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REVIEW

Treatment of vitiligo with topical ruxolitinib: a narrative review

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Abstract

Vitiligo is a chronic autoimmune disorder characterized by the selective destruction of melanocytes, leading to depigmented patches of skin. Whilst its pathogenesis is not fully understood, genetic predisposition, environmental triggers, oxidative stress, metabolic dysfunction and impaired cell adhesion are all implicated. Vitiligo occurs in two primary forms — non-segmental and segmental — and affects approximately 0.5–2% of the global population. Beyond its physical manifestations, vitiligo imposes a significant psychosocial burden on patients. Current treatments include topical corticosteroids, calcineurin inhibitors, systemic immunosuppressants and narrowband UVB phototherapy. More recently, Janus kinase (JAK) inhibitors have emerged as promising targeted therapies. Topical ruxolitinib 1.5% cream has been approved by both the FDA and EMA for the treatment of non-segmental vitiligo in adolescents and adults, following its demonstrated efficacy and favourable tolerability in clinical trials. Although some risks, such as infection, malignancy, major adverse cardiovascular events and thrombosis, have been raised due to class-wide JAK inhibition concerns, these events appear to be rare with topical use, as no systemic drug accumulation has been reported. Given its safe and therapeutic profile, ruxolitinib is an effective targeted therapy for non-segmental vitiligo. This narrative study aims to review and synthesize the current evidence on the safety, efficacy and therapeutic impact of topical ruxolitinib cream in vitiligo.

Keywords: drug therapy, efficacy, JAK–STAT signalling pathway, Janus kinase inhibitors, ruxolitinib, safety, topical administration, vitiligo.

Citation

Monteiro e Silva G, Mohamed A, Ferreira C, Torres T. Treatment of vitiligo with topical ruxolitinib: a narrative review. *Drugs Context*. 2025;14:2025-5-2. https://doi.org/10.7573/dic.2025-5-2

Introduction

Vitiligo is an acquired, chronic, immune-mediated skin disease characterized by the destruction of melanocytes.[1] It is the most common depigmenting condition, affecting 0.5–2% of the global population, with no significant differences in prevalence based on sex, ethnicity, Fitzpatrick skin type or geographic region.[2,3] The average age of onset ranges from 10 to 35 years. Clinically, it is characterized by sharply defined, non-scaly white patches of skin that can appear on any area of the body.[3–5] In individuals with darker skin tones, the contrast between affected and unaffected areas can lead to greater social and psychological impact.[5] Vitiligo is classified as either segmental or non-segmental, with the latter being more prevalent and categorized based on anatomical distribution.[1,5] Non-segmental vitiligo typically has a bilateral distribution, often crossing the midline, and follows a chronic, slowly progressive course of depigmentation. In contrast, segmental vitiligo is typically unilateral, rarely crosses the midline, and is marked by a rapid onset followed by early disease stabilization.[1,5] Diagnosis is primarily clinical, though the use of a Wood's lamp can aid in visualizing amelanotic areas.[5] Dermoscopy is another diagnostic tool used by clinicians to observe the morphological features of vitiligo lesions.[6] Whilst rarely required, a skin biopsy may be performed to confirm the diagnosis in atypical cases.[5]

Disease progression is unpredictable and has often been marked by flare-ups: episodes of increased dis-

ease activity of either new or expanding depigmented patches. Vitiligo has also been linked to various autoimmune diseases, the most reported being rheumatoid arthritis, alopecia areata, atopic dermatitis and psoriasis, amongst others.[7] The psychosocial burden of vitiligo cannot be understated, with many patients frequently reporting worsening self-esteem, depression, anxiety, suicide ideation, social phobia, and cognitive and emotional impairment.[3,4,7,8]

Despite the growing understanding of its burden, vitiligo has long remained an area of unmet therapeutic need, with treatment historically relying on topical corticosteroids, calcineurin inhibitors, systemic immunosuppressants and narrowband UVB (NB-UVB) phototherapy. Whilst these approaches may offer partial or temporary repigmentation, their efficacy is often limited, particularly in recalcitrant or extensive disease. Relapse, that is, the clinically observed reappearance or further enlargement of depigmented lesions after a period of remission, is frequently seen following treatment discontinuation. Recent findings implicate the Janus kinase signal transducer and activator of transcription (JAK–STAT) pathway as a central mediator of vitiligo pathogenesis, driving melanocyte loss via interferon-γ (IFNγ) and interleukin signalling. In this context, ruxolitinib cream, a selective topical JAK1/2 inhibitor, has garnered considerable attention after recently becoming the first treatment approved for non-segmental vitiligo.

Unmet needs in the treatment of vitiligo

Although European and British vitiligo guidelines recommend tailoring treatment based on disease activity and severity, management must be chosen on an individual basis.[2] Early initiation of therapy is recommended, as repigmentation largely depends on the affected body areas and the extent of depigmentation.[1,9] It should be noted that nearly 50% of vitiligo lesions recur in the first year after repigmentation without maintenance therapy. For instance, studies have shown that applying tacrolimus 0.1% twice weekly, without the need for sun exposure, reduces the risk of relapse from 40% to 9.7% for facial lesions.[9]

For localized disease, first-line therapies typically include once-daily use of topical corticosteroids or twice-daily use of topical calcineurin inhibitors. In rapidly progressing cases with unstable, widespread or recalcitrant vitiligo, systemic corticosteroids - administered either orally or intramuscularly for up to 6 months - is used initially.[1–3,9] Topical calcineurin inhibitors are often favoured over corticosteroids in both adults and children due to a lower risk of skin atrophy. However, their use should be avoided in cases of superficial infections, malignancy, immunosuppression, significant sun exposure or local irritation.[2,5]

Phototherapy with NB-UVB radiation can be used, either alone or in combination with other treatments, to promote repigmentation. UVB radiation is preferred over UVA radiation due to its lower risk of side-effects, more accurate targeting of skin lesions and the absence of a need for a photosensitizing agent.[9] Treatment may be administered two to three times per week, but only if repigmentation is actively occurring.[2] It is well known that treating the extremities with NB-UVB phototherapy can be particularly challenging.[2] The most common acute adverse effect is erythema, which is dependent on skin type and dosage, typically appearing 12–24 hours after irradiation.[2] This form of therapy is not related to an increased risk of skin cancer, up to at least 400 sessions.[9]

Surgical approaches, such as epidermal suspension transplantation, may be considered for patients with segmental vitiligo or stable non-segmental vitiligo unresponsive to medical therapy for at least 12 months.[5,9] For individuals with depigmentation affecting over 50% of their body surface area, depigmentation strategies using agents like monobenzyl ether of hydroquinone or depigmenting lasers may be appropriate.[5,9]

Despite these options, the limited efficacy and adverse effects of existing therapies underscore the urgent need for safer, more effective treatments that also address quality of life.[2,3] Recently, 1.5% topical ruxolitinib received FDA and EMA approval for non-segmental vitiligo, prompting this narrative review to summarize current evidence on its efficacy, safety and therapeutic potential within the broader treatment landscape.

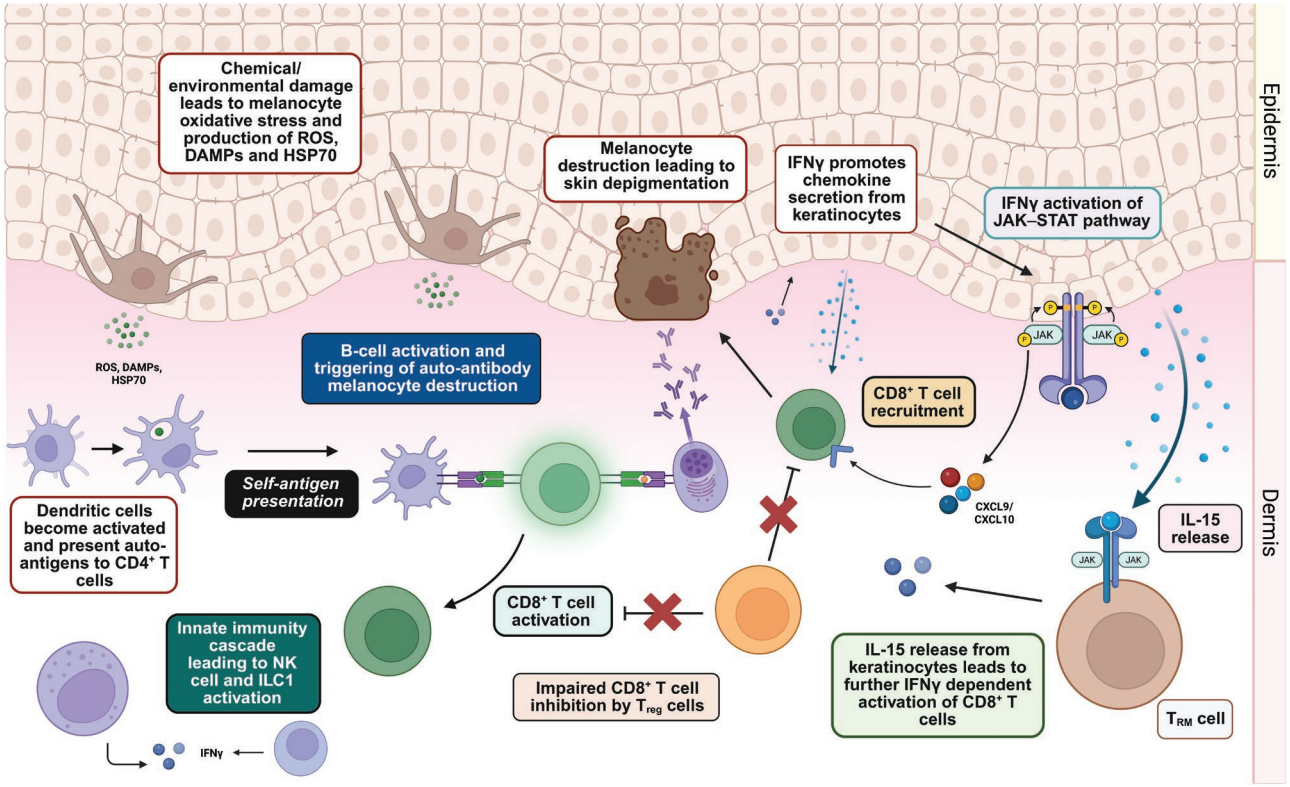
Review

Pathogenesis of vitiligo and role of the JAK–STAT pathway

The pathogenesis of vitiligo is primarily driven by autoreactive $CD8^+$ T cells, resulting in melanocyte destruction and subsequent depigmentation (Figure 1).[3,10] This process is influenced by a combination of genetic predisposition, oxidative stress and immune dysregulation.[2,10] Although vitiligo follows a polygenic inheritance pattern, environmental factors play a crucial role in its progression, often occurring unpredictably without a significant family history.[4]

The onset of vitiligo is commonly associated with external oxidative stressors, including UV radiation, chemical exposure and trauma, which cause melanocytes to release reactive oxygen species, heat shock protein 70 (HSP70) and damage-associated molecular patterns.[3] The accumulation of these molecules results in melanocyte dysfunction and increased antigen pres-

Figure 1. Immune pathogenesis of vitiligo. UV/chemical-induced oxidative stress leads to ROS production in melanocytes. Accumulation of HSP70 and DAMPs damages melanocytes, leading to antigen presentation and initiation of an autoimmune response. Autoreactive CD8⁺ T cells are activated and secrete IFNγ, leading to the activation of the JAK–STAT signalling pathway. Autoantibodies are also produced upon activation of B cells by CD4⁺ helper T cells. CD8⁺ T cell inhibition by T_{reg} cells is impaired. The subsequent downstream gene transcription drives an autoimmune response, leading to melanocyte apoptosis and hypopigmentation. Release of IL-15 by keratinocytes promotes further destruction of melanocytes via IFNγ release from T_{rm} cells.



CXCL9/10, C-X-C chemokine motif 9/10; DAMPs, damage-associated molecular patterns; HSP70, heat shock protein 70; IFNγ, interferon-γ; JAK, Janus kinase; NK, natural killer; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; T_{reg}, regulatory T; T_{rm}, tissue resident memory T.

entation, activating the innate immune system and initiating a cascade of downstream immune responses.[3] Autoreactive CD8⁺ T cells become activated, producing IFNγ, a key regulator in vitiligo.[1,3] External triggers induce IFNγ signalling, activating the JAK–STAT pathway, and promoting melanocyte apoptosis.[1–4,7,10] IFNγ binds to its associated receptor, triggering the activation of JAK, a transmembrane protein kinase, which then undergoes auto-phosphorylation. This leads to STAT phosphorylation and dimerization, activating the JAK–STAT pathway via JAK1 and JAK2.[3,4,7] The subsequent initiation of gene transcription drives an autoimmune response, leading to melanocyte apoptosis, cellular senescence and depigmentation.[7,10]

The JAK–STAT signalling cascade plays a central role in mediating cellular responses to cytokines, hormones and growth factors, thereby influencing immune regulation and maintaining cellular equilibrium.[10–12] JAK proteins are activated upon cytokine–receptor binding at the cell surface, initiating intracellular signalling that governs immune cell behaviour and gene expression.[7] This process begins with receptor dimerization, which positions two JAKs in close proximity, allowing for mutual phosphorylation and activation.[7,10–12] Subsequently, STAT proteins in the cytoplasm associate with these phosphorylated receptors, undergo phosphorylation themselves, form dimers, and migrate to the nucleus, where they trigger transcription of immune-related genes.[2,5,7,10,11] Distinct JAK pairings, such as JAK1 with either JAK2 or JAK3, and JAK2 homodimers, determine the specificity of downstream signalling and resultant cellular outcomes.[7,10,11]

In the context of vitiligo, activation of the JAK–STAT pathway prompts keratinocytes to release chemokines like CXCL9 and CXCL10, which signal through CXCR3 to attract additional immune cells.[2,3] This reinforces a chronic inflammatory loop maintained by these chemokines and

tissue-resident memory T (T_{RM}) cells, which are crucial for disease persistence.[2–4] T_{RM} cells contribute to relapse and chronic inflammation by supporting cytotoxic $CD8^+$ T cell recruitment and expansion via IL-15-dependent survival mechanisms.[3] Elevated circulating IL-15 levels in patients with vitiligo have been associated with greater disease activity.[3,12] During flare-ups, oxidative stress induces keratinocytes to express IL-15 and its receptor subunit IL-15Rα, facilitating T_{RM} cell survival and function through JAK1 and JAK3 signalling and downstream STAT3 and STAT5 phosphorylation.[3,12]

In parallel, regulatory T (T_{reg}) cells are critical for maintaining self-tolerance by suppressing autoreactive $CD8^+$ T cell activity, a process supported by IL-2 signalling.[3] Impaired function or decreased numbers of T_{reg} cells compromise immune tolerance, enabling autoreactive $CD8^+$ T cells to persist and target melanocytes.[3] As a result, disease relapses are frequently observed after treatment.[4]

Mechanism of action and pharmacology of ruxolitinib

Ruxolitinib is a selective, competitive JAK1 and JAK2 inhibitor that disrupts vitiligo pathogenesis by blocking IFNγ signalling, inhibiting dendritic cell migration and dampening cytotoxic T cell activity, thereby promoting melanocyte recruitment and facilitating repigmentation.[1–3,8,10] It demonstrates selectivity for JAK1 and JAK2 based on its half-maximal inhibitory concentration (IC_{50}); however, at lower concentrations, it functions as a pan-JAK inhibitor, as indicated by its inhibition constant value.[10] The major limitation of IC_{50} is its high variability, influenced by ATP levels, JAK concentration and assay conditions, making cross-study comparisons challenging.[10] In contrast, the inhibition constant, which reflects inhibitor dissociation, is more stable but can still be affected by receptor binding, pH and temperature.[10]

In a pharmacokinetic study, 429 patients with vitiligo aged ≥12 years applied topical ruxolitinib twice daily to the same skin sites for 24 weeks.[1] The average steady-state concentration in plasma reached 56.9 nM, with a calculated area under the curve of 683 h·nM.[1] In individuals with impaired renal function, systemic exposure (estimated by area under the curve) was nearly doubled.[1] Plasma concentrations of ruxolitinib were similar across two landmark ruxolitinib trials, TRuE-V1 and TRuE-V2, showing steady-state means of 55.8±56.7 nM and 58.0±68.1 nM, respectively, from weeks 4 through 24.[8] The average bioavailability following topical application was approximately 9.7%.[1] In vitro findings suggest that ~97% of ruxolitinib in circulation is bound to plasma proteins, predominantly albumin.[1] The elimination half-life of the topical formulation is estimated at around 3 hours.[1,12] Metabolism of ruxolitinib occurs primarily via the cytochrome P450 3A4 (CYP3A4) enzyme.[1] Consequently, coadministration with CYP3A4 inhibitors may elevate systemic drug levels, increasing the potential for adverse reactions.[1] However, topical ruxolitinib is not anticipated to significantly impact major CYP enzymes, nor does it appear to alter the activity of key transport proteins such as P-glycoprotein, breast cancer resistance protein or organic anion transporters.[1]

Additionally, ruxolitinib has undergone a comprehensive battery of genotoxicity assays, including bacterial mutagenicity, in vitro chromosomal aberration and rat bone marrow micronucleus tests, all of which demonstrated no evidence of genotoxic potential.[2] Carcinogenicity studies, including a 104-week dermal study in CD-1 mice, showed no significant drug-related toxicity or tumour development following daily application of 1.5% cream at a 100 µL dose.[2] Short-term stability studies demonstrated that the emulsion exhibited good physical stability without evidence of chemical degradation, findings that were further corroborated by longer-term stability studies.[12]

Clinical efficacy in vitiligo

Phase II trials

This open-label, phase II, proof-of-concept pilot trial (NCT02809976) (Table 1) was the first study to evaluate the efficacy of topical ruxolitinib 1.5% in promoting repigmentation of vitiligo lesions. It involved 11 participants, of whom 9 completed the trial. Participants applied ruxolitinib 1.5% cream twice daily for 20 weeks to all affected areas. Efficacy was assessed using several metrics: Vitiligo Area Scoring Index (VASI), Body Surface Area (BSA) involvement, the Vitiligo European Task Force (VETF) score, the Physician Global Vitiligo Assessment (PGVA) and the Dermatology Life Quality Index (DLQI). At week 20, the mean VASI improvement was 23%, BSA reduced by 11.2% and VETF scores improved by 4.5%. Two participants (18.2%) achieved a PGVA rating of 'clear' or 'almost clear'. Quality of life remained relatively stable with minimal change in DLQI scores. These findings suggest modest repigmentation benefits in patients with milder forms of vitiligo.[13]

The second trial (NCT03099304) was a larger, randomized, double-blind, dose-ranging study involving 157 participants with vitiligo affecting less than 20% of their BSA. Subjects received varying concentrations of ruxolitinib 1.5% cream or vehicle over 52 weeks, with an additional 104-week open-label extension phase allowing combination treatment with NB-UVB phototherapy. The 1.5% twice-daily dose yielded the most robust results: at week 52, 58% of patients achieved ≥50% improvement in Facial-VASI (F-VASI50), 52% achieved 75% improve-

Table 1. Summary of available results evaluating ruxolitinib in the management of vitiligo.

Trial	Study design	End points	Main results	Adverse events
NCT02809976 Phase I	Open-label, proof-of-concept *N* = 11 (aged 18–65 years) Vitiligo patches, BSA ≥1% BD of ruxolitinib 1.5% cream Follow-up 20 weeks No restriction on area of application	Primary: Percent change in VASI at week 20 Secondary: Percent change in BSA of repigmentation at week 20 Number of participants achieving a PGVA of 'clear' or 'almost clear' at week 20 Mean DLQI scores at week 20 Percent change in VETF assessment – disease staging at week 20 Percent change in VETF assessment – disease progression at week 20	Improvement in VASI on week 20 (mean): 23% BSA: 11.2% PGVA: 2 (18.2%) DLQI: 3 VETF – disease staging: 4.5% VETF – disease progression: –0.5%	Treatment-emergent adverse effects: most common: rim of hyperpigmentation surrounding vitiligo lesion, intermittent erythema over affected lesions, URI symptoms and transient acne
NCT03099304 Phase II	Randomized, double blind, dose ranging *N* = 157 (aged 18–65 years) Vitiligo patches, BSA <20% Randomly receive one of four doses of topical ruxolitinib cream (1.5% twice daily, 1.5% once daily, 0.5% once daily, 0.15% once daily) or vehicle (1:1:1:1:1) Application for 52 weeks. No restriction on the area of application 104-week open-label extension period (combination of topical ruxolitinib and NB-UVB phototherapy)	Primary: F-VASI50, F-VASI75 and F-VASI90 at weeks 24 and 52 Secondary: T-VASI50 at weeks 24 and 52 F-VASI and T-VASI improvement with a combined therapy (topical ruxolitinib and NB-UVB phototherapy)	Week 24 (1.5% ruxolitinib cream BD): F-VASI50: 45% F-VASI75: 30% T-VASI50: 20% Week 52 (1.5% ruxolitinib cream BD): F-VASI50: 58% F-VASI75: 52% F-VASI90: 33% T-VASI50: 45% 104-week open-label extension period: Additional NB-UVB phototherapy (for 12 weeks) improved facial and total body repigmentation	Contact dermatitis, application site pruritus, acne, application site erythema, rash, skin exfoliation and urticaria Most common adverse effects from other (non-dermatological) systems: bronchitis and nasopharyngitis

(*Continued*)

Table 1. (Continued)

Trial	Study design	End points	Main results	Adverse events
NCT05247489 Phase II	Interventional trial *N* = 55 participants (adolescents and adults) Non-segmental vitiligo and BSA <10% 20 received ruxolitinib 1.5% cream BD (group 1) and 35 received ruxolitinib 1.5% cream BD combined with NB-UVB phototherapy (group 2)	Primary: T-VASI25 at week 48 Secondary: Percentage of participants achieving F-VASI50 at week 48 Percentage of participants achieving F-VASI75 at week 48 Percentage of participants achieving F-VASI90 at week 48 Percentage of participants achieving T-VASI50 at week 48 Percentage of participants achieving T-VASI75 at week 48 Percentage of participants achieving T-VASI90 at week 48 Percentage change from baseline in F-BSA at week 48 Percentage change from baseline in T-BSA at week 48	Week 48 – (group 1): T-VASI25: -3.43 Week 48 – (group 2): T-VASI25: -3.46 Percentage of participants achieving F-VASI50 at week 48: (group 1) 100% *versus* (group 2) 96.2% Percentage of participants achieving F-VASI75 at week 48: (group 1) 100% *versus* (group 2) 84.6% Percentage of participants achieving F-VASI90 at week 48: (group 1) 66.7% *versus* (group 2) 53.8% Percentage of participants achieving T-VASI50 at week 48: (group 1) 83.3% *versus* (group 2) 57.7% Percentage of participants achieving T-VASI75 at week 48: (group 1) 50% *versus* (group 2) 19.2% Percentage of participants achieving T-VASI90 at week 48: (group 1) 16.7% *versus* (group 2) 7.7% Percentage change from baseline in F-BSA at week 48: (group 1) −78.06% *versus* (group 2) −60.51% Percentage change from baseline in T-BSA at week 48: (group 1) −47.03% *versus* (group 2) −27.3%	Most common adverse effects: application site acne (10.91%), upper respiratory tract infection (7.27%), procedural site reaction (7.27%), oral herpes (5.45%) and oropharyngeal pain (5.45%) Less serious adverse effects were generally higher in the group of participants treated with topical ruxolitinib monotherapy

(*Continued*)

Table 1. (Continued)

Trial	Study design	End points	Main results	Adverse events
NCT04052425 Phase III	TRuE-V1, multinational, double blind, randomized, vehicle-controlled *N* = 330 (adolescents >12 years and adults) Vitiligo patches and BSA ≤10% Ruxolitinib 1.5% cream applied BD for 24 weeks and then for 28-week additional period. No restriction on the area of application Randomly (2:1) receiving 1.5% ruxolitinib cream (group 1) or vehicle (group 2)	Primary: Percentage of participants achieving F-VASI25/50/75/90, T-VASI25/50/75/90, VNS of 4 or 5 at week 24 Secondary: Percentage of participants achieving F-VASI25/50/75/90, T-VASI25/50/75/90 at week 52	Week 24 – percentage of participants achieving: F-VASI75: (group 1) 29.8% *versus* (group 2) 7.4% F-VASI25: (group 1) 69.8% *versus* (group 2) 30% F-VASI50: (group 1) 51.2% *versus* (group 2) 16.9% F-VASI90: (group 1) 15.3% *versus* (group 2) 2.2% T-VASI25: (group 1) 48.8% *versus* (group 2) 23.8% T-VASI50: (group 1) 20.6% *versus* (group 2) 5.1% T-VASI75: (group 1) 4.1% *versus* (group 2) 1.8% T-VASI90: (group 1) 0.5% *versus* (group 2) 0% VNS of 4 or 5: (group 1) 24.5% *versus* (group 2) 3.3% Week 52 – percentage of participants achieving: F-VASI25: (group 1) 89.6% *versus* (group 2) 74.4% F-VASI50: (group 1) 75.1% *versus* (group 2) 56.1% F-VASI75: (group 1) 52.6% *versus* (group 2) 26.8% F-VASI90: (group 1) 32.9% *versus* (group 2) 12.2% T-VASI25: (group 1) 77.5% *versus* (group 2) 56.1% T-VASI50: (group 1) 53.2% *versus* (group 2) 31.7% T-VASI75: (group 1) 20.2% *versus* (group 2) 9.8% T-VASI90: (group 1) 3.5% *versus* (group 2) 2.4%	Systemic: nasopharyngitis, headache, urinary tract infection and pyrexia (their association with treatment was uncertain due to their low frequency) Other: application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, contusion, contact dermatitis, diarrhoea, ear infections, gastritis, gastroenteritis, hordeolum, influenza-like illness, insomnia, nasal congestion and vomiting No serious AEs were considered to be related to the trial medication

(*Continued*)

Table 1. (Continued)

Trial	Study design	End points	Main results	Adverse events
NCT04057573 Phase III	TRuE-V2, multinational, double blind, randomized, vehicle controlled *N* = 344 (adolescents >12 years and adults) Vitiligo patches and BSA ≤10% Ruxolitinib 1.5% cream applied BD for 24 weeks and then for 28-week additional period. No restriction on the area of application Randomly (2:1) receiving 1.5% ruxolitinib cream (group 1) or vehicle (group 2)	Primary: Percentage of participants achieving F-VASI25/50/75/90, T-VASI25/50/75/90, VNS of 4 or 5 at week 24 Secondary: Percentage of participants achieving F-VASI25/50/75/90, T-VASI25/50/75/90 at week 52	Week 24 – percentage of participants achieving: F-VASI75: (group 1) 30.9% *versus* (group 2) 11.4% F-VASI25: (group 1) 63.9% *versus* (group 2) 32% F-VASI50: (group 1) 51.4% *versus* (group 2) 20.9% F-VASI90: (group 1) 16.3% *versus* (group 2) 1.3% T-VASI25: (group 1) 50.2% *versus* (group 2) 21.2% T-VASI50: (group 1) 23.9% *versus* (group 2) 6.8% T-VASI75: (group 1) 8% *versus* (group 2) 1.8% T-VASI90: (group 1) 1% *versus* (group 2) 0% VNS of 4 or 5: (group 1) 20.5% *versus* (group 2) 4.9% Week 52 – percentage of participants achieving: F-VASI25: (group 1) 82.5% *versus* (group 2) 71.6% F-VASI50: (group 1) 74% *versus* (group 2) 49.4% F-VASI75: (group 1) 48% *versus* (group 2) 29.6% F-VASI90: (group 1) 27.7% *versus* (group 2) 16% T-VASI25: (group 1) 76.8% *versus* (2) 53.1% T-VASI50: (group 1) 49.2% *versus* (group 2) 22.2% T-VASI75: (group 1) 20.9% *versus* (group 2) 8.6% T-VASI90: (group 1) 6.8% *versus* (2) 1.2%	*(AEs equal to those presented above for TRuE-V1)* Treatment-related application site AEs: acne, pruritus and exfoliation Systemic AEs: nasopharyngitis, headache, urinary tract infection and pyrexia (their association with treatment was uncertain due to their low frequency) Other AEs: application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, contusion, contact dermatitis, diarrhoea, ear infections, gastritis, gastroenteritis, hordeolum, influenza-like illness, insomnia, nasal congestion and vomiting No serious AEs were considered to be related to the trial medication

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Table 1. (Continued)

Trial	Study design	End points	Main results	Adverse events
NCT04530344 Phase III	Double blind, vehicle-controlled, randomized, withdrawal and treatment extension *N* = 458 (adolescents >12 years and adults)	Primary: Percent change of F-VASI and T-VASI at week 104 in patients with no repigmentation or limited repigmentation of facial and non-facial lesions at week 24 of both TRuE-V1 and 2	Week 104: No previous repigmentation: improvement of F-VASI in 97.1% of patients and improvement of T-VASI in 93.3% of patients Previous limited repigmentation: improvement of F-VASI in 83.3% of patients and improvement of T-VASI in 81.6% patients Across both groups: 54.9% of patients achieved F-VASI and 50% achieved T-VASI50	Some serious AEs were reported in 2.62% of patients receiving continuously 1.5% ruxolitinib cream BD Other less serious AEs (such as COVID-19) occurred in 13% of patients treated with 1.5% ruxolitinib cream BD

AE, adverse event; BD, twice per day; BSA, body surface area; DLQI, Dermatology Life Quality Index; F-VASI25/F-VASI50/F-VASI75/F-VASI90, Facial Vitiligo Area Scoring Index 25%, 50%, 75%, 90% improvement; NB-UVB, narrowband ultraviolet B; PGVA, Physician Global Vitiligo Assessment; T-VASI25/T-VASI50/T-VASI75/T-VASI90, Total Vitiligo Area Scoring Index 25%, 50%, 75%, 90%; URI, upper respiratory infection; VASI, Vitiligo Area Scoring Index; VETF, Vitiligo European Task Force; VNS, Vitiligo Noticeability Scale.

ment (F-VASI75) and 33% reached 90% improvement (F-VASI90). Total VASI50 improvements also increased over time in a dose-dependent manner. Sub-group analysis showed no significant differences based on race, skin type or disease extent, though younger patients and females responded more favourably. Notably, patients with facial vitiligo had better outcomes than those with limb or acral involvement. During the extension phase, combining ruxolitinib with NB-UVB phototherapy was well tolerated and further enhanced repigmentation outcomes.[14]

Collectively, these trials support the efficacy and tolerability of topical ruxolitinib, especially at a 1.5% twice-daily dose, with improved outcomes when combined with NB-UVB phototherapy in select patients.

Phase III trials

Two multinational, phase III, double-blind, randomized, vehicle-controlled clinical trials were conducted to explore the efficacy and safety of ruxolitinib 1.5% cream in vitiligo treatment. TRuE-V1 (NCT04052425) and TRuE-V2 (NCT04057573) enrolled 330 and 344 patients, respectively (Table 1), who were then followed by a long-term extension study. These trials enrolled patients aged 12 years and older with vitiligo involving ≤10% of their total BSA (T-BSA), including both facial and non-facial involvement. Participants included in the study had a clinical diagnosis of non-segmental vitiligo, with depigmentation involving at least 0.5% BSA on the face (≥0.5 F-VASI), 3% BSA on non-facial areas (≥3 T-VASI) and not more than 10% total BSA affected. Individuals were excluded if they lacked pigmented hair in facial vitiligo patches, had other forms of vitiligo (for example, segmental) or similar skin conditions, had previously used depigmentation therapies like monobenzone, or had used restricted treatments within the specified washout period.[15,16]

In TRuE-V1 (330 participants) and TRuE-V2 (344 participants), participants were randomized 2:1 to receive either ruxolitinib cream or vehicle twice daily for 24 weeks, followed by an additional 28 weeks during which all participants received active treatment. At week 24, both trials showed significantly improved repigmentation outcomes in the ruxolitinib group across various thresholds of facial and total VASI improvement. In TRuE-V1, 51.2% achieved F-VASI50 and 29.8% achieved F-VASI75, compared to 16.9% and 7.4%, respectively, in the vehiclegroup. Total body responses were also superior, with 20.6% reaching T-VASI50 compared to 5.1% in the control group. Similar results were found in TRuE-V2, where 51.4% of patients on ruxolitinib achieved F-VASI50 *versus* 20.9% on vehicle, and 23.9% achieved T-VASI50 *versus* 6.8%. Notably, a higher proportion of patients reported noticeable improvement on the Vitiligo Noticeability Scale in the treatment arms of both studies.[15,16]

Following the 24-week double-blind phase, participants previously on vehicle began ruxolitinib, whilst those initially on ruxolitinib continued treatment. By week 52, those who started ruxolitinib earlier demonstrated consistently better outcomes. In TRuE-V1, 75.1% of early-treatment participants achieved F-VASI50 *versus* 56.1% of the delayed group; similar trends were observed in TRuE-V2. The data also showed higher T-VASI50 and F-VASI75/90 response rates in those with longer continuous use.[15–18]

An extension study (NCT04530344) further assessed long-term effects in 458 participants who completed either TRuE-V1 or TRuE-V2. This study examined both withdrawal and maintenance of response with continued ruxolitinib use. Even amongst patients who had minimal or no facial or body repigmentation at week 24, over 80% showed significant improvements by week 104 with continued therapy. Specifically, 97.1% of those with no initial facial repigmentation showed progress by week 104, and over half (54.9%) achieved F-VASI75. Improvements in T-VASI were also substantial, with 93.3% of initially non-responding patients showing progress by week 10.[19]

Together, these studies highlight that ruxolitinib cream is effective and well-tolerated for treating non-segmental vitiligo. Importantly, they emphasize the value of prolonged, continuous treatment, even in patients with slow initial response, for achieving meaningful and lasting repigmentation.

Therapeutic combinations with ruxolitinib

Following the FDA's approval of topical ruxolitinib, possible therapeutic combinations —particularly with NB-UVB phototherapy — have been explored to better understand treatment outcomes in patients with vitiligo. A double-blind, randomized, dose-ranging phase II study investigated the efficacy of combining ruxolitinib and NB-UVB therapy during a 52 and subsequent 104-week open-label period.[10,20] Following phototherapy initiation, 78.9% of patients showed improvement in F-VASI and 94.7% in T-VASI, with mean improvement rates of 50.2% and 29.5%, respectively, compared to ruxolitinib treatment alone.[10,20] Furthermore, amongst the 12 patients who had not reached F-VASI50 at week 24, 83.3% showed improvement in F-VASI and 91.7% in T-VASI, with mean improvement rates of 47.8% and 31.1%, respectively.[10] Notably, a separate 2024 study found that two patients who had failed to respond to either phototherapy or ruxolitinib monotherapy showed significant improvement in truncal lesions following combination therapy.[7] Together, these findings suggest that topical ruxolitinib 1.5% twice daily and NB-UVB phototherapy may be an

effective treatment strategy for vitiligo, especially in poor responders to ruxolitinib.[3,4,10,20]

Safety

Phase II trials

In an open-label, phase II, proof-of-concept pilot trial (NCT02809976) investigating ruxolitinib use, the most frequently reported side-effects included hyperpigmented rings around lesions (81.8%), intermittent erythema (72.7%), upper respiratory symptoms (36.4%) and transient acne (18.2%). Less common events included isolated cases of gastroenteritis, dental pain, myalgias and other minor conditions, all occurring in one patient.[13]

In a dose-ranging phase II study (NCT03099304) conducted over 180 weeks, no increased risk of mortality was observed across any dosing groups. Serious treatment-related adverse events were rare but included coronary artery occlusion, subdural haematoma and seizures. The highest rate of less serious adverse events occurred in the 0.15% once-daily group (61.3%). Common dermatological side-effects included contact dermatitis, pruritus, acne, application site erythema and rash. Non-dermatological side-effects most frequently involved bronchitis and nasopharyngitis.[14]

In another interventional trial (NCT05247489), adverse events were evaluated over 52 weeks for both ruxolitinib monotherapy and combination therapy with NB-UVB phototherapy. Serious adverse events, including intestinal obstruction and seizures, occurred only in the monotherapy group. However, less serious events like application site acne, oral herpes and procedural site reactions were slightly more common in the combination therapy group. Overall, adverse event rates were slightly lower in the combination group (42.9%) compared to monotherapy (45%), suggesting that ruxolitinib combined with NB-UVB phototherapy is not only effective but also well tolerated.[21]

Taken together, these findings suggest that topical ruxolitinib, whether used alone or with NB-UVB phototherapy, is generally safe for treating vitiligo, with most adverse effects being manageable and non-serious.

Phase III trials

Across two phase III double blind, randomized vehicle-controlled clinical trials (TRuE-V1 and TRuE-V2), topical ruxolitinib 1.5% cream demonstrated a favourable safety profile, with low systemic absorption and predominantly mild-to-moderate adverse events. During the 24-week double-blind treatment phase, adverse events were reported in approximately 50% of patients receiving ruxolitinib compared to 33% in the vehicle group. The most common treatment-related side-effects were localized application site reactions, including acne (5.8% *versus* 1.2%) and pruritus (5.1% *versus* 2.6%). Systemic adverse events, such as nasopharyngitis, urinary tract infection, headache and fever, were infrequent (<1%) and not clearly linked to the medication, as their rates were comparable between groups.

Some adverse events appeared exclusively in one group but occurred infrequently (0.5–1%). This included application site discoloration, folliculitis and contact dermatitis as well as non-dermatological conditions like diarrhoea, insomnia, vomiting and anxiety. Importantly, no serious adverse events were attributed to the study drug by investigators during these trials.[15–18]

A separate phase III extension and withdrawal study (NCT04530344) evaluated the long-term safety of ruxolitinib over 108 weeks in a population of 458 adults across the USA. In this extended period, serious adverse events were reported in 2.62% of patients treated continuously with 1.5% ruxolitinib cream. These included diverse conditions such as angina, spinal disorders, uterine prolapse and bipolar disorder. However, these events were not definitively linked to the treatment. Less serious adverse effects, most notably COVID-19 infections, were reported in 13% of participants.[19]

Discussion

Vitiligo is a chronic, autoimmune skin disorder that significantly impacts patients' quality of life. Its pathogenesis is unpredictable with a fluctuating, cyclical course of depigmentation and repigmentation. It involves progressive melanocyte destruction, primarily mediated by autoreactive $CD8^+$ cytotoxic T cells, resulting in depigmented macules. A key driver of this inflammatory process is the JAK–STAT signalling pathway, which regulates gene expression in response to various cytokines. In vitiligo, IFNγ activates JAK1/JAK2 and STAT1/STAT2, leading to inflammation and melanocyte apoptosis. JAK inhibitors (JAKi) disrupt this signalling cascade, thereby reducing the inflammatory response and skin depigmentation. However, because of their varying selectivity, JAKi can impact multiple immune pathways, necessitating a careful balance between therapeutic efficacy and safety.[7] Topical application is generally preferred over systemic application, as it offers localized benefits whilst minimizing systemic exposure and off-target effects.[7,10] In 2022, 1.5% ruxolitinib cream became the first topical JAKi approved by both the FDA and EMA for the treatment of non-segmental vitiligo. Its twice-daily application to affected areas (BSA ≤10%) is indicated for patients

aged ≥12 years with uncontrolled disease, since it has been shown to be effective and well tolerated.

Topical ruxolitinib 1.5% cream has demonstrated strong clinical efficacy and a favourable safety profile in the treatment of non-segmental vitiligo. In the previously mentioned open-label, phase II proof-of-concept trial, twice-daily application for 20 weeks led to a 23% reduction in VASI scores and improvements in disease staging and progression. Nearly one in five participants also achieved a favourable PGVA score. The subsequent randomized, double-blind, dose-ranging phase II trial confirmed dose-dependent efficacy: 45% of patients achieved F-VASI50 at week 24, increasing to 58% at week 52. Similarly, F-VASI75 increased from 30% to 52%, whilst F-VASI90 reached 33% by week 52. T-VASI50 responses also increased with time and dosage, from 20% at week 24 to 45% at week 52. However, the data also highlight a gradual treatment response, with only 30% of patients achieving F-VASI75 by week 26 and just over half reaching F-VASI50 by 1 year, indicating that whilst topical ruxolitinib is a valuable addition to the vitiligo treatment options currently available, it is not universally or rapidly effective. Efficacy was notably higher in facial lesions and amongst younger patients, women and those with prior treatment failures, regardless of race, skin type or disease status. Moreover, given the chronic and relapsing nature of vitiligo, topical ruxolitinib may play a role in maintenance therapy by helping sustain repigmentation and lower the risk of relapse, even after successful treatment. However, data on its long-term efficacy and safety in this setting are still limited.

These findings were reinforced in the phase III TRuE-V1 and TRuE-V2 trials. Specifically at week 24, results showed F-VASI75 was achieved by approximately 30% of patients using ruxolitinib cream compared to less than 12% with vehicle. These trials also showed clear advantages across other key thresholds, including F-VASI25, F-VASI50 and F-VASI90, as well as in T-VASI outcomes. After 52 weeks of continuous treatment, nearly 90% of patients in TRuE-V1 achieved F-VASI25, with similar rates in TRuE-V2. In the long-term extension study, even patients who had shown little to no repigmentation by week 24 demonstrated continued improvement, with over half achieving F-VASI75 and T-VASI50 by week 104. These results highlight the benefit of sustained therapy in maximizing treatment response.

Despite its promising clinical efficacy, the cost of ruxolitinib, particularly if used as a long-term maintenance therapy, raises important concerns around affordability and accessibility. Like other JAKi, ruxolitinib may require prolonged or indefinite use to sustain repigmentation, potentially placing a significant financial burden on patients. Access remains a global challenge as well, with the medication not yet approved or available in several regions, limiting treatment options for patients in those countries. Broader regulatory approval and strategies to improve affordability will be essential to ensure equitable access to care.[22]

In terms of safety, topical ruxolitinib was well tolerated across all phases of development. Early-phase trials reported mostly mild events such as erythema, acne and hyperpigmentation at lesion borders. Serious adverse events were rare and included isolated cases such as coronary artery occlusion and breast cancer. The most common mild dermatological events included contact dermatitis, pruritus and site-specific irritation, particularly at lower doses. In the TRuE-V trials, ~50% of patients in the ruxolitinib group experienced adverse events compared to 33% in the vehicle group.[15,16] Acne and pruritus were the most frequently reported side-effects, whilst systemic events like nasopharyngitis and headache were infrequent and not clearly treatment related. In the 108-week extension study, serious adverse events occurred in only 2.6% of patients, and non-serious events like mild infections occurred in 13%, confirming the overall safety of long-term use.[19] Additionally, combination therapy with ruxolitinib and NB-UVB phototherapy significantly improved outcomes in patients who were poor responders to monotherapy. As shown before, F-VASI and T-VASI improved in nearly 79% and 95% of patients, respectively, with mean improvement rates of 50.2% and 29.5%. The combination was also well tolerated and, in some cases, associated with fewer adverse effects than ruxolitinib alone. These findings support its potential as a valuable treatment strategy for refractory or difficult-to-treat vitiligo cases.

Some limitations remain, particularly regarding the use of JAKi during pregnancy. Data on the safety of ruxolitinib in pregnant or breastfeeding individuals and children are lacking, making management during conception, pregnancy and lactation particularly challenging. These groups are often excluded from clinical trials, leaving important gaps in our knowledge regarding potential risks and long-term effects. Addressing these gaps is essential to ensuring safe and informed use of the medication across a broader patient population.[23]

Additionally, most of the current evidence comes from studies with short-term to medium-term follow-up, typically not extending beyond 52–104 weeks, leaving the long-term safety and durability of response uncertain. Moreover, these trials predominantly enrolled participants with Fitzpatrick skin types II–IV, resulting in limited data on efficacy and pigmentary outcomes in individu-

als with darker skin tones. Regional differences in treatment response, particularly reduced effectiveness on areas like the hands, feet and bony prominences, also require further study. Moreover, factors such as real-world adherence, the necessity for ongoing treatment and financial barriers may substantially affect outcomes outside of clinical trial environments.

Finally, the predominance of North American study populations in published trials may limit the global generalizability of findings, and industry sponsorship of many of these studies raises the possibility of publication or reporting bias, underscoring the need for more independent, geographically and ethnically diverse research cohorts.

Overall, topical ruxolitinib 1.5% cream is a safe and effective treatment for non-segmental vitiligo, particularly for facial lesions. Its benefits are maximized with prolonged use and may be further enhanced when combined with NB-UVB phototherapy. The consistent safety profile and therapeutic clinical outcomes across diverse populations support its role as a new agent in the treatment of non-segmental vitiligo.

Conclusion

Ruxolitinib disrupts vitiligo pathogenesis by blocking IFNγ signalling, inhibiting dendritic cell migration and reducing cytotoxic T cell activity, thereby facilitating melanocyte recruitment and repigmentation. In clinical trials, topical use was generally well tolerated, with the most common adverse effects being cutaneous, including application site acne, pruritus, exfoliation and erythema. Slight increases in upper respiratory tract infections were also reported; however, this rarely led to trial discontinuation. Importantly, no systemic drug accumulation was observed, potentially minimizing the risk of side-effects if used in conjunction with other therapies. Topical ruxolitinib has demonstrated clinical efficacy and a favourable safety profile in patients with non-segmental vitiligo, particularly in those with limited disease who may benefit from localized treatment. Ongoing studies are further evaluating its role in paediatric populations and in anatomically sensitive areas such as the genitals. Collectively, current evidence supports the use of topical ruxolitinib as a targeted, well-tolerated and non-systemic therapeutic option in the management of vitiligo.

Contributions: GMS, AM, CF and TT: Conception of the work, critical review, and approval of the final version to be published. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: TT has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Arena Pharmaceuticals, BIOCAD, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, J&J, Eli Lilly, Fresenius Kabi, Janssen, LEO Pharma, Merck Sharp & Dohme, Mylan/Viatris, Novartis, Pfizer, Samsung Bioepis, Sandoz, Sanofi-Genzyme, STADA and UCB. He is also a Senior Editor for *Drugs in Context*. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2025/08/dic.2025-5-2-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/treatment-of-vitiligo-with-topical-ruxolitinib-a-narrative-review

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Provenance: Invited; externally peer reviewed.

Submitted: 11 May 2025; **Accepted:** 29 July 2025; **Published:** 15 September 2025.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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