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Association Between Topical Ruxolitinib Treatment and Psychiatric Outcomes in Adults With Vitiligo

Kermanjot Sidhu BS,[a] Kritin Verma MBA,[b] Sahil Kapur BS,[c] Kevin Nguyen BA,[b] Iltefat Hamzavi MD,[d] Henry Lim MD,[d] Karan Pandher MD[e]

[a]Michigan State University College of Human Medicine, Grand Rapids, MI
[b]Texas Tech University Health Sciences Center School of Medicine, Lubbock, TX
[c]University of Toledo College of Medicine and Life Sciences, Toledo, OH
[d]Center for Cutaneous Biology and Immunology Research, Department of Dermatology, Henry Ford Health, Detroit, MI
[e]Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA

INTRODUCTION

Vitiligo is a chronic autoimmune skin disorder characterized by progressive loss of epidermal melanocytes, resulting in depigmented macules and patches.[1] The visible nature of vitiligo can impose a substantial psychosocial burden, including diminished quality of life, reduced self-esteem, and impaired social functioning.[2,3] Psychiatric comorbidities, particularly depression and anxiety, occur at disproportionately high rates in this population and are frequently attributed to the visible and often stigmatizing nature of the disease.[4] Lesions commonly appear on cosmetically sensitive and visible areas, such as the face and hands, amplifying social scrutiny and emotional distress.[3,5]

Recent therapeutic advances have introduced topical Janus kinase (JAK) inhibitors, including ruxolitinib 1.5% cream, as targeted treatments for repigmentation in vitiligo.[6] Ruxolitinib inhibits JAK1 and JAK2 signaling pathways implicated in autoimmune melanocyte destruction, and phase three clinical trials have demonstrated meaningful clinical repigmentation with favorable tolerability profiles.[6,7] Despite the recognized psychiatric burden of vitiligo, limited evidence exists regarding whether effective treatments such as topical ruxolitinib confer measurable benefits in reducing incident psychiatric comorbidities. The present study leverages large-scale, real-world data to examine the association between topical ruxolitinib use and psychiatric disorders among adults with vitiligo.

MATERIALS AND METHODS

We performed a retrospective, propensity score–matched cohort analysis on TriNetX comparing adult patients with vitiligo treated with topical ruxolitinib to matched controls without ruxolitinib exposure. Adults with vitiligo were identified using the International Classification of Diseases (ICD-10) code L80 and matched 1:1 on age, sex, race, and ethnicity, resulting in two balanced cohorts of 4,936 patients each. Treatment status was determined from prescription records for ruxolitinib (RxNorm 1193326). Since no code distinguishes topical from oral formulations, prescriptions were restricted to those originating in dermatologic outpatient settings, and patients with hematologic or myeloproliferative diseases, typically treated with oral ruxolitinib (ICD-10 D47.4, D45, D89.810, D89.813, D76.1, D47.1, C94.3) were excluded.

Psychiatric and behavioral outcomes were identified using valid ICD-10 codes, while procedural and mental health service utilization outcomes were captured via Current Procedural Terminology (CPT) codes. Incidence rates were compared between groups using relative risk (RRs) with 95% confidence intervals (CIs) calculated using Wald's method. Statistical significance was determined by two-tailed *P*-values, with significance defined as $P<0.05$. The observation period for outcomes started one day after the index date, which was defined as the first topical ruxolitinib prescription date for treated patients or a matched index date for controls, and extended through available follow-up.

RESULTS

Patients treated with topical ruxolitinib exhibited significantly lower rates of multiple psychiatric comorbidities and mental health service utilization compared to untreated controls (Table 1). Depressive episodes occurred in 1.9% of the treated group versus 7.2% in controls (RR 0.26; CI 0.21–0.33). Recurrent major depressive disorder was similarly reduced (0.9% vs 3.3%; RR 0.27; CI 0.19–0.37). Significant risk reductions were also observed for phobic anxiety disorders (RR 0.43; CI 0.24–0.79), other anxiety disorders (RR 0.33; CI 0.28–0.39), persistent mood disorders (RR 0.297; CI 0.16–0.54), and unspecified mood disorders (RR 0.37; CI 0.22–0.62). Sleep disorders unrelated to substances or known physiological conditions were also reduced (0.73% vs 2.67%; RR 0.28; CI 0.19–0.40). Additionally, mental and behavioral disorders due to psychoactive substance use were less common in treated patients (1.09% vs 4.80%; RR 0.22; CI 0.17–0.30).

The association with obsessive–compulsive disorder did not achieve statistical significance (RR 0.53; CI 0.25–1.13). Although the point estimates for bipolar disorder (RR 0.23; CI 0.12–0.46)

TABLE 1.

Relative Risk of Psychiatric Comorbidities in Adults With Vitiligo Treated With Topical Ruxolitinib 1.5% Cream versus Without

Outcomes	Vitiligo Patients Treated with Topical Ruxolitinib ≥18 Years Old (n = 4,936)	%	Vitiligo Patients without Topical Ruxolitinib Treatment ≥18 Years Old (n = 4,936)	%	Relative Risk (95% CI)	*P*-value
Depressive episode	94	1.90%	355	7.19%	0.26 (0.21,0.33)	< 0.0001
Major depressive disorder, recurrent	43	0.87%	163	3.30%	0.27 (0.19,0.37)	< 0.0001
Phobic anxiety disorders	15	0.30%	35	0.71%	0.43 (0.24,0.79)	0.0049
Other anxiety disorders	152	3.08%	478	9.68%	0.33 (0.28,0.39)	< 0.0001
Persistent mood disorders	14	0.28%	47	0.95%	0.30 (0.16,0.54)	< 0.0001
Unspecified mood disorder	20	0.41%	54	1.09%	0.37 (0.22,0.62)	< 0.0001
Sleep disorders not due to a substance or known physiological condition	36	0.73%	132	2.67%	0.28 (0.19,0.40)	< 0.0001
Mental and behavioral disorders due to psychoactive substance use	54	1.09%	237	4.80%	0.22 (0.17,0.30)	< 0.0001
Obsessive-compulsive disorder	≤ 10*	-	19	0.38%	0.53 (0.25,1.13)	0.0952
Bipolar disorder	≤ 10*	-	43	0.87%	0.231 (0.12,0.46)	< 0.0001
Schizophrenia, schizotypal and delusional disorders	≤ 10*	-	37	0.75%	0.269 (0.13,0.54)	< 0.0001
Outpatient Visits	107	2.17%	563	11.41%	0.32 (0.27,0.39)	< 0.0001
Psychiatry Services and Procedures	45	0.91%	149	3.02%	0.31 (0.22,0.43)	< 0.0001

* Indicates outcomes with ≤10 patients; effect estimates for these outcomes should be interpreted with caution due to limited sample size or data availability.

and schizophrenia, schizotypal, and delusional disorders (RR 0.27; CI 0.13–0.54) suggested a reduced risk in treated patients, the small number of events limited the precision of these findings and should be interpreted with caution due to limited statistical power. Mental health service utilization was significantly reduced in treated patients, with outpatient psychiatric visits occurring in 2.17% versus 11.41% of treated versus untreated patients (RR 0.32; CI 0.27–0.39), and overall psychiatric services utilization similarly reduced (0.91% vs 3.02%; RR 0.31; CI 0.22–0.43).

DISCUSSION

Our large, multicenter analysis demonstrates that adults with vitiligo who were prescribed topical ruxolitinib exhibited markedly lower incidence of several psychiatric comorbidities compared with matched patients unexposed to the drug. Specifically, significant reductions in depressive episodes, recurrent major depressive disorder, multiple anxiety disorders, persistent mood disorders, substance use disorders, and sleep disturbances were identified. These findings extend beyond the established cutaneous efficacy of topical ruxolitinib by suggesting potential secondary mental health benefits associated with its use in vitiligo populations.

These findings raise the possibility that effective repigmentation treatment with topical ruxolitinib may mitigate psychiatric morbidity by alleviating psychosocial distress, restoring skin appearance, and modifying patient self-perception. While the psychiatric benefit is plausibly mediated by visible repigmentation and improved quality of life, the biological mechanism underlying these associations warrants further exploration.[8] Cytokines regulated through JAK signaling, including interleukins (eg, IL-1β, IL-6) and interferons (eg, IFN-γ), have been implicated in the pathogenesis of depression and

anxiety via neuroinflammatory activation of the JAK–signal transducer and activator of transcription (STAT) pathway.[9-11] Thus, ruxolitinib's effects may not only be symptomatic through cutaneous improvements but may also reflect systemic modulation of inflammatory signals relevant to neuropsychiatric health.1[2] Unraveling these mechanisms is a key avenue for future mechanistic and translational studies.

Despite these encouraging results, several considerations temper interpretation. First, the study design was retrospective and relied on administrative coding, which introduces inherent susceptibility to misclassification bias. Although ICD-10 and CPT code algorithms provide validated means for identifying outcomes, they cannot fully capture psychiatric symptom severity, subclinical distress, or patient-reported quality of life, which are often the most relevant outcomes to patients. Additionally, reliance on prescription records to classify exposure could not conclusively differentiate topical from oral ruxolitinib, and our exclusion of patients with hematologic disorders cannot fully eliminate potential misclassification. These limitations underscore the need for confirmatory studies with verified treatment exposure.

Furthermore, the observed psychiatric benefits may be confounded by healthcare utilization patterns. Patients prescribed novel, specialty dermatologic treatments may have greater healthcare access, closer physician follow-up, and enhanced psychosocial support compared to untreated patients. These factors could independently reduce psychiatric morbidity. Although propensity score matching balanced demographic variables, residual confounding by socioeconomic status, disease severity, and location, or access to mental health services cannot be excluded.

While the temporal design ensured that outcomes were assessed after treatment initiation, retrospective observational analyses cannot definitively exclude reverse causation or unmeasured confounding. Randomized controlled trials incorporating psychiatric endpoints or large-scale prospective registries would be necessary to establish causality. Finally, although our study suggests a link between topical ruxolitinib use and improved psychiatric outcomes, whether these benefits are attributable to the drug itself, the process of treatment engagement, or the downstream psychosocial impact of visible repigmentation remains unresolved. Integrating objective skin-related outcomes (eg, Vitiligo Area Scoring Index (VASI), Patient Global Impression (PGI) scale) with validated psychiatric assessment tools could clarify the mediating pathways in future research.

CONCLUSION

Topical ruxolitinib use in adults with vitiligo was associated with a significantly reduced risk of developing diverse psychiatric disorders, reflecting benefits that extend beyond its cutaneous effects. These novel findings highlight the complex and bidirectional relationship between dermatologic disease activity and psychosocial health, emphasizing the importance of treatments that address both the visible manifestations of vitiligo and its often profound emotional and mental health impacts.

DISCLOSURES

Iltefat Hamzavi has served as an advisory board member for AbbVie; a consultant for Boehringer Ingelheim, AVITA Medical, Galderma Laboratories LP, Incyte, Pfizer, and UCB; a principal investigator for AVITA, Bayer, Estee Lauder, Ferndale Laboratories, Incyte Corporation, Lenicura, L'Oreal, Pfizer, and Unigen; immediate past president of the HS Foundation; and a board member of the Global Vitiligo Foundation. Henry Lim reports receiving investigator/research grants to his institution from Incyte, L'Oreal, Pfizer, and PCORI, acting as a consultant for ISDIN, Beiersdorf, Ferndale, L'Oréal, Eli Lilly, Zerigo Health, Skinosive, Kenvue, NAOS, and Cantabria Labs, and as a speaker at general educational sessions for La Roche-Posay, Cantabria Labs, Pierre Fabre, NAOS, Uriage, Pfizer, and ISDIN. All other authors have no financial disclosures or conflicts of interest.

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AUTHOR CORRESPONDENCE

Kermanjot S. Sidhu BS

E-mail:..... sidhuker@msu.edu