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Managing Psoriasis with Topical Agents - Where Do We Stand?

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ABSTRACT

Psoriasis vulgaris is a chronic, immune-mediated inflammatory skin disease affecting 2-4% of the Canadian population. Lifelong management is required. While most psoriasis vulgaris cases are mild-to-moderate (>80%) and do not require systemic treatment, these cases can still be particularly challenging to treat as topical therapies present limitations, including efficacy and administration, leading to poor long-term treatment compliance and unsatisfactory treatment responses. The intent of this paper is to provide physicians with a clinically relevant review of the currently available and newly developed topical therapies for psoriasis, the practice guidelines for topical management of mild-to-moderate psoriasis, and the common pitfalls and mitigation strategies to encourage long-term treatment compliance.

Introduction

Psoriasis is a common immune-mediated skin disease affecting ~2-4% of the population in North America.[1] In nearly one-third of cases, disease begins during the first 2 decades of life and follows a chronic and persistent course, resulting in high cumulative lifetime disability.[2] Psoriasis is divided into 4 major clinical forms, including plaque psoriasis, guttate psoriasis, erythrodermic psoriasis and pustular psoriasis.[3] Plaque psoriasis represents >90% of cases and will be the focus of this

review. Classically, plaque psoriasis affects the trunk as well as the extensor surfaces of the elbows and knees; it can also affect other body sites, giving rise to regional variants such as scalp, face, intertriginous, palmoplantar, genital and nail psoriasis.[3]

Because psoriasis is often localized to visible and/or special body sites (knees, elbows, trunk and scalp) and is commonly associated with pain and itch, it often causes significant physical and psychological burdens.[4] Stigmatization is common and contributes to poor health-related quality of life (HRQoL), elevated risk of multiple health comorbidities, and increased barrier to treatment.[5] Indeed, a recent Global Burden of Disease (GBD) study ranked psoriasis as the second contributor to all skin-related Disability Adjusted Life Years (DALYs).[6] The GBD study highlighted an increase in prevalence and morbidity of psoriasis globally, with North America and Europe being particularly affected, emphasizing the significant burden that psoriasis imposes on both individuals and society as a whole.[6]

Mild, moderate, and severe psoriasis are defined as plaques affecting <3%, between 3-10%, and >10% of body surface area (BSA), respectively.[1] Much progress has been realized in regards to managing severe disease with the approval of numerous advanced systemic therapies, including biologics and small molecules.[7] Unfortunately, in contrast to severe disease, there has been very limited advancement in the management of mild-to-moderate disease, which affects >80% of the psoriatic patient population.[8,9] Mild psoriasis is typically managed with lifelong skin-directed topical therapies.[10] Topical therapies are also often used to treat severe psoriasis vulgaris, either as monotherapy or as an adjunct to phototherapy and/or systemic therapy.[10]

The most commonly used topical therapies in psoriasis include corticosteroids, vitamin D3 analogues, retinoids, calcineurin inhibitors, keratolytics and tar. Multiple fixed-ingredient combination products have become commercially available in the last 20 years with the aim to overcome challenges related to lack of efficacy, compliance and adverse events.[11]

Our objective is to review: 1) the currently available and newly developed topical therapies, both single and fixed-dose combination products; 2) clinical practice guidelines specific to the topical treatment of psoriasis; and 3) common pitfalls and mitigation strategies when managing psoriasis with topical therapies. While we recognize the importance of behavioural modification and skin care in the management of psoriasis vulgaris of all severities, we refer the reader to the review article by Ko et al. on the topic.[12]

Literature Search

This narrative literature review included studies that examined currently available therapies for psoriasis from 2010 to present. The review was conducted using the PubMed and Embase databases with the following search terms: (psoriasis) AND [(corticosteroids) OR (topical corticosteroids) OR (topical corticosteroids AND salicylic acid) OR (topical corticosteroids AND coal tar) OR (calcipotriol) OR (calcitriol) OR (tacalcitol) OR (pimecrolimus) OR (tacrolimus) OR (tazarotene) OR (retinoids) OR (corticosteroid* AND calcipotriol) OR (corticosteroid* AND calcitriol) OR (corticosteroids AND tazarotene) OR (roflumilast) OR (tapiranof) OR (topical treatment)] as either keywords or MeSH terms. Clinicaltrials.gov website was also searched for ongoing Phase II and III clinical trials. References of identified manuscripts were manually extracted to identify additional articles. Only articles published in English were considered. Articles were included if they reported on treatment of psoriasis in humans, regardless of study type. All publications were independently assessed by SG and EN first by screening titles, then abstract, followed by full-length manuscripts. Any discrepancies were discussed and resolved.

Topical Therapies for Psoriasis - Our Current Toolbox

Psoriasis is a chronic disease that requires a life-long treatment. Most patients are managed with topical treatments, therefore, it is important to recognize all presently available therapeutic options, taking into account their respective efficacy, safety profile, and usage considerations. Currently, available treatments that will be discussed include topical corticosteroids (TCS), vitamin D3 analogues, calcineurin inhibitors (TCI), tar-based preparations, retinoids, and combination therapies.[13] These therapies can be used to induce skin clearance and to maintain disease control.[14] Monotherapies with dithranol and salicylic acid will not be discussed, as their clinical use is limited. A clinical timeline of topical therapies for psoriasis is provided in Figure 1. This section will first discuss efficacy and safety considerations of monotherapies followed by

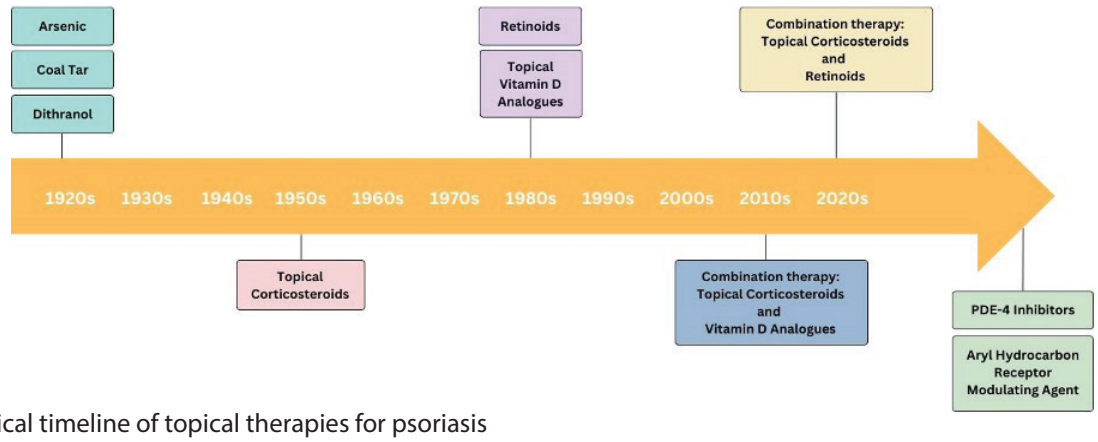

Figure 1: Clinical timeline of topical therapies for psoriasis

combination treatments. Novel therapies, established or previously published guidelines for topical medications use and general recommendations to improve compliance are discussed in following sections.

Monotherapies

Topical Corticosteroids (TCS)

TCS have been used to treat psoriasis for over 60 years.[15] TCS exert broad anti-inflammatory, immunosuppressive, and antimitotic effects.[16] The most recent systematic review that we have identified focusing on TCS efficacy and safety in psoriasis dates back to 2012.[15] It included 50 randomized controlled trials (RCTs), of which only 11 were placebo controlled. Potent and ultra-potent TCS were used in different formulations to induce and/or maintain disease control. Only 5 studies used the Psoriasis Area and Severity Index (PASI) assessment tool to measure efficacy outcomes. The mean percentage change in the PASI from baseline to 4-8 weeks ranged from 45-60%. However, the overall reported efficacy rating varied greatly depending on the study. An added benefit of occlusion was suggested (1 study), whereas no efficacy difference was established between different vehicles (2 studies). Three studies confirmed that weekend (or episodic) TCS treatment after achieving skin clearance was valuable to prevent plaque recurrence in 30-40% of patients at 6 months.

Since this publication, we identified 2 additional RCTs.[17,18] Desoximetasone 0.25% spray twice daily (BID) demonstrated statistically significant clinical success compared to the vehicle as measured by Physician Global Assessment (PGA) score 0/1 at 4 weeks (39% vs. 7%, respectively).[17] Efficacy was better among compliant patients who received reminders compared to those that were not reminded, suggesting that compliance is an important barrier to treatment success.[18-20] Another RCT compared once daily (QD) halobetasol propionate 0.05% cream vs. halobetasol propionate 0.01% lotion suggesting similar efficacy at 2 weeks.[21]

Despite corticosteroid-sparing alternatives and combination therapies (discussed below) being commercially available, TCS remain widely used because of the low cost of some products as well as their versatility. They are available in a wide range of vehicles and potencies, ranging from I (ultra-high potency) to VII (low potency). Available vehicles include creams, lotions, foams, gels, ointments, shampoo, sprays, and solutions[22] (Table 1). Typically, potent to ultra-potent TCS (class I-II) (*e.g.*, clobetasol propionate) are used for thick plaques on the trunk/limbs or special sites, such as the scalp and palmoplantar regions; moderate potency TCS (class III-IV) (*e.g.*, betamethasone valerate; triamcinolone acetonide) are suitable for thinner plaques on the trunk/limbs, whereas mild potency TCS (class VI-VII, *e.g.*, desonide; hydrocortisone) are recommended for intertriginous areas, genitals and/or face.[22] Milder potency preparations are also usually preferred to manage psoriasis in pediatric or pregnant patients.[23,24] The choice of the vehicle is made by the treating physician together with the patient. While some vehicles are preferred based on the anatomic site being treated and desired potency, patient preference is of utmost importance since this enhances treatment compliance. An RCT of vehicle preference among various TCS preparations assessed adherence to treatment and improvement of HRQoL among patients with psoriasis between spray, cream, ointment, gel, lotion, foam, and solution.[25] It was found that patient preference was highly variable, with less messy products favoured.[25] There was no overwhelming agreement on the effect of TCS vehicles in terms of efficacy, hence treatment should be individualized.

Adverse events (AEs) with TCS use are generally rare, but may occur with prolonged and/or inappropriate use. These include local AEs such as skin atrophy, telangiectasia, striae, poor wound healing and infections. When used on the face or acne-prone skin, acne exacerbation or *de novo* periorificial dermatitis/folliculitis may occur.[26] Furthermore, even class VII TCS used on eyelids for prolonged periods can lead to cataracts and/or glaucoma.[27] Systemic AEs related to hypothalamic-pituitary axis (HPA) suppression are exceedingly rare.[28,29] Two systematic reviews/meta-analyses evaluated TCS safety in psoriasis. Literature identified was reassuring, with <5% risk of skin atrophy[30] and <5% rate of HPA suppression when TCS were used long-term.[31] TCS withdrawal reactions, such as Red Skin Syndrome or topical steroid addiction, have also been reported with discontinuation of prolonged, frequent use of moderate to high potency TCS.[32] These severe reactions are rare and are more likely to occur with use on special areas, such as the face and the genitals. A recent review article concluded that TCS are generally safe and effective when used correctly for short periods of time or with short breaks in longer treatments.[32] Beside AEs, additional TCS related limitations include potential tachyphylaxis and corticophobia. Whether tachyphylaxis truly exists is debated among experts, as diminished efficacy over time may be related to low adherence to treatment among patients, especially when long-term treatment is required.[33] Corticophobia among patients and health care providers remains omnipresent and is a major barrier for treatment efficacy beyond inherent limitations associated with the drugs of this class.[34]

Vitamin D3 Analogues

The introduction of Vitamin D3 analogues ~30 years ago was met with much enthusiasm due to their steroid-sparing effect.[35] Commercially available vitamin D3 analogues in Canada are calcipotriol and calcitriol ointments. Vitamin D3 analogues may be used as monotherapy, as an adjunct to TCS, or as fixed-dose combination therapy. They work by regulating gene transcription, modulating keratinocyte proliferation, and differentiation.[36] The mechanism of action also involves the inhibition of T cell proliferation and downstream inflammatory mediators.[36]

There are several systematic reviews published assessing the efficacy of vitamin D3 analogues compared to vehicle or TCS.[37-41] As monotherapy, 1 review reported treatment success (defined as >90% reduction in the PASI score) with vitamin D3 analogues ranging from 4-40% after 6-12 weeks of therapy.[37] Another reported a decrease in the PASI ranging from 27.8-60.4% with calcipotriol monotherapy.[38] Further, BID use of vitamin D3 analogues was found to be at least as effective as TCS and more effective than placebo at 8 weeks.[38,39] A systematic review focused on efficacy of vitamin D3 analogues in pediatric

psoriasis patients found 5 studies reporting improvement in PASI from baseline ranging from 17.3-94%, 1 study reporting improvement in Psoriasis Scalp Severity Index (PSSI) of 32.1%, and 1 study reporting 100% clearance of skin lesions.[40]

In the last 10 years, only 2 new double-blind, vehicle-controlled phase III RCTs evaluated the efficacy and safety of calcipotriol 0.005% foam BID for mild-to-severe psoriasis (defined as plaque psoriasis involving 2-20% BSA) compared to vehicle.[42] Both studies demonstrated significant treatment success, defined as the Investigator's Static Global Assessment (ISGA) scores of 0/1 at 8 weeks. The primary outcome was achieved in 15% vs. 7% of calcipotriol vs. vehicle patients in the first study and 28% vs. 6% in the second study.[42]

The use of vitamin D3 analogues in psoriasis has been shown to be safe and well-tolerated, with less AEs than TCS. AEs are generally comparable to the vehicle, with application site reactions occurring in less than 2% of subjects.[42] Specifically, these include stinging, burning, and peeling of the skin.[37,43] Calcitriol may cause less irritation in sensitive areas compared to treatment with calcipotriol.[44] When used appropriately (maximum recommended dose of 100 g per week of calcipotriene or 200 g per week of calcitriol), the risk of hypercalcemia is very low.[43] Hypercalcemia risk was studied in 3 studies, occurring at a rate <1%.[37]

Retinoids

Vitamin A and its naturally occurring and synthetic derivatives are referred to as retinoids.[45] They were introduced as a treatment for cutaneous disorders in the 1960s and, with the development of safer synthetic retinoids, have become widely used.[45] There are many topical retinoids used in dermatology, however, only tazarotene has been studied and indicated for psoriasis. While tazarotene lotion 0.045% is the only formulation commercially available in Canada, it is indicated for acne and used off-label for psoriasis. Tazarotene binds and modulates activity of retinoic acid receptors (RAR)-β and -γ, thereby decreasing inflammation and keratinocyte proliferation.[46]

There were 2 systematic reviews assessing the efficacy of topical retinoids in psoriasis. The first contained 4 studies comparing tazarotene 0.05% or 0.1% gel or cream to placebo, finding tazarotene to be more effective in improving symptoms in the short-term (6-12 weeks).[39] However, the more recent systematic review comparing the same interventions found that symptom clearance as measured by Investigator's Global Assessment (IGA) ranged from 5.5-6.2% with tazarotene 0.05% and 0.1%

Class	Selected Preparation
I (ultra-high potency)	• Augmented betamethasone dipropionate 0.05% ointment, and lotion • Clobetasol propionate 0.05% cream, ointment and lotion, and solution (shampoo, spray aerosol) • Halobetasol propionate 0.05% cream and ointment
II (high potency)	• Amcinonide 0.1% ointment • Augmented betamethasone dipropionate 0.05% cream • Betamethasone dipropionate 0.05% cream and ointment • Desoximetasone 0.25% ointment • Desoximetasone 0.05% gel • Fluocinomide 0.05% cream, ointment, and gel • Halobetasol propionate 0.01% lotion • Mometasone furoate 0.1% ointment
III (mid-potency)	• Amcinonide 0.1% cream • Betamethasone valerate 0.1% ointment • Desoximetasone 0.05% cream and ointment • Fluocinonide 0.05% cream • Triamcinolone acetonide 0.5% cream
IV	• Hydrocortisone valerate 0.2% ointment • Mometasone furoate 0.1% cream and lotion • Triamcinolone acetonide 0.1% cream and ointment
V	• Betamethasone dipropionate 0.05% lotion • Betamethasone valerate 0.1% cream • Desonide 0.05% ointment • Hydrocortisone valerate 0.2% cream • Prednicarbate 0.1% cream and ointment
VI (low potency)	• Betamethasone valerate 0.1% lotion • Desonide 0.05% cream
VII	• Hydrocortisone 0.5% ointment • Hydrocortisone 1% cream, ointment, and lotion • Hydrocortisone 2.5% cream

Table 1. Topical Corticosteroid Classes of Potency
List of products obtained from Health Canada's Drug Product Database on April 25th, 2023.

cream at 12 weeks, which was not better than placebo.[47] In the last 10 years, there have been no new published RCTs assessing the efficacy of topical retinoid monotherapy in psoriasis. Most clinical trials have focused on combination therapy of tazarotene and TCS.

The most common AEs associated with use of tazarotene are cutaneous local irritations such as peeling, erythema, itching, and burning at the site of application.[46] Cutaneous absorption of topical retinoids is limited, and there are no known systemic toxicities. However, as retinoids are teratogenic, women of childbearing age must use appropriate contraception.[46]

Calcineurin Inhibitors (TCI)

Topical calcineurin inhibitors (TCI) have been approved since the early 2000s for the treatment of mild-to-moderate atopic dermatitis. While not indicated for psoriasis, TCI are often used off-label for facial and intertriginous psoriasis to avoid TCS-related AEs.[48] The available formulations are pimecrolimus 1% cream and tacrolimus 0.1% and 0.03% ointments. TCI bind to immunophilins, which lead to a decreased release of interleukin (IL)-2 and interferon (INF)-γ and thereby decreased T cell proliferation.[49]

Systematic reviews assessing the efficacy of TCI for psoriasis confirmed tacrolimus superiority to placebo, TCS and calcitriol in treating facial and intertriginous psoriasis with treatment duration of 8 weeks.[50,51] However, pimecrolimus was inferior to standard psoriasis treatments.[50,52] One systematic review looked at the synergistic effect of TCI and TCS, which found that there was no additional benefit by combining these agents as opposed to TCS alone.[53]

In the last 10 years, there have been 2 new RCTs published assessing the efficacy of TCI in psoriasis. The first studied the use of pimecrolimus 1% cream in the treatment of intertriginous psoriasis compared to placebo, finding that 71.4% in the treatment group reported an IGA of 0/1 at 8 weeks.[54] The second assessed tacrolimus 0.1% ointment in the treatment of nail psoriasis on 1 hand, using the other hand as a control. At 12 weeks, there was statistically significant improvement in the treated hand as evaluated by the Nail Psoriasis Severity Index (NAPSI) score.[55]

AEs for TCI include skin irritation and discoloration to the site of application.[56] In 2006, a black box warning was issued for a potential link with skin cancer and lymphoma.[56] However, as a result of subsequent large-scale studies disproving this association,[57] Health Canada lifted the black box warning in 2021.[58] The systematic reviews and RCTs found similar rates of AEs between treatment and placebo groups,[51,54] however patients should be counselled regarding transient burning sensation when prescribed tacrolimus ointment to improve treatment adherence.

Tar

Historically, coal tar was considered a classic anti-psoriatic therapy and was used as a first-line agent for more than 2,000 years to treat psoriasis and other skin diseases.[59] Recent studies shed light into the mechanism of action of tar, suggesting modulation of epidermal differentiation and anti-inflammatory effects are likely achieved through activation of the aryl hydrocarbon receptor (AHR).[59] The efficacy of coal tar or its distillate, liquor carbonis detergens (LCD), in treating psoriasis was seldom formally evaluated. The limited available data suggests inferior efficacy to other commercially available agents. Specifically, a Cochrane Review (last updated in 2013), identified tar (including LCD) as generally less effective than TCS and vitamin D3 analogue monotherapies.[41] Safety has been another important concern. As the "crude" word suggests, coal tar contains >10,000 organic compounds, including carcinogenic chemicals, such as benzene.[59] However, carcinogenic potential has not been proven.[60] Over-the-counter tar-containing products are available in different formats including lotions, creams, ointments, and shampoos, however, its application can be messy by staining hair, skin, nails, and clothing with a very unpleasant odour.[61] While it can be compounded with TCS and other active ingredients to enhance effectiveness and penetration, currently it is primarily used in shampoos for the treatment of scalp psoriasis.[61]

Combination Therapies

Combination therapies were developed to improve treatment efficacy as it provides 2 mechanisms of action simultaneously and may have additive or synergistic effects.[62] Further, they may decrease AEs related to each ingredient alone and are therefore better tolerated than monotherapy.[62] Specifically, vitamin D3 analogues and retinoids decrease the risk of skin atrophy, whereas TCS decreases the irritation associated with vitamin D3 analogues and retinoids. Additionally, most fixed-dose combination topical therapies are prescribed to be applied QD as opposed to BID, thereby potentially improving long-term compliance. Commonly prescribed fixed-dose combination topical therapies include TCS and salicylic acid, TCS and vitamin D3 analogues (commercially available since 2001 as ointment, 2012 as gel, and 2016 as aerosol) as well as TCS and retinoids (commercially available as lotion since 2020).

Topical Corticosteroids and Keratolytics

Keratolytic agents, such as salicylic acid and urea, can improve the efficacy of TCS, especially for thicker plaques, by enhancing penetration and improving skin barrier. They are commercially available in combination as salicylic acid 3.0% and betamethasone dipropionate 0.05% ointment and salicylic acid 2.0% and betamethasone dipropionate 0.05% lotion. Additional alternatives can be compounded. There were several RCTs assessing combination therapy of salicylic acid and TCS showing superiority to monotherapy of either salicylic acid or the TCS alone.[53,63] However, 2 RCTs compared combination therapy of TCS and salicylic acid to calcipotriol monotherapy, with no clinical difference.[64] HRQoL was however improved with the combination therapy and was preferred by patients.[63] Only 1 RCT assessed urea in combination with TCS, which found a greater percentage of patients with an improved clinical score compared to monotherapy (47% vs. 33%).[63] Similarly, recent data showed that even simple moisturizers containing lipid-ceramides improve the efficacy of TCS.[65,66] In the last 10 years, there have been no newly published RCTs assessing the efficacy of topical salicylic acid and TCS combination therapy in psoriasis. Although rare, there is a risk of salicylic acid toxicity with topical application.[67]

Calcipotriol and Betamethasone Dipropionate Fixed-Dose Combination

Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g (Cal/BD), available in ointment, gel, and foam formulations in Canada, allows for both anti-inflammatory and anti-proliferative effects. A large Cochrane systematic review published in 2013 assessed the efficacy of combination therapies in psoriasis. Cal/BD was superior to placebo[41,68] and monotherapy (Cal or BD alone) in all but 1 RCT as early as after 2-8 weeks of treatment.[41]

In the last 10 years, there have been many new RCTs assessing the efficacy of Cal/BD for psoriasis focusing on the newer foam formulation, which when used QD for 4-12 weeks demonstrated a significant decrease in PASI from baseline of ~70%, superior to vehicle or either monotherapy.[69-72] Further, approximately half of participants achieved an IGA of 0/1.[73] Two studies compared Cal/BD to betamethasone valerate 0.1% dressing, showing in the first trial no significant efficacy difference at 4 weeks with Cal/BD ointment[74] and the second trial demonstrated superiority of the Cal/BD foam (at 4 weeks).[75] Several additional RCTs re-iterated the superiority of Cal/BD therapy vs. vitamin D3 analogue monotherapy.[76,70,77-80]

Several RCTs focused on Cal/BD vehicle.[71,72,81] RCTs comparing different vehicles have shown better efficacy and superior HRQoL improvement with the use of Cal/BD foam compared to gel or ointment formulations[71,72,81] and cream compared to suspension.[82] However, RCTs assessing vehicle preference as determined by patients did not find any significant preferences when comparing gel vs. foam, gel vs. ointment, and ointment vs. topical suspension, determining that individual patient preference should dictate treatment.[83-85] One real-world study found that patients using gel reported greater satisfaction compared to ointment due to ease of use.[86]

One RCT focused on psoriasis relapse prevention following clinical clearance, defined as PGA score 0 or 1 (clear or almost clear).[87] In this study, both treatment arms received Cal/BD QD for 4 weeks initially to achieve skin clearance and were subsequently randomized into Cal/BD or vehicle biweekly as maintenance treatment. Patients that applied Cal/BD proactively experienced 3.1 relapses per year vs. 4.8 relapses (defined as PGA score 2 or higher) seen in the vehicle group. Median time to first relapse was also longer in the proactive management group (56 vs. 30 days) suggesting that proactive approach may be an interesting alternative to reactive approach for interested patients and could potentially be cost-effective.[87] As expected, both active treatment and proactive maintenance with Cal/BD were well-tolerated and no cases of skin atrophy were reported in either group.[87]

Tazarotene and Halobetasol Fixed-Dose Combination

The only combination treatment of retinoid with TCS commercially available in Canada is halobetasol 0.01%/tazarotene 0.045% (HP/TAZ) lotion. A systematic review published in 2012 included 7 studies assessing the combination of retinoids (in general) with TCS, supporting superiority of combination as opposed to retinoid monotherapy at 4 weeks.[88] A recently published systematic review of 5 RCTs demonstrated treatment success, defined as at least 2-grade improvement from baseline in the IGA score and IGA score of 0 or 1 (clear or almost clear), of 32.8-52.5% for HP/TAZ compared to 33.3-34% for HP alone and 18.6% for TAZ alone with treatment duration of 2-8 weeks.[89]

There have been several new RCTs published in the last 10 years assessing efficacy and safety of retinoids and TCS combination therapy. A combination tazarotene 0.05%/betamethasone diproprionate 0.05% (TAZ/BD) applied QD was superior to either agent used as monotherapy in 2 studies.[90,91] Treatment success of QD topical HP/TAZ lotion measured by the proportion of patients achieving IGA 0/1 ranged from 31.3-57.8% with treatment durations of 8-12 weeks,[92-99] which was significantly more effective than vehicle or either ingredient alone. The most frequent AEs reported were dermatitis, pruritus, pain, and irritation,[92,93,98] occurring in 6-20.8% of study participants.[91,97] A single RCT analyed the sensitization and irritation potential of HP/TAZ lotion with treatment duration of 4-6 weeks, finding that the topical did not induce contact sensitization and caused only minimal skin irritation, but significantly less than tazarotene alone.[100]

Topical Therapies for Psoriasis - The Pipeline

As reviewed above, our current toolbox of topical therapy options is limited to TCS and a handful of other agents, such as vitamin D3 analogues, retinoids, tar or their combination. While the marketing of steroid-sparing monotherapies and fixed-dose combinations with TCS represents a major step forward in the management of psoriasis, these treatment options possess limitations in terms of efficacy, AEs, cost, patient satisfaction, and real-world adherence. Hence, there remains an unmet need for new topical therapies.[101]

There is an exciting topical therapy pipeline in psoriasis (Table 2), roflumilast and tapirnarof will be discussed in this section as phase III RCT data was recently published. Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor that has been developed into 0.3% cream and foam formulations. Crisaborole, a topical PDE-4 inhibitor, was approved in 2016 for atopic dermatitis in adults and children.[102] Its use has been investigated for psoriasis in phase II RCTs, however, despite demonstrating efficacy and safety, results were not published. Rather, focus has shifted to roflumilast, a more potent PDE-4 inhibitor by 25-300X based on *in vitro* studies.[102] PDE-4 inhibition suppresses the breakdown of cyclic adenosine monophosphate (cAMP), decreasing the presence of proinflammatory cytokines involved in the pathogenesis of psoriasis, similar to apremilast used systemically or topical crisaborole.[103] Phase I and II RCT data have demonstrated that roflumilast cream QD was superior to the vehicle when used for 2-8 weeks.[104-106] Phase III RCT data regarding roflumilast 0.3% cream efficacy and safety has been recently published.[107] DERMIS-1 and DERMIS-2 were parallel double-blind RCTs including 439 and 442 patients, respectively. Patients aged ≥2 years with psoriasis affecting 2-20% BSA were recruited and randomized 2:1 into either roflumilast 0.3% cream or vehicle applied QD for 8 weeks. The primary outcome was IGA 0/1 response plus ≥2 grade improvement from baseline, which was achieved in 37.5-42.4% of roflumilast-treated patients vs. 6.1-6.9% vehicle-treated patients. Improvement of PASI ≥75% from baseline (PASI75)

Product	Class	Phase	Clinical Trial Number and Status*
BOS-475 0.5%, 1%, or 2% cream	Targets BD2 domain of bromodomain containing protein	I	NCT03960450,NCT04221906[124,125] – Studies completed
SAN021 serum containing 10% East Indian sandalwood oil	PDE-4 inhibitor	II	NCT03000608[126] – Study completed
Crisaborole ointment 0.3%, 0.5%, 1%, 2%, or 5%	PDE-4 inhibitor	I	NCT01258088, NCT00763204, NCT00762658[127-129] – Studies completed
Crisaborole ointment 0.5%, 2%, or 5%	PDE-4 inhibitor	II	NCT01300052, NCT00759161, NCT00755196, NCT01029405[130-133] – Studies completed
LAS41004 ointment (bexarotene/ betamethasone dipropionate)	Fixed combination retinoid and topical corticosteroid	II	NCT02180464, NCT01360944, NCT01283698, NCT01119339, NCT02111499, NCT01462643[134-139] – Studies completed
PH-10 0.002%, 0.005%, or 0.01% rose bengal aqueous hydrogel	Rose bengal disodium	II	NCT01247818, NCT02322086, NCT00941278[140-142] – Studies completed
SNA-120 (CT 327/pegcantratinib) 0.5% ointment	TrkA receptor antagonist	II	NCT03448081, NCT03322137[143,144] – Studies completed
Roflumilast 0.3% foam for scalp and body psoriasis	PDE-4 inhibitor	II	NCT04128007[145] – Study completed
Roflumilast 0.3% cream	PDE-4 inhibitor	II	NCT03764475, NCT04746911, NCT04655313[146-148] – Studies completed
Roflumilast 0.3% foam for scalp and body psoriasis	PDE-4 inhibitor	III	NCT05028582[149] – Study completed
Roflumilast 0.3% cream	PDE-4 inhibitor	III	NCT04286607, NCT05763083[150,151] – Actively recruiting
M518101 (pefcalcitol) ointment	Vitamin D3 analogue	III	NCT01908595, NCT01989429, NCT01878461, NCT01873677[152–155] – Study completed
MC2-01 cream (calcipotriene 0.05%/betamethasone dipropionate 0.064%)	Fixed combination vitamin D3 analogue and corticosteroid	III	NCT03462927[156] – Study completed
Tapinarof (DMVT-505) 1% cream	Aryl hydrocarbon receptor agonist	III	NCT04053387[157] – Study completed NCT05172726[158] – Actively recruiting NCT05680740, NCT05789576[159,160] – Active, not yet recruiting

Table 2. Topical antipsoriatic agents undergoing clinical trials
*Last update per ClinicalTrials.gov as of April 25, 2023

was achieved in 39.0-41.6% vs. 5.3-7.6% of roflumilast-treated vs. vehicle-treated patients, respectively. It was also shown to be effective for the treatment of intertriginous psoriasis (68.1-71.2% vs. 13.8-18.5%). The incidence of AEs was comparable to the vehicle, with the most commonly reported events being diarrhea and headache in the roflumilast group. Further, AE profiles were similar in individuals aged 12–17 years relative to adults.[107] Currently, roflumilast is approved by the US Food and Drug Administration (FDA) and Health Canada.

Tapinarof is an AHR-modulating agent that acts as an anti-inflammatory compound. It has a similar mechanism of action to tar, which also activates AHRs, however it does not contain carcinogenic chemical compounds.[108] Tapinarof is able to regulate innate and adaptive immune responses, affecting Th17 and regulatory T cells. It also has an important role in the development and maintenance of the skin barrier and upregulating barrier genes, such as filaggrin. Lastly, tapinarof inhibits the migration of T cells, decreasing the presence of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, INF-γ, IL-2, IL-13 and IL-17A.[103] Phase III RCT data has been recently published. In 2 parallel double-blind RCTs including >600 patients each, adults with mild-to-severe psoriasis (PGA 2-4, BSA 3-20%) were recruited and randomized 2:1 into either tapiranof 1% cream or vehicle applied QD for 12 weeks. The primary endpoint was IGA 0/1 and 2-point reduction from baseline at 12 weeks, which was achieved in 35.4-40.2% of tapinarof-treated patients vs. 6.0-6.3% of vehicle-treated patients.[109] While it was generally well-tolerated, increased rates of pruritus, contact dermatitis and folliculitis were seen in the active treatment group. A second RCT found that significantly more participants achieved a 75% reduction in the PASI score from baseline (PASI75) with tapinarof (50.4%) compared to calcipotriol (38.5%) and placebo (13.9%) when used QD for 12 weeks.[110] Tapinarof has been recently approved by the FDA.

Treatment Guidelines for Topical Antipsoriatic Agents

Treatment guidelines for severe psoriasis and psoriatic arthritis are beyond the scope of this manuscript. This section will focus on reviewing guidelines specific to the treatment of mild-to-moderate psoriasis or treatment focused on topical agents.

Current guidelines for the treatment of mild-to-moderate psoriasis recommend topical therapies which include monotherapy with TCS, vitamin D3 analogues, TCI, retinoids, anthralin, and tar as well as combination therapies as first-line options. In Canada specifically, treatment guidelines were initially published in 2011. At this point, Grade A recommendation for first-line topical therapies included TCS or vitamin D3 analogues (i.e. calcipotriol) monotherapy or Cal/BD fixed-dose combination therapy. The treatment guidelines noted that additional topical therapy options were superior to placebo (e.g., retinoids alone or in combination with TCS, 15% LCD) and may be used on a case-by-case basis.[10,111] An update of these treatment guidelines was published in 2016 adding topical calcitriol as an additional first-line topical therapy option for mild psoriasis.[10,111]

The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) have put forth the most recent guidelines in North America in 2020 focusing on topical therapies.[14] The AAD-NPF guidelines do not mention specific recommendations for first-line topical therapy options, but rather provide guidance for use within each class. For TCS, Grade A recommendations include using class I to V agents for up to 4 weeks for body psoriasis (excluding intertriginous areas) and class I to VII agents for scalp psoriasis. The use of TCS for prolonged periods (>12 weeks) may be done under the supervision of a physician (Grade C). However, gradual reduction in frequency of TCS is suggested upon clinical improvement, but without defined tapering protocol. Following clinical improvement, maintenance of response can be achieved by using a steroid-sparing agent (*e.g.*, vitamin D3 analogues or TCI) or by using TCS intermittently (*e.g.*, biweekly, this is also known as proactive approach). Additional recommendations made in regards to TCS use were as follows: the use of emollient was suggested to reduce itching and desquamation and to prevent relapse after TCS discontinuation (Grade B). As well, topical salicylic acid alone or in combination with TCS was recommended as an alternative to TCS monotherapy to achieve clear skin (8-16 weeks of treatment, Grade B).

AAD/NPF guidelines recommended vitamin D3 analogue monotherapy and/or in combination with TCS (*e.g.*, Cal/BD fixed-dose combinations) to induce clearance of scalp psoriasis (4-12 weeks treatment, Grade A), facial psoriasis (up to 8 weeks treatment, Grade B, caution to favour class VI-VII TCS agents) or body psoriasis (up to 52 weeks treatment, Grade A). Topical retinoids (*e.g.*, tazarotene) were recommended either as monotherapy, fixed-dose combination (*e.g.*, HP/Taz) or in combination with narrowband ultraviolet light phototherapy (NB-UVB) (Grade B) for plaque psoriasis and nail psoriasis. However, HP/Taz was preferred (Grade A) to induce clear skin (8-16 weeks treatment) due to better efficacy and tolerability.

The off-label use of TCI (*e.g.*, tacrolimus and pimecrolimus) was recommended by AAD/NPF guidelines for facial and inverse psoriasis to achieve clinical improvement (Grade B recommendation) and to maintain response (Grade C recommendation). They also suggested a combination of tacrolimus/6% salicylic acid for body psoriasis (Grade B recommendation).

Grade B recommendation was also stated for short contact anthralin use (≤2 hours per day, up to 8-12 weeks treatment) and Goeckerman therapy (coal tar and NB-UVB) for mild-to-moderate plaque psoriasis.[14] Coal tar preparations received Grade A recommendation as well.

Real-world Limitations with Topical Treatments and Strategies to Improve Compliance

As highlighted above, all current topical therapies come with limitations. Patient compliance is certainly among the most important barriers to success. Adherence rates with current topical therapies are low, estimated to range from 50-70% in general.[101] The compliance rates for TCS are even more variable and in some instances are thought to be as low 8%, due to prevalent corticophobia among dermatology patients.[101,112]

Adherence is an important concept that must be evaluated in patients as it is directly associated with better clinical outcomes. A recent RCT demonstrated that a decrease in adherence rate of 10% was associated with a 1-point increase in disease severity.[113]

Various interventions were studied to improve compliance. Three RCTs integrated reminders in the forms of BID telephone calls, text messages, or smartphone application to remind and motivate patients to use their topical therapy.[20,114,115] In all studies, adherence improved and almost doubled compared to non-interventional arms (65% vs. 38% adherence).[115] This translated into significantly better clinical outcomes, such as reduction in PGA.[20,115] Another RCT developed a web-based application to educate patients with videos, graphics, and text.[116] While knowledge was improved, this did not translate to increased treatment adherence.[116] Four RCTs approached adherence by offering more clinical support, such as teaching from nursing staff or internet-based reporting.[117-120] Compared to standard of care, these clinical trials demonstrated that additional support resulted in greater clinical outcomes as early as 4 weeks, which were sustained at 3 months.[117-120]

Vehicle selection is an important component of efficacy and adherence. Good vehicles can accelerate barrier restoration and enhance efficacy of active agents by promoting penetration and sustained drug release.[121] As discussed above, RCTs assessing patient satisfaction have found that treatment preferences are heterogeneous and may even change over time.[83,122] Factors that may influence preferences included age, sex, comorbidities, disease duration, and prior treatments.[122] Therefore, a vehicle should be selected to maximize efficacy and meet the diverse needs of the patient while considering bodily location of psoriasis, probability of improvement, and delivery method. An additional very important attribute for a topical therapy to improve patient adherence is convenience. While it may be patient-specific, an agent that does not need to be applied often (QD or less often), is universal (*e.g.*, same product that can be applied anywhere on the skin), is cosmetically acceptable (texture, colour, and odour) and is affordable will likely promote higher patient adherence and thereby achieve better clinical success rates.

As discussed in the guideline review section above, the first aim of psoriasis treatment is to achieve clear/almost clear skin with a topical agent of choice (combined physician/patient decision for agent selection). Prior to fixed-dose combination topical therapies, in order to increase efficacy while mitigating AEs, different strategies were used. These included rotational treatment where patients alternated between 2 agents, usually a TCS and a corticosteroid-sparing molecule;[123] or a sequential treatment approach where a superpotent agent (usually TCS class I-II) was used initially with subsequent step down to either a milder TCS, steroid-sparing molecule or a rotational treatment. However, nowadays fixed-dose combination topical therapies are more popular for their additive efficacy, simplicity, and convenience.[123] Once acceptable control is achieved, discussion of relapse prevention is important.

Because psoriasis is chronic and likely to recur upon discontinuation of the topical therapy, it is important to educate the patient about the chronicity of the disease and its treatment at the initial and subsequent visits. Two approaches following initial improvement of psoriasis are commonly used in clinical practice to maintain response over longer-term: the proactive and reactive approaches. Combined physician-patient decision-making may opt for either a proactive approach which consists of using the same agent to achieve clear skin (or another topical) intermittently (e.g., biweekly) to psoriasis-prone areas in order to prevent recurrence, or a reactive approach where all treatments are discontinued upon clinical resolution and restarted promptly with first signs of disease recurrence.

Conclusion

The vast majority of our psoriasis patients have a mild-to-moderate disease requiring topical therapies life-long. Consequently, the availability of safe, effective, and convenient products is essential to achieve and maintain clear/almost clear skin and promote long term treatment adherence. In this review, we provided clinicians an up to date safety and efficacy data of commercially available topical products as well as imminent pipeline topicals. North American guidelines for topical treatment of mild-to-moderate psoriasis are summarized as well as clinical tips are provided.

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