Topical Ruxolitinib for Treatment of Non-segmental Vitiligo

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Background:

Ruxolitinib, a selective Janus kinase (JAK) 1 and 2 inhibitor, has emerged as a novel targeted therapy for vitiligo based on advances in understanding its immunopathogenesis. Vitiligo is driven by interferon-γ (IFN-γ)–mediated activation of the JAK–STAT signaling pathway, which promotes recruitment of autoreactive $CD8^+$ T cells and subsequent melanocyte destruction. By inhibiting JAK1/2 activity, ruxolitinib effectively blocks downstream cytokine signaling, disrupts this autoimmune cascade, and creates a local environment conducive to melanocyte survival and repigmentation. Topical ruxolitinib 1.5% cream has shown promising results in clinical trials, notably the phase 3 TRuE-V1 and TRuE-V2 studies, demonstrating significant repigmentation and improved patient-reported outcomes compared with vehicle. Its favorable safety profile, minimal systemic absorption, and potential synergy with phototherapy make it a major advance in vitiligo management.

Introduction:

Ruxolitinib is a selective inhibitor of JAK1 and JAK2. Its topical formulation has recently been approved by FDA for the treatment of nonsegmental vitiligo in patients over the age of 12, based on findings from clinical studies **(Brumfiel C.M. *et al.*, 2022).**

On 23 February 2023, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending marketing authorization of 1.5% ruxolitinib cream for the treatment of non-segmental vitiligo **(Tavoletti G. *et al.*, 2023)**.

Mechanism of action:

JAK inhibitor designed to target IFN-γ and IL-15 signaling pathways. Ruxolitinib appears to be selective for JAK1 and 2 according to the half

maximal inhibitory concentration (IC50); however, it is considered as a pan-JAKinh that can inhibit all JAKs at low concentrations **(Sheikh et al., 2022).**

Although the exact mechanism of action of ruxolitinib cream in treating vitiligo remains unclear, studies on mice and human tissues suggest that, beyond blocking IFN-γ and JAK signaling, ruxolitinib also inhibits the differentiation and migration of human dendritic cells (DCs) ex vivo. This suppression reduces DC-induced antigen-specific CD4+ and CD8+ T cell responses, as well as the activation of CD8+ cytotoxic T cells, which are believed to play a crucial role in the pathogenesis of vitiligo **(Heine et al., 2013, Vannucchi et al., 2015).**

Also**, Rosmarin et al. (2020)** revealed that ruxolitinib cream (1.5% concentration) therapy may lower blood CXCL10 levels, which may impact CD8+ T cells. A recovery in the quantity and functionality of melanocytes may result from the anticipated decrease in T cell migration to the skin and the associated decrease in inflammatory mediators, which would be beneficial for repigmentation.

Due to wide variations of vitiligo clinical course, including the onset, expansion, persistence and resolution (re-pigmentation) phases, the use of phosphorylate transcription factor signal transducers and activators of transcription (STATs), after stimulation cytokines/growth factors receptors, thereby modifies signals for gene expressions associated with pathological conditions **(Murray, 2007).**

Ruxolitinib interferes with the STAT pathway, which is involved in the signaling of over 60 inflammatory cytokines related to immune function, including growth factors, interferons, and interleukins (IL) **(Howell et al., 2019).**

Pharmacotherapeutics:

Ruxolitinib cream is prescribed as a thin layer that should be applied twice a day to vitiligo patches that make up to 10% of the total surface area in vitiligo treatment. This formulation was previously approved for the topical short-term, non-continuous chronic treatment of mild to moderate atopic dermatitis. Also, researches indicates that it may be useful in the treatment of psoriasis and cutaneous lichen planus **(Brumfiel et al., 2022).**

Dependent on body region, patients should not use more than one 60 g tube per week or two 100 g tubes per month. Patients may require treatment for longer than 24 weeks; however, discontinuing ruxolitinib cream should be considered in the EU and UK if less than 25% repigmentation is achieved in the affected areas after 52 weeks of treatment **(Kang, 2024).**

Pharmacokinetics

The mean topical bioavailability of ruxolitinib was 9.7%. In vitro studies indicate that ruxolitinib is 97% bound to plasma proteins, primarily albumin. The mean elimination half-life of topical ruxolitinib was approximately 3 hours **(Kang, 2024)**

According to research compared topical administration of ruxolitnib with systemic use, topical treatment effectively reaches the skin while sparing other organs. Moreover, the steady-state epidermal concentration of ruxolitinib following topical administration was nearly 2000 times higher than that following oral administration, while the plasma concentration was only about one-thirteenth **(Persaud et al., 2020).**

Ruxolitinib is primarily metabolized by the cytochrome P450 (CYP3A4) enzyme and serves as its substrate. As a result, inhibitors of CYP3A4 can elevate systemic ruxolitinib levels, increasing the risk of adverse effects, while inducers of CYP3A4 can reduce its concentration, potentially diminishing its therapeutic efficacy **(Kang, 2024).**

Side effects:

There were just a few mild side effects noted, including acne, erythema, and a ring of hyperpigmentation around the vitiligo patches **(Rothstein et al., 2017).**

Topical ruxolitinib carries special warnings in the USA for major adverse cardiovascular events (MACE), blood clots, serious infections, cancer, and even death (associated with the use of oral JAK inhibitors), although low incidence rates have reported in clinical trials for these adverse events **(Kang, 2024).**

Ruxolitinib was examined in a comprehensive series of genotoxicity tests, which showed no signs of genotoxic potential in assays for rat bone marrow micronucleus, in vitro chromosomal aberration, and bacterial mutagenicity. When 1.5% ruxolitinib cream is applied at a dose of 100 μL per day, carcinogenicity investigations on mice have not reported any significant drug-related toxicity or tumors **(Tavoletti et al., 2023).**

Contraindication:

Due to lack of data, ruxolitinib cream is contraindicated during pregnancy in the EU and UK, and patients are advised to use effective contraception throughout treatment and for four weeks after discontinuation. In contrast, no recommendation has been made in the USA regarding use in pregnancy. Additionally, breastfeeding should be avoided during treatment and for approximately four weeks after the last dose. Ruxolitinib cream is also not recommended for patients with kidney failure **(Kang, 2024).**

Conclusion:

Topical ruxolitinib 1.5% cream offers a targeted and effective therapeutic approach for non-segmental vitiligo by inhibiting the JAK1/2–STAT pathway and interrupting IFN-γ–mediated immune signaling. Clinical evidence demonstrates meaningful repigmentation with an excellent safety profile and minimal systemic exposure and few adverse effects. Continued research is warranted to optimize treatment protocols, assess long-term durability, and explore combination strategies for enhanced and sustained outcomes.

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