISK FACTORS

Genetics play a key role in psoriasis, with a family history present in up to 30% of patients. In addition, environmental and lifestyle factors greatly influence the disease. Triggers include infection, physical trauma, psychological stress, climate and/or medications[9]. Multiple drugs have been implicated in drug-induced psoriasis, including lithium, interferon, antimalarials, beta-blockers, and withdrawal of systemic steroids[4,9].

Lifestyle factors associated with psoriasis include smoking, alcohol abuse, obesity and other features of the metabolic syndrome (e.g., dyslipidemia, hypertension, glucose intolerance)[10]. Evidence clearly links smoking, in a dose dependent relationship, to the development of psoriasis[10].

SIGNS & SYMPTOMS

Psoriasis can be categorized based on its morphology. The most common form is plaque psoriasis (in 90%), consisting of well defined, scaly, erythematous plaques, occurring either as single lesions or as generalized disease over a wider area [4]. Appearance of lesions varies with the location affected. In the classic form (e.g., trunk, extremities, scalp), plaques are thick with silvery scale; in flexural areas (such as skin folds in the groin or axillary), moisture and friction contribute to thinner, shiny plaques with less scale and possible breakdown or cracking of the skin[4].Non-plaque forms of psoriasis including pustular, guttate, and erythrodermic psoriasis[4].

Comorbidities in the form of cardiovascular disease, metabolic syndrome and other inflammatory disorders are common in psoriasis. Arthritis occurs in up to 40% of patients, often presenting as asymmetrical oligoarthritis (70%), or symmetrical polyarthritis (15%)[2, 4].

NON-PHARMACOLOGIC INTERVENTIONS

Targeting environmental and lifestyle risk factors is an integral component of psoriasis treatment. Minimizing trauma is helpful to avoid precipitation of new lesions. Smoking cessation, minimizing alcohol intake, and maintaining a healthy diet are advised to counteract metabolic syndrome and cardiovascular risk factors[4].

Non-medicated products such as emollients help retain moisture in the skin by forming a film over the surface and can be used liberally without concern of side effects. Thicker vehicles may provide a better barrier but are less cosmetically appealing. Petrolatum has added benefit due to anti-proliferative effects on epidermal cells[11]. Using a rim of ointment or thick cream around plaques can also minimize side effects of topical medications on surrounding normal skin.

PHARMACOTHERAPY

Topical therapy is used for mild, localized cases, when total body surface area involved is less than 5%[6]. Systemic options, either alone or in combination with topical, are reserved for more severe, widespread symptoms[9]. Table 1 lists treatment options and the evidence for their use.

Levels of Evidence Key Therapies

Topical Therapy

Topical pharmacotherapy plays an important role in the treatment of mild to moderate psoriasis as it can provide good control with few systemic side effects. Therapy targets the immune causes of disease to reduce symptoms of scale thickness, inflammation and dryness[9]. Although effective at controlling symptoms, it is not curative and chronic use is often needed[4]. Table 2 lists topical formulations available in Canada.

Steroids

Topical corticosteroids are very effective, and central to the treatment of psoriasis as they produce anti-inflammatory, anti-proliferative, immunosuppressive and vasoconstrictive effects[12]. They are considered first line in the treatment of mild plaque psoriasis, and an adjunct to systemic therapy in more severe forms[4-6].

Advantages of corticosteroids are their fast onset and ease of use. Comparative studies have not shown superiority with respect to potency, frequency of application, nor type of formulation[12]. In general, higher potency steroids are considered more effective than mild ones, especially for thicker plaques. Occlusion with gloves or plastic wrap overnight provides added benefit[12].

Although topical steroids can cause skin changes such as atrophy, telangiectasias (spider veins), and striae, this is unlikely while steroids are being applied to active lesions[13]. Once control is achieved and skin is of normal thickness, steroid-sparing topical agents (e.g., petrolatum) can be used to decrease the frequency of steroid application. Unfortunately, recurrence is common once active agents are discontinued, with a mean remission time of two months.[6] Intermittent use as infrequently as two to three times weekly after control is achieved can be effective in preventing rebound flares[12].

Calcipotriol

The vitamin D3 analogue, calcipotriol, exerts its therapeutic effect by regulating keratinocyte proliferation and differentiation as well as cytokine activity[14]. It is available alone or in combination with betamethasone (as a gel formulation). The combination of calcipotriol and steroid, used either once or twice daily, was more effective than calcipotriol alone, twice daily, in multiple studies[14]. Alternatively, calcipotriol on weekdays with corticosteroids on weekends is an effective maintenance regimen[14]. Response tends to be slow (taking up to two months) but efficacy is maintained, unlike tachyphylaxis seen with continued steroid use[9].

Although not as effective as topical corticosteroids on its own, calcipotriol may be better tolerated, with fewer adverse effects, the most common being contact dermatitis. Although rare, hypercalcemia has been reported; therefore, serum calcium levels should be monitored when using quantities greater than 5 mg calcipotriol (100 g ointment) per week[4].

Calcineurin Inhibitors

Pimecrolimus and tacrolimus inhibit calcineurin, thereby blocking the synthesis of inflammatory cytokines that contribute to psoriasis. Both are effective in plaque psoriasis, especially facial forms. Tacrolimus may be more effective than calcipotriol[15]. A greater benefit was seen on thinner skin areas such as the face or folds, possibly related to decreased penetration through thicker plaques[6]. Burning and itching on application is quite common but improves with continued use. Due to its cream base, pimecrolimus may be more cosmetically appealing to patients especially on the face.

Tazarotene

Tazarotene is a topical retinoid and acts to normalize keratinocyte differentiation and decrease hyper-proliferation[6]. Although effective as monotherapy, combination with corticosteroids led to greater efficacy and decreased side effects[16].

The most common side effect is skin irritation, both with gel and cream formulations[16]. Leaving product on for 30-60 minutes then washing off and moisturizing can minimize irritation. Frequency of administration can also be decreased to alternate days. Another side effect, photosensitization, can be mitigated with evening application.

Intralesional Triamcinolone

Intralesional injectable steroids

Table 1: Levels of Evidence for Key Psoriasis Therapies

	Canadian [4,5]	American [6-8]
Mild Psoriasis		
Topical Corticosteroids	LoE 1++	Class 1+3/4 =LoE 1 Class 2= LoE 2
Topical Calcipotriol	LoE 1++	LoE 1
Topical Combination Calipotriol/Beta-methasone	LoE 1++	LoE 1
Tazarotene	LoE 1+	LoE 1
Moderate-Severe Psoriasis		
Topical Combination Calcipotriol / Beta-methasone	LoE 1++	LoE 1
Methotrexate	LoE 1+	LoE 2
Acitretin	LoE 1-	LoE 2
Cyclosporine	LoE 1++	LoE 2
UV Therapy	PUVA LoE 2++ UVB LoE 2++	PUVA LoE 1-2 NB-UVB LoE 2
TNF Antagonists	Infliximab LoE 1++ Etanercept LoE 1++ Adalimumab LoE 1++	Infliximab LoE 1 Etanercept LoE 1 Adalimumab LoE 1
Ustekinumab	NA	LoE 1
Apremilast	NA	NA

Canadian Level of Evidence (LoE):
1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
American Level of Evidence (LoE):
1. Good-quality patient-oriented evidence.
2. Limited-quality patient-oriented evidence

Table 2: Available Topical Formulations in Canada[34]

Calcipotriol *Dovonex*	50 mcg/mL soln 50 mcg/g cream/ ung
Calcipotriol With Betamethasone *Dovobet*	50 mcg/mL gel
Tazarotene *Tazorac*	0.05% gel /cream 0.1% gel /cream
Calcineurin Inhibitors *Protopic (tacrolimus)* *Elidel (pimecrolimus)*	0.03, 0.1% ointment 1% cream
Coal Tar *T/Gel* *Tersa Tar* *Targel* *Denorex* *Psoriasin* *Doak Oil* *Exorex 1, 2*	0.5, 1% Shampoo 3% Shampoo 10% Shampoo 7.5, 10% Shampoo 2% ung, 1.25% gel, 0.66% liquid 2%, 10% liquid 1%, 2% gel
Combination Coal Tar + Salicylic Acid *X-Seb T Plus, Targel SA* *X-Seb T, Sebcur T* *Tardan SHP*	Shampoos: 10% CT/ 3% SA 10% CT/ 4% SA 5% CT/ 2% SA

are considered a fast and effective method of treating thick resistant plaques, despite minimal published data on use or effectiveness [4].

Other topical medications

Coal Tar decreases epidermal hyperproliferation and appears to be antimicrobial and antipruritic[17]. Although comparable in efficacy, it has a slower onset of action and is less tolerated than calcipotriol products[18]. Its advantages are the low cost and wide availability of shampoos and solutions, ideal for scalp application. Disadvantages include odor and ability to stain[17]. When applying, a downward stroke in the same direction as hair growth can minimize inflammation and folliculitis in hair follicles. It is used up to four times daily on the skin, or twice weekly as a shampoo. If combined with phototherapy, it should be fully removed 2 hours before treatments[17].

Salicylic acid acts by breaking up keratinocytes to soften plaques and decrease scaling[4]. It is rarely used on its own, but combined with betamethasone in topical ointments and with coal tar in shampoo products to maximize efficacy.

Systemic Therapy

When psoriatic symptoms become more severe and/or too extensive for topical therapy, systemic therapy, in the form of oral medications, biologics or phototherapy is preferred. Methotrexate, cyclosporine and acitretin are the systemic oral agents of choice. When these fail or are not tolerated, there is evidence for other systemic agents (e.g., sulfasalazine, leflunomide, tacrolimus, azathioprine, mycophenolate mofetil and hydroxyurea) that will not be discussed in this review[19].

UV light

UV light therapies include narrowband UVB (NB-UVB) and psoralen-UVA (PUVA). They cause death of dermal and epidermal lymphocytes, macrophages and dendritic cells[7]. UVB is given three times weekly, and PUVA is given with oral or bath Psoralen for sensitization 3-4 times a week. Light therapies can achieve full clearance rapidly, but are inconvenient for some patients. The concern of carcinogenesis linked to long-term light therapy, especially PUVA, has led to recommended limits on total cumulative dose[4].

Methotrexate

Methotrexate is very effective in treating both psoriasis and psoriatic arthritis. It competitively inhibits dihydrofolate reductase, impairing DNA and RNA replication and producing immunomodulatory and antiproliferative effects[20].

Methotrexate is dosed on a weekly basis to maximize dose-dependent effect and minimize toxicity. The usual dose is 7.5-25mg weekly. In general, 75-80% of patients respond within 1-4 weeks, but full benefit takes 2-3 months[19]. Reinforcement of the weekly dose is important as serious effects result if patients take their weekly dose every day.

The most serious adverse effects of methotrexate are bone marrow toxicity and hepatotoxicity. Pancytopenia is more commonly reported in patients taking methotrexate for rheumatologic conditions. Risk factors include age >65, decreased renal function, absence of folic acid supplementation, and concurrent medications affecting the folic acid pathway or causing bone marrow suppression[21].

Hepatic fibrosis and cirrhosis are recognized side effects of methotrexate. Risk of liver toxicity is highest in those with concurrent liver disease, hepatotoxic medications, alcohol intake >100g weekly, and/or higher cumulative methotrexate dose. Current guidelines suggest less stringent monitoring for patients without risk factors[22].

Folic acid supplementation is controversial. Although most studies confirm that folic acid can minimize hepatotoxicity and gastrointestinal toxicity (nausea, vomiting, and oral ulcers) of methotrexate, two small studies demonstrated that efficacy of methotrexate was decreased when folic acid was taken[23]. If indicated, it is ideally dosed at 5mg daily on days when the methotrexate is not taken[23].

Methotrexate can cause birth defects and abortions. Paternal methotrexate may not be harmful, but data is limited[24]. For now, advise women to use reliable contraception up to one ovulation cycle after stopping methotrexate, men for three months afterwards[5].

Acitretin

Acitretin is a systemic Vitamin A derivative that works in the same way as tazarotene. It is possibly more effective than methotrexate, and has no immunosuppressive effects[16, 25]. Doses start at 10mg daily and are increased on a biweekly basis up to 70 mg daily. It can take 3-6 months to achieve a full response at a stable dose[7].

The most important adverse effect with acitretin is teratogenicity[16]. Contraception should be started one month prior to starting therapy and continued for three months afterwards[19].

Acitretin can transform into etretinate which has a half life of 168 days and a potential total wash out time of three years. Alcohol can increase this conversion; therefore, its avoidance is important while taking acitretin[19].

Dryness of the eyes, lips, nares and skin can be a significant dose limiting side effect for some patients. Severity can be minimized by an intense moisturizing regimen, including petrolatum for lips and nares (especially overnight), natural tear products for the eyes, and a humidifier for the bedroom.

Hypertriglyceridemia is another common and well-recognized side effect in 25-50% of patients, and a low fat diet is recommended to prevent or reduce hyperlipidemia[7].

Cyclosporine

Cyclosporine is highly effective with a fast onset. It inhibits calcineurin leading to decreased production of inflammatory cytokines involved in psoriasis[26].

Doses generally start at 2.5-3mg/kg/day for 4 weeks, then increase by 0.5mg/kg/day until control is achieved (max 5mg/kg/day)[19].

Major adverse effects of cyclosporine

include dose dependent renal toxicity and hypertension, likely secondary to vasoconstriction. Intermittent 12 week courses may decrease the risk of irreversible nephrotoxicity[7]. Cyclosporine is metabolized via CYP450 3A4 resulting in many potential drug interactions, so a comprehensive drug interaction check is important[7].

Apremilast
The newest medication in the management of psoriasis is apremilast (Otezla), an oral agent that inhibits phosphodiesterase (PDE-4), resulting in decreased inflammatory cytokines[27]. It appears to be less effective than cyclosporine and biologics, with only up to 41% of patients achieving 75% improvement after 12 weeks[27]. Apremilast is well tolerated, with nausea, loose stools and weight loss being the main side effects[27]. No routine bloodwork monitoring is required. Monitoring for drug interactions is necessary since clearance occurs via CYP-450 3A4. Dose reductions are necessary in renally impaired patients. apremilast is currently contraindicated in pregnancy (and in women who are breastfeeding).

Biologics
Biologics are the most effective therapy for psoriasis, but much more expensive than traditional systemic agents[28]. Patients are required to fail two traditional systemic medications (including UV light) to qualify for biologic therapy in Canada. A biologic may be used in combination with another systemic agent, especially methotrexate, if there is suboptimal response to monotherapy[29]. The available biologics differ according to mechanism of action:

1) **TNF antagonists** include adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). Infliximab is the only one given as an intravenous infusion[the others are given via subcuteous administration. TNF antagonists can re-activate TB or hepatitis B, and worsen heart failure[30]. Of the TNF antagonists, etanercept appears to be the least effective[31].

2) **Blockage of IL-12/23** is achieved by the subcutaneous biologic ustekinumab (Stelara). It has similar efficacy as the TNF antagonists, and does not appear to significantly increase the risk of serious infections[31, 32].

Table 3: Dosing of Biologics[5, 33]

	Dose	Half Life (d)
Adalimumab (Humira)	80mg SC x1 then 40mg q2wks	10-20
Etanercept (Enbrel)	50mg SC 2x/wk x 12 wks then 50mg/wk	4.25
Infliximab (Remicade)	5mg/kg IV @ 0,2,6 wks then q8wks	7.7-10
Ustekinumab (Stelara)	45mg @ 0, 4 wks then q12wks (90mg if >100kg)	15 - 32

Table 3 lists available biologics and their dosing.

SPECIAL SITUATIONS

Pregnancy
Fortunately more than 50% of pregnant patients observe significant improvement in their psoriasis during pregnancy[5]. Topical corticosteroids and calcitriol are options for mild symptoms, with UVB as a systemic alternative[5]. If these are not feasible, cyclosporine or biologics can be considered (Category C). Retinoids and methotrexate are contraindicated (Categories X and D)[4]

Vaccinations
Vaccine administration may be problematic with all systemic medications, with the exception of acitretin and apremilast, because of their immunosuppressive effects. An inadequate immune response may decrease effectiveness of an inactivated vaccine or lead to infection with a live attenuated vaccines[5]. If a patient taking a biologic requires a live vaccine, the biologic should be stopped for approximately one month before, and resumed one week following vaccination[5]. Biologics should be held during serious or febrile illnesses including pneumonia, wound infections and cellulitis, but can be continued through uncomplicated upper respiratory tract infections or cystitis[33].

Surgery
Holding immunosuppressant medications to minimize increased risk of infection during perioperative periods may be recommended. TNF-alpha inhibitors may additionally impair wound healing[33]. For elective surgeries, some advise suspending biologics for the duration of five half-lives before surgery and then resuming once the surgery site is healed without signs of infection[33].

Treatment of psoriasis can appear complex with multiple topical and systemic agents used concurrently, and continuously changing regimens. Pharmacists can play a critical role in educating patients about their various treatments, and reviewing optimal administration to ensure efficacy and minimize side effects.

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