Advancements in Targeted Therapies for Vitiligo: Prioritizing Equity in Drug Development

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PRACTICE POINTS

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- Individuals with skin of color are underrepresented in patient cohorts for JAK inhibitor clinical trials for vitiligo, mirroring a phenomenon seen in the majority of clinical trials. Ensuring diverse participant enrollment and measuring quality-of-life metrics will strengthen future clinical trials for treatment of vitiligo and other skin diseases impacting patients with skin of color.

Vitiligo is a common acquired autoimmune disease that causes depigmented patches to develop throughout the skin, with descriptions dating back more than 3000 years to the earliest known Indian and Egyptian texts. Approximately 1.4% of the worldwide population has vitiligo, and onset follows a bimodal age distribution with an early-onset population (mean age at onset, 10.3 years) as well as an adult-onset population (mean age at onset, 34 years). Vitiligo manifests as well-defined, irregular, depigmented macules and patches surrounded by normal skin. The patches can vary in size from a few millimeters to several centimeters. There may be signs of inflammation, and the lesions can be itchy, but in most cases vitiligo is asymptomatic. In nonsegmental vitiligo, the depigmented patches are symmetrical, can appear in any area of the body, and commonly progress slowly. In segmental vitiligo, the patches are unilateral, rarely cross the midline of the body, and are localized to one area. Segmental vitiligo commonly appears in childhood and progresses rapidly.

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but stops abruptly within 6 to 12 months and remains stable, usually for life.\(^3\) Although the condition may be more apparent in patients with skin of color, vitiligo manifests at a similar rate in individuals of all races and ethnicities.\(^4\)

Similar to most autoimmune diseases, vitiligo has a strong genetic predisposition. Although the overall prevalence of vitiligo is less than 2%, having a family history of vitiligo (ie, a first-degree relative with vitiligo) increases an individual’s risk to 6%, while concordance in identical twins is 23%.\(^5\) Beyond genetic predisposition, there is strong evidence that environmental exposures, such as hair dyes, contribute to risk for disease.\(^6\)

Interestingly, vitiligo is associated with polyautoimmunity—the presence of multiple autoimmune diseases in a single patient,\(^7\) such as type 1 diabetes mellitus, rheumatoid arthritis, autoimmune thyroid disease, pernicious anemia, and Addison disease. Similar to vitiligo itself, polyautoimmunity is likely driven by a combination of genetic and environmental factors.\(^8\)

We provide a brief overview of clinical trial results of Janus kinase (JAK) inhibitors for treating vitiligo and discuss the trial cohorts, with an emphasis on the impact of cohort demographic composition for individuals with skin of color. We recommend factors that investigators should consider to ensure equitable representation of individuals with skin of color in future clinical trials.

**Autoimmune Pathogenesis and Treatment With JAK Inhibitors**

Vitiligo is driven by autoreactive CD8\(^+\) T cells that target melanocytes and secrete IFN-\(\gamma\). Signaling of IFN-\(\gamma\) occurs through the JAK–signal transducer and activator of transcription (JAK–STAT) pathway, leading to transcriptional changes that activate proinflammatory genes such as the chemokine CXCL10, which is required for the directed accumulation of melanocyte-specific CD8\(^+\) T cells at the epidermis where melanocytes reside.\(^8\) Once vitiligo has been initiated, the disease persists due to the presence of resident memory T cells that remain in the skin and destroy new melanocytes.\(^9,10\)

Given the central role of IFN-\(\gamma\) signaling in the pathogenesis of vitiligo, drugs that inhibit JAK signaling are appealing to treat the disease. These JAK inhibitors bind to the kinase domain of JAK to prevent its activation, thus preventing downstream signaling events including STAT phosphorylation and its translocation to the nucleus, which ultimately stops the upregulation of inflammatory gene transcription. This process attenuates the autoimmune response in the skin and results in repigmentation of vitiligo lesions. In 2022, the US Food and Drug Administration approved the topical JAK inhibitor ruxolitinib for the treatment of vitiligo. Additional clinical trials have been initiated to test oral JAK inhibitors—ritlecitinib (ClinicalTrials.gov identifiers NCT06163326, NCT06072183, NCT05583526), povo-ricitinib (NCT04818346, NCT06113445, NCT06113471), and upadacitinib (NCT04927975, NCT06118411)—with strong results reported so far.\(^11\)

The effects of JAK inhibitors can be striking, as shown in the Figure. A patient of one of the authors (J.E.H.) used topical ruxolitinib on only the left arm for approximately 36 weeks and results were as expected—strong repigmentation of only the treated area, which is possible with JAK inhibitors. Indeed, 2 phase 3 studies—Topical Ruxolitinib Evaluation in Vitiligo (TRuE-V1 and TRuE-V2)—showed that approximately 30% of participants in TRuE-V1 (\(N=330\)) and 30.9% of participants in TRuE-V2 (\(N=344\)) achieved at least 75% improvement over baseline in the facial vitiligo area scoring index (VASI).\(^12\) In the oral ritlecitinib phase 2b study, 12.1% of the 187 participants on the highest tested dose of ritlecitinib (loading dose of 200 mg/d for 28 days, followed by 50 mg/d maintenance dose) achieved at least 75% improvement over baseline in the VASI at 24 weeks.\(^13\) Although this rate is lower than for topical ruxolitinib, this trial required all participants to have active disease (unlike the TRuE-V trials of ruxolitinib), which likely created a higher bar for repigmentation and thus resulted in fewer participants achieving the primary outcome at the early 6-month end point. Extension of treatment through 48 weeks demonstrated continued improvement over baseline without any evidence of plateau.\(^11\) Although treatment with JAK inhibitors can result in dramatic repigmentation of vitiligo patches, it falls short of providing a permanent cure, as stopping treatment results in relapse (ie, the return of depigmented lesions).
Racial Disparities in Clinical Trials

Even though vitiligo affects all skin types and races/ethnicities with similar prevalence and severity, the proportion of individuals with darker skin types enrolled in these clinical trials fails to match their representation in the population as a whole. A study examining the prevalence of vitiligo in the United States reported that Black or African American individuals represented 15.8% of vitiligo diagnoses in the United States even though they are only 12.7% of the total US population. However, Black or African American individuals comprised only 5% of the combined participants in the TRuE-V clinical trials for topical ruxolitinib and 2.7% of the participants in the phase 2b study of oral ritlecitinib. This lack of appropriate representation is not unique to JAK inhibitors or other vitiligo trials. Indeed, the US Food and Drug Administration reported that Black or African American individuals comprised only 8% of participants for all clinical trials in 2020.

Efficacy Metrics Beyond Repigmentation

Disparities in quality-of-life (QOL) metrics in diseases affecting individuals with skin of color also exist. In vitiligo, the contrast between affected and unaffected skin is greater in patients with skin of color, which means that for a given VASI score, the visibility of depigmentation as well as repigmentation may be variable among patients. Additionally, there is evidence that QOL concerns vary between patients with skin of color and those with lighter skin types. Ezzedine et al observed that QOL concerns in vitiligo patients with darker skin focused more on appearance, while concerns in vitiligo patients with lighter skin focused more on skin cancer risk. In addition to QOL differences among individuals with different skin types, there are also well-documented differences in attitudes to vitiligo among certain ethnic or cultural groups. For example, the Rigveda (an ancient Hindu text) indicates that individuals with vitiligo and their progeny are disqualified from marriage. Although the JAK inhibitor clinical trials for vitiligo did not appear to show differences in the degree of repigmentation among different skin types or races/ethnicities, QOL measures were not collected as a secondary end point in these studies—despite the fact that at least 1 study had documented that QOL measures were not uniform across patients when stratified by age and extent of disease. This same study also presented limited data suggestive of lower QOL in patients with the darkest skin phototype.

Considerations for Future Clinical Trials

It is logical to assume that every clinical trialist in dermatology seeks equitable representation among a diverse set of races, ethnicities, and skin types, but achieving this goal remains elusive. Two recent publications outlined the challenges and examined solutions to address enrollment disparities, including several barriers to diversity among clinical trial participants: awareness of the clinical trials among minority populations; easy access to clinical trial sites; reluctance to participate because of prior experiences of discrimination, even if unrelated to clinical trials; and a lack of workforce diversity among the clinical trialist teams. To overcome these barriers, a multifaceted approach is needed that requires action at the level of the patient, provider, community, and institution. Once diverse representation is achieved, investigators should consider the need for QOL metrics as a secondary outcome in their trials, which will ensure that the intended clinical effect is matched by patient expectations.

REFERENCES