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Review Article

Ruxolitinib: A novel molecule in the management of dermatological disorders

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ABSTRACT

Ruxolitinib (RUX) cream 1.5%, a selective Janus kinase (JAK) 1 and 2 inhibitor initially developed for myelofibrosis, has emerged as a novel therapeutic agent in dermatology. It is the first topical JAK inhibitor approved by the Food and Drug Administration for atopic dermatitis (AD) and non-segmental vitiligo. This article reviews the pharmacological profile, mechanism of action, and clinical efficacy of topical RUX in immune-mediated skin conditions. RUX inhibits cytokine-induced JAK-signal transducer and activator of transcription signaling, reducing inflammation and pruritus with minimal systemic absorption and a favorable safety profile. In phase III TRuE-AD1/AD2 trials, RUX demonstrated significant improvements in the investigator's global assessment, eczema area and severity index scores, and pruritus in patients with mild-to-moderate AD. Similarly, in the TRuE-V1/V2 studies for vitiligo, RUX achieved superior rates of facial vitiligo area scoring index (F-VASI75) and other repigmentation measures compared to vehicle, with sustained benefits at week 52. Common adverse effects included application site reactions such as burning, acne, and pruritus. Beyond its approved indications, emerging evidence supports off-label use in conditions such as lichen planus, alopecia areata, and cutaneous lupus, among others. While preliminary data suggest a positive impact on the skin microbiome, further studies are warranted. RUX cream represents a promising advancement in targeted dermatological therapy, offering localized efficacy with minimal systemic risk.

Keywords: Atopic dermatitis, Janus kinase inhibitor, Psoriasis, Ruxolitinib

INTRODUCTION

Immune-mediated skin conditions are common and associated with significant morbidity and increased use of healthcare resources.[1,2] Historically, their management relied on symptom control and broad immunosuppression. However, recent advances in understanding the underlying immune mechanisms have led to the identification of novel therapeutic targets.[2]

A wide range of cytokines plays a key role in the pathogenesis of inflammatory and immune-related skin disorders. The major signaling pathways implicated include the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) and spleen tyrosine kinase pathways. The JAK family comprises four members: JAK1, JAK2, JAK3, and tyrosine kinase 2. Multiple pro-inflammatory cytokines – including interleukin (IL)-4, IL-5, IL-13, IL-31, and thymic stromal lymphopoietin – utilize these pathways to convey signals from the cell membrane to the nucleus.

The classical JAK-STAT signaling model proposes that cytokine binding to its receptor activates the associated JAKs, leading to phosphorylation of the receptor's intracellular domain. This modification allows STAT proteins to bind, become phosphorylated, dimerize, and translocate into the nucleus, where they bind to specific Deoxyribonucleic Acid (DNA sequences to drive gene transcription.[3] JAK-mediated phosphorylation generates docking sites for STAT proteins through their Src homology 2 domains. Once recruited, STATs are phosphorylated – mainly on tyrosine residues, and sometimes on serine – by JAKs and other kinases, facilitating their nuclear entry and activity.[4] However, the exact dynamics and proportions of STAT homo- and heterodimers in cells before, during, and after cytokine signaling are not fully understood.[5]

In a significant therapeutic development, the US Food and Drug Administration (FDA) approved 1.5% ruxolitinib (RUX) cream in September 2021 for the treatment of atopic dermatitis (AD), followed by its approval for non-segmental vitiligo in July 2022.[6]

PHARMACOLOGY

Pharmacokinetics

In vitro studies show that RUX binds 97% to plasma proteins, mainly albumin. Its average elimination half-life following topical application is around 3 hours.[7-9] RUX is primarily

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metabolized by cytochrome P450 (CYP) 3A4, making it susceptible to interactions with CYP3A4 modulators – levels may increase with inhibitors and decrease with inducers.[9] Topical RUX is not expected to inhibit or induce major CYP enzymes, nor affect P-gp, breast cancer resistance protein, or key organic anion transporters. Systemic absorption is minimal, indicating a low risk of drug–drug interactions.[7,8]

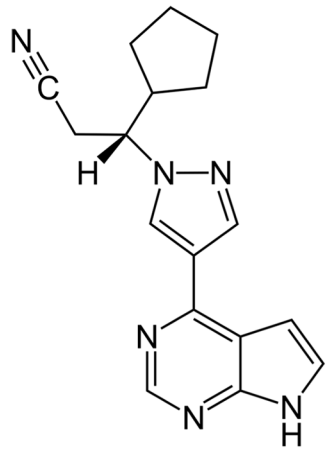

Figure 1: Molecular structure of ruxolitinib.

Pharmacodynamics

Preclinical studies in cell and animal models show that RUX cream effectively inhibits cytokine-induced STAT signaling and reduces tissue inflammation.[10] Its half-maximal inhibitory concentration is below 100 nM.[10] *In vivo*, twice-daily application of 1.5% RUX cream resulted in low systemic exposure and higher dermal drug concentrations compared to oral dosing.[11] Topical RUX sustained JAK-STAT inhibition in the dermis, suggesting prolonged efficacy with reduced risk of systemic side effects.[11]

Molecular characteristics

RUX is available as RUX phosphate and has a molecular weight of 404.36 g/moL. The molecular formula is C17H21N6O4P, chemically identified as (R)-3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-

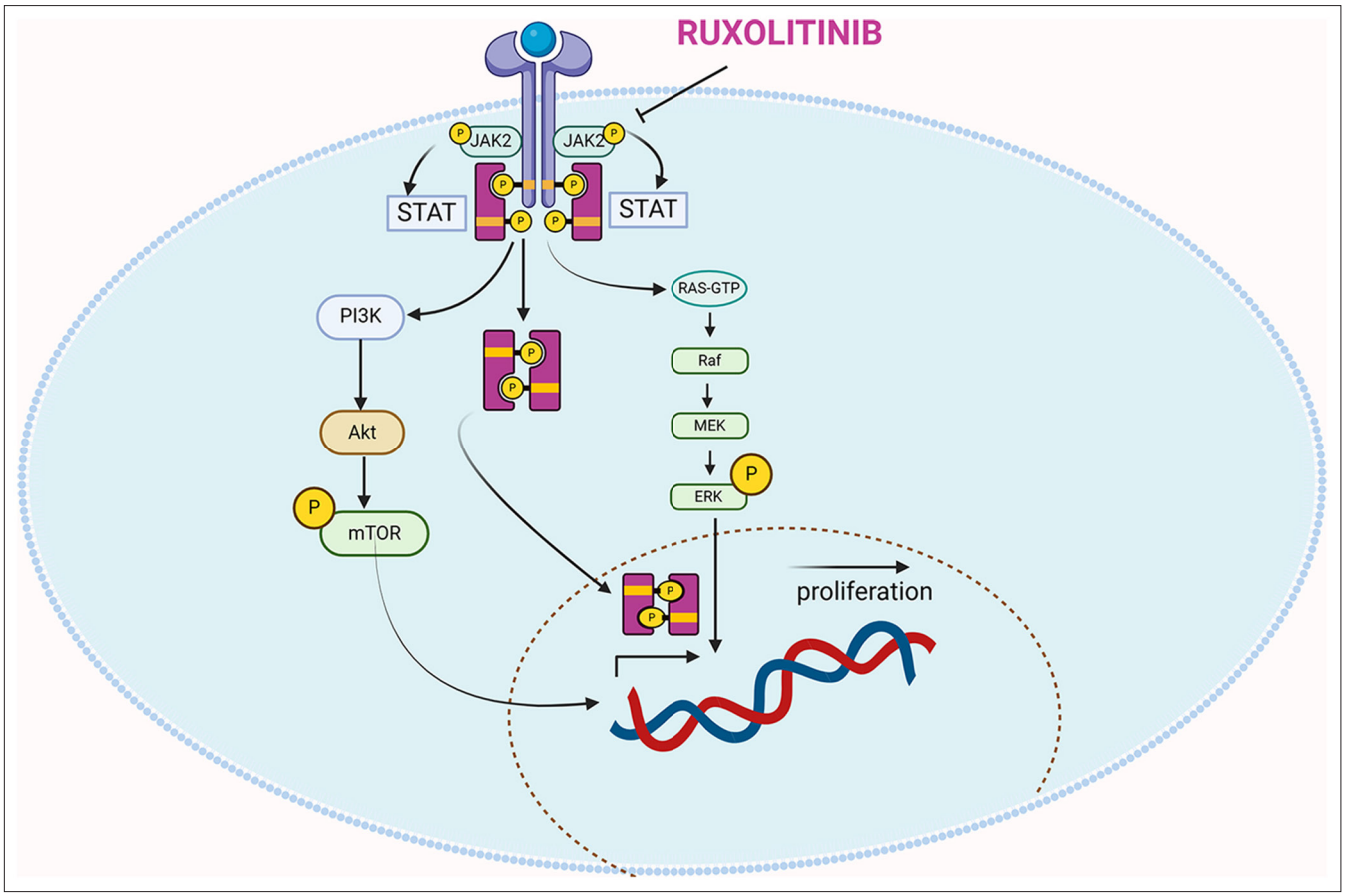

Figure 2: Mechanism of action of ruxolitinib. Akt: Protein kinase B, ERK: Extracellular signal-regulated kinase, JAK: Janus kinase, mTOR: Mammalian target of rapamycin, PI3K: Phosphatidylinositol 3-kinase, STAT: Signal transducer and activator of transcription, MEK: Mitogen-activated protein kinase.

cyclopentyl propanenitrile phosphate. The drug substance in an aqueous medium is pH-dependent. It is most soluble in pH 1.0 buffer (0.54 mg/mL) and least soluble in pH 7.4 medium (0.15 mg/mL)[12] [Figure 1].

Mechanism of action

RUX is a JAK inhibitor that selectively targets JAK1 and JAK2 by competitively blocking their Adenosine Triphosphate (ATP)-binding sites. This disrupts cytokine and growth factor signaling, leading to reduced levels of proinflammatory cytokines and chemokines commonly elevated in inflammatory conditions. JAK-STAT pathway inhibition by RUX results in decreased phosphorylation of STAT-3/5, protein kinase B,, and Extracellular signal-regulated kinase (ERK).[13] In addition, RUX has been shown to suppress cytokine-independent colony formation of erythroid progenitors[14] [Figure 2].

CLINICAL INDICATIONS

FDA-approved indications

Atopic Dermatitis (AD)

AD, or atopic eczema, is a chronic, relapsing inflammatory skin condition that primarily affects children but also occurs in adults.[15] It is characterized by eczematous lesions and intense pruritus, which significantly impairs quality of life through sleep disruption, anxiety, and depression. AD pathogenesis involves abnormal activation of Th2 and Th22 cells, with a lesser role played by Th17 cells.[16] The JAK-STAT pathway mediates the signaling of key cytokines in AD, including Th2 cytokines IL-4, IL-13, and the pruritogenic IL-31, as well as the Th22 cytokine IL-22[16] [Figure 3].

RUX 1.5% cream is the first topical JAK inhibitor licensed by the FDA. The efficacy was assessed in two similar, randomized, double-blind, vehicle-controlled, global

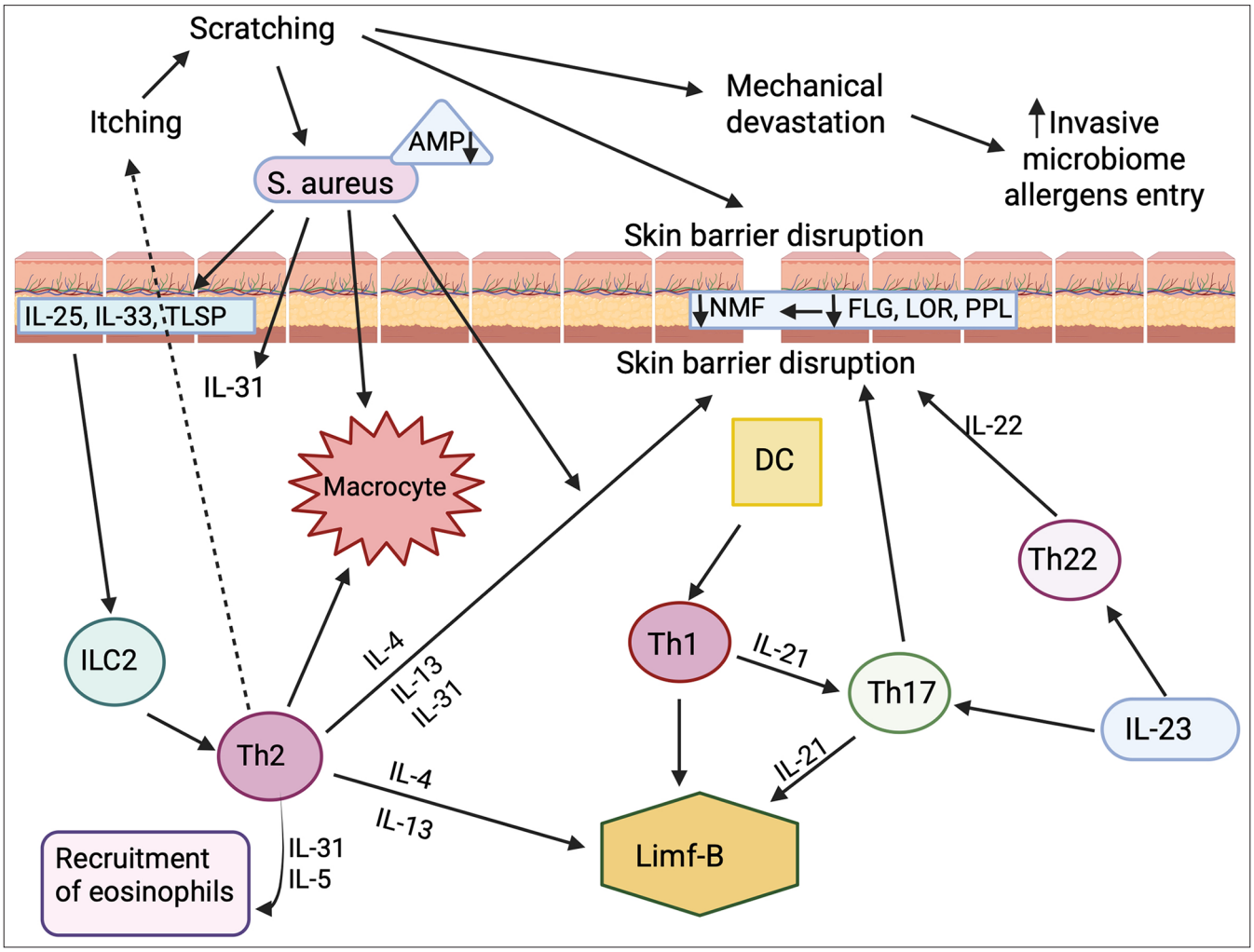

Figure 3: Pathogenies of atopic dermatitis. NMF: natural moisturizing factor, filaggrin (FLG), loricrin (LOR), and involucrin (PPL), Staphylococcus aureus (S. aureus), AMPs: antimicrobial peptides, IL:interleukin, IL-33:interleukin-33, TSLP: thymic stromal lymphopoietin . ILC2: innate lymphoid cells, Th: T helper, Lymph-B: B-lymphocyte, DCs: Dendritic cells.

phase III trials – TRuE-AD1 and TRuE-AD2. The studies comprised patients aged 12 years or older with mild-to-moderate AD for a minimum of 2 years, an investigator's global assessment (IGA) score of 2 (mild) or 3 (moderate), and 3–20% body surface area (BSA) involvement, excluding the scalp. Patients exhibiting unstable AD (defined by spontaneous improvement or quick deterioration), alternative eczema types, immunocompromised conditions, or recent administration of AD therapies during the washout period or study duration were excluded.[17,18]

The bi-daily administration of RUX 1.5% cream for 8 weeks resulted in substantial improvements in disease severity, pruritus, and sleep disruptions among patients with AD. At week 8, a markedly greater percentage of patients utilizing RUX attained the primary endpoint – successful response on the IGA – in comparison to the vehicle.[18] RUX cream has shown significant efficacy in attaining eczema area and severity index (EASI)-75, indicating a 75% enhancement from baseline in the EASI.[18,19] By week 52, 77.8% of 428 patients initially administered RUX and 74.1% of 96 patients who transitioned from vehicle to RUX at week 8 attained IGA scores of 0 (clean) or 1 (near clear). The mean affected BSA was 1.4% and 1.7%, respectively.[18] In patients using RUX throughout the 44-week extended duration including individuals who commenced therapy with RUX and those who transitioned from vehicle-maintained treatment- free intervals of 44% and 38% of the time, respectively, owing to lesion resolution. In a cohort of 63 patients who attained

Table 1: Off-label uses of RUX.

Disease	Population	Study type	Efficacy	Treatment duration and dose	Citation
Frontal fibrosing alopecia	Adult	Case report	RUX 1.5% cream effectively cleared face papules and resolved symptoms in addition to stabilizing the frontal hairline	3 months, once daily	Desai *et al.*[23]
Necrobiosis lipoidica	Adult	Case report	improvement in the color and size of plaque	3 months, twice daily application	Nugent *et al.*[24]
Lichen planus pigmentosus	Adult	Case report	Stabilization of hyperpigmentation and mild lightening of the affected area at 3 months with significant decrease in symptoms at 3 months	9 months, twice daily	Cornman *et al.*[25]
Cutaneous lupus erythematosus	Adult	Case report	Improvement in plaques with hair growth	2 months	Park *et al.*[26]
Alopecia areata	Pediatric	Case report	Complete resolution of lesions at 12 months	12 months, twice daily with fluocinonide 0.05% topical solution	Tembunde and Kindred[27]
Alopecia areata	Adult	Double-blind, randomized, vehicle-controlled phase 2 study	No significant difference on comparison to vehicle	48 weeks, twice daily	Olsen *et al.*[28]
Sarcoidosis	Adult	Case report	Complete resolution of the plaque in 6 weeks	6 weeks, twice daily	Smith *et al.*[29]
Prurigo nodularis	Adult	Phase 3, double-blind, randomized, vehicle-controlled	Ongoing study	40 weeks	Incyte Corporation©[30]
Lichen planus	Adult	A prospective, open-label study	Significant improvement in lesions and improvement in mean modified composite assessment of index lesion severity from week 4	12 weeks, twice daily	Brumfiel *et al.*[31]
Granuloma annulare	Adult	Case report	Compete resolution of lesions at 12 weeks	12 weeks, twice daily	Piontkowski *et al.*[32]

RUX: Ruxolitinib

clear skin (IGA 0) by week 8, the median duration until initial retreatment was 12 days.[18]

RUX 1.5% cream was well tolerated in patients aged 12 years and older with mild-to-moderate AD in the TRuE-AD1 and TRuE-AD2 trials. No safety signals indicative of systemic JAK inhibition were observed.[18] The most commonly reported adverse event was application site burning. Other treatment-emergent adverse effects included nasopharyngitis, headache, and upper respiratory tract infection. According to prescribing guidelines, RUX cream should be applied as a thin layer to affected areas twice daily, covering no more than 20% of total BSA, with a maximum of 60 g/week. Treatment should be discontinued once symptoms, such as itching, rash, and redness, have resolved. Patients who show no improvement within 8 weeks should be re-evaluated.[7]

Vitiligo

Vitiligo is a persistent autoimmune disorder characterized by a loss of epidermal melanocytes, resulting in depigmented white spots on the skin. JAK inhibitors have emerged as a new therapeutic alternative for non-segmental vitiligo. RUX 1.5% cream is the inaugural FDA-approved topical therapy for those aged 12 and older with non-segmental vitiligo. The effectiveness of RUX cream was assessed in two identical, multicenter, double-blind, vehicle-controlled phase III trials – TRuE-V1 and TRuE-V2. Eligible patients were those aged ≥12 years with non-segmental vitiligo impacting ≤10% of BSA, comprising at least 0.5% BSA on the face and ≥3% BSA on non-facial regions. The inclusion criteria mandated an F-VASI score of at least 0.5 and a total VASI value of no <3. Primary exclusion criteria encompassed total leukotrichia in facial lesions, coexisting dermatological conditions that might impede treatment, and recent administration of JAK inhibitors, biologics, experimental therapies (within 12 weeks), phototherapy (within 8 weeks), immunomodulators (within 4 weeks), or topical vitiligo treatments (within 1 week).[20] After 24 weeks, RUX cream resulted in markedly enhanced skin repigmentation compared to the vehicle. The primary endpoint – F-VASI75 (≥75% improvement in face depigmentation) – was attained at a markedly greater rate in the RUX group (P<0.001), with a fourfold increased probability of achieving F-VASI75 compared to the vehicle group.[20]

Pooled analysis from the TRuE-V1 and TRuE-V2 trials showed that patients using RUX cream achieved significantly higher rates of F-VASI50, F-VASI90, T-VASI50, and Vitiligo Noticeability Scale (VNS) responses at week 24 compared to vehicle (P<0.0001).[21,22] While overall health-related quality of life was similar between the two groups, treatment satisfaction was significantly higher in the RUX cream group at week 24 (P<0.05).[21,22] At week 52, pooled long-term follow-up data showed that F-VASI, T-VASI, and VNS responses were either sustained or improved compared to week 24.

The most commonly reported treatment-related adverse events were application-site acne and pruritus.[13-32]

The recommended dosage is a thin layer of RUX cream applied twice daily (at least 8 hours apart) to depigmented areas, avoiding the lips to prevent ingestion. The application should not exceed 10% of the total BSA – roughly the size of ten handprints.[7] Usage should not exceed one 60 g tube/week or two 100 g tubes/month, depending on the treated body area.[9] While some patients may require treatment beyond 24 weeks, discontinuation should be considered if <25% repigmentation is observed after 52 weeks.[7-9]

Off-label uses

RUX 1.5% cream has been used in a variety of dermatological conditions. A summary of all the off-label uses of RUX 1.5% cream in dermatology has been summarized in Table 1.

CONCLUSION

Originally developed for myelofibrosis, RUX 1.5% cream has since demonstrated effectiveness in a range of skin disorders. Based on strong clinical trial outcomes, the FDA has approved its use for AD and non-segmental vitiligo. As a potent JAK1 and JAK2 inhibitor with a favorable safety profile and strong anti-pruritic effects, RUX has significantly reduced the symptoms and severity of AD. Preliminary research also suggests a beneficial impact on the atopic skin microbiome, though further studies are needed to confirm this.

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Declaration of patient consent: Patient's consent is not required as there are no patients in this study.

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