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Masterful Topical JAK Inhibitor

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VEHICLES MATTER: DESIGNED FOR PURPOSE

Leon Kircik MD

Janus kinase (JAK) inhibitors, which have been used in a range of disease states from rheumatology to gastroenterology, have been finally adopted into dermatology. These agents are rapidly changing the ways that dermatologists treat a range of inflammatory skin diseases, particularly atopic dermatitis (AD).[1]

There are several oral JAK formulations available in the United States market. The first topical cream formulation of a JAK inhibitor is ruxolitinib cream 1.5%, which is approved for the management of nonsegmental vitiligo and short-term non-continuous use for mild to moderate atopic dermatitis in adults and children 12 or older. Current guidelines of care for the management of atopic dermatitis from the American Academy of Dermatology give a strong recommendation for ruxolitinib cream for adults with AD.[2]

The cream formulation contains several emollient and hydrating ingredients that leave no greasy residue after application. Both clinical trial data and real-world experience show that this unique topical JAK formulation offers versatility for prescribers and their patients with eczema as a safe and effective alternative to topical steroids.

As described in the pages ahead, the pivotal trials for ruxolitinib cream show that it provides notable and sustained skin clearance in individuals as young as age 12. In the randomized, double-blind, vehicle-controlled, 8-week phase 3 clinical trials (TRuE-AD1/2), 53.8% and 51.3% (TRuE-AD1 and TRuE-AD2, respectively) of subjects treated with ruxolitinib cream 1.5% achieved IGA success vs 15.1% and 7.6% in the vehicle arms, respectively, at week 8. Greater percentages of ruxolitinib-treated subjects achieved EASI-75 compared to vehicle (62.1% and 61.8% vs 24.6% and 14.4%, respectively).[3] Given the incidence and impact of eczema on pediatric patients, it is worth noting that a pooled analysis of data from the two phase 3 trials found that 8-week treatment success (IGA) and EASI-75 rates for subjects aged 12 to 17 were comparable to the rates for those aged 18 and older.[4]

There is also favorable data to support the use of ruxolitinib cream on various anatomic areas. For example, when it was assessed for the treatment of AD in the head and neck region, nearly two-thirds of patients were clear or almost clear at the first follow up.[5] As noted in the pages ahead, other topical treatments indicated for AD may be associated with increased irritation and burning when applied to the head and neck area.[2] For the management of chronic hand eczema, ruxolitinib is associated with significant rates of skin clearance at week 4, even among patients who had failed other topical and oral therapies.[6,8]

What may be most striking in the clinical trial data and real-world experience with ruxolitinib cream 1.5% is the rapid reduction of itch. Among multiple data analyses demonstrating substantial and rapid reduction of itch, a pooled analysis of the phase 3 trials found ruxolitinib cream to improve itch as early as 12 hours following the first application.[7] Considering that eczema is often called "the itch that rashes," the rapid and substantial improvement in pruritus associated with ruxolitinib cream use may be an important asset in patient care. Despite these impactful findings, there remains hesitation to steer away from topical steroids in daily practice. One possible reason for this is the perception of the safety profile of JAK inhibitors.

While the label for ruxolitinib cream 1.5% has a boxed warning consistent with other JAK inhibitors, oral ruxolitinib, which was approved for intermediate or high-risk myelofibrosis and polycythemia vera in 2011, has no boxed warning! This is certainly perplexing and challenging to explain, especially since the data for the cream overall show low rates of significant adverse events.[2]

The topical cream formulation of ruxolitinib cream 1.5% has emerged as an effective and safe non-steroidal treatment option for a chronic disease where long-term topical steroid use is not recommended. Additionally, this cream's moisturizing, non-greasy formulation makes it a very user friendly and favorable option for our patients.

As always, "VEHICLES MATTER".

Leon Kircik MD

Clinical Professor of Dermatology; Icahn School of Medicine at Mount Sinai, New York, NY; Adjunct Clinical Professor of Dermatology; Indiana University School of Medicine, Indianapolis, IN; Medical Director, Physicians Skin Care, PLLC Louisville, KY; DermResearch, PLLC Louisville, KY, Skin Sciences, PLLC Louisville, KY

DISCLOSURE

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 ORIGINAL ARTICLE

Appraisal of Ruxolitinib 1.5% Cream as a First-Line Topical Therapeutic Agent for Adolescents and Adults With Mild-to-Moderate Atopic Dermatitis

Naiem T. Issa MD PhD,[a] Pearl Kwong MD,[b] Christopher G. Bunick MD PhD,[c] Leon Kircik, MD[d]

[a]Forefront Dermatology, Vienna, VA; Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL; George Washington University School of Medicine and Health Sciences, Washington, DC
[b]Suncoast Skin Solutions, Inc, Jacksonville, FL; Apex Clinical trials, Jacksonville, FL
[c]Department of Dermatology and Program in Translational Biomedicine, Yale University School of Medicine, New Haven, CT
[d]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University School of Medicine, Indianapolis, IN; Physicians Skin Care, PLLC Louisville, KY; DermResearch, PLLC Louisville, KY; Skin Sciences, PLLC Louisville, KY

ABSTRACT

Dermatology has entered the long-awaited paradigm shift from steroidal to non-steroidal therapeutics for the topical treatment of atopic dermatitis. Topical Janus kinase (JAK) inhibitors have garnered a strong recommendation for the treatment of adult atopic dermatitis (AD) by the American Academy of Dermatology in the most recent updated guidelines as of 2023. Ruxolitinib 1.5% cream is the only FDA-approved topical JAK inhibitor available in the US and is approved for the short-term and intermittent chronic treatment of mild-to-moderate AD in adolescents and adults aged >= 12 years with up to 20% affected body surface area (BSA). Since approval in 2021, ruxolitinib cream has been shown to be consistently effective across disease severities, age groups, and anatomic sites of special interest (ie, head and neck region, hands). Real-world usage as monotherapy and in combination with other topicals have confirmed its efficacy in practice and further led to reduced usage of topical corticosteroids. Ruxolitinib cream also has the potential to reduce economic costs due to AD-related decline in work productivity. Here, we review the most up-to-date clinical trial and real-world efficacy data that position ruxolitinib 1.5% cream as a first-line AD therapeutic.

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INTRODUCTION

The topical therapeutic landscape of atopic dermatitis (AD) has entered the "golden age" of drug development. Until now, the landscape was comprised of 3 major mechanistic classes: (1) corticosteroids, calcineurin inhibitors (tacrolimus and pimecrolimus), and phosphodiesterase-4 (PDE-4) inhibitors (crisaborole and, more recently, roflumilast). The current topical pipeline also includes the aryl hydrocarbon receptor (AhR) agonist tapinarof, which is undergoing the regulatory approval process in the United States (US).[1]

Janus kinase (JAK) proteins are critical transducers of cytokine inflammatory signals intracellularly. In particular, JAK1 and JAK2 are activated by the core AD cytokines interleukin (IL)-4, IL-13, IL-22, IL-31, thymic stromal lymphopoietin (TSLP), among others, to recruit signal transducer and activator of transcription (STAT) proteins that are then phosphorylated. STAT proteins subsequently dimerize and cause DNA transcriptional changes in various immune and non-immune cell types to ultimately cause increased expression of additional pro-inflammatory cytokines. As such, targeting JAK1/2 has been a highly sought-after therapeutic approach for AD, resulting in 2 oral

FDA-approved JAK1 inhibitors (abrocitinib and upadacitinib) and 1 topical JAK 1/2 (ruxolitinib cream 1.5%). Ruxolitinib inhibits JAK family kinases with the following IC_{50} values: JAK1, 6.4 nM; JAK2, 8.8 nM; JAK3, 487 nM; and TYK2, 30.1 nM.[2] JAK inhibitors have garnered much attention given their ability to rapidly clear skin and reduce itch.[3]

With the rapidly evolving landscape in topical AD therapeutics, the American Academy of Dermatology has recently updated its guidelines for topical management of AD in 2023.[4] Topical JAK inhibitors have been given a strong recommendation for adults with mild-to-moderate AD. At this time, topical ruxolitinib 1.5% cream is the only FDA-approved topical JAK inhibitor therapy for AD currently available in the US. Here, we gather the currently available up-to-date data on ruxolitinib cream with respect to efficacy and safety in clinical trials as well as real-world usage.

AD Skin Clearance With Ruxolitinib Cream

Treatment with ruxolitinib 1.5% cream twice daily as monotherapy has shown significant improvements in Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) scores in adolescents and adults (age >= 12 years of age) with mild-to-moderate AD. IGA treatment success (IGA-TS) is defined as a score of 0 (clear) or 1 (almost clear) with a >= 2-grade improvement from baseline.

In the 2 pivotal randomized, double-blind, vehicle-controlled, 8-week phase 3 clinical trials (TRuE-AD1/2), ruxolitinib 1.5% cream twice daily as monotherapy again showed superiority to the vehicle in obtaining skin clearance in subjects >= 12 years of age.[5] At baseline, subjects exhibited an IGA of 2 or 3, mean affected BSA of 10.0 +/- 5.4, and mean EASI of 8.0 +/- 5.0 with median duration of disease of 16.0 (0-70.7) years. At week 8, 53.8% and 51.3% (TRuE-AD1 and TRuE-AD2, respectively) of subjects in the ruxolitinib 1.5% treatment group achieved IGA success vs 15.1% and 7.6% in the vehicle arms, respectively. A greater percentage of subjects in the ruxolitinib 1.5% treatment group achieved EASI-75 compared with the vehicle group (62.1% and 61.8% vs 24.6% and 14.4%, respectively).

With respect to the 44-week long-term safety (LTS) period of the study subsequent to the vehicle-controlled period, subjects initially randomized to ruxolitinib 1.5% cream twice daily and continued to receive ruxolitinib after week 8, whereas those initially randomized to the vehicle were re-randomized to either ruxolitinib 0.75% or 1.5% cream.[6] Of note, ruxolitinib was used on an as-needed basis to simulate real-world usage (ie, subjects were instructed to treat only active AD lesions, stop treatment 3 days after lesion clearance, and restart treatment at first signs of recurrence). At week 52, disease control was maintained in subjects who initially started on and continued with ruxolitinib 1.5% cream (77.8% achieved IGA 0/1, mean total affected BSA 1.4%). Similar efficacy was also observed in the vehicle-to-ruxolitinib 1.5% cream group (74.1% achieved IGA 0/1, mean total affected BSA 1.7%).

Sub-analyses based on age stratification have also been conducted. Eichenfield et al performed a pooled analysis of adolescents from the 2 phase 3 randomized trials and found at week 8, significantly more adolescent (age >= 12-17 years) subjects receiving ruxolitinib 1.5% cream vs vehicle to achieve IGA-TS (50.6% and 14.0%, respectively) and EASI-75 (60.9% and 34.9%, respectively).[7] Moreover, adolescent IGA-TS and EASI-75 with ruxolitinib cream was comparable to subjects 18-64 years of age (52.2% and 61.0%, respectively) and >= 65 years of age (60.5% and 73.7%, respectively). In the long-term safety (LTS) period with as-needed use of ruxolitinib cream, 68.8% (53/77) of those who continued on ruxolitinib cream had clear or almost clear skin (IGA 0/1). For those who switched from vehicle to ruxolitinib cream, there was a substantial increase in the percentage of subjects achieving clear or almost clear skin at week 12 compared to week 8 [60% (12/20) vs 28.6% (6/21)]. This success was sustained through week 52 [63.2% (12/19)].

Simpson et al. further performed a post hoc analysis of the pivotal phase 3 trials (TRuE-AD1/2), which included subjects who, at baseline, had an IGA score of 3, EASI >= 16, and affected BSA >= 10%.[8] This analysis intended to assess the success of ruxolitinib cream in a subset of subjects with moderate and/or more extensive disease who meet the severity threshold for systemic therapy. At week 8, ruxolitinib cream was superior to the vehicle with respect to skin clearance (IGA 0/1), with 59.4% (19/32) and 0.0% (0/13), respectively, achieving success. Ruxolitinib cream also outperformed vehicle with respect to EASI-75 with success rates of 71.9% (23/32) and 7.7% (1/13), respectively. During the LTS period with as-needed ruxolitinib cream usage, the percent of subjects achieving clear or almost clear skin (IGA 0/1) further increased in those who initially applied ruxolitinib cream from the vehicle-controlled period [78.3% (18/23)]. Mean affected BSA also decreased from 18.0% at baseline to 5.2% and 2.5% at weeks 8 and 52, respectively. Percentages of subjects achieving IGA 0/1 and reduction in mean affected BSA were similar among patients who applied ruxolitinib cream from day 1 and those who crossed over from the vehicle.

Recent findings from the TRuE-AD3 trial, which followed a similar design to the TRuE-AD1/2 studies and the LTS extension, also demonstrated that significantly more patients aged 2-11 years who applied ruxolitinib 1.5% cream achieved both IGA-TS (56.5%) and EASI-75 (67.2%) by week 8 compared to those treated with vehicle (10.8% and 15.4%, respectively).[9] Efficacies were sustained during the 44-week as-needed treatment period of the LTS. These results highlight the efficacy of ruxolitinib cream in younger pediatric populations with AD.

Atopic Dermatitis of the Head and Neck

Patient quality of life is not only related to disease severity but also to body regions that are differentially affected.[10] For example, AD involvement in highly visible areas (ie, the face) is associated with a greater reduction of quality of life compared with other non-visible areas (ie, the back).[11,12] The head and neck region is also particularly challenging to treat, given that irritation and burning may be exacerbated with topical crisaborole and calcineurin inhibitors.[4,13] Adverse events from topical corticosteroid use (ie, hypopigmentation, skin atrophy, periorificial dermatitis, rebound dermatitis, striae, etc.) may also be amplified in the head and neck.[14,15]

A pooled sub-group analysis by Simpson et al examined the efficacy of ruxolitinib cream monotherapy across the head and neck from the phase 3 TRuE-AD studies.[16] 663 subjects (age >= 12 years of age) at baseline had head and neck involvement. Least squares mean (LSM) percentage improvements from baseline in total EASI score in the head and neck region were significantly greater than vehicle at all time points (weeks 2, 4, and 8) with EASI subscores for induration, erythema, excoriation, and lichenification all exhibiting significantly greater improvements over vehicle as early as week 2. The pooled total percentages of subjects achieving EASI-50, EASI-75, and EASI-90, as well as IGA treatment success (defined as an IGA-TS score of 0/1 with ≥2-point improvement), were significantly greater with ruxolitinib cream compared with vehicle at week 8 (P<.0001). Itch NRS4 success was also significantly greater with ruxolitinib cream (P<.0001). These treatment successes correlated with significant improvements in the Dermatology Life Quality Index (DLQI) observed at week 2 and sustained through week 8.

Improvement of Chronic Hand Eczema With Ruxolitinib Cream

Chronic hand eczema (CHE) is a condition of multifactorial etiology, and a subset of CHE patients have atopic dermatitis of the hands (~34%).[17] A systematic review and meta-analysis encompassing over 17,000 patients found that hand eczema has a moderate-to-severe impact on quality of life that is comparable to other chronic diseases.[18] Disease severity is measured by the validated Hand Eczema Severity Index (HECSI), a clinical severity scoring tool ranging from 0 to 360 points based on assessments of severity across 6 different morphological signs (erythema, infiltration/papulation, vesicles, fissures, scaling and edema).[19] Higher HECSI scores strongly correlated with DLQI scores.[18] Furthermore, patients afflicted with CHE exhibit substantial concern over the use of topical corticosteroids for the treatment of their condition.[20]

Although therapeutic advancements in CHE treatment have been notable, particularly with systemic therapies (eg, dupilumab, abrocitinib, upadacitinib), significant progress in the topical space remains a major unmet need. To date, there is no FDA-approved medication for the treatment of CHE; however, oral alitretinoin and topical delgocitinib (a pan-JAK inhibitor available in 2024) are approved in Europe.[21] Ruxolitinib 1.5% cream has been preliminarily studied for CHE by Smith et al in an investigator-initiated, open-label, single-site study.[22] Recruited subjects exhibited moderate-to-severe CHE, and all had failed topicals (corticosteroid and/or calcineurin inhibitors) and, in some cases, systemic (eg, oral corticosteroids, methotrexate, and phototherapy) treatments. Treatment with ruxolitinib 1.5% cream twice daily for 4 weeks resulted in 100% and 64% of subjects achieving 50% (HECSI-50) and 75% (HECSI-75) improvement, respectively. Significant improvement in DLQI scores was also noted. Given this success, a phase 2 randomized controlled trial for chronic hand eczema is underway (NCT05906628).

Real-World Efficacy and Reduced Utilization of Topical and Oral Corticosteroids and Biologics

In addition to the aforementioned trials, the real-world efficacy of ruxolitinib cream for AD has been noted in the literature. A single-center retrospective study assessed 92 adult patients with mild-to-moderate AD.[23] Majority of patients had moderate disease (63%), were female (64%) and White (59%). Most patients (63%) achieved clear or almost clear skin at their first follow-up visit, with the average time between initiation of ruxolitinib cream and follow up being 3.5 months.

Real-world physician satisfaction of AD disease control with ruxolitinib cream was demonstrated in a US Adelphi study.[24] A cross-sectional survey of physician-reported data between 2022 and 2023 captured 149 patients (84.6% with moderate AD) who received ruxolitinib cream as monotherapy or in combination for >= 1 month (median duration of treatment, 26 weeks). After treatment, 48.3% of patients achieved clear or almost clear skin (IGA 0/1), and 81.2% were not currently experiencing a flare of their condition. Physicians were satisfied with disease control for 87.3% of all treated patients and for 91.5% of those who received monotherapy.

Furthermore, real-world U.S. claims data studies revealed that within 6 months following ruxolitinib cream initiation, there was a decrease in utilization of other AD treatments, including topical and oral corticosteroids, topical calcineurin inhibitors, topical PDE4 inhibitors, and biologics.[25] This continued through the following 7 to 12 months after treatment initiation.[26] Among patients who did not receive AD biologic therapy during the baseline period, >90% remained off biologics during the follow-up periods. Among patients who received AD biologic therapy during the

baseline period, 26% did not continue biologics. The mean cumulative prednisone-equivalent dose was also reduced by 44% during months 7 to 12 of the follow-up period. This helps lower healthcare costs while also reducing the safety risks associated with prolonged use of systemic agents, offering a safer, more cost-effective alternative for long-term disease management.

Effect of Ruxolitinib 1.5% Cream on Itch

Itch has been cited as the most burdensome symptom by patients afflicted with atopic dermatitis; reducing itch is the cornerstone of breaking the "itch-scratch" cycle that perpetuates AD.[27] In the TRuE-AD1/2 phase 3 pivotal trials, baseline mean worst itch numerical rating scale (NRS) was 5.1 +/- 2.5 out of a maximum score of 10.[5] The proportion of subjects achieving success in itch reduction (defined as a 4-point reduction in NRS [NRS4]) at week 8 was significantly greater in the ruxolitinib 1.5% cream treatment group (52.2% and 50.7%) vs vehicle (15.4% and 16.3%). For subjects with baseline itch NRS >= 4, NRS4 success was also significantly greater by day 2 (~36 hours after the first treatment application) for ruxolitinib 1.5% cream (11.6% and 10.8%, respectively) vs vehicle (2.9% and 1.3%, respectively).

A pooled analysis of the phase 3 trials using itch NRS2 (2-point reduction in worst itch NRS, which is clinically relevant[28]) found ruxolitinib cream to improve itch as early as 12 hours following the first application.[29]The median time to reach itch NRS2 was also shorter for subjects applying ruxolitinib 1.5% cream (4.0 days) vs vehicle (17.0 days). The median time to reach itch NRS4 was 13.0 days for the ruxolitinib 1.5% cream treatment group; however, this endpoint was not met in the vehicle group. When stratified by age (12-17 years, 18-64 years, >= 65 years), itch NRS4 was achieved by 52.1%, 51.1%, and 53.8% of subjects, respectively, receiving ruxolitinib 1.5% cream compared to vehicle (17.4%, 15.3% and 17.6%, respectively).[7] This suggests that ruxolitinib cream has a comparable positive effect on itch reduction regardless of age. In a subset analysis of TRuE-AD1 & True-AD2 subjects with extensive disease who met the severity threshold for systemic therapy (IGA = 3, EASI >= 16, BSA >= 10%), 61.1% vs 27.3% achieved itch NRS4 at week 8 in the ruxolitinib 1.5% cream and vehicle groups, respectively, compared to 51.5% in the overall TRuE-AD1/2 population.[8]

Blauvelt et al further evaluated the achievement of an itch-free state (defined as worst itch NRS 0/1) in another pooled analysis of TRuE-AD1 and TRuE-AD2.[30] Achievement of itch NRS 0/1 was significantly greater in the ruxolitinib 1.5% cream group compared to vehicle (19.0% vs 4.6%, respectively) as early as day 2 (~36 hours after first application) and remained significant through week 8. The median time to achieve itch NRS 0/1 was 9.0 days for ruxolitinib 1.5% cream vs not estimable for vehicle. Of note, a multivariable proportional hazards regression model found age to be the only demographic factor associated with faster itch response (<18 years, median 11.0 days; >= 18 years, median 17.0 days). A greater percentage of subjects who applied ruxolitinib cream vs vehicle reported no days of itch. Furthermore, a serum proteomic analysis of 1,012 proteins comparing subjects from the Phase 2b trial (NCT03011892) who achieved itch NRS 0/1 vs those who did not at week 8 revealed a total of 53 proteins to be more downregulated and 4 proteins to be more upregulated in those who achieved an itch-free state, thus correlating with reduced systemic inflammation.[31]

With regards to the younger pediatric population (ages 2-11), Eichenfield et al. found greater success in itch reduction (NRS4) in patients treated with ruxolitinib 1.5% cream (43.5%) vs vehicle (29.7%).[9] This outcome was similar to phase 3 results in adolescents and adults.

A 28-day phase 2, open-label, single-site study (SCRATCH-AD; NCT04839380) in adult subjects aged 18 to 65 years with AD for >= 6 months also assessed the short-term benefits of ruxolitinib 1.5% cream twice daily to control itch.[32] The study assessed change from baseline in modified peak pruritus numerical rating scale (mPP-NRS; current itch intensity) at short intervals on day 1 (15 and 30 minutes, and at 1, 2, 4, 6, and 12 hours post-treatment) as well as days 2 through 29. At baseline, subjects exhibited a mean (SD) pretreatment mPP-NRS score of 6.4 (1.72), and 89.1% had an IGA of 3. Itch reduction was observed as early as 15 minutes [mPP-NRS -2.3 (2.34)], peaked at 4 hours post-treatment [-4.2 (2.12)], and was further improved and sustained through 28 days of treatment. Of note, transepidermal water loss (TEWL) of lesional AD skin was also measured from baseline through the 4 weeks, and it substantially decreased to levels similar to nonlesional skin with ruxolitinib treatment.

Efficacy of Ruxolitinib Cream Directly Compared to Topical Corticosteroid

A phase 2, randomized, double-blind, dose-ranging, vehicle- and active-controlled 8-week study in adult patients (age 18 - 70 years) with mild-to-moderate AD >= 2-year history of disease assessed the efficacy of vehicle twice daily (n=52), ruxolitinib 1.5% cream twice daily (n=51) and triamcinolone 0.1% cream twice daily (n=51) over 4 weeks in the initial portion of the trial.[33] Mean percentage improvement from baseline in EASI score for ruxolitinib, triamcinolone, and vehicle were 71.6%, 59.8%, and 15.5%, respectively. The proportion of IGA responders were also 38.0%, 25.5%, and 7.7%, respectively. Of note, the authors found a direct correlation between serum concentration of thymus and activation-regulated cytokine (TARC) and EASI score. This is in agreement with the prior notion of TARC serum levels being a biomarker of disease severity.[34] Ruxolitinib 1.5% cream applied twice daily resulted in the greatest reduction in TARC concentrations.

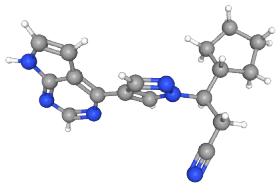
CONCLUSION

Ruxolitinib 1.5% cream is the first FDA-approved topical JAK inhibitor for mild-to-moderate AD in patients >= 12 years of age up to 20% affected BSA without any topical drug interaction warning (ie, it can be used as monotherapy or in combination with other topical medications as deemed fit). It can also be used on a non-continuous as-needed basis, given its efficacy in the pivotal 44-week as-needed treatment period (LTS). JAK inhibitors are appreciated for their rapidity of effect on itch and skin clearance, along with their magnitude of effect. The 2023 AAD guidelines have given a strong recommendation for topical JAK inhibition, with ruxolitinib cream being the first and only in class while exhibiting numerous advantages (Figures 1 and 2).[4] Not only has ruxolitinib cream shown superiority to vehicle cream in the pivotal phase 3 trials,it has also shown favorable efficacy compared to triamcinolone 0.1% cream in a phase 2 active comparator study. Utility of ruxolitinib cream has also been demonstrated in various special anatomic sites, such as the head and neck region, and treatment-recalcitrant chronic hand eczema. Real-world assessments have repeatedly shown a quick onset of action, especially when ruxolitinib cream is used in combination therapy (due to lack of drug interactions), suggesting that it can be used across the spectrum of AD. These outcomes correlate with high physician and patient satisfaction. Ruxolitinib 1.5% cream is also associated with improved work productivity with expected incremental annual indirect cost savings of over $4000.[35] Lastly, ruxolitinib cream is very well tolerated with minimal systemic absorption and a clean safety profile (detailed in the second portion of this supplement). As such, ruxolitinib 1.5% cream is a welcomed first-line topical therapeutic for any AD patient over the age of 12 years with less <= 20% affected BSA to be used either as monotherapy or in combination with other topical AD treatments without need for lab monitoring, and offers flexibility for long-term management, as it can be applied on an as-needed basis for chronic treatment, providing both efficacy and convenience in maintaining disease control.

FIGURE 1. Current landscape of topical ruxolitinib 1.5% cream for the treatment of adolescent and adult patients with atopic dermatitis. Nitrogen atoms are colored blue, while carbon atoms are colored gray.

Significant Skin Clearance

- Superior to vehicle at week 8, but as early as week 2
- Similar effectiveness in adolescents and adults
- Effective in anatomic sites of special interest (i.e. head and neck, chronic hand eczema)
- Improvement in skin barrier with reduction in transepidermal water loss (TEWL)



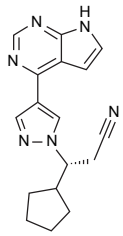
Ruxolitinib 1.5% Cream

Established Safety Profile

- Comparable to vehicle in pivotal phase 3 trials
- Infrequent and unrelated adverse events of special interest in long-term safety (LTS) trial
- Maximal-use and pharmacokinetic profiling consistently revealed plasma concentrations below that required for bone marrow suppression

Powerful Itch Reduction

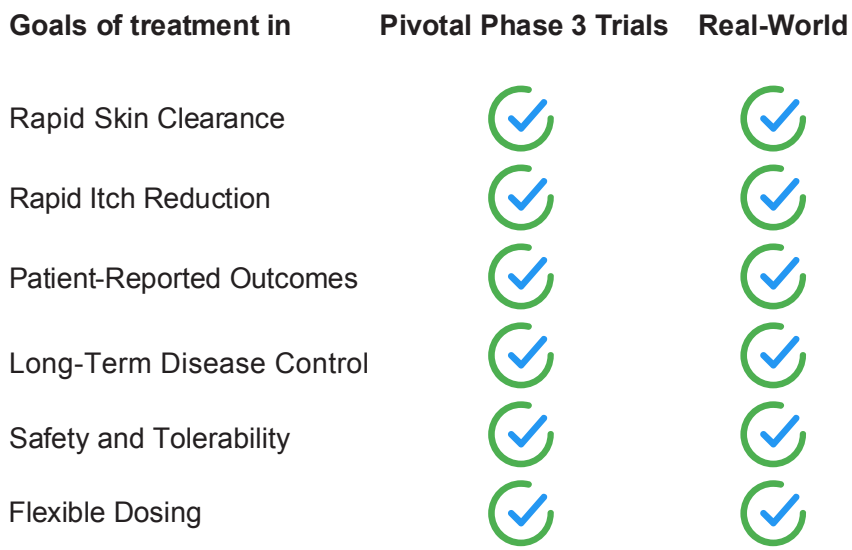
- Clinically meaningful reduction in itch as early as 12 hours (NRS2) and 36 hours (NRS4)
- 15-minute rapid itch reduction in open-label, single-arm monotherapy Phase 2b study
- Itch-free state (NRS 0/1) achieved by ~20% of subjects treated in phase 3 trials within 36 hours



Improved Patient Reported-Outcomes

- DLQI and other QoL indices significantly improved
- Increased patient work productivity and reduction in activity impairment resulting in significant annual indirect cost savings

FIGURE 2. Goals of treatment in atopic dermatitis achieved in pivotal phase 3 clinical trials as well as real-world usage data.



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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AUTHOR CORRESPONDENCE

Naiem T. Issa MD PhD

E-mail:..... drnaiemissa@gmail.com

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 ORIGINAL ARTICLE

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

Naiem T. Issa MD PhD,[a] Pearl Kwong MD,[b] Christopher G. Bunick MD PhD,[c] Leon Kircik MD[d]

[a]Forefront Dermatology, Vienna, VA; Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL; George Washington University School of Medicine and Health Sciences, Washington, DC
[b]Suncoast Skin Solutions, Inc, Jacksonville, FL; Apex Clinical trials, Jacksonville, FL
[c]Department of Dermatology and Program in Translational Biomedicine, Yale University School of Medicine, New Haven, CT
[d]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University School of Medicine, Indianapolis, IN; Physicians Skin Care, PLLC Louisville, KY; DermResearch, PLLC Louisville, KY; Skin Sciences, PLLC Louisville, KY

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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AUTHOR CORRESPONDENCE

Naiem T. Issa MD PhD

E-mail:..... drnaiemissa@gmail.com

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