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 ORIGINAL ARTICLE

Ruxolitinib 1.5% Cream and the "Boxed Warning Paradox": Reappraisal of Safety Through the Lens of Pharmacokinetics

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ABSTRACT

Ruxolitinib 1.5% cream is the first-in-class topical Janus kinase (JAK) inhibitor approved for the treatment of atopic dermatitis in patients 12 years of age and older. The US Food and Drug Administration (FDA) issued a "boxed warning" for ruxolitinib cream, cautioning about increased risks of serious infections, malignancies, blood clots, and cardiovascular events because it is a JAK inhibitor. Despite clinical trials and real-world data demonstrating the safety of ruxolitinib cream, the boxed warning remains in place, even though oral ruxolitinib—known for its significantly higher bioavailability and plasma concentration—has not been assigned this warning. As a result, this warning has caused hesitation in its use and has been a barrier to the broader, appropriate adoption of ruxolitinib cream despite its strong recommendation for use in atopic dermatitis (AD) by the American Academy of Dermatology in 2023. Here, we provide an in-depth overview of in vivo and ex vivo pharmacokinetic (PK) data from studies in minipigs and human cadaver skin, along with human PK data from pediatric and adult atopic dermatitis (AD) patients aged 2 years and older, as well as safety data from both clinical trials and real-world studies in AD patients. Together, this data reinforces the safety of topical ruxolitinib and reassures clinicians that they can utilize this medication in everyday practice.

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INTRODUCTION

Janus kinase (JAK) proteins are key, evolutionarily conserved mediators of external-to-internal cellular signaling, activated when external cytokines bind to their respective transmembrane receptors, triggering phosphorylation of JAK proteins, then STAT proteins, inside the cell. Dysregulated signaling through JAK1 and JAK2 has been implicated in various inflammatory-driven cutaneous conditions, including atopic dermatitis (AD) and vitiligo.[1] Both topical and oral JAK inhibitors have been developed and continue to be explored for these diseases, aiming to modulate these crucial immune pathways. Oral JAK inhibitors offer systemic control for more severe cases, while topical formulations provide localized treatment with minimal systemic absorption, reducing the potential for side effects.

All JAK kinase domain inhibitors used for treating chronic inflammatory conditions have received a "boxed warning." The boxed warning encompasses 4 safety risk categories: (1) serious infections, (2) malignancies, (3) major adverse cardiovascular events (MACE), and (4) thromboembolic events (ie, deep vein thrombosis (DVT), pulmonary emboli (PE), and arterial thrombosis).[2]This warning was derived from the Oral Surveillance study, a post-marketing trial evaluating tofacitinib in rheumatoid arthritis patients 50 years of age and older and at least one additional cardiovascular risk factor,, with concomitant methotrexate use, which revealed increased risks of MACE, malignancies, and death compared to tumor necrosis factor (TNF) inhibitors.[3] These findings prompted the FDA to extend its boxed warning to all JAK inhibitors with a similar mechanism of action to tofacitinib,

which preferentially inhibits JAK-1/3 as well as JAK-2 to a lesser extent.[4] Of note, the boxed warning does not apply to JAK inhibitors used for the treatment of non-inflammatory conditions (eg, oral ruxolitinib for myelofibrosis).[5]

In 2023, the American Academy of Dermatology (AAD) presented updated guidelines for the topical treatment of atopic dermatitis and strongly recommended the use of topical JAK inhibitors, such as ruxolitinib cream, for appropriate patients, acknowledging their efficacy in reducing inflammation and symptoms.[6] Despite this endorsement, concerns surrounding the FDA-imposed boxed warning on JAK inhibitors have led to cautious use, even though the risks from topical formulations are considered lower.

Ruxolitinib 1.5% cream is the first FDA-approved topical JAK inhibitor, indicated for the short-term and intermittent chronic treatment of mild-to-moderate atopic dermatitis in patients aged 12 and older with up to 20% body surface area (BSA) involvement. It is also approved for nonsegmental vitiligo in patients 12 years and older, with affected BSA of up to 10%, marking a significant advancement in the management of these conditions by offering a targeted, localized, and effective therapy with minimal systemic absorption.[7] Despite its topical formulation, ruxolitinib cream carries the boxed warning, which has led to hesitation among clinicians and their patients, creating a barrier to its broader, appropriate use. Here, we present a comprehensive analysis of the available pharmacokinetic and safety data for ruxolitinib cream, focusing on its safety profile in the context of AD, where absorption may be greater due to altered skin barrier integrity. We explore findings from clinical trials and real-world studies that assess plasma concentrations, adverse events, and overall patient outcomes, aiming to clarify the risk-benefit profile of ruxolitinib cream. Our goal is to provide clinicians with the necessary information to make informed treatment decisions and to encourage the appropriate use of this innovative therapy in managing atopic dermatitis.

In Vivo and Ex Vivo Pharmacokinetic Characterization of Ruxolitinib Cream

Ruxolitinib cream has been uniquely formulated to concentrate in the skin while minimizing systemic absorption. A preclinical in vivo study utilizing minipigs compared the plasma concentrations and distribution of ruxolitinib following topical administration (1.5% cream applied to 10% BSA twice daily) vs oral dosing (40 mg/kg ingested twice daily) over a 4-day period.[8] The oral dosing regimen of 40 mg/kg achieves steady-state plasma concentration levels similarly to human oral dosing of 10 to 15 mg twice daily in clinical trials.[9] Plasma concentrations were measured over a 24-hour period post-dose. Minipigs treated with oral ruxolitinib had approximately 38-fold higher average plasma concentration (C_{max}) than those treated topically (153 ± 173 nM and 3.98 ± 3.5 nM, respectively). When evaluating overall drug exposure, as measured by the area under the concentration vs time curve (AUC), the orally dosed group exhibited about 30-fold greater average exposure compared to the topically treated group. Furthermore, average daily plasma concentrations were also 30-fold higher in the orally treated group (88.34 ± 87.79 nM vs 2.88 ± 1.95 nM, respectively). Importantly, the ex vivo half-maximal inhibitory concentration (IC50) of thrombopoietin-stimulated phosphorylation of STAT3 in human whole blood is 281 nM, underscoring the relevance of these pharmacokinetic findings relating to safety.[10]

Concentrations of ruxolitinib were assessed in the epidermis and dermis of minipig skin using liquid chromatography-tandem mass spectrometry (LC/MS/MS) after the separation of these skin layers. At 74 hours post the first daily dose, the epidermal concentrations of ruxolitinib were measured at 0.57 ± 0.21 μM for the orally treated group and 1249.00 ± 495.81 μM for the topically treated group. When averaged over all time points, topical administration resulted in a 1989-fold higher total epidermal concentration compared to oral administration. A similar trend was observed in dermal concentrations; at the 74-hour mark, orally dosed minipigs

showed total dermal concentrations of 0.19 ± 0.08 μM, while those receiving topical treatment had concentrations of 66.40 ± 26.21 μM. Averaging these values across all time points revealed that topical ruxolitinib administration achieved a 507-fold higher total dermal concentration compared to oral administration.

Ruxolitinib cream formulations (1.0%, 1.5%, and 2.0%) were also evaluated in a cutaneous transport experiment using ex vivo human cadaver skin. After applying 20 mg of cream (corresponding to 200 μg, 300 μg, and 400 μg of ruxolitinib, respectively), only 0.09%, 0.10%, and 0.07% of the applied dose permeated the dermis after 24 hours. This indicates that the flux of ruxolitinib across the skin is limited. Moreover, this permeation is independent of the ruxolitinib concentration in cream, as less than 1% of the applied dose was found to permeate human cadaver skin after 24 hours across all tested concentrations.

Human Safety of Ruxolitinib Cream in Atopic Dermatitis

Ruxolitinib 1.5% cream applied twice daily is overall well tolerated with unremarkable safety concerns. An open-label maximum-use trial assessed the plasma concentration of ruxolitinib in subjects aged >= 12 to a 1-year post-marketing safety analysis of real-world use of ruxolitinib 1.5% cream (queried from the Incyte global safety database up to 30 September 2022), a total of 294 individual case safety reports (ICSRs) were identified out of an estimated 13,833 patient-years of treatment.[23] The majority of ICSRs were spontaneous, and consumer reported. VTE

65 years, AD disease severity IGA >= 2, and >= 25% affected BSA (average of 37.5% BSA, range 25.0-90.0%).[11] The mean steady-state plasma concentration remained consistently below the level expected (5-fold lower) to cause bone marrow suppression (expected IC50 = 281 nM). Of note, the mean daily application amount of ruxolitinib 1.5% cream here is 3.7-fold higher than in the phase 3 trials which only included subjects with affected BSA <= 20%. Furthermore, in the phase 3 and LTS trials, the mean ruxolitinib steady-state plasma concentrations (C_{ss}) were also consistently below that required to cause myelosuppression.[12,13]

The safety profile of ruxolitinib 1.5% cream (applied to up to 20% affected BSA) was found to be comparable to that of the vehicle in phase 3, 8-week, vehicle-controlled trials.[14] Application site reactions occurred more frequently in the vehicle group (4.4%) than in the ruxolitinib group (0.8%). No serious treatment-emergent AEs were considered related to treatment, and discontinuation rates were less frequent in the ruxolitinib treatment group. There were no reported cases of serious infections, malignancies, MACE, or thrombosis during the 8-week vehicle-controlled trials. Additionally, no specific pattern of changes was observed in hematologic laboratory patterns. With respect to the head and neck region, subjects who applied ruxolitinib cream experienced less frequent (<3%) and mild application site reactions compared to vehicle, and did not experience treatment discontinuations.[15] The safety profile of ruxolitinib cream in systemic-worthy AD subjects (defined as IGA = 3, EASI >= 16, BSA >= 10%) was also consistent with the overall study population.[16]There were no discontinuations as a result of a treatment-emergent adverse event, and no notable infections, MACE, malignancy, or thromboses were reported in this subgroup. Moreover, in an open-label interventional study using ruxolitinib 1.5% cream for the treatment of recalcitrant moderate-to-severe chronic hand dermatitis, no treatment-related adverse events were noted.[17]

Adverse events (AEs) of special interest were infrequent during the LTS period (52 weeks), with none considered to be related to as-needed treatment with ruxolitinib cream.[18] There were no discontinuations due to an AE, and application site reactions were also infrequent. Two cases of acne were reported among all subjects who applied ruxolitinib cream; both cases were mild-to-moderate in severity and resolved spontaneously without the need for treatment interruption. A total of 5 serious infections were noted (pneumonia, n=4; sepsis, n=1), but all resolved, and no patients discontinued. Eight events of herpes zoster were noted but not observed at application sites. Six malignancies were reported (basal cell carcinoma, n = 2; squamous cell carcinoma, n = 4 [1 patient had both basal and squamous cell carcinoma]; renal cell cancer, n = 1); the non-melanoma skin cancers did not occur at sites of ruxolitinib cream application. A total of 3 MACE events occurred (myocardial infarction, n =1; cerebrovascular accident, n=2) in patients with known hypertension and other cardiovascular risk factors. Three thromboembolic events (DVT, n=1; PE, n=2) occurred in 2 patients with known risk factors as well. Incidence rates of these AEs of special interest were infrequent and consistent with expected rates among patients with AD.[19-21] Regarding hematologic AEs, neutropenia was reported in 2 patients (1 with ruxolitinib plasma concentration below the quantifiable limit and the other with 56.5 nM at week 12) and were nonserious.[12] Neither case required treatment interruption. Moreover, there were no significant trends in laboratory parameters indicative of anemia, thrombocytopenia, or neutropenia across all patients. Fluctuations in lipid or liver enzyme elevations were infrequent, considered minor, and deemed clinically irrelevant. Ruxolitinib plasma concentrations at steady state observed prior to the occurrence of HZ, MACE, thrombosis, and NMSC were similar to or lower than those recorded in the VC period, and all remained significantly below the 281 nM threshold, which represents the IC50 for thrombopoietin-stimulated STAT3 activation. Furthermore, no correlations were found between ruxolitinib plasma concentrations and decreases in hemoglobin levels, absolute neutrophil count, mean platelet volume, or platelet counts.

In the pediatric population, a phase 1, open-label, age-descending study was conducted to assess the safety and pharmacokinetics of ruxolitinib cream in subjects aged 2 to 17 years with mild to severe atopic dermatitis (IGA ≥ 2) affecting 8-20% of body surface area (excluding the scalp). Participants received various dosages applied twice daily for 28 days.[22] Average steady-state plasma concentrations of ruxolitinib were low, ranging from 23.1 nM to 97.9 nM, which were significantly lower than the levels observed after administration of oral ruxolitinib at 15 mg twice daily (226 nM) and below the IC50 for thrombopoietin-stimulated phosphorylation of STAT3 in human whole blood (281 nM). Furthermore, mean steady-state plasma concentrations across cohorts were comparable to those found in adolescent and adult patients in the TRuE-AD trials, with values of 23.8 nM and 35.7 nM for the 0.75% and 1.5% cream, respectively. Although 4 of the 71 patients reported headaches, these were deemed unlikely to be related to the study treatment. There were no observed patterns in changes to serum bone biomarker levels, suggesting no impact on bone formation or metabolism. Ruxolitinib plasma concentrations remained generally low and did not show a proportionate increase with higher concentrations of the cream, consistent with prior pharmacokinetic studies in minipigs. Additionally, no significant effects on mean blood cell counts were noted.

In a 1-year post-marketing safety analysis of real-world use of ruxolitinib 1.5% cream (queried from the Incyte global safety database up to September 30, 2022), a total of 294 individual case safety reports (ICSRs) were identified out of an estimated 13,833 patient-years of treatment.[23]The majority of ICSRs were spontaneous and reported by consumers. The most frequently (>2%) reported AEs were application site pain, atopic dermatitis, skin irritation, scratch, and 'condition aggravated' (lack of improvement or worsening of the underlying condition for which the patient was being treated). Only 4 serious AEs were reported: 'skin cancer' (n=2), pericarditis (n=1), and thrombocytopenia (n=1). However, there was insufficient information to conclude whether these serious AEs were related to ruxolitinib cream. With respect to AEs of special interest, there were 2 events of 'skin cancer' as mentioned. There were no cases of serious infections, MACE, thromboembolic events, lymphoma, or other malignancies.

DISCUSSION

The JAK inhibitor boxed warning in chronic inflammatory conditions stems from the findings of the Oral Surveillance study, which evaluated the safety of oral tofacitinib in patients with rheumatoid arthritis, concomitantly receiving methotrexate, who were also at higher risk for cardiovascular events.[3] The study found that patients taking tofacitinib had a significantly increased risk of MACE, including myocardial infarctions and strokes, as well as higher incidences of malignancies such as lung cancer and lymphoma, compared to those on tumor necrosis factor (TNF) inhibitors. In response, the FDA applied this warning to the entire class of JAK inhibitors, citing a class effect, and emphasized the importance of assessing these risks, particularly in older patients who have a history of smoking or have other cardiovascular or malignancy risk factors.

While rheumatologic and dermatologic diseases exhibit significant differences in their co-morbidity risk profiles, there remains a substantial knowledge gap regarding the safety of JAK inhibitors in dermatologic populations, particularly across various age groups. For example, the lower observed risks of MACE and VTEs in pooled safety analyses may be attributed to the younger, healthier patients enrolled in clinical trials for dermatologic indications such as atopic dermatitis.[24] Daniele and Bunick evaluated the incidence of these adverse events of special interest for JAK inhibitors compared to traditional systemic therapies (e.g., oral corticosteroids, methotrexate, cyclosporine) and found that the use of upadacitinib and abrocitinib was associated with either comparable or lower rates of malignancy (excluding non-melanoma skin cancer), MACE, and VTE relative to baseline incidence rates in atopic dermatitis and control populations.[25] Furthermore, a meta-analysis of phase 3 dermatology randomized clinical trials indicated that short-term use of JAK inhibitors (less than 5 months) for dermatologic indications is unlikely to be associated with an increased risk of all-cause mortality, MACE, or VTE.[24] This meta-analysis included data from 4 phase 3 trials assessing ruxolitinib cream in the contexts of atopic dermatitis and vitiligo.[14,26]

Ruxolitinib cream is specifically formulated to concentrate within the skin layers (epidermis and dermis) while minimizing systemic absorption. This targeted delivery system has been demonstrated in preclinical studies using minipigs, which compared the effects of topical application to those of oral dosing, as well as in ex vivo studies with human cadaveric skin. Pharmacokinetic (PK) studies in both minipigs and human patients with atopic dermatitis, including children aged 2 years and older and covering a wide range of affected BSA, consistently showed plasma concentrations well below the IC50 required to inhibit thrombopoietin-stimulated STAT3 phosphorylation in human whole blood—a surrogate marker for myelosuppression.[27] Additionally, safety assessments from numerous clinical trials and real-world studies have consistently confirmed the safety of ruxolitinib cream across various age groups and anatomical sites (eg, head/neck, hands), with low discontinuation rates and minimal, mild, and transient changes in clinical laboratory parameters. Moreover, AEs of special interest noted in the LTS were considered unrelated to ruxolitinib cream. These findings further support the favorable safety profile of ruxolitinib cream.

The American Academy of Dermatology's 2023 guidelines for atopic dermatitis strongly recommend the use of topical JAK inhibitors. However, the existing boxed warning creates a skewed perception of safety, which may hinder the appropriate utilization of topical agents like ruxolitinib cream. Therefore, clinicians must critically reassess the "boxed warning paradox" surrounding ruxolitinib cream, taking into account the plethora of pharmacokinetic and safety data available.

DISCLOSURES

Christopher G. Bunick has served as an investigator for AbbVie, Almirall, Apogee, Daiichi Sankyo, LEO Pharma, Ortho Dermatologics, Sun Pharma, Timber, and Palvella; a consultant for AbbVie, Almirall, Apogee, Arcutis, Connect BioPharma, Eli Lilly, EPI Health/Novan, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, Takeda, and UCB; and a speaker for and received honoraria from Allergan, Almirall, LEO Pharma, and UCB.

Pearl Kwong MD PhD serves on the speaker bureau, advisory board, and/or as a consultant or principal investigator for the following pharmaceutical companies: Abbvie, Arcutis, Apogee, Dermavant, Eli Lilly, Pfizer, Sanofi, Regeneron, Ortho, Leo, Galderma, L'Oréal, Incyte, Sun, UCB, Verrica, and Pelthos.

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Leon Kircik MD has served on as an Investigator, consultant, speaker, and/or advisory board member for Abbvie, Acambis, Amgen, Inc., Anacor Pharmaceuticals, Anaptys, Arcutis, Arena, Assos Pharma, Astellas Pharma US, Inc., Asubio, Biomimetrix, Biosion, Dermavant, Dermira, Dow Pharmaceutical Sciences, Inc., Eli Lilly, Ferndale Laboratories, Inc., Galderma, Genentech, Inc., GlaxoSmithKline, PLC, Glenmark, Health Point, LTD, Incyte, Innocutis, Innovail, Kyowakirin, Leo, L'Oreal, Nano Bio, Nektar, Novartis AG, Nucryst Pharmaceuticals Corp, Onset, OrthoDermatologics, OrthoNeutrogena, Promius, PediaPharma, PharmaDerm, Pfizer, PuraCap, Quinnova, Rapt, Regeneron, Sanofi, SkinMedica, Inc., Stiefel Laboratories, Inc., Sun Pharma, Taro, Triax, and Valeant Pharmaceuticals Intl.

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