Integrated Safety Analysis of Ruxolitinib Cream: Data From 20 Clinical Studies in Inflammatory Dermatologic Conditions

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Christopher G. Bunick, MD, PhD,[1] Khaled Ezzedine, MD, PhD,[2] Lawrence F. Eichenfield, MD,[3] Robert Bissonnette, MD,[4] Thierry Passeron, MD, PhD,[5,6] Daniel Sturm, PharmD,[7] Haobo Ren, PhD,[7] Yun Su, MD, MPH,[7] David Rosmarin, MD[8]

[1]Yale School of Medicine, New Haven, CT, USA; [2]Henri Mondor University Hospital and Université Paris-Est Créteil Val de Marne, Paris, France; [3]University of California San Diego School of Medicine, La Jolla, CA, USA; [4]Innovaderm Research, Montreal, QC, Canada; [5]Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France; [6]INSERM U1065, C3M, Université Côte d'Azur, Nice, France; [7]Incyte Corporation, Wilmington, DE, USA; [8]Indiana University School of Medicine, Indianapolis, IN, USA

Objective

- To investigate the incidence of JAK inhibitor warning adverse events among 20 clinical studies of ruxolitinib cream in patients with AA, AD, HS, LP, LS, or vitiligo

Conclusions

- **With >2000 PY of follow-up and up to 3 years of exposure, EAIRs of adverse events in the JAK inhibitor safety warning (serious infections, MACE, thromboembolic events, malignancies, and mortality) among patients who applied 1.5% ruxolitinib cream twice daily were generally low or absent and consistent with available published literature**
- **These findings may be attributable to low systemic exposure owing to topical administration of ruxolitinib cream**
- **No new safety signals were identified across the studies**

Abbreviations

AA, alopecia areata; AE, adverse event; AD, atopic dermatitis; BID, twice daily; EAIR, exposure-adjusted incidence rate; HS, hidradenitis suppurativa; IC_{50}, half-maximal inhibitory concentration; JAK, Janus kinase; LP, lichen planus; LS, lichen sclerosus; MACE, major adverse cardiac event; NMSC, nonmelanoma skin cancer; PY, person-year; STAT, signal transducer and activator of transcription.

Disclosures

CGB has served as an investigator for AbbVie, Almirall, Apogee, Daiichi Sankyo, LEO Pharma, Ortho Dermatologics, Palvella, Sun Pharma, and Timber; a consultant for AbbVie, Almirall, Apogee, Arcutis, Connect BioPharma, Eli Lilly, EPI Health/Novan, Incyte Corporation, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, Takeda, Teladoc, and UCB; and a speaker for and received honoraria from Allergan, Almirall, LEO Pharma, and UCB. KE has served as a consultant for AbbVie, Almirall, Bristol Myers Squibb, Incyte Corporation, La Roche-Posay, Lilly, Pfizer, Pierre Fabre Pharmaceuticals, and Sanofi. LFE has served as a consultant; speaker; advisory board member; or investigator for AbbVie, Almirall, Amgen, Apogee, Arcutis, Attovia, Bristol Myers Squibb, Castle Biosciences, CorEvitas, Dermavant, Eli Lilly, Forte, Galderma, Incyte Corporation, Janssen, Johnson & Johnson, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Target RWE, T-Rex, and UCB. RB has served as an advisory board member; consultant, speaker and/or investigator for and has received honoraria and/or grants from AbbVie, Actavis, Amgen, Apogee, Arcutis, Arrtetea, Asana BioSciences, Bellus, BioMimetix, Bluefin, Biomedicine, Boehringer Ingelheim, Boston Pharma, CARA, Dermavant, Eli Lilly, Escient, Evidera, Fresh Tracks (Brickell), Galderma, GlaxoSmithKline, Incyte Corporation, Innagreex Bio, Janssen, LEO Pharma, Merck, Novartis, Opsidio, Pfizer, RAPT, Sanofi, Stiryx, Target RWE, Vyne Therapeutics, and Zencor and is an employee and shareholder of Innovaderm Research. TP has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Calyopsis, Celgene, Eli Lilly, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte Corporation, Janssen, LEO Pharma, Novartis, Pfizer, Sun Pharmaceuticals, Takeda, UCB, and Vyne Therapeutics; is the cofounder of NIKAIA Pharmaceuticals; and has patents on WNT agonists and GSK3b antagonists for repigmentation of vitiligo and on the use of CXCR3B blockers in vitiligo. DS, HR, and YS are employees and shareholders of Incyte Corporation. DR has served as a consultant, speaker, or investigator for AbbVie, Abcuro, Almirall, Altrubio, Amgen, Arena, Astria, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Concert, CSL Behring, Dermavant Sciences, Dermira, Dualtas, EMD Serono, Galderma, Incyte Corporation, Janssen, Kymera, Kyowa Kirin, Lilly, Merck, Nektar, Novartis, Pfizer, RAPT Therapeutics, Recludix, Regeneron Pharmaceuticals, Revolo Biotherapeutics, Sanofi, Sun Pharmaceuticals, UCB, Viela Bio, and Zura Bio.

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Introduction

- JAK inhibitors are an effective therapy in a variety of inflammatory conditions[1-6]
- A safety warning for serious infections, MACE, thromboembolic events, malignancies, and mortality accompanies most of the US and Canadian labels of JAK inhibitors for inflammatory conditions[7,8]
  - This warning is based on safety findings from the use of a systemic pan-JAK inhibitor (tofacitinib) when compared with a tumor necrosis factor inhibitor in patients with rheumatoid arthritis aged ≥50 years and ≥1 additional cardiovascular disease risk factor while on concomitant methotrexate[9,10]
- Ruxolitinib cream, a selective JAK1/JAK2 inhibitor, is currently approved in patients aged ≥2 years with AD in the US,[7] patients aged ≥12 years with AD in Canada,[8] and patients aged ≥12 years with nonsegmental vitiligo (US, Canada, UK, and various European and Asian countries)[7,8,11-13]
  - In clinical studies with ruxolitinib cream, plasma concentrations of ruxolitinib were low,[2,3] suggesting minimal systemic exposure and limited systemic JAK inhibition

Methods

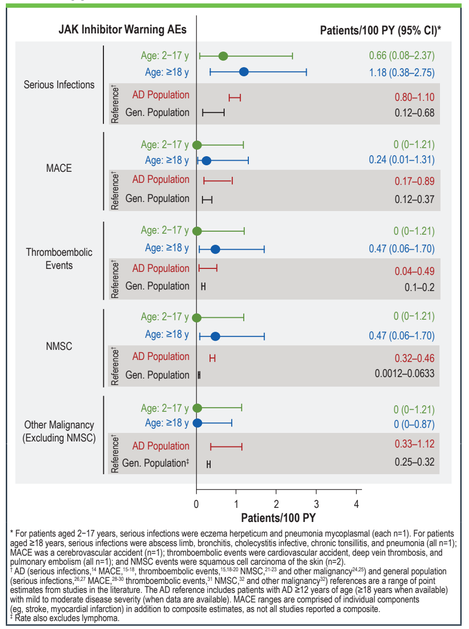
Study Design and Patients

- EAIRs (number of patients experiencing the event per 100 PY of exposure) of adverse events in the JAK inhibitor safety warning were calculated for patients who applied 1.5% ruxolitinib cream twice daily
- Data were derived from clinical studies in patients with AD (10 studies; ages 2−17 y, n=461, 304.98 PY; ages ≥18 y, n=882, 423.98 PY); vitiligo (6 studies; n=877; 1157.08 PY); and AA (n=89; 73.51 PY), HS (n=66; 24.22 PY), LP (n=60; 25.17 PY), and LS (N=58; 19.20 PY; all 1 study each), with exposure durations ranging from approximately 4 weeks to 3 years
  - For study design details, please scan the QR code

Results

- Patients with AD aged 2−17 years who applied 1.5% ruxolitinib cream had an EAIR (95% CI) of 0.66 (0.08−2.37) for serious infections, with no MACE, thromboembolic events, or malignancies (**Figure 1**)
- Patients with AD aged ≥18 years who applied 1.5% ruxolitinib cream had EAIRs (95% CI) of 1.18 (0.38−2.75) for serious infections, 0.24 (0.01−1.31) for MACE, 0.47 (0.06−1.70) for thromboembolic events, 0.47 (0.06−1.70) for NMSC, and 0 (0–0.87) for malignancies excluding NMSC

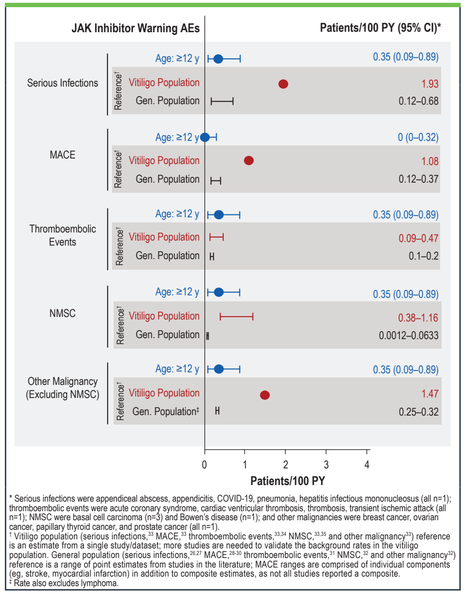
Figure 1. Atopic Dermatitis EAIRs With 1.5% Ruxolitinib Cream Application



* For patients aged 2–17 years, serious infections were eczema herpeticum and pneumonia mycoplasmal (each n=1). For patients aged ≥18 years, serious infections were abscess limb, bronchitis, cholecystitis infective, chronic tonsillitis, and pneumonia (all n=1); MACE was a cerebrovascular accident (n=1); thromboembolic events were cardiovascular accident, deep vein thrombosis, and pulmonary embolism (all n=1); and NMSC events were squamous cell carcinoma of the skin (n=2).
† AD (serious infections,[14] MACE,[15-19], thromboembolic events,[15,19,20] NMSC,[21,22] and other malignancy[24,25]) and general population (serious infections,[26,27] MACE,[28,29] thromboembolic events,[31] NMSC,[32] and other malignancy[30]) references are a range of point estimates from studies in the literature. The AD reference includes patients with AD ≥12 years of age (≥18 years when available) with mild to moderate disease severity (when data are available). MACE ranges are comprised of individual components (eg, stroke, myocardial infarction) in addition to composite estimates, as not all studies reported a composite.
‡ Rate also excludes lymphoma.

- AD EAIRs were generally consistent with rates observed in adolescents and adults with AD reported in the literature
- Patients with vitiligo who applied 1.5% ruxolitinib cream had EAIRs (95% CI) of 0.35 (0.09−0.89) for serious infections, 0 (0−0.32) for MACE, 0.35 (0.09−0.89) for thromboembolic events, 0.35 (0.09−0.89) for NMSC, and 0.35 (0.09−0.89) for malignancies excluding NMSC, which are consistent with disease-specific rates reported in the literature (**Figure 2**)

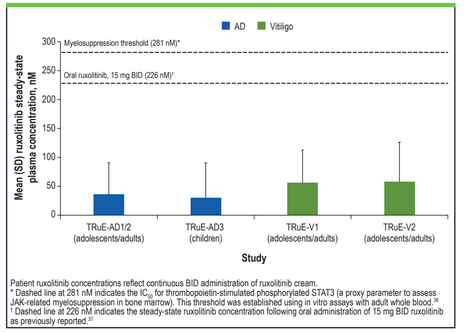
Figure 2. Vitiligo EAIRs With 1.5% Ruxolitinib Cream Application



* Serious infections were appendiceal abscess, appendicitis, COVID-19, pneumonia, hepatitis infectious mononucleosus (all n=1); thromboembolic events were acute coronary syndrome, cardiac ventricular thrombosis, thrombosis, transient ischemic attack (all n=1); NMSC were basal cell carcinoma (n=3) and Bowen's disease (n=1); and other malignancies were breast cancer, ovarian cancer, papillary thyroid cancer, and prostate cancer (all n=1).
† Vitiligo population (serious infections,[33] MACE,[34] thromboembolic events,[33,34] NMSC,[33,35] and other malignancy[33]) reference is an estimate from a single study/dataset; more studies are needed to validate the background rates in the vitiligo population. General population (serious infections,[26,27] MACE,[28,29] thromboembolic events,[31] NMSC,[32] and other malignancy[30]) reference is a range of point estimates from studies in the literature; MACE ranges are comprised of individual components (eg, stroke, myocardial infarction) in addition to composite estimates, as not all studies reported a composite.
‡ Rate also excludes lymphoma.

- In studies of patients applying 1.5% ruxolitinib cream having other diseases in which patient years were limited, patients with AA experienced serious infections (diverticulitis [n=1] and sepsis [n=1]) and a malignancy excluding NMSC (lentigo maligna, n=1); patients with LP experienced NMSC (squamous cell carcinoma of skin, n=1), and patients with LS experienced NMSC (basal cell carcinoma, n=1)
- No patients with HS had serious infections, MACE, thromboembolic events, NMSC, or other malignancies
- No fatalities occurred in any study
- Ruxolitinib plasma concentrations, as measured in the pivotal studies of patients with AD or vitiligo, generally remained low (eg, well below the threshold of 281 nM associated with JAK-mediated myelosuppression using in vitro assays in whole blood in adults[36]; **Figure 3**)

Figure 3. Ruxolitinib Plasma Concentrations With 1.5% Ruxolitinib Cream Application in Pivotal Studies for AD and Vitiligo



Patient ruxolitinib concentrations reflect continuous BID administration of ruxolitinib cream.
* Dashed line at 281 nM indicates the IC_{50} for thrombopoietin-stimulated phosphorylated STAT3 (a proxy parameter to assess JAK-related myelosuppression in bone marrow). This threshold was established using in vitro assays with adult whole blood.[36]
† Dashed line at 226 nM indicates the steady-state ruxolitinib concentration following oral administration of 15 mg BID ruxolitinib as previously reported.[37]

Limitations

- Pooled results combine studies with differing designs, durations, populations, and event ascertainment
- Background EAIRs based on published literature may vary due to differences in patient characteristics, case definitions, follow-up windows, and whether rates reflect first events vs overall incidence; ranges may span broad intervals and are provided for reference only and not for direct comparison
- Additional cumulative exposure to ruxolitinib cream and further peer-reviewed epidemiologic research will continue to contextualize these findings over time