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Review Article

Janus kinase inhibitors and the changing landscape of vitiligo management: a scoping review

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Abstract

Vitiligo is a chronic skin condition caused by an autoimmune response that results in the progressive loss of melanocytes and recent studies have suggested that Janus kinase inhibitors (JAKi) are emerging as a promising new treatment modality. Therefore, to assess and understand the extent of knowledge in the emerging field of JAKi use in vitiligo, a scoping review of the literature was undertaken. The reviewed articles explored a wide variety of JAKi administered either orally or topically for vitiligo. There were no injectable JAKi studied. Tofacitinib was the most commonly studied oral JAKi in 16 of the 35 studies selected for review, followed by baricitinib (n = 3), and one study each with ritlecitinib, ruxolitinib, and upadacitinib. Ruxolitinib (n = 6) and tofacitinib (n = 6) were the most often studied topical JAKi, followed by delgocitinib (n = 1). Potential benefits may vary between JAKi based on their receptor selectivity profile and coexistent autoimmune diseases. A topical JAKi would be advantageous in limited body area involvement and in adolescents. Concurrent use of JAKi with phototherapy or sun exposure appears beneficial. Most studies permitted the use of other topical agents. Acne-related events, though frequent yet mild, were reported with both oral and topical JAKi. Nasopharyngitis, upper respiratory tract infections, and headaches were the most common adverse effects seen in the larger trials with JAKi. No serious or clinically meaningful hematology or thromboembolic events were detected. Treatment of vitiligo with oral or topical JAKi seems to be promising and the growing evidence shows a favorable risk-benefit profile.

Introduction

Vitiligo is a chronic, depigmenting skin disorder caused by an autoimmune response that results in the progressive loss of melanocytes. The pathogenetic mechanisms involved in the destruction of melanocytes and the resultant depigmentation are complex and varied, with numerous genetic markers, oxidative stress, and cytotoxic lymphocytes, among several other mechanisms.[1] Recent developments describe vitiligo as a condition mediated by T-helper cells that infiltrate the dermal-epidermal junction and participate in the destruction of melanocytes, leading to the loss of pigmentation.

Janus kinases (JAKs) are enzymes belonging to the family of tyrosine kinases and bound to the intracellular domains of type I and type II receptors. Type I receptors bind several interleukins, colony-stimulating factors, and hormones such as erythropoietin, prolactin, and growth hormone. Type II receptors bind pro-inflammatory interferons and cytokines. JAKs transmit signals arising from cytokine-receptor interactions on the cellular membrane to influence cellular processes and immune cell function. This signaling occurs through the pairing of JAKs, specifically through combinations such as JAK1/JAK3 and JAK1/JAK2, among others. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which modulate intracellular activity, including gene expression. There are four different types of JAKs (JAK1, JAK2, JAK3, and TYK2) and seven different STATs (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6), which can variously combine and give rise to different biologic cascades. Janus kinase inhibitors (JAKi) are typically designed to block the specific adenosine triphosphate (ATP) binding pocket of JAKs, preventing the phosphorylation and activation of STATs, ultimately leading to a reduction in JAK-STAT signaling and dampening the inflammatory effect (Figure 1).[2–6]

An existing scoping review on the potential use of JAKi for the treatment of vitiligo[7] was available at the time this review

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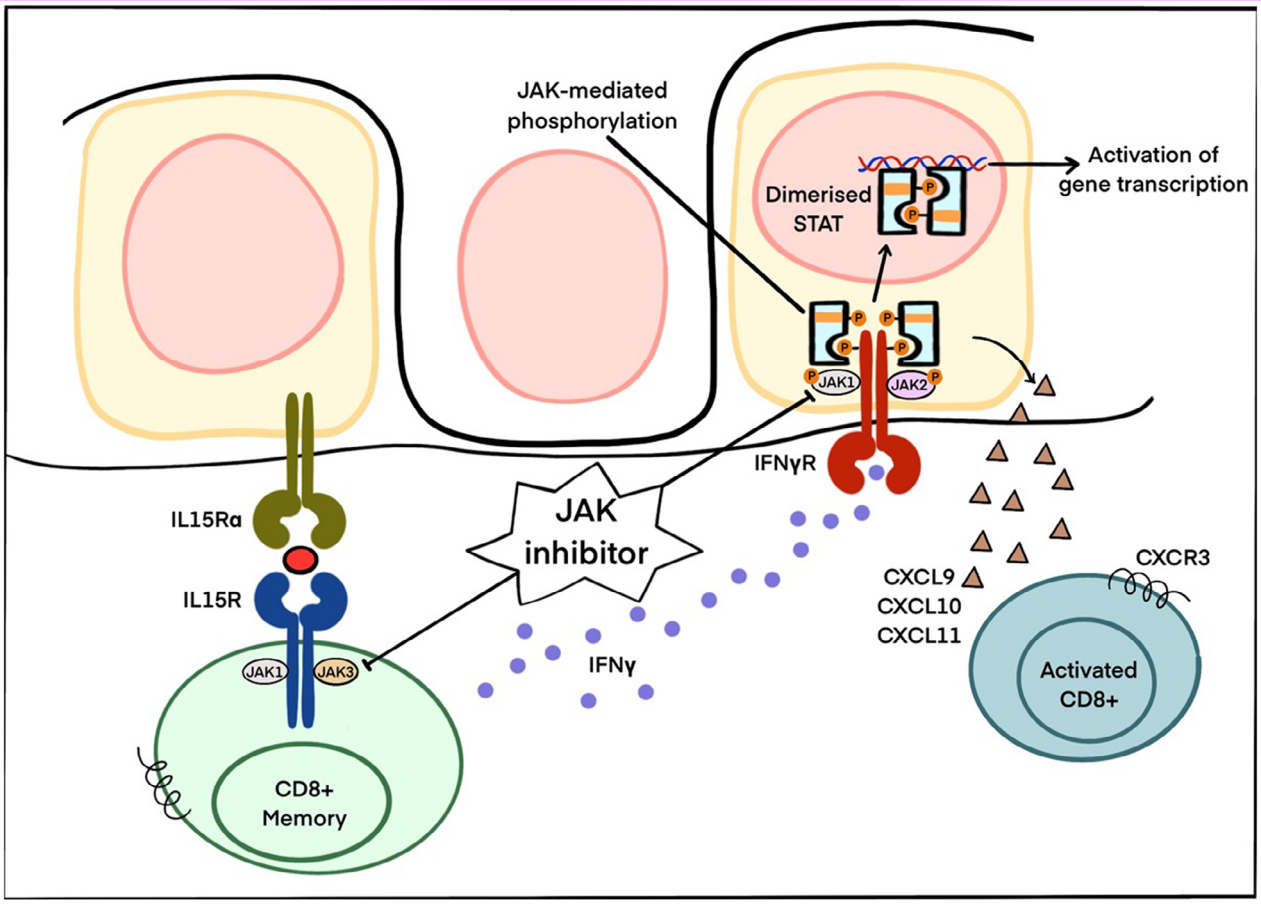

Figure 1 Pathophysiology of vitiligo and the role of JAK inhibitors.[1,6,47] Damage to melanocytes, triggered by genetic factors, oxidative stress, or autoimmune factors, promotes cytokine secretion and antigen presentation. The binding of interleukin (IL)-15 to IL-15 receptor (IL-15R) on memory CD8$^+$ T cells and IL-15 receptor alpha (IL-15R) on keratinocytes, activate the memory CD8$^+$ T cells resulting in the subsequent production of inflammatory cytokines such as interferon-gamma (IFN-γ) through Janus kinase (JAK1/3) signaling. IFN-γ, in turn, binds to its cell surface receptor (IFN-γR) and stimulates the transmembrane protein kinase JAK, initiating self-phosphorylation. Following this event, phosphorylation and dimerization of signal transducers and transcription activators (STAT)s take place, activating the JAK-STAT pathway via JAK1/2 signaling and initiating gene transcription, ultimately propagating autoimmune destruction and depigmentation of melanocytes. JAK1 expression is found to be higher in the lesional skin of vitiligo patients. Furthermore, IFN-γ facilitates the production of CXC chemokine ligands (CXCL9, CXCL10, and CXCL11), responsible for the recruitment of autoreactive effector CD8$^+$ T cells through their cognate CXC chemokine receptor 3 (CXCR3) to target melanocyte destruction. CXC chemokine ligands and CD8$^+$ T cells are found in higher numbers in vitiligo patients and correlate with disease activity. JAK inhibitors intervene in vitiligo pathogenesis by targeting the inactivation of both IFN- and IL-15-mediated downstream signaling, thereby disrupting autoimmune responses and mitigating melanocyte destruction.

was conducted; however, since then, a topical JAKi has been approved for the treatment of vitiligo. Thus, gaining a comprehensive understanding is crucial for establishing a well-informed assessment of the efficacy and safety profile of JAKi, as well as their application in the treatment of vitiligo.

Methods

Study design and objectives

A systematic scoping review was undertaken in accordance with the PRISMA-ScR framework[8] and a protocol published for scoping reviews.[9] The review aimed to organize the available literature with regard to the efficacy and safety of JAKi in the treatment of vitiligo, identify potential gaps in the evidence, and generate new queries that can be explored further.

Eligibility criteria

Publications reporting approved or off-label use of JAKi, with or without concomitant therapy, and in humans for the treatment of all types of vitiligo, designed as randomized controlled trials, observational studies, cross-sectional studies, case series, or case reports, were included. Literature reviews, animal studies, in vitro studies, and gray literature were excluded.

Search strategy and data extraction

MEDLINE and EMBASE databases were searched by two authors (AU and RW) independently for articles from inception to May 30, 2023, using the following search query: ("jak inhibitor" OR "Janus kinase inhibitor") AND ("vitiligo" OR "Hypopigmentation" OR "hypomelanosis"). The text was analyzed, keywords identified, and the search was repeated using additional databases, including CINAHL, Scopus, and Web of Science, until August 31, 2023. Other relevant articles were sourced by examining the reference lists of all selected articles. The search was limited to full-text articles written in English. See Table S1 for the detailed search strategy. The articles searched were exported to the EndNote reference manager, and those deemed eligible were selected for full-text examination. AU and RW conducted the data extraction process according to a predefined charting template. The quality of evidence and risk of bias in all studies that met eligibility for inclusion was assessed using the GRADE criteria.[10]

Extracting and charting results

Figure 2 illustrates the PRISMA flow diagram of the process of study selection. A total of 35 studies were identified for the review (Table 1). The majority were observational (n = 25), and others were experimental (n = 10). Additional information is presented in Tables S2 and S3.

Discussion

Lesion location and repigmentation response

The goal of vitiligo treatment varied from stabilizing the disease, achieving repigmentation, and/or preventing recurrence. All topical JAKi identified were studied on the face except delgocitinib. The treatment duration ranged from 2 to 60 months in observational studies and up to 52 weeks in experimental studies. The assessment of JAKi efficacy was conducted through validated scales and subjectively using terms such as "significant repigmentation" and "much improved," rendering a comparison of efficacy impractical.

Ruxolitinib 1.5% cream, the first and only JAKi approved for the treatment of vitiligo in adults and children over 12 years old,[11] when applied twice daily, exhibited more pronounced repigmentation in facial lesions, with responses seen as early as 4 weeks. The disease duration or disease activity at baseline may not be a factor in determining the response.[12] Facial repigmentation improved significantly with an extended 32-week treatment in

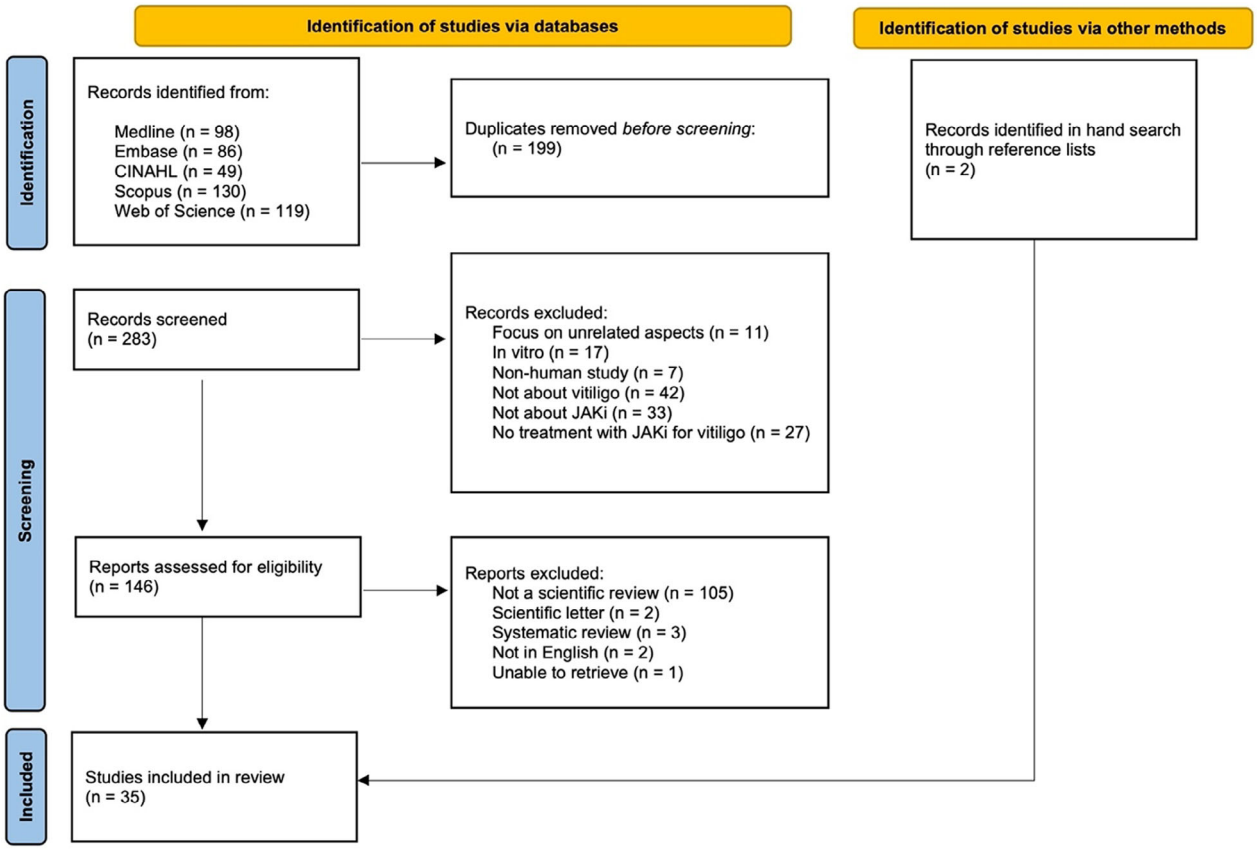

Figure 2 PRISMA flowchart of scoping literature.

Table 1 Summary of clinical studies on the use of JAK inhibitors in the treatment of vitiligo.

Author (year)	Study type and risk of bias (GRADE)	Study population	Age (years) (mean/range)	Treatment	Adjunctive treatment	Duration (weeks)	Area affected	Efficacy for vitiligo	Safety
Mumford et al. (2020)[37]	Case report (high)	1	67	PO baricitinib 4 mg QD	Not reported	32	Hands and forearms	No improvement seen with tofacitinib 5 mg BID; baricitinib substitution achieved almost complete repigmentation	No adverse effects Laboratory abnormalities not reported
Li et al. (2023)[36]	Case series (high)	2	(#1) 17 (#2) 56	PO baricitinib 2 mg BID	(#1) Levothyroxine, TOP tacrolimus BID, NBUVB 2XW (#2) Betamethasone injection, TOP tacrolimus and mometasone, NBUVB	(#1) 32 (#2) 24	(#1) Trunk, and extremities (#2) Face, trunk, and extremities (60% BSA)	(#1) Significant repigmentation with good tolerance (#2) ≥75% repigmentation	No adverse effects Laboratory abnormalities not reported
Doh et al. (2023)[42]	Case report (high)	2	(#1) 63 (#2) 65	PO baricitinib 4 mg QD	Not reported	6–18	(#1) Face, neck trunk, both arms, hands, and feet (#2) Forehead, neck, upper trunk, both arms, hands	Not reported	(#1) Acneiform eruptions on trunk and chest; *Rhodotorula mucilaginosa* resolved with ketoconazole (#2) Pruritic, erythematous papules and pustules on upper chest; *Tintelnotia destructans* resolved with ketoconazole Laboratory findings unremarkable
Ezzedine et al. (2022)[38]	RCT (low)	364	45	PO ritlecitinib 200/50 mg QD,100/50 mg QD,50 mg QD, 30 mg QD, 10 mg QD, placebo	None	48	BSA 4%–50% excluding palms, soles, and feet; ≥0.25% facial involvement	Significant change from baseline in F-VASI at week 24 for 50 mg groups with or without a loading dose, and 30 mg group; accelerated improvement seen at weeks 24–48 in 200/50 mg group	Nasopharyngitis (15.9%–20.3%), URTI (11.5–17.1%), headache (8.8%–13.4%) leading to drug discontinuation by 5.2%; herpes zoster (four patients) with treatment interruption for 20 days, NMSC (two patients); no significant laboratory abnormalities

Table 1 Continued

Author (year)	Study type and risk of bias (GRADE)	Study population	Age (years) (mean/range)	Treatment	Adjunctive treatment	Duration (weeks)	Area affected	Efficacy for vitiligo	Safety
Harris et al. (2016)[14]	Case report (high)	1	35	PO ruxolitinib 20 mg BID	Not reported	20	Face, trunk, extremities	Facial repigmentation improved from 0.8% to 51% in 20 weeks, but regressed 12 weeks after JAKi discontinuation. Hair growth was maintained	Laboratory abnormalities and adverse effects not reported
Craiglow et al. (2015)[16]	Case report (high)	1	50s	PO tofacitinib 5 mg QOD for 3 weeks, then 5 mg QD	Not reported	20	Forehead, trunk, extremities	Depigmented area reduced from BSA 10% to 5%; near-complete repigmentation of the forehead and hands	No adverse effects; no laboratory abnormalities
Vu et al. (2017)[40]	Case report (high)	1	44	PO tofacitinib 5 mg BID	Prednisolone 5 mg QD stopped after 6 weeks of JAKi initiation; betamethasone ointment reduced from 35 g/week to 2 g/week at 3 months	24	Trunk, extremities, scalp, and body hair	VASI decreased marginally from 4.68 at baseline to 3.95 at 5 months; substantial improvement in atopic dermatitis and alopecia areata	URTI and diarrhea resolved; no treatment interruption; no laboratory abnormalities
Liu et al. (2017)[22]	Case series (high)	10	47	PO tofacitinib 5–10 mg up to BID	Sunlight exposure or low-dose NBUVB	40 (average)	Face, acral, arms, torso, legs	50% responded with a mean decrease of 5.4% BSA; majority repigmentation seen in sun or NBUVB exposed areas	URTI, weight gain, arthralgia, mild lipid elevations
Kim et al. (2018)[18]	Case report (high)	2	(#1) 30s (#2) 50s	PO tofacitinib 5 mg BID	(#1): Full-body NBUVB 2XW (#2): Face NBUVB 2-3XW	12–18	Face, neck, chest, forearms, shins, hands	(#1) Near-complete repigmentation on face; >75% on other areas in 12 weeks (#2): 75% repigmentation on face in 18 weeks; no response in other areas	No adverse effects; no laboratory abnormalities
Photiou and Sinclair (2018)[46]	Open label (high)	25	14–72	PO tofacitinib 2.5 mg QD titrated up or down	Not reported	Not reported	Not reported	Not reported	Laboratory abnormalities and adverse effects not reported

Table 1 Continued

Author (year)	Study type and risk of bias (GRADE)	Study population	Age (years) (mean/range)	Treatment	Adjunctive treatment	Duration (weeks)	Area affected	Efficacy for vitiligo	Safety
AlMutairi (2019)[17]	Open label (high)	17	21–58	PO tofacitinib 5 mg BID	Not reported	Treatment 24 weeks Follow-up off-therapy 12 weeks	10% BSA including face and acral regions	16/17 experienced >25% VASI improvement at week 12; 9/15 experienced >75% F-VASI improvement (2 dropped out after 12 weeks); 5/15 experienced up to 25% acral VASI improvement; repigmentation maintained after discontinuation	No significant adverse effects Laboratory abnormalities not reported
Nguyen et al. (2020)[45]	Case report (high)	1	36	PO tofacitinib 11 mg QD (extended release)	Levothyroxine for hyperthyroidism	16	Neck, chest, arms, dorsal hands	Paradoxical, new onset vitiligo reported after 4 months of tofacitinib given for rheumatoid arthritis	Irreversible, de novo vitiligo lesions remained unchanged upon tofacitinib withdrawal ESR decreased 15 mm/hr with other routine labs being stable
Komnitski et al. (2020)[15]	Case report (high)	1	40	PO tofacitinib 5 mg BID	Not reported	32–104	Inguinal region, face, neck, elbows, hands, and feet, chest	Complete forehead and perilabial repigmentation; partial neck and upper chest repigmentation; noticeable hand, face, chest, cervical region repigmentation	Laboratory abnormalities and adverse effects not reported
Moore and Maberry (2021)[44]	Case report (high)	1	56	PO tofacitinib 5 mg BID for 5 months, then QD	Levothyroxine for Hashimoto thyroiditis	20	35% BSA	BSA decreased from 35% to 12% with accompanying improvement in alopecia, psoriatic arthritis, and psoriasis	Gastrointestinal adverse effects with BID dosing required dose reduction to QD; increased TPO and TG normalized within 1 month
Fang et al. (2021)[24]	Open label (high)	4	43	PO tofacitinib 5 mg QD	NBUVB	16	Face, trunk, arms, hands, legs, feet	24.9% VES reduction in two patients; repigmentation seen on trunk (50%) and head and neck (43.8%); no response to lesions on hands, legs	No adverse effects Laboratory abnormalities not reported

Table 1 Continued

Author (year)	Study type and risk of bias (GRADE)	Study population	Age (years) (mean/range)	Treatment	Adjunctive treatment	Duration (weeks)	Area affected	Efficacy for vitiligo	Safety
Fang et al. (2022)[23]	Case series (high)	3	37	PO tofacitinib 5 mg QD	308 nm excimer light 3XW	12	Face, trunk, arms, hands, legs, feet	32.7% VES reduction; at least 25% repigmentation in each patient; 43% repigmentation in total lesions not exposed to sunlight; poor response in acral lesions	No adverse effects Laboratory abnormalities not reported
Perche et al. (2022)[21]	Case report (high)	1	49	PO tofacitinib 5 mg BID	Not reported	104	10% BSA; face, chest, bilateral arms	Small patches of repigmentation in all areas in 2 months; moderate hand repigmentation in 8 months	No adverse effects Laboratory abnormalities not reported
Song et al. (2022)[32]	Open label (high)	42	31	PO tofacitinib 5 mg BID	(#1 Experimental group) Tofacitinib + other treatment; (#2 Control group) Other treatment alone: TOP halometasone, tacrolimus, or pimecrolimus, NBUVB 3XW	16	Face and neck, acral, trunk, extremity lesions VASI baseline: (#1) 15.55 (#2) 18.14	No difference in face and neck lesions between groups at week 16 ($P > 0.05$) Significant repigmentation in acral, trunk, and extremities in group (#1) at week 16 ($P < 0.05$)	Mild pain in hand and foot joints subsided with tofacitinib withdrawal in one patient; lipid levels fluctuated and uric acid levels trended upward in six patients
Aickara et al. (2023)[19]	Case report (high)	1	66	PO tofacitinib 5 mg BID	NBUVB 2XW for 6 m, TOP tacrolimus BID (body), TOP pimecrolimus BID (face)	260 (5 years)	70% BSA including face and scalp	Almost complete repigmentation of face and scalp after 11 months; no improvement in axillary and inguinal folds	No adverse effects; routine laboratory tests within limits after 5 years
Tajalli et al. (2020)[20]	Case report (high)	1	30	PO tofacitinib 5 mg BID for 4 months, stop for 1 month, then 5 mg QD	NBUVB 3XW	16	Face, chest, both elbows, dorsum of hands, and both legs	Perifollicular repigmentation of all vitiligo lesions at 3 months with tofacitinib 5 mg BID, and continuous improvement with a dose reduction to 5 mg QD	3–4 episodes of headache and flu-like symptoms led to JAKi discontinuation for 1 month Laboratory abnormalities not reported
Gianfaldoni et al. (2018)[33]	Observational (high)	67	25–61	PO tofacitinib10 mg QD	(#1 Group A) NBUVB 3XW (#2 Group B) NBUVB 3XW with tofacitinib	36	Not reported	Group B achieved 92% repigmentation compared to 77% in Group A	No adverse effects Laboratory abnormalities not reported

Table 1 Continued

Author (year)	Study type and risk of bias (GRADE)	Study population	Age (years) (mean/range)	Treatment	Adjunctive treatment	Duration (weeks)	Area affected	Efficacy for vitiligo	Safety
Pan et al. (2023)[29]	Case report (high)	1	16	PO upadacitinib 15 mg QD for 4 months, then 7.5 mg QD 3 months	Crisaborole for atopic dermatitis	28	Face, neck, chest, extremities	90% face and neck repigmentation, 60% chest repigmentation, and minimal repigmentation of extremities; relief of pruritus related to eczema within 24 h	Transient worsening of acne at 3 months requiring topical acne treatment No laboratory abnormalities
Yagi et al. (2021)[30]	Case report (high)	2	(#1) 39 (#2) 45	TOP delgocitinib BID	Not reported	8–12	(#1) Neck, dorsal hands (#2) Elbow	(#1) Significant neck repigmentation (#2) No elbow repigmentation	No adverse effects Laboratory abnormalities not reported
Narla et al. (2020)[43]	Case report (high)	2	(#1) 58 (#2) 44	TOP ruxolitinib1.5% cream BID (compounded, noncommercial product)	(#1) Dexamethasone 2 mg on weekends for 10 weeks before and after MKTP (#2) Pulse dexamethasone 4 mg on weekends	Not reported	(#1) BSA 2%; forehead, neck, upperback, elbow, knees (#2) BSA 4%; acrofacial	Not reported	(#1) Severe myalgias (shoulder, upper and lower extremities) with elevated CPK, resolved 2 months after discontinuation #2 Severe myalgias (left hip) resolved after discontinuation
Rosmarin et al. (2020)[39]	RCT (low)	157	48.3	TOP Ruxolitinib 1.5% BID;1.5% QD;0.5% QD;0.15% QD; vehicle	None	24–52	Face and body with ≤20% BSA	F-VASI50 at week 24 reached by 45% on 1.5% BID and 50% on 1.5% daily; F-VASI90 at week 52 reached by 33% on 1.5% BID; T-VASI50 at week 52 reached by 36% on 1.5% BID	Application-site pruritus 3%–19%; acne 3% –18%; pruritus 3% –13%; headache 3% leading to treatment discontinuation; no clinically relevant laboratory abnormalities
Rosmarin et al. (2022)[11]	RCT (low)	674	39.6	TOP ruxolitinib 1.5% cream BID; vehicle	None	24–52	Face and body with ≤10% BSA	F-VASI75 at week 24 reached by 29.8% in TRuE-V1 and 30.9% in TruE-V2 trials	Application-site acne 6.3%–6.6%; nasopharyngitis 5.4% –6.1%; pruritus 5.3% –5.4% No clinically relevant laboratory abnormalities

Table 1 Continued

Author (year)	Study type and risk of bias (GRADE)	Study population	Age (years) (mean/range)	Treatment	Adjunctive treatment	Duration (weeks)	Area affected	Efficacy for vitiligo	Safety
Rothstein et al. (2017)[12]	Open label (high)	11	52	TOP ruxolitinib 1.5% cream BID	Not reported	20	≥1% BSA; face, acral, nonacral extremity, trunk	Nine completed the study; Four achieved 76% F-VASI; All achieved 23% T-VASI	Erythema in 8; Perilesional hyperpigmentation in 9; Transient papular eruptions in 2; Laboratory testing not repeated at study completion
Joshipura et al. (2018)[13]	Open label extension of Rothstein et al (2017) (high)	8	Not reported	TOP ruxolitinib 1.5% Cream BID	Optional NBUVB (three patients)	52	≥1% BSA; face, acral, nonacral extremity, trunk	Four achieved 92% F-VASI (including three with NBUVB); All achieved 37.6% T-VASI; five maintained response at 6-month follow-up after ruxolitinib discontinuation	Erythema in 3 (38%); Transient acne in 2 (25%) Laboratory abnormalities not reported
Joshipura et al. (2018)[31]	Case report (high)	2	(#1) 49 (#2) 43	TOP ruxolitinib 1.5% Cream BID (#1) PO tofacitinib 5 mg BID (#2)	Sun exposure	12–38	Face, arms, and forearms	(#1) 90% facial involvement at baseline improved significantly after sun exposure (#2) 80% BSA involvement at baseline improved along sun-exposed dorsal hands	Not reported Laboratory abnormalities not reported
McKesey and Pandya (2019)[35]	Case series (high)	11	44	TOP tofacitinib 2% Cream BID	NBUVB 3XW	16	Face	0.80–0.23 decrease in F-VASI; 70% mean improvement (range 50%–87%)	No adverse effects Laboratory abnormalities not reported
McKesey and Pandya (2019)[34]	Case series (high)	5	43	TOP tofacitinib 2% Cream BID	NBUVB 3XW	12	Face	0.64–0.22 decrease in F-VASI; 66% improvement	No adverse effects Laboratory abnormalities not reported
Mobasher et al. (2020)[28]	Open label (high)	16	55	TOP tofacitinib 2% Cream BID	Topical steroids, topical calcineurin inhibitor, NBUVB, PUVA, excimer laser treatment	22	Face and nonfacial areas	13 experienced repigmentation, with 4 ≥90%; greater improvement seen in FST>IV, facial lesions	Acne like papules; skin contour changes on chin; required treatment discontinuation Laboratory abnormalities not reported

Table 1 Continued

Author (year)	Study type and risk of bias (GRADE)	Study population	Age (years) (mean/range)	Treatment	Adjunctive treatment	Duration (weeks)	Area affected	Efficacy for vitiligo	Safety
Olamiju and Craiglow (2020)[27]	Case report (high)	1	14	TOP tofacitinib 2% Cream BID	NBUVB 3XW	12–24	Right chin, anterior neck	Complete repigmentation after 6 months; recurrence 6 months after treatment discontinuation prompted restarting prior treatment	No adverse effects Laboratory abnormalities not reported
Kim and Craiglow (2021)[25]	Case report (high)	1	17	TOP tofacitinib 2% Cream BID	Sun exposure	20	Bilateral upper eyelids with leukotrichia	Near-complete eyelash repigmentation; partial repigmentation of upper eyelids	No adverse effects Laboratory abnormalities not reported
Berbert Ferreira et al. (2021)[26]	Case report (high)	1	17	TOP tofacitinib 2% Ointment BID	NBUVB 3XW	36	Acrofacial areas	Significant repigmentation of the forehead, nose, eyes, and lips	Erythema and transient acne; no laboratory abnormalities

2XW, twice a week; 3XW, three times a week; BID, twice a day; BSA, body surface area; CPK, creatine phosphokinase; ESR, erythrocyte sedimentation rate; FST>IV, Fitzpatrick skin type IV; F-VASI, facial-vitiligo area scoring index; MKTP, melanocyte keratinocyte transplant procedure; NBUVB, narrow band ultraviolet B; NMSC, nonmelanoma skin cancer; PO, per os; QD, once daily; QOD, every other day; RCT, randomized controlled trial; TG, thyroglobulin antibody; TOP, topical; TPO, thyroid peroxidase antibody; T-VASI, total-vitiligo area scoring index; URTI, upper respiratory tract infection; VES, vitiligo extent score.

those who opted for concomitant narrow band ultraviolet B (NBUVB).[13] Near-complete facial repigmentation achieved with oral ruxolitinib reversed following discontinuation.[14]

Oral tofacitinib monotherapy achieved near-complete forehead repigmentation,[15,16] with facial lesions responding earlier in as much as 4 weeks[17] and up to 5 months,[18] with the response being maintained for another 3 months postdiscontinuation.[17] Complete repigmentation seen on face,[19,20] scalp,[19] elbow, and hand and leg[20] lesions required concomitant phototherapy. Two months post oral tofacitinib initiation, significant improvement occurred in formerly treatment-resistant lesions on bilateral dorsal hands.[21]

A case of restarting oral tofacitinib with a lower dose after discontinuation for 1 month maintained the JAKi response.[20] Authors suggested that high doses achieve suppression of immunity and low doses promote melanocyte regeneration[22] and help avoid unwanted systemic adverse effects.[23] Nevertheless, for treatment-refractory vitiligo, a higher dose or longer duration of treatment may be needed.[24]

Topical tofacitinib was tried in adolescents for bilateral upper eyelid vitiligo associated with eyelash leukotrichia,[25] refractory acrofacial vitiligo,[26] and chin and neck lesions in combination with phototherapy,[27] with favorable results. Topical tofacitinib was also used in combination with topical steroids or calcineurin inhibitors for refractory vitiligo, with better improvement observed in facial areas.[28]

The thinner epidermis on the face may facilitate rapid and complete absorption of topicals further enhanced by sun exposure.[12,29] The higher density of hair follicles on the face leads to higher repigmentation rates compared to hands and feet with a lower density.[11]

Mixed results were seen with the use of topical delgocitinib, which were attributed to variations in skin thickness, disease duration, and areas with sun exposure. The authors proposed that treatment on thickened skin (i.e., elbow) would be more effective with occlusion, higher concentrations, or frequent application of a topical JAKi. Starting a JAKi early on and on active disease may also yield better results.[30]

Interestingly, three patients achieved repigmentation on their untreated eyelids following the application of ruxolitinib cream to the skin adjacent to the eyelids.[12,31] Authors suggested that JAKi decreases the inflammation of the normal-appearing perilesional skin, enabling periocular repigmentation of the eyelids.[12] Those followed up post discontinuation of ruxolitinib, maintained response to a maximum duration of 10 months.[13] Conversely, two patients developed new lesions in untreated areas, while treated areas remained the same.[13]

Combination light therapy

The synergistic use of JAKi with phototherapy or sun exposure was explored in several studies and is supported by the hypothesis that repigmentation requires a dual approach involving immune suppression by JAKi and melanocyte stimulation through low-dose phototherapy or sun exposure.

For successful oral tofacitinib treatment, concomitant sunlight or phototherapy exposure, retreatment following discontinuation, and maintenance monotherapy in those previously exposed to light may be beneficial.[15,18,22,24] Oral tofacitinib, in combination with NBUVB, was also effective in treating those with refractory vitiligo with poor response to conventional therapies.[32] However, there are reports[18,23,24] of poor to no response on acral lesions despite achieving overall repigmentation while on oral tofacitinib and phototherapy.

The combination of low-dose tofacitinib and excimer light resulted in higher repigmentation rates, including face and eyelid areas,[23] compared to the combination with NBUVB.[24] In another study, NBUVB microfocused phototherapy with a starting dose set at 20% less than the minimal erythema dose (MED) was progressively increased by 20% until erythema was noted. Thereafter, the irradiation dose was decreased by 20% in the following session, achieving near-complete repigmentation in combination with oral tofacitinib.[33] The addition of low-dose tofacitinib to NBUVB may be useful for prior NBUVB failures.[24]

Tofacitinib 2% cream in combination with NBUVB showed the best response in the facial region.[26,34,35] In contrast, there was no clear pattern of response seen in a series of 16 patients undergoing concomitant phototherapy. The authors suggested that younger age, darker skin type, and focal disease may be favorable prognostic indicators of this combination.[28]

When oral baricitinib was tried as an adjunct to phototherapy along with other topical treatments, patients experienced significant repigmentation in the extremities.[36] Similarly, it was noted that the curative effect was superior on sun-exposed areas in a patient who received oral upadacitinib.[29]

Two patients who have failed prior phototherapy or topical ruxolitinib monotherapy administered individually responded well for truncal lesions when treated with the combination simultaneously.[13]

Suction blister sampling demonstrated that the autoimmune response of both responding and nonresponding lesions was inhibited during treatment, suggesting that light, rather than immunosuppression, was the primary requirement for melanocyte regeneration,[22] and that the patient counseling recommendation of sun avoidance may be reconsidered.[31]

JAKi biomarkers and treatment selection

Vitiligo, affecting those genetically predisposed, is primarily driven by autoimmune attacks on melanocytes by $CD8^+$ T cells, among other mechanisms. The cytokines IFN-γ and IL-15 play key roles. For example, IFN-γ depends on JAK1/2 signaling to promote the infiltration of autoreactive $CD8^+$ T cells and pathogenic gene upregulation, whereas IL-15 depends on JAK1/3 for the proliferation and survival of memory T cells and regulatory T cells.[6]

Table 2 JAK inhibitors studied in the treatment of vitiligo and their target kinases.[3,6]

JAK inhibitor	Target kinase family	JAK selectivity	Inhibited cytokine receptor
Baricitinib	JAK1, JAK2	Nonselective	IFN-γ
Delgocitinib	JAK1, JAK2, JAK3, TYK2	Nonselective	IFN-γ, IL-15
Ritlecitinib	JAK3, TEC	Selective	IL-15
Ruxolitinib	JAK1, JAK2	Nonselective	IFN-γ
Tofacitinib	JAK1, JAK3	Nonselective	IFN-γ, IL-15
Upadacitinib	JAK1	Selective	IFN-γ

IFN-γ, interferon-gamma; IL, interleukin; JAK, Janus kinase; TEC, tyrosine kinases expressed in the hepatocellular carcinoma; TYK, tyrosine kinase.

Table 2 represents the JAKi investigated in the treatment of vitiligo, their specific target kinases, and the corresponding cytokine receptors they inhibit. JAKi can be directed toward one or multiple isoforms of JAKs, yet the pharmacological specificity of binding remains uncertain. Consequently, this lack of binding selectivity may not reliably predict consistent clinical outcomes, even when employing JAKi that target the same JAKs.[5] Nonselective JAKi inhibit many cytokines simultaneously, and more selective inhibitors may inhibit the signaling of a narrower range of cytokines.[6] It is worth noting that the lack of selectivity in JAKi may raise concerns regarding optimal dosing, safety, and clinical applications.[4,5] Therefore, it becomes imperative to incorporate data derived from both clinical trials and real-world evidence to comprehensively evaluate the efficacy and safety of treatment protocols.[5]

The role of JAKi biomarkers in informing the choice of treatment strategies was investigated in several articles:

1 One study reported that the lack of response to tofacitinib along with light exposure may be due to its inhibition of JAK1/3, which leads to the process of IFN-dependent attack of melanocytes, suggesting ruxolitinib, a JAK1/2 inhibitor, likely being more efficacious instead.[22] Similar observation was reported when baricitinib was substituted to compensate for tofacitinib nonresponse. Baricitinib, similar to ruxolitinib in action, preferentially inhibits JAK1/2, suggesting exhibiting greater efficacy than other JAKi.[37]
2 Authors of a clinical trial suggested that oral ritlecitinib may decrease the production of IFN-γ via an indirect mechanism by inhibiting JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma kinase family (JAK3/TEC) and would be a favorable choice for the treatment of large vitiligo lesions with a body surface area (BSA) of 4%–50%.[38]
3 Recent studies have shown an increased risk of vitiligo in atopic dermatitis patients, suggesting overlapping genetic and immune mechanisms. Upadacitinib with increased JAK1 selectivity may contribute with dual effects to provide itch relief in atopic dermatitis and repigmentation in vitiligo.[29]
4 Oral ruxolitinib efficacy was demonstrated by measuring a patient's serum CXC motif chemokine ligand 10 (CXCL10) level, which showed a decrease in 3 months into treatment.[14] Topical ruxolitinib once or twice daily treatment showed significant downregulation of CXCL9 and CXCL10 in serum samples.[39] Similarly, oral tofacitinib treatment decreased $CD8_+$ T-cell numbers, and CXCL9 and CXCL10 protein levels were measured in vitiligo lesions.[22]

Concomitant autoimmune diseases

Vitiligo has been associated with a number of other autoimmune diseases, as well as a wide range of psychosocial difficulties, significantly impacting the quality of life.[6,20] The most frequently reported comorbidities are rheumatoid arthritis (RA), alopecia areata (AA), atopic dermatitis (AD), psoriasis, among others.[6] According to this review findings, initiation of a JAKi may improve concomitant autoimmune conditions.

Tofacitinib was one of the earliest JAKi to be explored for the treatment of autoimmune conditions, including vitiligo. As a result, it has accumulated a substantial body of evidence supporting its efficacy for the treatment of autoimmune conditions beyond vitiligo, including AA, AD, RA, and psoriasis.[6]

1 In a patient with refractory alopecia and vitiligo, noticeable scalp and eyebrow hair regrowth was seen 2 months after initiation of oral tofacitinib.[21] Another with psoriasis, vitiligo, and alopecia areata universalis involving scalp, eyebrows, and hair achieved near-complete improvement in psoriasis, perifollicular repigmentation, and regrowth of all scalp and body hair, with low-dose tofacitinib.[20]
2 Examination of skin biopsies from individuals with AA has identified heightened levels of JAK3, with JAK1 and JAK2 also being expressed, though to a lesser degree, indicating a possible role for tofacitinib.[6] JAK3 expression is known to be markedly increased in psoriasis as well as AD.[6] A case of treatment-refractory AD, AA, and vitiligo, when treated with oral tofacitinib, saw the greatest response in AD. However, the patient being on concurrent oral prednisolone and topical betamethasone confounded the individual impact of the drugs concerned. The marginal improvement seen in AA and vitiligo was attributed to these diseases being stable at the start of treatment.[40]
3 Oral tofacitinib initiated for the treatment of RA, coincidentally helped improve repigmentation of vitiligo lesions on the hands and face after 8 months of use.[15] A similar case of tofacitinib given for RA and augmented by NBUVB microphototherapy, achieved near-complete repigmentation in several patients.[33]

Besides tofacitinib, there were reports indicating the use of ruxolitinib and upadacitinib for managing concomitant autoimmune disorders alongside vitiligo.

1 In a case involving a patient with AA and vitiligo, both conditions improved while on oral ruxolitinib, but repigmentation regressed while hair regrowth was maintained after discontinuation.[14]
2 Using oral upadacitinib in conjunction with topical crisaborole effectively treated both coexisting AD and vitiligo lesions on the face and neck.[29] However, crisaborole utilization as monotherapy for vitiligo[41] introduces a confounding element, complicating the assessment of individual therapy effectiveness.

Safety

Systemic JAKi with increased selectivity may have an improved safety profile. However, this may present challenges due to the intricate network of cytokine interactions and the widespread presence of JAK-STAT signaling in nonimmune cells. While expanding the therapeutic scope for various diseases, such selectivity might inadvertently increase off-target adverse effects.[3,4] Treatment with a JAKi may also affect the function of T and B lymphocytes and natural killer cells and can lead to an increased susceptibility to infections, particularly affecting the upper respiratory tract. Additionally, reactivation of Herpes Zoster virus (HZV) and altered blood lipid profiles are commonly reported, with a potential dose-dependent relationship.[3,5] Chronic infectious diseases such as viral hepatitis, HIV infections, and latent or active tuberculosis should be excluded prior to the start of JAKi. The risk of varicella-zoster reactivation should be addressed by pretreatment vaccination.[5] While JAKi can elevate blood cholesterol levels, this rise has not been linked to an increased risk of cardiovascular disease in clinical studies.[3] Elevated serum creatinine or liver transaminase levels have also been reported and are somewhat more common in older patients. Currently, the relevance of increased risk of malignancy and thromboembolic events is unclear.[4,5] Recommended baseline laboratory investigations for oral JAKi are indicated in Table 3.

Table 3 Recommended pretreatment laboratory investigations for oral JAK inhibitors.[5]

Laboratory investigation	Recommendations
Complete blood count	Precaution: hemoglobin <8 g/dL, thrombocytes <150 x 10^9 cells/L
Differential blood count	Precaution: neutrophils <1 × 10^9 cells/L, lymphocytes 0.5 × 10^9 cells/L
Renal function tests	Creatinine, creatine phosphokinase
Liver function tests	Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase
Lipid panel	Total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein
Hepatitis B and C	Hepatitis B and C virus serology
HIV	HIV serology
TB QuantiFERON and chest X-ray	Exclude latent or active tuberculosis infection

HIV, human immunodeficiency virus; TB, tuberculosis.

Mild elevations of lipid levels were reported in one study[22] and fluctuations seen in another[32] with oral tofacitinib treatment did not warrant interventions. Clinically significant hematology or thromboembolic events were not found despite the black box warning associated with cardiovascular risks, fatal blood clots, and malignancies for all JAKi. In a 5-year trial, one patient experienced no discernible adverse effects with oral tofacitinib.[19] Elevated baseline uric acid levels in six patients generally trended upward for a 16-week treatment with oral tofacitinib, suggesting a potential impact on renal function or metabolic processes.[32] However, it is not clear if these patients were asymptomatic or presented with crystalluria.

Amid safety concerns regarding systemic JAK inhibition, certain JAKi have been investigated for topical application, aiming to provide localized benefits while potentially mitigating off-target systemic effects. Acne-related adverse events, though frequent yet mild, were reported as acneiform eruptions and transient acne in several studies using topical JAKi.[11,12,26,28,29,39] An adolescent who reported the worsening of facial acne with oral upadacitinib required topical acne treatment.[29] Two patients with truncal acne revealed commensal fungal species when cultured, which nevertheless resolved with topical ketoconazole while undergoing oral baricitinib treatment. The authors postulated that blocking JAK1 receptors might cause a shift in the immune response, resulting in microbiome dysbiosis and susceptibility to unusual infections.[42]

The development of myalgias observed following the use of oral tofacitinib[32] and topical ruxolitinib,[43] and with elevations of creatinine phosphokinase levels, were hypothesized to be a sudden increase in myocyte differentiation and proliferation, leading to muscle cell fragility and damage.

In the largest study with oral ritlecitinib, common adverse effects included nasopharyngitis, upper respiratory tract infections, and headaches. Nonmelanoma skin cancer, assessed as unrelated to ritlecitinib with full recovery, and localized herpes zoster, assessed as related to drug and resolution with a short interruption, were reported as nonserious adverse effects.[38] Acne, pruritus, and nasopharyngitis were the most significant adverse effects in clinical trials with topical ruxolitinib,[11,39] with continuation of treatment or a temporary dose reduction.[11]

Recurrent episodes of headache and flu-like symptoms led to the discontinuation of oral tofacitinib and reinitiation at the lower dose.[20] Another study reported a patient with gastrointestinal side effects while on tofacitinib requiring a dose reduction to 5 mg once daily. The authors noted that tofacitinib in addition to its JAKi activity, was known to decrease thyroid peroxidase and thyroglobulin antibodies within 1 month of initiation, suggesting that unresponsive vitiligo may be associated with elevated antithyroid autoantibodies, warranting testing and treatment.[44]

Interestingly, a case of a paradoxical presentation of new-onset vitiligo was reported within 4 months of starting oral tofacitinib XR prescribed for RA. The authors postulated that the trigger may have been a JAK1/3 blockade causing a paradoxical upregulation of IFN-γ signaling via JAK2, in addition to the alteration of the inflammatory cascade resulting in the production of multiple proinflammatory cytokines.[45]

In summary, while the use of JAKi carries the potential for specific adverse effects, including infections, HZV reactivation, and altered lipid profiles, current evidence from this review suggests a low incidence of major complications, such as cardiovascular events.

Limitations

Most of the reviewed studies were observational, which translated into moderate-tolow-quality evidence, likely resulting in observer and publication bias. Confounders to the interpretation of JAKi safety and efficacy include disease activity at recruitment, varying years of history of vitiligo, inability to monitor natural sun exposure, and concomitant treatment with phototherapy or topical applications. Small sample sizes in studies diminished the power of this review, limiting the validity and reproducibility of results.

Knowledge gaps and implications for further study

Notwithstanding the evidence presented in this review, notable knowledge gaps exist in our understanding of the utilization of JAKi in vitiligo. This highlights the necessity for continued research efforts to address these gaps.

1 Long-term safety and efficacy: Considering the life-long chronicity of the condition, existing studies on the use of JAKi for vitiligo may be limited in duration. Long-term data could offer insights into the sustained effectiveness, relapses post-discontinuation, and potential adverse effects.
2 Repigmentation rates: Diverse measurement tools for repigmentation assessment posed challenges. Standardized scales would enhance objectivity in evaluating repigmentation from both clinical and patient perspectives, all the more so for observational case reports.
3 Lesion type and location: Certain body areas may be more challenging to treat. Analyzing JAKi based on lesion activity, histological changes, disease duration, and location could provide valuable insights.
4 Dose-response relationship: Studies reveal notable dosage titrations, warranting future investigation into a potential dose-response relationship to explore whether higher doses yield better outcomes without proportional adverse effects.
5 Optimal treatment protocols: Identifying effective and well-tolerated regimens is crucial. Explore variations in dosages, treatment durations, and JAKi use as monotherapy or in combination, assessing synergistic effects for optimal outcomes.
6 Related autoimmune conditions: Considering vitiligo's association with autoimmune diseases, a judicious approach to JAKi treatment is crucial. Select JAKi addressing both vitiligo and coexisting autoimmune conditions for optimized therapeutic outcomes.
7 Comparison with standard treatments: With JAKi's recent emergence, comparative research against standard treatments is imperative. Head-to-head trials or meta-analyses can elucidate relative benefits and drawbacks.
8 Mechanisms of action and biomarkers: Understanding JAKi targets of action, biomarkers, and molecular pathways may predict treatment response and guide intervention strategies.
9 Patient subpopulations: Assess JAKi responses in diverse subpopulations, including adolescents. Tailoring treatments based on age, gender, and ethnic background could enhance personalized medicine approaches.
10 Quality of life outcomes: Explore the impact of JAKi on vitiligo patients' quality of life. Qualitative assessments of patient-reported outcomes can address physical, psychological, and social aspects of living with vitiligo.
11 Cost-effectiveness: This research did not uncover economic evaluations. Understanding the economic implications informs healthcare decision-makers.
12 Prevention of relapse: Considering the mechanism of action of JAKi, there is a potential to induce stability of vitiligo and prevention of relapse via memory T cells. To date, there are no treatments capable of preventing relapse, and if JAKi can fill in this gap, this would be a game changer.

Conclusion

In this review, we have introduced new perspectives and findings that enrich the existing body of literature on JAKi for the treatment of vitiligo. Vitiligo treatment with JAKi, whether oral or topical, shows promise, with a favorable risk-benefit profile. Benefits may vary based on the JAKi receptor selectivity profile. A gap in knowledge exists regarding the switch between JAKi for cases with concurrent inflammatory diseases lacking improvement. Remarkably, facial vitiligo responds well to JAKi, and sustained responses post-JAKi discontinuation are observed. A topical JAKi is advantageous for limited body areas, especially in adolescents, an area where further research could add substantial value.

No studies utilized oral and topical formulations of JAKi in parallel. Combining a JAKi with NBUVB or sun exposure appears beneficial for melanocyte stimulation. Most investigations allowed concurrent use of other topical agents, mirroring real-world scenarios. For oral JAKi, discontinuation and restart with a dose reduction may be helpful if found intolerable. Adverse effects, generally mild and consistent, seldom led to

complications or hospitalization. It is of note that postmarketing, follow-up for published studies may be ongoing.

This scoping review not only illuminates the evolving landscape of vitiligo treatment with JAKi emphasizing the need for ongoing research to refine treatment strategies and improve outcomes, but also introduces new findings and identifies gaps in the current knowledge, thereby adding substantial value.

References

1 Karagaiah P, Valle Y, Sigova J, Zerbinati N, Vojvodic P, Parsad D, et al. Emerging drugs for the treatment of vitiligo. *Expert Opin Emerg Drugs*. 2020;**25**(1):7–24.
2 Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. A comprehensive overview of globally approved JAK inhibitors. *Pharmaceutics*. 2022;**14**(5):1–66.
3 Angelini J, Talotta R, Roncato R, Fornasier G, Barbiero G, Dal Cin L, et al. JAK-Inhibitors for the treatment of rheumatoid arthritis: a focus on the present and an outlook on the future. *Biomolecules*. 2020;**10**(7):1–40.
4 Wood H, Chandler A, Nezamololama N, Papp K, Gooderham MJ. Safety of Janus kinase (JAK) inhibitors in the short-term treatment of atopic dermatitis. *Int J Dermatol*. 2022;**61**(6):746–54.
5 Eichner A, Wohlrab J. Pharmacology of inhibitors of Janus kinases—part 2: pharmacodynamics. *J Dtsch Dermatol Ges*. 2022;**20**(12):1621–31.
6 Garcia-Melendo C, Cubiró X, Puig L. Janus kinase inhibitors in dermatology: part 1—general considerations and applications in vitiligo and alopecia areata. *Actas Dermosifiliogr (English Edition)*. 2021;**112**(6):503–15.
7 Montilla AM, Gómez-García F, Gómez-Arias PJ, Gay-Mimbrera J, Hernández-Parada J, Isla-Tejera B, et al. Scoping review on the use of drugs targeting JAK/STAT pathway in atopic dermatitis, vitiligo, and alopecia areata. *Dermatol Ther*. 2019;**9**(4):655–83.
8 Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;**169**(7):467–73.
9 Gómez-García F, Gómez-Arias PJ, Hernandez J, Montilla AM, Gay-Mimbrera J, Aguilar-Luque M, et al. Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review. *BMJ Open*. 2019;**9**(5):e028303.
10 Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol*. 2011;**64**(4):407–15.
11 Rosmarin D, Passeron T, Pandya AG, Grimes P, Harris JE, Desai SR, et al. Two phase 3, randomized, controlled trials of ruxolitinib cream for vitiligo. *N Engl J Med*. 2022;**387**(16):1445–55.
12 Rothstein B, Joshipura D, Saraiya A, Abdat R, Ashkar H, Turkowski Y, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol*. 2017;**76**(6):1054–1060 e1.
13 Joshipura D, Alomran A, Zancanaro P, Rosmarin D. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib: a 32-week open-label extension study with optional narrow-band ultraviolet B. *J Am Acad Dermatol*. 2018;**78**(6):1205–1207 e1.
14 Harris JE, Rashighi M, Nguyen N, Jabbari A, Ulerio G, Clynes R, et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). *J Am Acad Dermatol*. 2016;**74**(2):370–1.
15 Komnitski M, Komnitski A, Komnitski Junior A, Silva de Castro CC. Partial repigmentation of vitiligo with tofacitinib, without exposure to ultraviolet radiation. *An Bras Dermatol*. 2020;**95**(4):473–6.
16 Craiglow BG, King BA. Tofacitinib citrate for the treatment of vitiligo: a pathogenesis-directed therapy. *JAMA Dermatol*. 2015;**151**(10):1110–2.
17 AlMutairi N. Progressive vitiligo in adults treated with Janus kinase inhibitor tofacitinib: an open label study. *J Am Acad Dermatol*. 2019;**81**(4):AB109.
18 Kim SR, Heaton H, Liu LY, King BA. Rapid repigmentation of vitiligo using tofacitinib plus low-dose, narrowband UV-B phototherapy. *JAMA Dermatol*. 2018;**154**(3):370–1.
19 Aickara DJ, Patel S, Rosen J, Alonso-Llamazares J. Significant improvement of vitiligo with oral tofacitinib treatment. *Int J Dermatol*. 2023;**62**(6):e358–60.
20 Tajalli M, Kabir S, Vance TM, Qureshi AA. Effective use of oral tofacitinib and phototherapy in a patient with concomitant alopecia areata, vitiligo, and plaque and inverse psoriasis. *Clin Case Rep*. 2020;**8**(5):819–22.
21 Perche P, Purvis C, Pichardo R. Refractory alopecia areata and vitiligo responding to tofacitinib monotherapy. *J Drugs Dermatol*. 2022;**21**(12):1366–8.
22 Liu LY, Strassner JP, Refat MA, Harris JE, King BA. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J Am Acad Dermatol*. 2017;**77**(4):675–682 e1.
23 Fang WC, Lin SY, Huang SM, Lan CE. Low-dose tofacitinib with 308-nm excimer therapy successfully induced repigmentation in patients with refractory vitiligo. *Clin Exp Dermatol*. 2022;**47**(4):782–3.
24 Fang WC, Chiu SH, Lin SY, Huang SM, Lan CE. Evaluation of low-dose tofacitinib combining narrowband UVB therapy for treating vitiligo patients who had failed previous therapy: a pilot study. *Photodermatol Photoimmunol Photomed*. 2021;**37**(4):345–7.
25 Kim SR, Craiglow BG. Repigmentation of vitiligo-associated eyelash leukotrichia with topical tofacitinib. *JAAD Case Rep*. 2021;**16**:90–1.
26 Berbert Ferreira S, Berbert Ferreira R, Neves Neto AC, Assef SMC, Scheinberg M. Topical tofacitinib: a janus kinase inhibitor for the treatment of vitiligo in an adolescent patient. *Case Rep Dermatol*. 2021;**13**(1):190–4.
27 Olamiju B, Craiglow BG. Tofacitinib cream plus narrowband ultraviolet B phototherapy for segmental vitiligo in a child. *Pediatr Dermatol*. 2020;**37**(4):754–5.
28 Mobasher P, Guerra R, Li SJ, Frangos J, Ganesan AK, Huang V. Open-label pilot study of tofacitinib 2% for the treatment of refractory vitiligo. *Br J Dermatol*. 2020;**182**(4):1047–9.
29 Pan T, Mu Y, Shi X, Chen L. Concurrent vitiligo and atopic dermatitis successfully treated with upadacitinib: a case report. *J Dermatolog Treat*. 2023;**34**(1):2200873.
30 Yagi K, Ishida Y, Otsuka A, Kabashima K. Two cases of vitiligo vulgaris treated with topical Janus kinase inhibitor delgocitinib. *Australas J Dermatol*. 2021;**62**(3):433–4.
31 Joshipura D, Plotnikova N, Goldminz A, Deverapalli S, Turkowski Y, Gottlieb A, et al. Importance of light in the treatment of vitiligo with JAK-inhibitors. *J Dermatolog Treat*. 2018;**29**(1):98–9.
32 Song H, Hu Z, Zhang S, Yang L, Liu Y, Wang T. Effectiveness and safety of tofacitinib combined with narrowband ultraviolet B

phototherapy for patients with refractory vitiligo in real-world clinical practice. *Dermatol Ther*. 2022;**35**(11):e15821.
33 Gianfaldoni S, Tchernev G, Wollina U, Roccia MG, Fioranelli M, Lotti J, et al. Micro-focused phototherapy associated to janus kinase inhibitor: a promising valid therapeutic option for patients with localized vitiligo. *Open Access Maced J Med Sci*. 2018;**6**(1):46–8.
34 Mckesey J, Pandya A. *Topical Janus kinase inhibitor tofacitinib for the treatment of vitiligo*. Milan: Italy; 2019.
35 McKesey J, Pandya AG. A pilot study of 2% tofacitinib cream with narrowband ultraviolet B for the treatment of facial vitiligo. *J Am Acad Dermatol*. 2019;**81**(2):646–8.
36 Li X, Sun Y, Du J, Wang F, Ding X. Excellent Repigmentation of Generalized Vitiligo with Oral Baricitinib Combined with NB-UVB Phototherapy. *Clin Cosmet Investig Dermatol*. 2023;**16**:635–8.
37 Mumford BP, Gibson A, Chong AH. Repigmentation of vitiligo with oral baricitinib. *Australas J Dermatol*. 2020;**61**(4):374–6.
38 Ezzedine K, Peeva E, Yamaguchi Y, Cox LA, Banerjee A, Han G, et al. Efficacy and safety of oral ritlecitinib for the treatment of active nonsegmental vitiligo: a randomized phase 2b clinical trial. *J Am Acad Dermatol*. 2023;**88**(2):395–403.
39 Rosmarin D, Pandya AG, Lebwohl M, Grimes P, Hamzavi I, Gottlieb AB, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. *Lancet*. 2020;**396**(10244):110–20.
40 Vu M, Heyes C, Robertson SJ, Varigos GA, Ross G. Oral tofacitinib: a promising treatment in atopic dermatitis, alopecia areata and vitiligo. *Clin Exp Dermatol*. 2017;**42**(8):942–4.
41 Tam I, Kahn JS, Rosmarin D. Repigmentation in a patient with vitiligo on crisaborole 2% ointment. *JAAD Case Rep*. 2021;**11**:99–101.
42 Doh JY, Rintarhat P, Jung WH, Kim HS. Truncal acne following JAK inhibitor use in vitiligo with rare opportunistic fungal infections: two case reports. *JAAD Case Rep*. 2023;**37**:123–7.
43 Narla S, Oska S, Lyons AB, Lim HW, Hamzavi IH. Association of myalgias with compounded topical Janus kinase inhibitor use in vitiligo. *JAAD Case Rep*. 2020;**6**(7):637–9.
44 Moore AY, Maberry S. Tofacitinib treats unresponsive vitiligo and elevated thyroid peroxidase antibodies. *J Am Acad Dermatol*. 2021;**85**(3):AB124.
45 Nguyen JK, Schlichte MJ, Jogi R, Alikhan M, Patel AB. A case of new-onset vitiligo in a patient on tofacitinib and brief review of paradoxical presentations with other novel targeted therapies. *Dermatol Online J*. 2020;**26**(3):9.
46 Photiou L, Sinclair R. An open label study of tofacitinib in the treatment of vitiligo. *Austral J Dermatol*. 2018;**59**(S1):32–129.
47 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**(4):478–90.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Database search strategies.

Table S2. List of included studies.

Table S3. Additional characteristics of included studies.