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Exploring Newer Topical Therapies for Inflammatory Skin Diseases: A Guide for Rheumatologists

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Introduction

Understanding the pathogenesis of many inflammatory skin diseases and their associated signalling pathways has revealed multiple promising therapeutic targets. Given the chronic nature of many of these conditions, products with long-term safety and efficacy are desired. While topical corticosteroids have been the mainstay of topical therapies for years, they are burdened by concerns over long-term safety (i.e., atrophy, striae, telangiectasias), risk of absorption with systemic glucocorticoid side effects, and patient apprehension regarding steroid use. Similarly, topical calcipotriol and retinoids may be ineffective and can cause irritation. Although topical calcineurin inhibitors (i.e., pimecrolimus, tacrolimus) have been approved for atopic dermatitis, their off-label use for many inflammatory conditions may be limited by tolerability issues such as stinging and burning, and lack of effectiveness. The emergence of newer targeted small molecules for topical application, including topical phosphodiesterase-4 inhibitors (PDE4i), topical Janus kinase inhibitors (JAKi), and a therapeutic aryl hydrocarbon modulating agent (TAMA), offer promising new options and will be reviewed here and summarized in **Table 1.**

Phosphodiesterase-4 Inhibitors (PDE4i)

Cyclic adenosine monophosphate (cAMP) serves as the principal secondary messenger governing the regulation of immune responses. Phosphodiesterase 4 (PDE4) stands out as the key enzyme responsible for cAMP degradation and is present in both immune cells and non-immune cells such as keratinocytes.[1] Inhibitors targeting PDE4 can extend or amplify the effects of cAMP, which can lead to the suppression of both Th1 and Th2 immune responses, thereby making this an attractive target for managing inflammatory skin diseases.[1,2]

Class	Product	Indication	Trade name
Calcineurin inhibitors			
Pimecrolimus	**Pimecrolimus 2% cream BID**	Mild-to-moderate atopic dermatitis	Elidel cream
Tacrolimus	**Tacrolimus 0.03%, Tacrolimus 0.1% ointment**	Moderate-to-severe atopic dermatitis	Protopic ointment
PDE4 inhibitors			
Crisaborole	**Crisaborole 2% ointment BID**	Mild-to-moderate atopic dermatitis, ages 3 months and above	Eucrisa ointment
Roflumilast	**Roflumilast 0.3% cream OD**	Plaque psoriasis, ages 9 years and above	Zoryve cream 0.3%
	Roflumilast 0.3% foam	Seborrheic dermatitis	Zoryve foam 0.3%
	Roflumilast 0.15% cream* OD	Atopic dermatitis	Zoryve cream 0.15%
JAK inhibitors			
Delgocitinib	Delgocitinib 20mg/g cream* BID	Chronic hand eczema	Unknown
Ruxolitinib	Ruxolitinib 1.5% cream** BID	Atopic dermatitis and vitiligo, ages 12 years and above	Opzelura cream
AhR modulating agents (TAMA)			
Tapinarof	Tapinarof 1% cream** OD	Plaque psoriasis Atopic dermatitis	Vtama cream

Table 1: Summary and indications of non-steroidal topical agents for inflammatory skin diseases; *courtesy of Melinda Gooderham, MSc, MD, FRCPC.*

Abbreviations: BID: twice a day, **OD:** once daily

Bolded medications are approved by Health Canada
* Not yet approved by Health Canada
** Not yet approved and under review by Health Canada

This mechanism of action is well proven with the oral PDE4i, apremilast, which is approved for use in moderate-to-severe psoriasis, psoriatic arthritis, and Behçet's disease.[3] Topical PDE4i are also approved for use in inflammatory skin diseases. Specifically, topical crisaborole 2% ointment is approved for atopic dermatitis for ages three months and above,[4] and more recently, topical roflumilast 0.3% cream has been approved for plaque psoriasis in individuals 12 years and above.[5]

Roflumilast, a highly potent PDE4i, has been approved as an oral therapy for chronic obstructive pulmonary disease since 2011.[2] In 2023, Health Canada approved topical roflumilast 0.3% cream, for treating plaque psoriasis, including intertriginous psoriasis for ages 12 and older.[5] This topical formulation of roflumilast is an elegant, moisturizing, water-based cream that is applied once daily. Notably, it exhibits superior potency compared to other PDE4 inhibitors, ranging from 25 to 300 times more potent than apremilast or crisaborole, depending on the specific comparator and PDE4 isoform.[2]

The phase 3 trials, DERMIS-1 and DERMIS-2, included 881 participants aged 2 years and above with plaque psoriasis covering 2–20% of their body surface area. These multicentre trials evaluated the daily use of roflumilast 0.3% cream over an 8-week period. Roflumilast showed significant improvements in key outcomes, including the primary outcome of Investigator Global Assessment (IGA) success (achieving an IGA of clear or almost clear and at least a 2-grade

improvement from baseline) and a key secondary outcome, 75% improvement in Psoriasis Area Severity Index (PASI-75). Pruritus also improved with the use of roflumilast, showing a reduction of at least 4-points in the Worst Itch Numeric Rating Scale (WI-NRS) scores observed as early as week 2, and this improvement was more prominent by week 8. Adverse events associated with roflumilast were comparable between roflumilast and vehicle (placebo) groups which were uncommon and likely unrelated to treatment.[6]

Future approvals and formats of topical roflumilast include a roflumilast 0.3% foam for once daily use to treat seborrheic dermatitis,[7] which is already approved by the FDA for use in ages 9 years and above in the United States. The roflumilast foam product has also been studied in scalp and body psoriasis (NCT05028582) and may have a future indication for the use of roflumilast. A topical roflumilast 0.15% cream is being investigated for use in atopic dermatitis,[8] and was approved by the FDA in July 2024.

Janus Kinase Inhibitors

The Janus kinases (JAKs), including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), are predominantly found in hematopoietic cells, residing on the cytoplasmic side of Type I and II cytokine receptors.[9] Upon cytokine binding, JAKs activate signal transducers and activators of transcription (STATs). This activation process leads to the phosphorylation of the STATS. Once phosphorylated, they dimerize and translocate to the nucleus to regulate gene transcription. Inhibition of this pathway, which plays a crucial role in immune defence, has shown promise in treating multiple immune-mediated diseases. JAKi, which are small molecules that modulate immune responses by uncoupling cytokine receptor signalling from downstream STAT transcription activation; and, can be effective also as topical preparations.[9] Ruxolitinib 1.5% cream is the first topical JAKi that targets JAK1 and JAK2, which is currently approved by the FDA for use in atopic dermatitis and vitiligo.[10]

The atopic dermatitis pivotal trials, TRuE-AD1 and TRuE-AD2, involved 1249 participants aged 12 years and above with mild-to-moderate atopic dermatitis (IGA 2 or 3) covering 3–20% of their body surface area.[11] These multicentre trials evaluated the use of ruxolitinib 1.5% cream twice daily over an 8-week period. The findings of these trials demonstrated significant improvements of ruxolitinib cream in key outcomes, including the primary outcome, IGA treatment success (IGA-TS), and a 75% improvement in the Eczema Area Severity Index (EASI-75). A treatment effect was noted as early as week 2 in both studies. Pruritus also showed significant improvement with the use of ruxolitinib cream, with at least a 4-point reduction in the Itch Numeric Rating Scale (NRS) scores that were observed as early as day 2 of treatment, with a clinically significant difference at week 2, and the improvement was more prominent by week 8 of treatment in both studies. The most commonly reported adverse events were comparable between the ruxolitinib and vehicle groups, and included nasopharyngitis, upper respiratory tract infection, and headache.[11] There were no reported adverse events associated with systemic JAK absorption.

The pivotal trials in vitiligo, TRuE-V1 and TRuE-V2, included 674 participants 12 years of age or older who had non-segmental vitiligo covering 10% or less of their body surface area.[12] Participants applied either ruxolitinib 1.5% cream twice daily or vehicle to all involved areas for a 24-week period. After this time point, all patients, regardless of their initial group assignment, applied ruxolitinib cream until the 52-week time point. The primary endpoint was a 75% improvement in the Facial Vitiligo Area Scoring Index (F-VASI75) at week 24. The study found significantly greater repigmentation in the ruxolitinib group, with approximately one-third of participants achieving this target, compared to the vehicle group by week 24.[12] Other secondary endpoints included a 50% improvement in the total VASI (T-VASI50), which was significantly greater in the ruxolitinib group and achieved in approximately one-fifth on active treatment with ruxolitinib. After 52 weeks of topical ruxolitinib application, adverse events were infrequent and included acne, nasopharyngitis, and application site pruritus.[12] Topical ruxolitinib 1.5% cream is also currently being studied for conditions such as mild hidradenitis suppurativa (NCT05635838) and prurigo nodularis (NCT05755438, NCT05764161).

Another JAKi, delgocitinib, is a topical pan-JAK inhibitor that is under investigation for chronic hand eczema. Delgocitinib is approved for use in atopic dermatitis in Japan in a 0.5% ointment formulation.[13] The phase 3 pivotal trials, DELTA-1 and DELTA-2, included 960 participants aged 18 years and above who were treated with twice daily delgocitinib cream 20 mg/g or vehicle for 16 weeks.[14,15] The most common reported adverse effects were nasopharyngitis, dermatitis, and

Inflammatory Skin Condition	PDE4 Inhibitors	JAK Inhibitors	AhR Modulating Agent
Psoriasis	**Roflumilast 0.3% cream OD**		Tapinarof 1% cream** OD
Atopic Dermatitis	**Crisaborole 2% ointment BID** **Roflumilast 0.15% cream* OD**	Ruxolitinib 1.5% cream** BID	Tapinarof 1% cream* OD
Chronic Hand Eczema		Delgocitinib 20 mg/g cream* BID	
Seborrheic Dermatitis	Roflumilast 0.3% foam* OD		
Vitiligo		Ruxolitinib 1.5% cream** BID	

Table 2: Approved and upcoming indications for topical therapies; *courtesy of Melinda Gooderham, MSc, MD, FRCPC.*

Abbreviations: BID: twice a day, **OD:** once daily

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headache. DELTA-3 was a 36-week extension trial that evaluated the long-term safety and efficacy of delgocitinib cream. The results showed good maintenance of effect and no new safety concerns over 36 weeks of as-needed use.[16]

Aryl hydrocarbon receptor antagonists

Aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor, regulates gene expression in immune and epithelial cells, and is necessary for maintaining skin homeostasis.[17] Through heterodimerization with the AhR nuclear translocator (ARNT), an AhR-ARNT complex is formed that binds to specific DNA sites, to control the transcription of AhR-responsive genes. Activation by different ligands can induce a variety of biological responses, making AhR a suitable therapeutic target for inflammatory skin diseases due to its role in regulating inflammation and homeostasis.[17] For instance, topical inhibition of the AhR pathway, by tapinarof, a topical Therapeutic Aryl hydrocarbon receptor-Modulating Agent (TAMA), is a novel way to target skin inflammation.[17]

In the pivotal trials for topical tapinarof, PSOARING-1 and PSOARING-2, 1025 participants aged 18 to 75 years with a physician global assessment (PGA) score of at least mild (2) and a body surface area of 3 to 20% affected by psoriasis were treated with tapinarof 1% cream or vehicle once daily for 12 weeks.[18] PGA response, reflected by the PGA score (clear [0] or almost clear [1] with at least a 2-point improvement from baseline) was the primary trial endpoint. Other key endpoints, such as the PASI-75 score, were met in a significantly greater proportion of patients in the tapinarof 1% cream arm than in the vehicle arm. Also, long-term efficacy was observed in the PSOARING-3 trial; a long-term extension study. In this trial, participants with a PGA score of 1 or greater applied tapinarof 1% cream for an additional 40 weeks, observing that some patients achieved a remittive effect (the maintenance of clear or almost clear while off therapy). Adverse events such as folliculitis, headache, back pain, and pruritus were most commonly reported.[18] Tapinarof is also being assessed for its use in atopic dermatitis (NCT05014568, NCT05032859).

Future Directions

The need for safe, long-term therapies continues in chronic inflammatory skin conditions. Current treatment options may have cumulative toxicities or tolerability issues, which underscores the excitement surrounding the emergence of novel topical therapies. The recent approval of topical roflumilast 0.3% cream, which offers a convenient once-daily treatment for plaque psoriasis, including the intertriginous areas, opens a promising new avenue for patients to manage their condition. The imminent approvals of other topical treatments, including PDE4i, JAKi, and TAMA for conditions such as psoriasis, atopic dermatitis, seborrheic dermatitis, and vitiligo, with hopefully many more conditions being added to this list adds to therapeutic topical treatments for many patients with inflammatory skin conditions (**Table 2** which

lists various diseases where the new topical agents are being studied). These and other treatments continue to improve outcomes for patients.

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