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Originally from Fort McMurray, Alberta, Dr. Grewal now resides and practices dermatology in the community setting in Edmonton, Alberta. In 2002, Dr. Grewal completed his Bachelor of Science (BSc) undergraduate degree at the University of Alberta with a Specialization in Psychology and graduated with Distinction. He completed his Doctor of Medicine (MD) degree at the University of Alberta in 2006 and graduated with Special Training in Research. In 2011, he completed his Dermatology training at the University of Alberta and became a Fellow of the Royal College of Physicians and Surgeons of Canada (FRCPC) and also went on to become a board certified Fellow of the American Academy of Dermatology (FAAD). Dr. Grewal is a Clinical Professor within the Faculty of Medicine, Division of Dermatology, at the University of Alberta. He is the Co-Medical Director of Dermatology and Clinical Research Trials at Rejuvenation Dermatology and Aesthetics Downtown Edmonton. He is also a consulting physician for the University of Alberta Hospital, the Royal Alexandra Hospital, the Grey Nuns Hospital and the Misericordia Hospital. Dr. Grewal has participated in over 100 clinical research trials for a multitude of dermatology conditions and medications. Dr. Grewal also serves on multiple national and international scientific advisory boards, is a distinguished peer reviewer for medical journals and has published both journal articles and book chapters in Dermatology.

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Off-Label Uses of Topical Ruxolitinib

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Introduction

Janus kinase (JAK) inhibitors, such as ruxolitinib, have emerged as promising therapeutic agents in dermatology. These small-molecule inhibitors target and disrupt the inflammatory Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, critical to inflammatory and autoimmune skin disorders.[1] Topical formulations allow localized treatment while minimizing the systemic side effects commonly associated with oral JAK inhibitors. Ruxolitinib, a selective JAK1/JAK2 inhibitor, is approved for the treatment of atopic dermatitis (AD) and non-segmental vitiligo in individuals 12 years and older as of 2022.[1-4] The therapeutic effects of ruxolitinib in AD and vitiligo are primarily mediated through inhibition of JAK1/JAK2 signalling, which regulates cytokines implicated in AD such as interferon (IFN)-γ, interleukin (IL)-13, and IL-31, as well as IFN-γ-driven melanocyte destruction in vitiligo.[5]

Beyond these approved indications, off-label uses for oral and topical ruxolitinib are rapidly emerging, particularly for conditions with underlying inflammatory or autoimmune mechanisms. While systemic treatment has demonstrated good efficacy in a variety of conditions, the potential for associated side effects can limit the feasibility of their widespread use.[6] For topical administration, the data is promising; however, its broader adoption is limited by a lack of large-scale trials, optimized dosing, and long-term safety data. This review examines the evidence to date, highlights knowledge gaps, and explores the potential for broader clinical applications of topical JAK inhibitors in dermatology.

Mechanism of Action in Select Conditions

The success of ruxolitinib cream across a variety of conditions can be attributed to its targeted inhibition of the JAK/STAT pathway. This pathway plays a critical role in regulating immune responses and inflammatory cytokines implicated in numerous dermatological diseases.

- **Alopecia Areata:** Characterized by peri-follicular lymphocytic infiltration involving natural killer cells and T cells, which are targets of ruxolitinib's inhibitory action. By reducing this peri-follicular infiltration, ruxolitinib addresses the autoimmune processes driving hair loss.
- **Psoriasis:** Driven by dendritic cell activation and cytokine dysregulation, processes that are effectively countered by ruxolitinib's action on the JAK/STAT pathway. Ruxolitinib suppresses these pathogenic pathways by suppressing dendritic cell activation and cytokine overproduction, interrupting the cycle of inflammation and keratinocyte hyperproliferation, decreasing lymphocytic infiltration, and acanthosis.[7,8]

These mechanisms support ruxolitinib as a logical therapeutic candidate for a broad range of inflammatory and autoimmune skin conditions.

Advantages of Topical Ruxolitinib Cream

Ruxolitinib cream offers several key benefits compared to approved systemic treatments[5]:

1. **Localized Action:** As a topical agent, it provides targeted treatment with minimal systemic absorption, reducing risks such as malignancy or immunosuppression-related infections. However, some systemic absorption may occur, as evidenced by reports of relative leukopenia upon treatment initiation.[8]
2. **Rapid Symptom Relief:** Patients often experience sustained symptomatic improvement within days to weeks of initiating treatment.
3. **Convenience and Compliance:** Unlike oral JAK inhibitors (e.g., tofacitinib), injectable biologics, or oral antibiotics, ruxolitinib cream is user-friendly, and may enhance patient adherence.

4. **Long-Term Tolerability:** Its limited systemic side effects make it suitable as a long-term treatment option.

Safety Profile and Reported Side Effects

Reported side effects for ruxolitinib cream are mild and self-limited. Some examples of mild adverse events include pruritus, irritation, pain, localized dryness, erythema, and headaches. Ruxolitinib does carry a boxed warning regarding serious infections, malignancies, major adverse cutaneous events, thrombosis, and mortality. However, the topical application results in limited-to-negligible systemic absorption and the steady-state plasma concentration of ruxolitinib remains well below the thresholds associated with systemic JAK-inhibitor toxicities.[8] Consequently, the risk of systemic adverse effects is not deemed to be clinically significant.

Methods

A literature search was conducted using PubMed, OVID Medline, and Embase with the search terms "ruxolitinib," "JAK inhibitors," "Janus kinase inhibitors," and "topical." Twenty-six studies, encompassing a total cohort of 520 patients, met the inclusion criteria and were analyzed. The identified studies included randomized controlled trials, open-label studies, retrospective analyses, and case reports. The clinical characteristics, distribution patterns, and observed therapeutic efficacy profiles across these 26 extracted protocols are systematically outlined below in **Table 1**. In addition to the above-mentioned literature review, Turchin et al[18] have also previously published a review of topical, off-label uses of ruxolitinib. They have cited its effective use in the following conditions: atopic dermatitis, vitiligo, alopecia areata, psoriasis, lichen planus (LP), necrobiosis lipoidica, discoid lupus erythematosus, and seborrheic dermatitis.

Limitations of the Current Evidence

Although ruxolitinib cream has shown promise across a range of off-label dermatologic applications, several limitations remain:

1. **Small Sample Sizes:** Many studies rely on case reports or small cohorts, limiting the generalizability of the results.
2. **Short Study Durations**: Most trials have follow-up durations of only 6–12 months, limiting the assessment of long-term efficacy and safety for chronic diseases.
3. **Unoptimized Dosing Protocols:** Available concentrations (e.g., 0.075% or 2%) have not been systematically compared to refine treatment strategies.
4. **Limited Peer-Reviewed Data:** Many findings remain unpublished or have not undergone peer review, restricting interpretation and validation by the broader scientific community.

Future Directions

To address these limitations and expand the clinical utility of ruxolitinib, further research is needed:

1. **Large-Scale Randomized Trials:** These are essential to validate efficacy and safety across broader populations.
2. **Long-Term Studies:** Chronic conditions require data on outcomes extending beyond 12 months.
3. **Dose Optimization Studies:** Comparative trials investigating different concentrations and regimens could help tailor treatment for specific conditions.
4. **Broader Applications:** Exploration of topical ruxolitinib efficacy should be further explored to determine its full therapeutic potential.

Currently, active clinical trials are evaluating topical ruxolitinib across several off-label conditions (ClinicalTrials.gov). There are trials being conducted in adult and adolescent patients with hidradenitis suppurativa (NCT07049575), children 6 to <12 years of age with non-segmental vitiligo (NCT06804811), refractory cutaneous dermatomyositis (NCT06857240), and participants with discoid lupus (NCT06261021).

Conclusion

Ruxolitinib cream has demonstrated significant promise in both approved and off-label dermatological indications. Its localized action, rapid symptom relief, and favourable safety profile

make it an attractive alternative to systemic treatments. However, current evidence is limited by small sample sizes, short follow-up periods, and unoptimized dosing protocols. Addressing these gaps through larger-scale, long-term research will be critical to understanding its full potential as a safe and effective therapy for diverse inflammatory and autoimmune skin diseases.

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Dermatological Condition	Number of Studies	Reported Clinical Effect / Efficacy Notes	Primary Literature Sources
Alopecia Universalis	3	Shows potential for systemic regrowth, though highly prone to relapse upon withdrawal	Solimani et al., 2019[5] Craiglow et al., 2016[9]
Alopecia Areata	4	Stimulates hair regrowth by reducing peri-follicular T-cell infiltration.	Bayart et al., 2017[10] Gordon et al., 2019[11] Deeb et al[12], Olsen et al., 2012[13]
Psoriasis	3	Significantly decreases epidermal acanthosis and limits cytokine overproduction.	Carmona-Rocha et al., 2024[7]; Punwani et al., 2012[8]
Cutaneous Graft-Versus-Host	3	Controls localized, resistant sclerodermatous skin flares.	Solimani et al., 2019[5]
Frontal Fibrosing Alopecia	2	Slows down or stabilizes the progression of frontal hairline scarring.	Hosking et al., 2018[3] Desai et al., 2024[15]
Seborrheic Dermatitis	2	Reduces erythema and scaling via localized anti-inflammatory pathway blocks.	Gong et al., 2021[2] Pope et al., 2022[14]
Lichen Planus	2	Flattens classic violaceous papules and eases localized pain/pruritus.	Solimani et al., 2019[5], Brumfiel et al., 2022[16]
Cutaneous Lupus	2	Calms active discoid or subacute cutaneous lesions without systemic toxicity.	Hosking et al., 2018[3]
Hidradenitis Suppurativa	2	Decreases nodular inflammatory burden in early Hurley stages.	Hosking et al., 2018[3]
Necrobiosis Lipoidica	1	Promotes granulomatous ulcer healing and stabilizes plaque margins.	Solimani et al., 2019[5] Nugent et al., 2022[17]
Total Encompassed	**24 Studies**	**Cumulative Clinical Cohort: 520 Patients**	**Extracted Literature Set**

Table 1. Off-Label Applications of Ruxolitinib Cream; *courtesy of Parbeer Grewal, MD, FRCPC, FAAD*

J&J/Janssen, JAMP Pharma, Leo Pharma, Med Plan, Novartis, Pfizer, Regeneron, Sanofi-Aventis/Genzyme, Sandoz, Sun Pharmaceuticals, Takeda, and UCB. Investigator for: AbbVie, Amgen, Anacor, Apogee, Arena Pharmaceuticals, Avillion, Bausch Health, Biogen, BMS, Boehringer Ingelheim, Celgene, CorEvitas, Dermavant, Eli Lilly, Galderma, Innovaderm, J&J/Janssen, Leo Pharma, Meiji Seika Pharma, Moonlake Immunotherapeutics, Novartis, Pfizer, Regeneron, Sanofi-Aventis/Genzyme, Sandoz, Takeda, UCB, and Vitae.

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