

Topical Ruxolitinib for Alopecia Areata: Current Evidence and Future Perspectives

Soheir Ghonemy, Mariam Ibrahim Abdelmonem Elsherbiny*

Dermatology, Venereology and Andrology Department, Faculty of Medicine, Zagazig University, Egypt

*Corresponding author: Mariam Ibrahim Abdelmonem Elsherbiny

Email: mariam.elsherbeny.6@gmail.com,

Abstract:

Alopecia areata (AA) is an immune-mediated, non-scarring hair-loss disorder in which dysregulation of the JAK–STAT pathway plays an important role in follicular inflammation. Ruxolitinib is a selective Janus kinase 1/2 (JAK1/JAK2) inhibitor that suppresses key inflammatory signaling pathways, particularly interferon- γ and interleukin-15, thereby reducing T-cell activation and helping restore hair-follicle immune privilege. Topical ruxolitinib 1.5% cream has been developed to provide targeted local immunomodulation while minimizing the systemic adverse effects associated with oral JAK inhibitors. Its topical formulation achieves low systemic exposure while enhancing drug delivery through the skin toward affected follicles. In alopecia areata, topical JAK inhibitors may be beneficial particularly in localized patchy disease, although reported clinical responses remain variable because adequate drug penetration to the deep hair bulb can be limited. Dermoscopic evaluation is useful for objectively monitoring treatment response through changes in disease-activity markers, such as black dots, and the appearance of signs of follicular recovery. Therefore, clinical and dermoscopic assessment of topical ruxolitinib may provide valuable information regarding its efficacy, response pattern, and potential role in the treatment of patchy AA.

Keywords: Alopecia areata; Ruxolitinib; Topical ruxolitinib; JAK inhibitors; JAK–STAT pathway; Dermoscopy; Trichoscopy; Hair regrowth.

Introduction:

Ruxolitinib is a potent, a targeted JAK1/JAK2 inhibitor initially developed and approved for hematologic and immune-mediated conditions, including myelofibrosis, polycythemia vera, and steroid-refractory graft-versus-host disease (GVHD) (1,2), receiving sequential FDA and EMA approvals between 2011 and 2022 (3). It is uniquely available in both systemic and topical formulations (4,5).

Systemically, oral ruxolitinib exhibits rapid absorption (Time to maximum plasma concentration (T_{max}) 1–2 hours), high oral bioavailability (~95%), a 3- to 6-hour elimination half-life, and steady-state kinetics within 4 days of twice-daily dosing (6). It is highly protein-bound (~97%, primarily albumin) and undergoes hepatic metabolism via CYP3A4 with renal excretion, necessitating dose adjustments in hepatic or renal impairment (1,7).

Advancing this molecule, the US FDA approved its deuterated oral analog, deuruxolitinib (Leqselvi™), in July 2024 for severe AA ($\geq 50\%$ scalp hair loss). Deuteration—substituting hydrogen with deuterium—reduces CYP3A4 metabolic clearance without altering target affinity, enabling twice-daily 8 mg dosing (8).

Mechanism of Action

Ruxolitinib is a potent, selective JAK1/2 inhibitor acting via the JAK–STAT signaling pathway. It targets Type 2 inflammatory cytokines (IL-4, IL-13, IL-31, TSLP) in atopic conditions, its therapeutic efficacy in AA primarily derives from blocking IFN- γ and IL-15 signaling, thereby halting T-cell activation and restoring HFIP (9).

Recent evidence highlights a novel "triple-mechanism effect" of ruxolitinib in AA: (1) targeted JAK–STAT pathway inhibition, (2) reduction of localized OS (evidenced by decreased malondialdehyde [MDA] levels), and (3) modulation of keratinocyte apoptosis, collectively disrupting the self-amplifying autoimmune cascade driving follicular injury (10). The cellular mechanisms underlying this therapeutic approach, along with

the specific targets of approved and investigational JAKi within intracellular signaling pathways, are summarized in **Figure 1**.

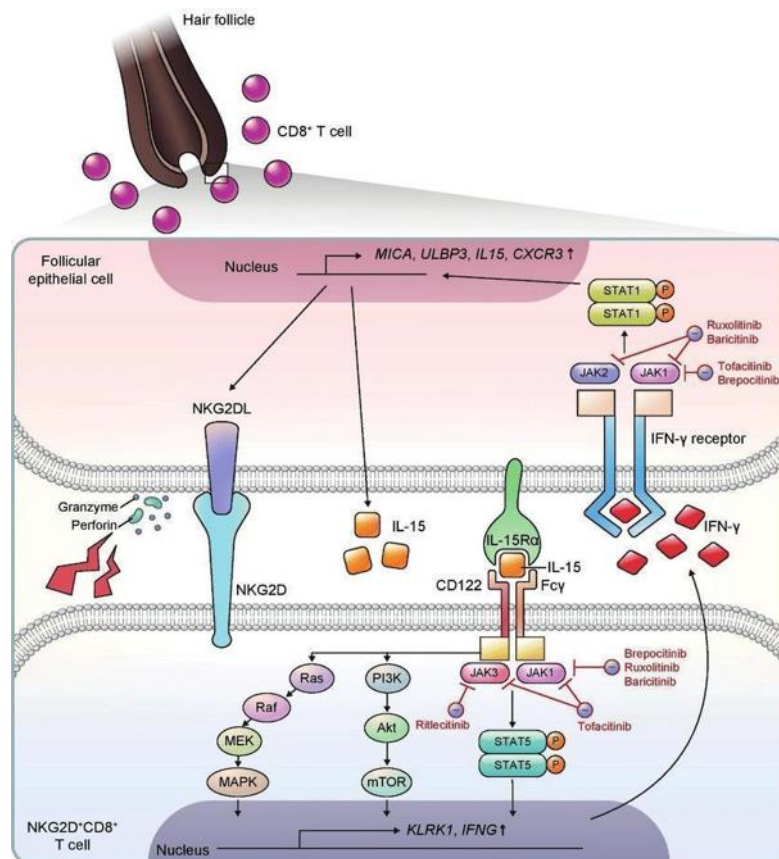


Figure 1: JAK Inhibitors and the JAK-STAT Pathway in AA. The figure demonstrates how activation of IFN- γ and IL-15 receptors triggers several intracellular signaling pathways, including Ras-Raf-MEK-MAPK, PI3K-Akt-mTOR, and JAK-STAT pathways, leading to increased expression of inflammatory markers involved in AA pathogenesis. It also highlights the targets of different JAKi: Baricitinib and Ruxolitinib block JAK1/JAK2; Brepocitinib targets JAK1; Tofacitinib block JAK1/JAK3; and Ritlecitinib selectively inhibits JAK3/TEC family kinases. (11).

Topical Formulation (1.5% Cream)

Topical ruxolitinib represents a pivotal shift in modern dermatology, engineered to deliver targeted local immunomodulation within inflamed cutaneous tissues while minimizing systemic toxicity. Following twice-daily application of ruxolitinib 1.5% cream (Opzelura), plasma concentrations remain minimal and stay well below safety thresholds associated with oral JAKi therapy (7). Furthermore, this 1.5% formulation optimizes cutaneous bioavailability, enhancing drug penetration through the stratum corneum to reach hair follicles (12).

Currently, topical ruxolitinib holds FDA approvals for mild-to-moderate atopic dermatitis and nonsegmental vitiligo (13), with off-label application across various T-cell-mediated and granulomatous skin disorders—including lichen planus, morphea, and cutaneous sarcoidosis—(14).

In AA, topical JAKi show benefits in localized patches, eyebrows, and eyelashes. However, clinical trial outcomes vary: phase 2 trials demonstrated initial open-label responses (50%) but failed to show statistically significant differences versus vehicle in randomized phases. This discrepancy is largely driven by restricted transdermal penetration to the deep hair bulb as well as variations in disease chronicity (15,16).

Consequently, while topical ruxolitinib rapidly suppresses acute perifollicular inflammation—achieving marked clearance of active dermoscopic markers such as black dots—volumetric hair regrowth remains moderate

relative to oral formulations (17). Lacking formal FDA approval for AA, topical ruxolitinib is currently positioned as an off-label targeted option for localized patches or post-systemic maintenance therapy (18).

Safety Profile

Systemic oral JAKi therapy carries notable risks, including upper respiratory infections (17.2%), acneiform eruptions, hyperlipidemia, cytopenias (requiring treatment pause if platelet counts drop below $50 \times 10^9/L$), and CYP3A4 drug interactions (19). Consequently, baseline monitoring requires CBC, LFTs, lipid panels, and infection screening (e.g., tuberculosis and hepatitis) alongside underlying malignancies. Furthermore, mandatory dosage adjustments are indicated in patients with moderate-to-severe renal or hepatic impairment (6).

In contrast, topical ruxolitinib 1.5% cream avoids systemic toxicity, illustrating the "Boxed Warning Paradox" (20). This concept highlights the discrepancy between FDA class-wide boxed warnings for oral JAKis (major adverse cardiovascular events (MACE), malignancies, thromboembolism) and the localized safety of topical application. Topical ruxolitinib 1.5% cream maintains steady-state plasma levels well below the toxicity threshold (281 nM), avoids bone marrow suppression or QT interval prolongation, and requires no routine lab monitoring (20,21).

Conclusion

Topical ruxolitinib offers a targeted option for inflammatory skin disorders, avoiding the systemic toxicities associated with oral JAKi therapy. However, therapeutic efficacy in AA remains variable, primarily constrained by insufficient percutaneous penetration to deep hair follicles, alongside inconsistencies in dosing schedules and vehicle concentrations. Furthermore, most clinical evaluations are limited by short follow-up durations ranging from 4 weeks to 2 years (17). Future investigations should prioritize optimizing vehicles for enhanced transfollicular delivery, establishing standardized clinical protocols, and evaluating topical ruxolitinib as an alternative for refractory AA or as a post-systemic maintenance regimen (22).

References:

1. Mesa, R.A., Gotlib, J. and Gupta, V., 2021. Ruxolitinib in hematologic malignancies: Mechanism of action, clinical pharmacology, and dosage adjustments in renal and hepatic impairment. *Journal of Hematology & Oncology*, 14(1), pp.42–55.
2. Harrison, C.N., Kiladjian, J.J. and Vannucchi, A.M., 2023. Efficacy and long-term safety of JAK inhibitors in myeloproliferative neoplasms and steroid-refractory graft-versus-host disease. *Blood Reviews*, 58, p.101015.
3. Passamonti, F., Palandri, F. and Barbui, T., 2024. Evolution of JAK inhibitor approvals in Europe and the US: A decade of clinical translational medicine. *The Lancet Haematology*, 11(2), pp.e145–e154.
4. Samuel, C., Cornman, H., Kambala, A. and Kwatra, S.G., 2023. A review on the safety of using JAK inhibitors in dermatology: Clinical and laboratory monitoring. *Dermatology and Therapy*, 13(3), pp.729–749.
5. Incyte Corporation, 2023. *Jakafi (ruxolitinib) Prescribing Information*. Wilmington, DE: Incyte Corporation.
6. Gong, X., Zhang, Y. and Liu, Z., 2023. Pharmacokinetic characteristics, clinical safety, and adverse event profiles of oral ruxolitinib: A comprehensive meta-analysis. *Frontiers in Pharmacology*, 14, p.1084210.
7. Sun Pharmaceutical Industries, 2024. *Leqselvi (deuruxolitinib) Prescribing Information*. Silver Spring, MD: U.S. Food and Drug Administration.
8. Xing, L., Dai, Z., Jabbari, A., Cerise, J.E., Higgins, C.A., Gong, W., de Jong, A., Christensen, B.J., Farber, G.M., Gelb, B.E., Christiano, A.M. and Clynes, R., 2014. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. *Nature Medicine*, 20(9), pp.1043–1049.
9. Song, A., Lee, S.E. and Kim, J.H., 2022. Immunopathology and immunotherapy of inflammatory skin

diseases. *Immune Network*, 22(1), p.e7.

10. Rosmarin, D., Passeron, T., Pandya, A.G., Grimes, P., Harris, J.E., Desai, S.R., Lebwohl, M., Ruer-Mulard, M., Seneschal, J., Zdybski, J., Bissonnette, R., Stein Gold, L., Papp, K., Venturanza, M.E., Sun, K., Butler, K. and Hamzavi, I.H., 2022. Two Phase 3 trials of ruxolitinib cream for vitiligo. *The New England Journal of Medicine*, 387(16), pp.1445–1455.
11. Hosking, A.M., Juhasz, M. and Mesinkovska, N.A., 2018. Topical Janus kinase inhibitors: a review of applications in dermatology. *Journal of the American Academy of Dermatology*, 79(3), pp.535–544.
12. Mackay-Wiggan, J., Jabbari, A., Nguyen, N., Bizjak, B., Merola, J.F., Shapiro, J., Cline, A., Gong, Z., Christiano, A.M., Hordinsky, M. and Olsen, E., 2020. Ruxolitinib cream for the treatment of patients with alopecia areata: A 2-part, double-blind, randomized, vehicle-controlled phase 2 study. *Journal of the American Academy of Dermatology*, 82(2), pp.412–419.
13. Tembunde, Y. and Kindred, C., 2024. Ruxolitinib 1.5% topical cream for the treatment of alopecia areata. *Journal of Drugs in Dermatology*, 23(5), pp.378–382.
14. King, B.A., Senna, M.M., Ohyama, M., Tosti, A., Sinclair, R.D., Ball, S., et al., 2022. Defining severity in alopecia areata: current perspectives and a multidimensional framework. *Dermatology and Therapy*, 12(3), pp.825–834. doi: 10.1007/s13555-022-00711-3.
15. Punwani, N., Yeleswaram, S., Chen, X., Bowman, J., Soloviev, M. and Williams, W., 2014. Evaluation of the effect of ruxolitinib on cardiac repolarization: A thorough QT study. *Clinical Pharmacology in Drug Development*, 3(3), pp.207–214.