Emerging Insights in Vitiligo Therapeutics: A Focus on Oral and Topical JAK Inhibitors

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Vitiligo is a common autoimmune disorder characterized by cutaneous depigmentation that has a substantial impact on patient quality of life.[1] Vitiligo affects approximately 28.5 million individuals globally, with the highest lifetime prevalence occurring in Central Europe and South Asia.[2] In the United States, Asian American and Hispanic/Latine populations most commonly are affected.[3] The accompanying psychosocial burdens of vitiligo are particularly substantial among individuals with darker skin types, as evidenced by higher rates of concomitant anxiety and depression in these patients.[4] Despite this, patients with skin of color are underrepresented in vitiligo research.[2]

Treatment algorithms developed based on worldwide expert consensus recommendations provide valuable insights into the management of segmental and nonsegmental vitiligo.[5] The mainstay therapeutics include topical and oral corticosteroids, topical calcineurin inhibitors, and phototherapy. While vitiligo pathogenesis is not completely understood, recent advances have focused on the role of the Janus kinase (JAK)/signal transducer and activator of transcription pathway. Interferon gamma drives vitiligo pathogenesis through this pathway, upregulating C-X-C motif chemokine ligand 10 and promoting CD8+ T-cell recruitment, resulting in targeted melanocyte destruction.[6] The emergence of targeted therapeutics may address equity and inclusion gaps. Herein, we highlight innovations in vitiligo treatment with a focus on oral and topical JAK inhibitors.

Oral JAK Inhibitors for Vitiligo

The therapeutic potential of JAK inhibitors for vitiligo was first reported when patients with alopecia areata and comorbid vitiligo experienced repigmentation of the skin following administration of oral ruxolitinib.[7] Since this discovery, other oral JAK inhibitors have been investigated for vitiligo treatment. A phase 2b randomized clinical trial (RCT) of 364 patients examined oral ritlecitinib, a JAK3 inhibitor, and found it to be effective in treating active nonsegmental vitiligo.[8] Patients aged 18 to 65 years with active nonsegmental vitiligo that had been present for 3 months or more as well as 4% to 50% body surface area (BSA) affected excluding acral surfaces and at least 0.25% facial involvement were included. Treatment groups received 50 mg (with or without a 100- or 200-mg loading dose), 30 mg, or 10 mg daily for 24 weeks. The primary endpoint measured the percentage change in Facial Vitiligo Area Scoring Index (F-VASI) score. Significant differences in F-VASI percentage change compared with placebo occurred for those in the 50-mg group who received a loading dose (−21.2 vs 2.1 [$P<.001$]) and those who did not receive a loading dose (–18.5 vs

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Iain Noel Encarnacion and Noelle Desir have no relevant financial disclosures to report. Dr. Taylor has served as a consultant, advisory board member, investigator, and/or speaker for AbbVie, Allergan Aesthetics, Arcutis, Armis Biopharma, Avita Medical, Beiersdorf, Biorez, Bristol-Myers Squibb, Cara Therapeutics, Catalyst Medical Education, Concert Pharmaceuticals, Croma-Pharma GmbH, Dermsquared, Dior, Eli Lilly and Company, EPI Health, Estée Lauder, Evolus, Galderma, GloGetter, Hugel America, Incyte, Johnson & Johnson Innovative Medicine, LearnSkin, L'Oreal USA, MedScape, MJH LifeSciences, Pfizer, Piction Health, Sanofi, Scientis US, UCB, and Vichy Laboratories. Dr. Taylor also serves on the board of directors for Mercer Strategies; has received stock options for Armis Biopharma, GloGetter, and Piction Health; and has received royalties from McGraw-Hill.

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Cutis. 2025 March;115(3):73-75. doi:10.12788/cutis.1178

2.1 [$P<.001$]) as well as the 30-mg group (−14.6 vs 2.1 [$P=.01$]). Continued repigmentation of the skin was observed in the 24-week extension period, indicating that longer treatment periods may be necessary for optimal repigmentation results. Ritlecitinib generally was well tolerated, and the most common treatment-emergent adverse events were nasopharyngitis (15.9%), upper respiratory tract infection (11.5%), and headache (8.8%). Most patients identified as White (67.6%), with 23.6% identifying as Asian and 2.7% identifying as Black. The authors stated that continued improvement was observed in the extension period across all skin types; however, the data were not reported.[8]

Upadacitnib, an oral selective JAK1 inhibitor, also has demonstrated efficacy in nonsegmental vitiligo in a phase 2 RCT.[9] Adult patients (N=185) with nonsegmental vitiligo were randomized to receive upadacitinib 6 mg, 11 mg, or 22 mg or placebo (the placebo group subsequently was switched to upadacitinib 11 mg or 22 mg after 24 weeks). The primary endpoint measured the percentage change in F-VASI score at 24 weeks. The higher doses of upadacitinib resulted in significant changes in F-VASI scored compared with placebo (6 mg: −7.60 [95% CI, −22.18 to 6.97][$P=.30$]; 11 mg: −21.27 [95% CI, −36.02 to −6.52][$P=.01$]; 22 mg: −19.60 [95% CI, −35.04 to –4.16][$P=.01$]). As with ritlecitinib, continued repigmentation was observed beyond the initial 24-week period. Of the 185 participants, 5.9% identified as Black and 13.5% identified as Asian. The investigators reported that the percentage change in F-VASI score was consistent across skin types.[9] The results of these phase 2 RCTs are encouraging, and we anticipate the findings of 2 phase 3 RCTs for ritlecitinib and upadacitinib that currently are underway (Clinicaltrials.gov identifiers NCT05583526 and NCT06118411).

Topical JAK Inhibitors for Vitiligo

Tofacitinib cream 2%, a selective JAK3 inhibitor, has shown therapeutic potential for treatment of vitiligo. One of the earliest pilot studies on topical tofacitinib examined the efficacy of tofacitinib cream 2% applied twice daily combined with narrowband UVB therapy 3 times weekly for facial vitiligo. The investigators reported repigmentation of the skin in all 11 patients (which included 4 Asian patients and 1 Hispanic patient), with a mean improvement of 70% in F-VASI score (range, 50%-87%).[10] In a nonrandomized cohort study of 16 patients later that year, twice-daily application of tofacitinib cream 2% on facial and nonfacial vitiligo lesions resulted in partial repigmentation in 81.3% of patients: 4 (25%) achieved greater than 90% improvement, 5 (31.3%) achieved improvement of 25% to 75%, and 4 (25%) achieved 5% to 15% improvement.[11] The researchers also found that tofacitinib cream 2% was significantly more effective in facial than nonfacial lesions ($P=.02$).

While tofacitinib has shown promise in early studies, recent advancements have led to US Food and Drug Administration approval of ruxolitinib cream 1.5%, another topical JAK inhibitor that has undergone robust clinical testing for vitiligo.[12-14] Ruxolitinib, a JAK1, JAK2, and JAK3 inhibitor, is the first and only US Food and Drug Administration–approved topical JAK inhibitor for vitiligo.[14,15] Two phase 3, double-blind, vehicle-controlled trials of identical design conducted across 101 centers in North America and Europe (TRuE-V1 and TRuE-V2) assessed the efficacy of ruxolitinib cream 1.5% in 674 patients aged 12 years and older with nonsegmental vitiligo covering 10% or lower total BSA.[13] In both trials, twice-daily application of topical ruxolitinib resulted in greater facial repigmentation and improvement in F-VASI75 score (ie, a reduction of at least 75% from baseline) at 24 weeks in 29.9% (66/221) and 30.1% (69/222) of patients in TRuE-V1 and TRuE-V2, respectively. Continued application through 52 weeks resulted in F-VASI75 response in 52.6% (91/173) and 48.0% (85/177) of patients in TRuE-V1 and TRuE-V2, respectively. The most frequently reported adverse events were acne (6.3% [14/221] and 6.6% [15/228]), nasopharyngitis (5.4% [12/221] and 6.1% [14/228]), and pruritus (5.4% [12/221] and 5.3% [12/228]). These findings align with prior subgroup analyses of an earlier phase 2 double-blind RCT of ruxolitinib cream 1.5% that indicated similar improvement in vitiligo among patients with differing skin tones.[17]

There are no additional large-scale RCTs examining topical JAK inhibitors with intentional subanalysis of diverse skin tones.[16,17,18] Studies examining topical JAK inhibitors have expanded to be more inclusive, providing hope for the future of topical vitiligo therapeutics for all patients.

Final Thoughts

It is imperative to increase racial/ethnic and skin type diversity in research on JAK inhibitors for vitiligo. While the studies mentioned here are inclusive of an array of races and skin tones, it is crucial that future research continue to expand the number of diverse participants, especially given the increased psychosocial burdens of vitiligo in patients with darker skin types.[4] Intentional subgroup analyses across skin tones are vital to characterize and unmask potential differences between lighter and darker skin types. This point was exemplified by a 2024 RCT that investigated ritlecitinib efficacy with biomarker analysis across skin types.[19] For patients receiving ritlecitinib 50 mg, IL-9 and IL-22 expression were decreased in darker vs lighter skin tones ($P<.05$). This intentional and inclusive analysis revealed a potential immunologic mechanism for why darker skin tones respond to JAK inhibitor therapy earlier than lighter skin tones.[19]

In the expanding landscape of oral and topical JAK inhibitors for vitiligo, continued efforts to assess these therapies across a range of skin tones and racial/ethnic groups are critical. The efficacy of JAK inhibitors in other populations, including pediatric patients

and patients with refractory segmental disease, have been reported.[20,21] As larger studies are developed based on the success of individual cases, researchers should investigate the efficacy of JAK inhibitors for various vitiligo subtypes (eg, segmental, nonsegmental) and recalcitrant disease and conduct direct comparisons with traditional treatments across diverse skin tones and racial/ethnic subgroup analyses to ensure broad therapeutic applicability.

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