Review Article

Review of Ruxolitinib for Treatment of Non-Segmental Vitiligo

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Abstract

Objective: To review the pharmacokinetics, efficacy, and safety of topical ruxolitinib for treatment of nonsegmental vitiligo. **Data Sources:** Literature published between January 1983 and October 2022 was reviewed from MEDLINE and ClinicalTrials.gov. **Study Selection and Data Extraction:** Relevant articles in English and data from clinical trials were included. **Data Synthesis:** In 2 phase II trials, treatment with ruxolitinib cream showed significant improvements in Vitiligo Area Scoring Index (VASI) scores compared with controls. The 1.5% concentration applied twice daily showed the best results after 52 weeks, with 50% VASI improvement in 58% of patients, 75% VASI improvement in 52% of patients, and 90% VASI improvement in 33% of patients. In 2 phase III trials, more patients achieved at least 75% improvement in facial VASI at 24 weeks (primary endpoint; trial 1: 29.9%, trial 2: 29.9%) than controls (trial 1: 7.5% [$P < 0.0001$], trial 2: 12.9% [$P < 0.01$]). Common adverse effects were erythema, pruritus, and acne; all events were mild. **Relevance to Patient Care and Clinical Practice in Comparison to Existing Drugs:** This review summarizes the pharmacokinetics, efficacy, and safety data regarding topical ruxolitinib for vitiligo. Ruxolitinib is associated with significant clinical improvements with low bioavailability and minimal adverse effects compared with conventional topical steroids, calcineurin inhibitors, phototherapy, and depigmentation agents. **Conclusions:** Ruxolitinib cream is the first therapy approved by the Food and Drug Administration for repigmentation of nonsegmental vitiligo. Clinicians should consider these benefits when recommending treatment as conventional therapies may be time-intensive and carry greater risks of adverse effects.

Keywords
vitiligo, ruxolitinib, dermatology, clinical pharmacology

Introduction

Vitiligo is a chronic depigmenting skin disease caused by autoimmune destruction of melanocytes. The proposed pathogenesis is likely multifactorial, involving genetic, autoimmune, and oxidative stress components. In the United States, approximately 1.9 to 2.8 million people are affected with an estimated prevalence between 0.76% and 1.11%. The condition affects males and females equally and people of all types of races, ethnicities, and socioeconomic statuses.[1] It may appear at any age, with peak incidences in the second and third decades of life. Approximately one-third of patients with vitiligo are children, and 70% to 80% of adult patients develop vitiligo prior to age 30 years.[2]

Vitiligo commonly presents as depigmented macules and patches anywhere on the body and can have profound effects on a patient's well-being and identity.[2] The condition is classified in 2 main categories: nonsegmental and segmental. Nonsegmental vitiligo is the most common type, and the lesions often appear symmetrically and bilaterally. Segmental vitiligo is unilateral and asymmetric with an earlier age of onset.[3] Vitiligo is often associated with other autoimmune comorbid conditions including but not limited to thyroid disease, type 1 diabetes mellitus, psoriasis, alopecia areata, inflammatory bowel disease, and rheumatoid arthritis.[4] Unlike most autoimmune disorders, vitiligo can be reversible, and repigmentation can occur with proper treatment. The pigment often returns in a speckled perifollicular pattern because melanocytes within the hair follicles are often spared due to immune privilege in this area. Hair follicles also contain melanocyte stem cells capable of regeneration.[2] However, if left untreated, vitiligo lesions may spread diffusely throughout the skin. Because the disease course is unpredictable as lesions can flare-up, progress at various rates, or remain stable, it is important to

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recognize this condition early and begin treatment as soon as possible.

On July 18, 2022, the Food and Drug Administration (FDA) approved topical ruxolitinib 1.5% cream for treatment of nonsegmental vitiligo.[5] This is the first and only approved medication for repigmentation of vitiligo in adults and children aged 12 years and older. This article aims to provide an overview of the pharmacokinetics, efficacy, and safety of ruxolitinib and discuss the benefits of this drug formulation as a treatment option for vitiligo.

Data Selection

Literature published between January 1983 and October 2022 was reviewed from MEDLINE and ClinicalTrials.gov. Relevant articles in English and results from human clinical trials discussing the use of ruxolitinib for vitiligo were included.

Mechanism of Action/ Pharmacodynamics

Inflammatory damage induced by CD8+ cytotoxic T cells is 1 of the key immune responses leading to depigmentation and destruction of melanocytes in vitiligo. In early molecular studies, abundant amounts of CD8+ T cells were noted on both histology and flow cytometry in active disease cases.[6,7] Activation of CD8+ T cells begins with the binding of interferon-γ to its heterodimeric receptor on keratinocytes, which stimulates Janus kinase 1/2 (JAK1/JAK2) and signal transducer and activator of transcription 1 (STAT1) to induce the production of chemokine ligand 9 and 10 (CXCL9 and CXCL10).[8]

The primary role of CXCL9 appears to be in the recruitment of T cells, as the absence of CXCL9 was shown to reduce the number of T cells by 10-fold. Meanwhile, CXCL10 is thought to play a role in the localization of T cells to the epidermis, as the number of T cells in the epidermis is reduced in the absence of CXCL10. Interestingly, only the lack of CXCL10 was associated with reduced vitiligo severity rather than a change in the number of T cells, suggesting CXCL10 may also contribute to the function of T cells.[9]

Once released, CXCL9 and CXCL10 bind to the CXCR3 receptor on CD8+ cytotoxic T cells to further activate the JAK/STAT pathway and recruit more T cells that destroy melanocytes. The cycle continues in a positive feedback loop. Of note, expression of all 3 markers was significantly elevated in the serum and skin of patients with vitiligo and was higher in patients with progressive disease than in those with a stable disease.[10] Ruxolitinib prevents this inflammatory signaling pathway by inhibiting the JAK/STAT signaling pathway. Ruxolitinib specifically targets JAK1 and JAK2, which reduces the production of CXCL9 and CXCL10 to prevent T-cell recruitment.

Pharmacokinetics

For any topical medication, it is important to assess the steady-state concentration and bioavailability to better understand the systemic safety profile. The pharmacokinetics of ruxolitinib 1.5% cream was assessed using blood samples collected in phase II and III trials for atopic dermatitis.[11] The average bioavailability was 6.2% ± 7.7%, and the mean steady-state concentration (C_{ss}) on day 28 was 35.7 ± 55.0 nM.[12] The mean terminal half-life of ruxolitinib following topical application is around 116 hours, and plasma protein binding is approximately 97%.[13]

Oral formulations of ruxolitinib have been used for patients with myelofibrosis at a dose of 25 mg twice daily. This formulation has an increased systemic exposure with a reported C_{ss} of 350 nM on day 10. Thrombocytopenia and anemia have also been noted at a half-maximal inhibitory concentration value of 281 nM.[14,15]

Clinical Trial Results

Phase II—NCT02809976

The first study to assess topical ruxolitinib in vitiligo was an open-label, phase II, proof-of-concept trial (NCT02809976) (Table 1).[16] A total of 11 patients were enrolled, and 9 patients completed the study as 2 patients were lost to follow-up. All patients had a minimum of 1% body surface area (BSA) affected, with the mean BSA of 11%. Patients were asked to apply topical ruxolitinib 1.5% cream twice a day (BID) and were limited to 10% BSA to minimize systemic exposure. All other treatment agents for vitiligo were prohibited during this study. Five patients had vitiligo that was progressive at their baseline visit, and the remaining 6 had a stable disease within the 4 weeks before ruxolitinib initiation.

At the end of the 20-week treatment period, all enrolled patients exhibited a statistically significant 23% improvement in overall Vitiligo Area Scoring Index (VASI) scores (95% CI, 4%-43%; $P = 0.02$). The VASI score is calculated by the summation of the percentage of vitiligo involvement at 6 body regions (head/neck, trunk, arms, legs, hands, and feet) multiplied by residual depigmentation.[17] The most notable repigmentation response was on the face as 4 patients with significant facial involvement at baseline (BSA > 0.5%) had an improvement in VASI scoring of 76% (95% CI, 53%-99%; $P = 0.001$). Repigmentation in other areas was not statistically significant as only 3 of 8 patients with vitiligo on the extremities and the trunk had a mean 0.3% change in VASI score, and 1 of 8 patients with vitiligo on the acral surfaces had a mean 1.5% change in VASI score. The differences in the efficacy of repigmentation of the face compared with the acral surfaces highlight how repigmentation patterns can differ greatly depending on the availability of melanocyte precursors and stem cells in the epidermis or in hair follicles.

Table 1. Summary of the Results From Phase II Clinical Trial NCT02809976.

	Ruxolitinib 1.5% cream twice daily (N = 11)
Patient demographics	
Age, years	52
Baseline VASI score	9.8 (18.3)
Baseline BSA involved, %	11.1 (19.6)
Duration of disease, years	8.45
Previous steroid use, # of patients	2
Areas affected by vitiligo, # of patients	
>0.5% BSA of face	4
Acral surfaces	8
Nonacral extremities	8
Trunk	4
Results	
Average improvement in overall VASI scores	23% (4-43%)
Average improvement in overall VASI scores in the 4 patients with significant facial involvement	*76% (53-99%)
Adverse effects, # of patients	
Hyperpigmented rim	9
Erythema	5
Upper respiratory symptoms	4
Acne	2

Data is listed as mean (SD) or mean (range).
Abbreviations: BSA, body surface area; VASI, Vitiligo Area Scoring Index.
*$P < 0.001$ vs vehicle at week 20.

All reported adverse effects were mild, and no adverse effects were serious enough to lead to study discontinuation. The most common adverse effects reported were a hyperpigmented rim around vitiligo lesions, erythema, upper respiratory symptoms, and transient facial acne. The limitations of this study are the small sample size, lack of randomization and blinding, short duration, and limited application of ruxolitinib to only 10% BSA.

Phase II—NCT03099304

One year later, a randomized, double-blind phase II trial was performed across 26 hospitals in the United States (NCT03099304) (Table 2).[18] A total of 157 patients were enrolled and assigned in a 1:1:1:1:1 ratio to either the vehicle control group or treatment with 0.15% ruxolitinib cream once daily (QD), 0.5% cream QD, 1.5% cream QD, or 1.5% cream BID for 24 weeks. Patients were limited to treating 20% of their BSA during the trial. After 24 weeks, patients initially assigned to the vehicle control group and to 0.15% QD who did not achieve at least a 25% improvement from baseline in facial VASI (F-VASI) score were randomly assigned to 1 of 3 higher dosing groups for an additional 28 weeks. Eligibility criteria for this study included patients with affected areas greater than or equal to 0.5% of facial BSA and 3% of nonfacial BSA. Patients were excluded if they received phototherapy within 8 weeks of screening, any biologic or experimental therapy within 12 weeks of screening, or immunomodulating oral or topical medications (ie, corticosteroids, methotrexate, cyclosporine, tacrolimus/pimecrolimus, retinoids) within 4 weeks of screening. All other treatment agents for vitiligo were prohibited during this study.

The primary endpoint was the proportion of patients achieving a 50% or higher improvement from baseline in facial VASI score (F-VASI50) at week 24. Results showed F-VASI50 at week 24 was reached by significantly more patients treated with ruxolitinib 1.5% cream BID (45%) and QD (50%) than by those in the vehicle control group (3%). At week 52, a dose-dependent response was seen in T-VASI50 scores as well (36% in the 1.5% BID, 30% in 1.5% QD, 26% in 0.5% QD). Patients receiving the highest dose of 1.5% cream BID continued to show the greatest improvements after 52 weeks, with 58% of patients reaching F-VASI50, 52% of patients reaching 75% VASI improvement (F-VASI75), and 33% of patients reaching 90% VASI improvement (F-VASI90).

All doses were well tolerated with mild adverse effects. The most reported treatment-emergent adverse effects were acne, viral upper respiratory tract infection, and application site pruritus. Interestingly, the lowest dose of 0.15% QD had the greatest percentage of application site pruritus (19%), and the highest dose of 1.5% BID had the lowest (3%). The limitations of this study are the small sample size, short duration, and limited application of ruxolitinib to lesions constituting 20% or less of total BSA. To better understand the duration of effectiveness and recurrence of lesions, this study allowed patients to receive open-label ruxolitinib cream 1.5% twice daily for an additional 104 weeks with optional concurrent narrow-band ultraviolet light B (NBUVB) phototherapy, but the results from this extension period are not currently available.

Phase III—TRuE-V1 (NCT04052425) and TRuE-V2 (NCT04057573)

There were 2 pivotal randomized, double-blinded, phase III clinical trials, TRuE-V1 (NCT04052425) and TRuE-V2 (NCT04057573), that assessed the safety and efficacy of ruxolitinib cream in patients with vitiligo (Table 3).[19] Each study enrolled over 300 patients aged 12 years and older who had an official diagnosis of nonsegmental vitiligo. Key inclusion criteria included depigmented areas ≥0.5% of the BSA on the face, ≥0.5 F-VASI score, at least 3% of BSA on nonfacial areas, ≥3 T-VASI score, and a total BSA involvement of no greater than 10%. Key exclusion criteria included anyone who lacked pigmented hair on the facial vitiligo

Table 2. Summary of the Results From Phase II Trial NCT03099304.

	Vehicle cream twice daily (N = 32)	0.15% Ruxolitinib cream once daily (N = 31)	0.5% Ruxolitinib cream once daily (N = 31)	1.5% Ruxolitinib cream once daily (N = 30)	1.5% Ruxolitinib cream twice daily (N = 33)
Patient demographics					
Age, years	46.3 (13.1)	45.1 (11.5)	53.8 (14.3)	46.7 (11.7)	49.5 (12.3)
Baseline F-VASI	1.21 (0.85)	1.19 (0.75)	1.22 (0.71)	1.45 (0.98)	1.26 (0.81)
Baseline T-VASI	19.4 (18.5)	14.6 (9.1)	18.4 (15.4)	20.6 (18.5)	16.9 (12.3)
Duration of disease, years	15.4	13.7	10.8	14.7	13.5
Previous therapy, # of patients (%)					
Topical corticosteroids	16 (50%)	16 (52%)	12 (39%)	14 (47%)	14 (42%)
Calcineurin inhibitors	18 (56%)	14 (45%)	13 (42%)	11 (37%)	14 (42%)
Phototherapy	14 (44%)	5 (16%)	13 (42%)	11 (37%)	12 (36%)
Results, # of patients (%)					
Proportion of patients with F-VASI50 response (%) at week 24	1 (3%)	10 (32%)	8 (26%)	15 (50%)*	15 (45%)*
Proportion of patients with T-VASI50 response (%) at week 52	0	0	8 (26%)	9 (30%)	12 (36%)
Adverse effects, # of patients (%)					
Acne	1 (3%)	4 (13%)	5 (16%)	3 (10%)	6 (18%)
Viral upper respiratory tract infection	5 (16%)	3 (10%)	3 (10%)	6 (20%)	1 (3%)
Application site pruritus	3 (9%)	6 (19%)	3 (10%)	3 (10%)	1 (3%)

Data are listed as n (%) or mean (SD).
Abbreviations: F-VASI50, facial Vitiligo Area Scoring Index improvement of 50% or more; T-VASI50, total Vitiligo Area Scoring Index improvement of 50% or more.
*$P < 0.0001$ vs vehicle at week 24.

areas (poor prognostic indicator for repigmentation), forms of vitiligo other than nonsegmental (eg, segmental) or other skin depigmentation disorders, or prior use of depigmentation treatments (eg, monobenzone). All prior treatment agents for vitiligo were prohibited during this study.

Participants were randomized into 2 groups either receiving 1.5% ruxolitinib cream BID or a vehicle control for 24 weeks. Patients who successfully completed baseline and week-24 assessments were offered treatment extension with 1.5% ruxolitinib cream BID for an additional 28 weeks. After 24 weeks, the vehicle control group was crossed over to treatment with ruxolitinib 1.5% cream BID for the following 28 weeks. The primary endpoint of both studies was defined as the proportion of patients achieving F-VASI75 at week 24. Secondary endpoints assessed for the following changes at week 24: percent change from baseline in facial BSA and the proportion of patients achieving F-VASI50, T-VASI50, and F-VASI90.

A comparison of the results at week 24 and 52 showed overall clinical improvements in each of the endpoints, with greater improvements reported at the end of 52 weeks. The primary endpoint of F-VASI75 at week 24 was reported in 29.8% (TRuE-V1) and 30.9% (TRuE-V2) of patients in the ruxolitinib cream group compared with 7.4% (TRuE-V1) and 11.4% (TRuE-V2) in the vehicle group. At 52 weeks, an F-VASI75 response was observed in 52.6% of particioants in the TRuE-V1 trial and 48.0% of participants in the TRuE-V2 trial who applied ruxolitinib cream for 52 weeks. For patients who crossed over from vehicle cream to ruxolitinib cream for weeks 24 to 52, an F-VASI75 response was noted in 27% of participants in the TRuE-V1 trial and 30% of participants in the TRuE-V2 trial. For secondary endpoints, F-VASI50 was reported in approximately 51% of patients applying ruxolitinib at 24 weeks compared with 20% of patients applying the vehicle cream. An F-VASI90 response at week 24 occurred in 15.3% of patients in the TRuE-V1 trial and 16.3% of patients in the TRuE-V2 trial treated with ruxolitinib cream, compared with 2.2% and 1.3%, respectively, among those using vehicle cream. Results at week 52 in crossover patients who received 28 weeks of treatment with ruxolitinib cream after 24 weeks of vehicle cream showed similar results to the week 24 data in patients who applied ruxolitinib cream from day 1.

Throughout the studies, there were no serious treatment-related adverse events. The most reported adverse events were application site acne, application site pruritus, and nasopharyngitis.[19] Hematopoietic adverse events occurred in less than 1% of the study subjects and were not considered to be related to the trial agent. Plasma concentrations of ruxolitinib were similar in the 2 trials, with the mean ± SD steady-state concentration (average of week 4 and 24) reported to be 55.8 ± 56.7 nM in TRuE-V1 and 58.0 ± 68.1

Table 3. Summary of the Results From Phase III Trials TRuE-V1 (NCT04052425) and TRuE-V2 (NCT04057573).

	TRuE-V1		*TRuE-V2*	
	Vehicle (N = 109)	1.5% Ruxolitinib cream twice daily (N = 221)	Vehicle (N = 115)	1.5% Ruxolitinib cream twice daily (N = 228)
Patient demographics				
Age, years	39.7 (16.7)	40.5 (15.4)	39.8 (12.1)	38.4 (15.2)
Baseline F-VASI	1.00 (0.59)	0.93 (0.58)	0.83 (0.52)	0.90 (0.52)
Baseline T-VASI	6.42 (1.92)	6.49 (2.02)	7.02 (2.20)	6.84 (2.06)
Duration of disease, years	13.2	13.9	16.0	15.9
Previous treatment, # of patients (%)				
Topical corticosteroids	28 (26%)	67 (30%)	28 (24%)	66 (29%)
Calcineurin inhibitors	31 (28%)	72 (33%)	37 (32%)	74 (33%)
Phototherapy	20 (18%)	41 (18%)	27 (24%)	52 (23%)
Results, # of patients (%)				
Proportion of patients with F-VASI75 response (%) at week 24	8 (7.4%)	*66 (29.8%)	12 (11.4%)	69 (30.9%)*
Proportion of patients with F-VASI50 response (%) at week 24	18 (16.9%)	113 (51.2%)*	23 (20.9%)	114 (51.4%)*
Proportion of patients with F-VASI90 response (%) at week 24	2 (2.2%)	34 (15.3%)	1 (1.3%)	36 (16.3%)
Proportion of patients with T-VASI50 response (%) at week 24	6 (5.1%)	46 (20.6%)*	7 (6.8%)	53 (23.9%)*
Adverse effects, # of patients (%)				
Application site acne	0 (0%)	13 (6%)	3 (3%)	13 (6%)
Application site pruritus	4 (4%)	11 (5%)	2 (2%)	10 (4%)
Nasopharyngitis	4 (4%)	9 (4%)	1 (1%)	10 (4%)

Data is listed as n (%) or mean (SD).
Abbreviations: F-VASI75, facial Vitiligo Area Scoring Index improvement of 75% or more; F-VASI50, facial Vitiligo Area Scoring Index improvement of 50% or more; F-VASI90, facial Vitiligo Area Scoring Index improvement of 90% or more; T-VASI50, total Vitiligo Area Scoring Index improvement of 50% or more.
*$P < 0.001$ vs vehicle at week 24.

nM in TRuE-V2. The limitations of this study include the 10% BSA restriction, the exclusion of facial vitiligo patients who lacked pigmented hair, and the lack of diverse skin representation as the majority of patients had Fitzpatrick skin types I to III.

Dosage and Administration

The recommended dosage and administration of topical ruxolitinib cream for vitiligo is a 1.5% concentration applied as a thin layer twice daily in up to 10% of BSA, with a maximum dose of 60 g per week or 100 g per 2 weeks.[13] For reference, 1% BSA is equivalent to the surface area of 1 entire hand (palm and fingers), and 9% BSA is equivalent to the surface area of 1 anterior leg (from hip to sole of foot). The cream is supplied in 60-g or 100-g tubes by the providing pharmacy. Patients should be advised to avoid applying the cream to ophthalmic, oral, or intravaginal areas. Ruxolitinib use is contraindicated during any active infection or concurrent use of biologics, other JAK inhibitors, and azathioprine or cyclosporine. Patients should be advised to follow up with their care provider if significant repigmentation does not occur after 24 weeks of use. If repigmentation does occur, patients should follow up with their care provider to discuss continued use or adjusting application to different sites as there are no current standard guidelines at this time.

Of note, topical ruxolitinib cream 1.5% is also FDA-approved for atopic dermatitis. The maximum dosage and contraindications are the same for topical use in vitiligo. However, the 2 main differences in prescribing information for atopic dermatitis are (1) the cream can be applied up to 20% of BSA and (2) patients are advised to follow up with their care provider at 8 weeks if signs and symptoms do not improve.

Adverse Effects

The FDA issued multiple black box warnings over the use of ruxolitinib, based on the adverse effects of oral JAK inhibitors, which include increased risk of serious infections, major heart issues, blood clots, thrombocytopenia, anemia, neutropenia, cancer, increases in cholesterol, and death. However, in clinical trials assessing topical ruxolitinib for

both atopic dermatitis and vitiligo, none of the black boxed adverse effects were reported to be associated with the trial agent, and the measured plasma steady-state concentrations were much lower than those found in patients taking the oral form. However, due to the limited long-term safety studies, black box warnings remain listed as a potential adverse event associated with the topical formulation. Reported adverse effects for the topical formulation in vitiligo patients were generally mild to moderate and included erythema, application site pruritus, acne, nasopharyngitis, headache, and urinary tract infection.[13,16,18] Less than 1% of subjects in the TRuE-V1 and TruE-V2 trials experienced hypertension, anxiety, discoloration, folliculitis, contact dermatitis, diarrhea, ear infection, gastritis, gastroenteritis, influenza-like illness, insomnia, nasal congestion, and vomiting.[13]

Drug Interactions

Ruxolitinib is known to be a substrate for cytochrome P450 3A4. Inhibitors of CYP3A4 (ie, ketoconazole, erythromycin) may increase ruxolitinib systemic concentrations, whereas inducers of CYP3A4 (ie, rifampin) may decrease ruxolitinib systemic concentrations. There is also a potential interaction between topical ruxolitinib and pacritinib due to the inhibition of CYP450 1A2 and 3A4 by pacritinib.[13,20] Clinical data demonstrating the interaction are currently lacking, but concomitant use of pacritinib should be avoided if possible.

Relevance to Patient Care and Clinical Practice in Comparison to Existing Agents

Vitiligo can dramatically impact a patient's self-esteem, quality of life, and well-being. Psychological comorbidities associated with vitiligo include depression, anxiety, social phobia, feelings of stigmatization, sexual dysfunction, suicidality, and avoidance and restriction behavior.[21] In a study assessing common misperceptions about the disease, vitiligo was mistaken to be contagious or caused by external forces (ie, witchcraft or evil spirits), lack of hygiene, or infection.[22] Common coping strategies are concealment of lesions through clothing, camouflage, and altered body movements. Given the considerable psychosocial effects, efficacious treatment options and increased public awareness about the disease may help reduce the psychosocial burden among patients with vitiligo and allow them to feel more comfortable in their skin.

Prior to ruxolitinib, the conventional treatment options for vitiligo often required prolonged treatment courses, and the adverse effects varied widely. For repigmentation, topical corticosteroids are the most used agents for vitiligo, involving less than 10% of BSA. Corticosteroids are relatively affordable and easily accessible to the general population but are used off-label, and prolonged use can cause atrophy, telangiectasias, hypertrichosis, irregular pigmentation, acneiform eruptions, and perioral dermatitis. Topical calcineurin inhibitors such as tacrolimus ointment or pimecrolimus cream have fewer reported adverse effects but are off-label and associated with local reactions (ie, burning).[23] For patients with BSA involvement greater than 10%, phototherapy with NBUVB can be an effective treatment.[24] This treatment uses ultraviolet lamps with a peak emission of 311 nm. The proposed mechanism of repigmentation is due to the induction of local apoptosis, stimulation of melanocyte-stimulating hormones, and increase in melanocyte proliferation and melanogenesis.[25] However, this process requires multiple weekly visits to a dermatologist, and many patients are challenged by the intense time commitment.

When comparing the efficacy of conventional repigmentation agents to that of ruxolitinib, current research suggests ruxolitinib has shown greater improvements in repigmentation. In 1 study assessing the efficacy of corticosteroids and calcineurin inhibitors at 6 months, only 33% and 22% of patients showed 50% repigmentation, respectively.[26] In another study assessing responses with the NBUVB therapy, 37.4% of patients experienced 50% repigmentation at 6 months.[27] Relapse rates with conventional repigmentation products are as high as 40% within the first year after discontinuation.[4] However, further long-term studies are needed to assess the relapse rates of ruxolitinib. Recently, a 104-week study assessing the efficacy and safety of ruxolitinib cream 1.5% twice daily was completed. Results are pending at this time but will provide a better understanding of the long-term safety of ruxolitinib.

For patients with extensive depigmentation due to vitiligo when repigmentation therapies have failed, the depigmenting agent topical monobenzyl ether of hydroquinone (MBEH) is the only other FDA-approved medication for vitiligo. It received approval in 1952 as a depigmentation agent and is currently available as a 20% or 40% cream. The depigmentation effects are often irreversible as MBEH induces necrosis of melanocytes. Adverse effects include contact irritant dermatitis, loss of color (leukoderma), and ashy brown pigmentation (ochronosis). Prolonged use of MBEH may also lead to pigment deposition in the conjunctiva and cornea of the eyes.[28] Alternative topical therapies that have been used for depigmentation are 88% phenol, lasers, and imatinib. However, each therapy carries its own risks. Phenols are toxic at high doses and must be used cautiously because they can cause severe chemical burns, heart arrhythmias, and liver/kidney damage.[24] Lasers are expensive, require local anesthetics for pain, and have high rates of recurrence. Imatinib can cause periorbital edema, fluid retention, diarrhea, follicular mucinosis, erythroderma, and lichenoid eruption.[29]

Because vitiligo is a disorder of pigmentation and does not usually have any other major symptoms or life-threatening

potential, treatment may be declined by insurers. In a study of insurance coverage by 17 different organizations, the 2 most cited reasons for denial of coverage were (1) vitiligo is considered a cosmetic condition and (2) certain therapies are not FDA-approved for vitiligo.[30] The current wholesale acquisition cost of a 60-g tube of ruxolitinib 1.5% cream is $1,950, which is a financial challenge for many patients.[13] The recommended maximum weekly dose is 60 g, and patients are advised to apply a thin layer twice a day in up to 10% of BSA. Although the cost of ruxolitinib will vary based on the patient's insurance coverage and the amount needed, the official FDA approval will likely help improve access to the medication by validating the safety and efficacy of this medication.

Conclusions

Multiple phase II and III trials have shown treatment of nonsegmental vitiligo with ruxolitinib cream to yield clinically significant repigmentation with minimal adverse events. Further research studies with larger and more diverse patient populations are needed to assess the long-term safety data and the efficacy of ruxolitinib compared with other monotherapies or in combination with current treatment options. One clinical trial investigating ruxolitinib cream in combination with NBUVB phototherapy is in progress (ClinicalTrials.gov number: NCT05247489), and data from a 104-week open-label study are currently being evaluated.

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References

1. Gandhi K, Ezzedine K, Anastassopoulos KP, et al. Prevalence of vitiligo among adults in the United States. *JAMA Dermatol*. 2022;158:43-50. doi:10.1001/jamadermatol.2021.4724
2. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. *Lancet*. 2015;386:74-84. doi:10.1016/S0140-6736(14)60763-7
3. Ezzedine K, Lim HW, Suzuki T, et al. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res. 2012;25(3):E1-E13. doi:10.1111/j.1755-148X.2012.00997.x
4. Frisoli ML, Essien K, Harris JE. Vitiligo: mechanisms of pathogenesis and treatment. *Annu Rev Immunol*. 2020;38:621-648. doi:10.1146/annurev-immunol-100919-023531
5. US Food and Drug Administration. FDA approves topical treatment addressing repigmentation in vitiligo in patients aged 12 and older. Date unknown. Accessed August 6, 2022. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-topical-treatment-addressing-repigmentation-vitiligo-patients-aged-12-and-older.
6. Strassner JP, Rashighi M, Ahmed Refat M, Richmond JM, Harris JE. Suction blistering the lesional skin of vitiligo patients reveals useful biomarkers of disease activity. *J Am Acad Dermatol*. 2017;76(5):847-855.e5. doi:10.1016/j.jaad.2016.12.021
7. Le Poole IC, van den Wijngaard RM, Westerhof W, Das PK. Presence of T cells and macrophages in inflammatory vitiligo skin parallels melanocyte disappearance. *Am J Pathol*. 1996;148(4):1219-1228.
8. Marchioro HZ, Silva de Castro CC, Fava VM, Sakiyama PH, Dellatorre G, Miot HA. Update on the pathogenesis of vitiligo. *An Bras Dermatol*. 2022;97:478-490. doi:10.1016/j.abd.2021.09.008
9. Rashighi M, Agarwal P, Richmond JM, et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci Transl Med*. 2014;6:223ra23. doi:10.1126/scitranslmed.3007811
10. Wang XX, Wang QQ, Wu JQ, et al. Increased expression of CXCR3 and its ligands in patients with vitiligo and CXCL10 as a potential clinical marker for vitiligo. *Br J Dermatol*. 2016;174(6):1318-1326. doi:10.1111/bjd.14416
11. Gong X, Chen X, Kuligowski ME, et al. Pharmacokinetics of ruxolitinib in patients with atopic dermatitis treated with ruxolitinib cream: data from phase II and III studies. *Am J Clin Dermatol*. 2021;22(4):555-566. doi:10.1007/s40257-021-00610-x
12. Bissonnette R, Call RS, Raoof T, et al. A maximum-use trial of ruxolitinib cream in adolescents and adults with atopic dermatitis. *Am J Clin Dermatol*. 2022;23(3):355-364. doi:10.1007/s40257-022-00690-3
13. Opzelura (ruxolitinib) [package insert]. Wilmington, DE: Incyte Corporation; 2022. Accessed August 6, 2022. https://www.opzelura.com/prescribing-information.pdf.
14. Quintás-Cardama A, Vaddi K, Liu P, et al. Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms. *Blood*. 2010;115:3109-3117. doi:10.1182/blood-2009-04-214957
15. Chen X, Williams W, v Sandor V, Yeleswaram S. Population pharmacokinetic analysis of orally-administered ruxolitinib (INCB018424 Phosphate) in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. *J Clin Pharmacol*. 2013;53:721-730. doi:10.1002/jcph.102
16. Rothstein B, Joshipura D, Saraiya A, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol*. 2017;76:1054-1060.e1. doi:10.1016/j.jaad.2017.02.049
17. Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. Parametric modeling of narrowband UV-B phototherapy for vitiligo ssing a novel quantitative tool: the Vitiligo Area Scoring Index. *Arch Dermatol*. 2004;140:677-683. doi:10.1001/archderm.140.6.677

18. Rosmarin D, Pandya AG, Lebwohl M, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. *Lancet*. 2020;396:110-120. doi:10.1016/S0140-6736(20)30609-7
19. Rosmarin D, Passeron T, Pandya AG, et al. Two phase 3, randomized, controlled trials of ruxolitinib cream for vitiligo. *N Engl J Med*. 2022;387:1445-1455. doi:10.1056/NEJMoa2118828
20. Vonjo (pacritinib) [package insert]. Seattle, WA: CTI BioPharma Corporation; 2022. Accessed August 6, 2022. https://www.ctibiopharma.com/VONJO_USPI.pdf.
21. Ezzedine K, Eleftheriadou V, Jones H, et al. Psychosocial effects of vitiligo: a systematic literature review. *Am J Clin Dermatol*. 2021;22(6):757-774. doi:10.1007/s40257-021-00631-6
22. Tsadik AG, Teklemedhin MZ, Mehari Atey T, Gidey MT, Desta DM. Public knowledge and attitudes towards vitiligo: a survey in Mekelle City, Northern Ethiopia. *Dermatol Res Pract*. 2020;2020:3495165. doi:10.1155/2020/3495165
23. Eleftheriadou V, Atkar R, Batchelor J, et al. British Association of Dermatologists guidelines for the management of people with vitiligo 2021. *Br J Dermatol*. 2022;186(1):18-29. doi:10.1111/bjd.20596
24. AlGhamdi KM, Kumar A. Depigmentation therapies for normal skin in vitiligo universalis. *J Eur Acad Dermatol Venereol*. 2011;25(7):749-757. doi:10.1111/j.1468-3083.2010.03876.x
25. Yones SS, Palmer RA, Garibaldinos TM, Hawk JL. Randomized double-blind trial of treatment of vitiligo: efficacy of psoralen-UV-A therapy vs narrowband-UV-B therapy. *Arch Dermatol*. 2007;143(5):578-584. doi:10.1001/archderm.143.5.578
26. Silpa-Archa N, Nitayavardhana S, Thanomkitti K, Chularojanamontri L, Varothai S, Wongpraparut C. Comparison of the efficacy and safety of 0.1% tacrolimus ointment and 0.1% mometasone furoate cream for adult vitiligo: a single-blinded pilot study. *Dermatol. Sin*. 2016;34:177-179. doi:10.1016/j.dsi.2016.05.005
27. Bae JM, Jung HM, Hong BY, et al. Phototherapy for vitiligo: a systematic review and meta-analysis. *JAMA Dermatol*. 2017;153:666-674. doi:10.1001/jamadermatol.2017.0002
28. Hedges TR III, Kenyon KR, Hanninen LA, Mosher DB. Corneal and conjunctival effects of monobenzone in patients with vitiligo. *Arch Ophthalmol*. 1983;101(1):64-68. doi:10.1001/archopht.1983.01040010066010
29. Tsao AS, Kantarjian H, Cortes J, O'Brien S, Talpaz M. Imatinib mesylate causes hypopigmentation in the skin. *Cancer*. 2003;98:2483-2487. doi:10.1002/cncr.1181230.
30. Blundell A, Sachar M, Gabel CK, Bercovitch LG. The scope of health insurance coverage of vitiligo treatments in the United States: implications for health care outcomes and disparities in children of color. *Pediatr Dermatol*. 2021;38(suppl 2):79-85. doi:10.1111/pde.14714