

The Use of Janus Kinase Inhibitors in Vitiligo: A Review of the Literature

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Abstract

Vitiligo is a common acquired depigmenting disorder characterized by the development of white macules and patches due to the loss of melanocytes. Patients with vitiligo can be stigmatized by society, making the disease a source of psychological stress that can considerably affect quality of life. The goal of vitiligo treatment is to obtain skin repigmentation in the majority of cases, and less commonly to depigment the remaining normal skin. There is no consistent, long-term, durable therapy for vitiligo for all patients, highlighting the unmet need for new safe and effective therapies to control this disease. Recently, JAK inhibitors have been explored as a promising novel treatment option in vitiligo. The JAK and signal transducers and activators of transcription (STAT) pathway is an attractive therapeutic target because IFN- γ -dependent cytokines produced through this pathway have been implicated in the pathogenesis of disease. This literature review describes vitiligo pathophysiology, explains the usefulness of the JAK inhibitors for treatment, and summarizes published case reports, case series, and open-label studies. Research outlined here shows JAK inhibitors in patients with vitiligo have a favorable safety profile and effectively produce repigmentation of lesions, especially with concomitant ultraviolet exposure. Additional studies are required to confirm efficacy, establish safety, and investigate durability of repigmentation.

Keywords

JAK inhibitor, Janus kinase, ruxolitinib, tofacitinib, vitiligo

Introduction

Vitiligo is the most common depigmenting disorder, with an estimated prevalence of 0.5% to 1% in most populations.^{1–3} It is an acquired chronic skin disease characterized by the development of well-circumscribed, white, nonscaly macules and patches due to the destruction of melanocytes in the skin, hair, or both. No epidemiologic differences in vitiligo prevalence according to gender or race have been reported.³ Disease onset can occur at any age, but usually occurs between the ages of 10 to 30 years.^{4,5}

At all ages, vitiligo can be psychologically devastating and considerably affect quality of life (QoL).⁶ Patients with vitiligo can be distressed and feel discriminated against because of their altered skin appearance. In some countries, vitiligo is confused with other diseases such as leprosy, and patients can be rejected from their community.⁷ Many patients in India face severe stigma; for example, in some regions vitiligo is considered a punishment of past sins and can lead to marital problems, especially in young women.⁸ Given that patients often have significant psychological difficulties such as depression, anxiety, and low self-esteem,^{9–11} it would be irresponsible to dismiss vitiligo as simply a cosmetic problem. A QoL assessment should be performed during initial consultation to elucidate the patient's perception

of disease severity and be monitored throughout treatment as an objective measure of patient satisfaction and well-being. The Dermatology Life Quality Index (DLQI) is recommended to assess QoL as it has been used widely for patients with vitiligo and is the most studied instrument in the literature.¹² It has been shown that the DLQI is a reliable and valid instrument to measure the impact of vitiligo in an Iranian population.¹³ The DLQI has also been shown to have a significant correlation with psychiatric morbidity in 200 vitiligo patients.¹⁴

Classification

Vitiligo lesions are classified into 2 major categories: segmental vitiligo (SV) and nonsegmental vitiligo (NSV); the latter includes several subtypes (generalized vitiligo, universal vitiligo, and acrofacial vitiligo).¹⁵ These multiple forms

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of vitiligo differ in clinical features and disease progression. NSV is the most common form, is characterized by white patches that are typically symmetrical and bilaterally distributed, and has a chronic course that usually results in increasing depigmentation over time.¹⁵ In contrast, SV is characterized by a unilateral, segmental distribution, with rapid disease onset and usually disease stabilization.¹⁶ Focal vitiligo can occur both in NSV and SV, where the affected patch is small (10-15 cm²) without an obvious distribution pattern.¹⁵ Mixed vitiligo refers to the coexistence of nonsegmental and segmental lesions in the same patient, and in this case segmental lesions tend to be refractory to treatment.¹⁷ Patches of vitiligo often occur in response to friction or pressure, termed Koebner phenomenon.¹⁸ Patients should be counselled on avoiding triggers that induce new areas of depigmentation. Diagnosis of vitiligo is made clinically with a thorough history and physical examination, often accompanied by an examination with a Wood lamp. A Wood lamp emits long-wave ultraviolet (UV) radiation generated by a high-pressure mercury arc covered with a filter made of barium silicate with 9% nickel oxide and emits light between 320 and 400 nm with a peak at 365 nm.¹⁹ It is helpful in making the diagnosis of vitiligo and differentiating from conditions of hypopigmentation by inducing autofluorescence of dermal collagen in depigmented skin. It may also be of particular use in fair-skinned patients, in whom early lesions of vitiligo are more difficult to diagnose.¹⁹ A skin biopsy is rarely required to confirm the diagnosis.

Pathophysiology of Vitiligo

The pathogenesis of vitiligo is insufficiently understood, making the development of new treatment options a challenge. Histological examination shows a loss of melanocytes in skin lesions. The cause of melanocyte loss is likely multifactorial, and the causal mechanisms may be different for each individual. There have been multiple factors implicated in vitiligo pathogenesis such as physical and emotional stress, trauma, infection, immune mechanisms, neuroendocrine pathology, and genetic predisposition.^{20,21}

There are 4 main theories that attempt to explain the pathophysiology of vitiligo. The *autoimmune hypothesis* is the most popular. This hypothesis is supported by the association of NSV with autoimmune conditions such as Addison disease, alopecia areata (AA), rheumatoid arthritis (RA), insulin-dependent diabetes mellitus, and thyroiditis.²²⁻²⁵ In a systematic review, autoimmune thyroid disease was found in 14.3% of patients with vitiligo, and this risk seems to increase with age.²⁶ Furthermore, genome-wide association studies identified several susceptibility loci for vitiligo, many of which are shared with other autoimmune disorders.²⁷⁻²⁹

The second theory, the *neural hypothesis*, proposes that dysregulation of the nervous system may damage melanocytes in vitiligo. This theory is supported by the fact that melanocytes and nerves arise from neural crest cells, and

that segmental depigmentation in some patients follows the distribution of nerves.³⁰ The third is the *destruction hypothesis*, which suggests that melanocytes in patients with vitiligo have defective intracellular protective mechanisms to eliminate toxic melanin precursors, leading to an accumulation of indoles and free radicals.³¹ The final theory is the *convergence theory*, which proposes that a combined theory rather than 1 individual theory is more likely to explain the etiology of vitiligo.³²

Treatment of vitiligo

Overall, the aim of vitiligo therapy is to obtain skin repigmentation in the majority of patients, and less commonly to depigment the remaining normal skin. This often involves a multifaceted approach that includes topical therapy, phototherapy, systemic therapy, surgical therapy, depigmentation, and camouflage.

Topical Therapy

First-line treatment for vitiligo consists of topical therapy with corticosteroids and calcineurin inhibitors.³³ Topical corticosteroid (TCS) therapy is most common, but should be used appropriately on a discontinuous schedule to avoid well-known side effects such as cutaneous atrophy, striae, and telangiectasia.^{27,33} Topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus impair T-cell activity and decrease production of proinflammatory cytokines. TCIs are often used as an alternative to TCS especially in areas of sensitive skin (eg, the face), and if treatment with TCS was not successful or produced undesirable adverse effects. Small studies and case reports on the use of TCI in vitiligo report good efficacy, with superior repigmentation on face and neck lesions, and a better safety profile compared with TCS.³⁴⁻³⁶ The most common side effect of TCI is a burning sensation on the skin with application, which resolves with continued use in the majority of patients.³⁷

Phototherapy and Photochemotherapy

Second-line therapy involves phototherapy or systemic steroid treatment. Phototherapy options include narrow-band UVB (NB-UVB) or monochromatic excimer light, and photochemotherapy includes UVA and psoralens (PUVA therapy). Psoralens can be administered topically (topical PUVA) or orally (oral PUVA) prior to exposure to UVA.³¹ These options are limited by regional availability. A recent randomized, double-blind trial in patients with vitiligo found that NB-UVB had superior efficacy, better colour match, and fewer adverse events when compared to PUVA therapy.³⁸ Risks of PUVA therapy include higher cumulative UV exposure, systemic effects from psoralens, ocular toxicity, more burning incidents, and more long-term effects such as hyperkeratosis.^{31,39,40} The benefit of topical PUVA over oral PUVA

is the lack of systemic and ocular effects and lower required doses of UVA.³¹ In patients with psoriasis, NB-UVB therapy is not associated with an increased risk of skin cancers, but PUVA therapy has been linked to an increase in keratinocyte carcinomas and melanoma.⁴¹⁻⁴³ In contrast to those with psoriasis, in patients with vitiligo PUVA therapy has not been associated with an increase in nonmelanoma skin cancers; however, these studies have minimal patient numbers and short follow-up periods.⁴⁴⁻⁴⁶

Systemic Therapy

Oral corticosteroid minipulse therapy has been shown to be effective in halting rapidly progressive disease, but studies have shown failure of repigmentation.⁴⁷⁻⁴⁹ Oral corticosteroids are not used in the long-term because of known systemic side effects, such as weight gain, sleep disturbance, agitation, acne, and hypertrichosis.⁴⁷ Interestingly, 1 study reported that methotrexate halted progression of vitiligo lesions and was well tolerated, but did not induce any repigmentation.⁵⁰

It has been recognized that most systemic immunosuppressive therapy is effective at inducing repigmentation when given in combination with phototherapy; once inflammation is controlled, the melanocyte stem cells need to be reactivated for repigmentation to occur.³⁷ Systemic therapy with L-phenylalanine, *Polypodium leucotomos*, khellin, and antioxidant vitamins have also shown some benefit in combination with phototherapy.⁵¹ The traditional Chinese herb ginkgo biloba has been shown to decrease disease progression and contribute to repigmentation.⁵¹ Supplementation with zinc improved response rates compared to corticosteroids alone,⁵² as zinc may prevent apoptosis of melanocytes.^{51,53}

Surgical Therapy

Further options for therapy consist of surgical methods in patients with SV and those with NSV with stable disease, defined as failing medical therapy for at least 1 year and absence of Koebner phenomenon.²⁷ Several surgical techniques with varying difficulty have been employed in patients with variable success. Specimens containing melanocytes are grafted from healthy skin in procedures such as grafting of epidermal blisters,⁵⁴ split-thickness skin grafting, punch grafting, and autologous melanocyte transplant methods.^{31,55}

Emerging Therapeutic Approaches

A recent Cochrane review assessing all interventions used to manage vitiligo found that, in general, combination therapies were superior to monotherapies.⁵⁶ The authors also concluded there is no cure or way of restricting the spread of disease. This highlights the unmet need for new safe and effective therapies to control this condition.

A novel therapeutic target being explored for vitiligo is the JAK and signal transducers and activators of transcription (STAT) pathway. Drugs that inhibit this pathway are an emerging therapeutic class attracting interest in the literature for a wide variety of immune-mediated diseases, including vitiligo. Recently, chemokine profiling in human patients with vitiligo elucidated a T helper-1 (T_H1) cytokine signature in the skin that includes the IFN- γ -dependent chemokines CXCL9, 10, and 11.⁵⁷ CXCL10 promotes recruitment of autoreactive CD8+ T cells to the epidermis, where they attack melanocytes resulting in depigmentation. In vitiligo mouse models, treatment with a CXCL10-neutralizing antibody induced repigmentation of vitiligo skin lesions.⁵⁷ Thus, JAK inhibitors may be an important therapeutic options for vitiligo by downregulating IFN- γ signalling and thereby its downstream chemokines. The use of JAK inhibitors in vitiligo is a new area being explored and will be further discussed in this review.

Depigmentation and Cosmetic Camouflage

In patients with extensive disease (> 30% to 40% BSA), depigmentation of remaining pigmented areas can be considered, usually after failing other treatment modalities.⁵⁸ Methods of depigmentation include bleaching creams (monobenzone ethyl ester, 4-methoxyphenol, or phenol),⁵⁹ laser treatment,⁶⁰ or cryotherapy.^{37,61,62} Interestingly, some cases of vitiligo repigmentation from wounding post-phenol have been reported.⁶³ Cosmetic camouflage using tinted covering creams or self-tanning products may be a viable option for patients who wish to conceal vitiligo on exposed areas day to day.

JAK Inhibitors

The JAK-STAT pathway is critical for the downstream signalling of inflammatory cytokines and growth hormones.⁶⁴ JAKs are tyrosine kinases that are associated with the cytoplasmic domain of type I and type II chemokine receptors, with ligands such as IFN- γ . Extracellular binding of cytokines activates their receptors, inducing apposition of JAKs and self-activation by autophosphorylation. Activated JAKs bind STATs, which undergo JAK-mediated phosphorylation leading to STAT dimerization, translocation to the nucleus, DNA binding, and regulation of gene expression.⁶⁵

First-Generation JAK Inhibitors

JAK inhibitors are medications that inhibit the tyrosine kinases JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) either selectively or broadly.⁶⁵ First-generation JAK inhibitors include tofacitinib, ruxolitinib, and baricitinib, which block multiple JAKs. Tofacitinib, a potent JAK1 and JAK3 inhibitor, was the first JAK inhibitor to be tested in humans. It is approved for the treatment of moderate to severe rheumatoid arthritis (RA) in Canada, the United States (US),

and the European Union, for psoriatic arthritis in Canada and the US, and for ulcerative colitis in the US. Ruxolitinib, a potent JAK1 and JAK2 inhibitor, was the first FDA-approved JAK-inhibitor for myelofibrosis and polycythemia vera also approved in Canada and the European Union. Baricitinib, a JAK1 and JAK2 inhibitor, differs from tofacitinib and ruxolitinib in that it is cleared by the kidneys and not metabolized by the cytochrome P450 system.⁶⁶ Baricitinib has recently been approved for use in patients with RA in Canada, the US, and the European Union.⁶⁷ It has shown clinically significant improvements in RA disease activity in treatment-naïve and treatment-refractory patients, proving to be superior to methotrexate.⁶⁸⁻⁷⁰ The discovery that JAKs contribute substantially to the immunologic process in inflammatory disease has led to the use of JAK inhibitors for therapeutic immunosuppression in dermatologic conditions such as AA, atopic dermatitis (AD), and vitiligo.^{71,72}

Side Effects of JAK Inhibitors

The side effects of broad JAK inhibitors are intuitively related to their mode of action as an immunosuppressant. Increased risk of infection is the greatest concern. However, RA trials revealed that most infections are not severe and do not warrant treatment discontinuation, and the risk of serious infections is comparable to biologic therapy in that population.^{73,74} The use of JAK inhibitors may increase the risk of malignancy by impairing immunosurveillance; however, further monitoring is needed to better define this risk.⁶⁵ Other notable side effects include hematologic cytopenias, dyslipidemia, and gastrointestinal perforation.^{65,66,68,73} For baricitinib and tofacitinib, there has been recent concern about increased risk of thromboembolism (DVT and pulmonary embolism [PE]).⁷⁵ However, a recent safety review of 3 FDA-approved JAK inhibitors (ruxolitinib, tofacitinib, and tofacitinib XR) did not find elevated reporting rates for DVT and PE.⁷⁶ Instead, data indicated that pulmonary thrombosis was elevated with these JAK inhibitors. It is felt that thromboembolic events may be a class-wide issue with JAK inhibitors although the precise nature is still not appreciated.⁷⁶ Therefore, prescribers should be aware that caution is required in patients with thromboembolic risk factors such as older age, obesity, recent surgery, immobility, malignancy, and personal or family history.⁷⁵

Next-Generation JAK Inhibitors

Next-generation JAK inhibitors are being developed with a narrowed spectrum of action to create a more desirable safety profile by reducing undesirable off target effects.⁷⁶ Selective JAK1 inhibitors to date include filgotinib, upadacitinib, and solicitinib; selective JAK3 inhibitors include decernotinib and PF-06651600; and selective TYK2 inhibitors include

BMS986165, NDI0021232, NDI-031407, PF-06700841, and SAR-20347.⁶⁵

Case Discussion

The first report of the use of JAK inhibitors in vitiligo came after scientific advances suggested IFN- γ -induced expression of CXCL-10 in keratinocytes is an important mediator of depigmentation in vitiligo.²⁵ Craiglow et al⁷⁷ were the first to report a case of a 50-year-old woman with acrofacial vitiligo treated with a JAK inhibitor; her disease had been widespread and progressive despite treatment with triamcinolone ointment, tacrolimus ointment, and NB-UVB therapy. Oral tofacitinib 5 mg every other day was initiated, and was increased to 5 mg daily after 3 weeks. Partial repigmentation was evident at 2 months, and after 5 months of therapy depigmentation was reduced from 10% at baseline to 5% BSA.⁷⁷ This case, and others, is summarized in Table 1.

A number of case reports of JAK inhibitor use in patients with vitiligo and other coexisting dermatological conditions highlight similarities in disease pathogenesis. For example, vitiligo and AA are both IFN- γ driven, share genetic risk factors, and can coexist in some patients.^{57,86,87} Harris and colleagues⁸³ reported a case of rapid, but not long-lasting, repigmentation and hair growth in a 35-year-old man with concurrent vitiligo and AA during treatment with oral ruxolitinib. Similarly, Vu et al⁷⁸ reported clinical response of AD, AA, and NSV in a 44-year-old man treated with oral tofacitinib 5 mg twice daily for 6 months. In this patient, the AD demonstrated complete remission, while there was only slight improvement in vitiligo with a decrease in the Vitiligo Area Scoring Index (VASI) from 4.68 at baseline to 3.95 at 5 months.⁷⁸ The VASI is a reliable, clinician-reported outcome measure that divides the body into 6 regions (face and neck, hands, upper extremities, trunk, lower extremities, and feet) and is the product of the vitiligo area of each region in hand units (1% BSA) and the pattern of depigmentation in each hand unit (possible 10, 25, 50, 75, 90 or 100%).⁸⁸

It appears that vitiligo located on the face responds more robustly to therapy than nonfacial lesions. A 20-week, open-label, proof-of-concept trial of twice-daily ruxolitinib 1.5% cream in 12 patients showed a 23% improvement in VASI scores at week 20.⁸⁴ Four patients had significant facial involvement at baseline and had a 76% improvement in facial VASI scores.

Several studies have shown superior repigmentation rates in patients treated with JAK inhibitors and concomitant UV exposure. Joshipura and colleagues⁷⁹ reported significant repigmentation in sun-exposed areas such as the face and extensor surface of forearms in 2 patients treated with either topical ruxolitinib 1.5% twice daily or oral tofacitinib 5 mg twice daily. In a 32-week, open-label extension study in 8 patients, improvement in VASI score was seen with topical ruxolitinib alone but response rates improved significantly when combined with NB-UVB, particularly for facial

Table 1. Summary of Reports of JAK Inhibitor Use in Vitiligo.

Study	Dose/Formulation	Duration of Therapy	Adjunct Therapy	Report Type	N	Patients	Vitiligo Type	Results
Oral Tofacitinib/JAK 1,3								
Craiglow, et al (2015) ⁷⁷	Tofacitinib 5 mg PO every other day × 3 wks, then 5 mg PO daily	20 weeks total	None	CR	1	50 y F: vitiligo	Facial and acral	Near complete repigmentation. Improvement in depigmentation from 10% to 5% BSA
Vu et al (2017) ⁷⁸	Tofacitinib 5 mg PO BID	6 months	None	CR	1	44 y M: AD, AA, NSV	NSV	Marginal vitiligo improvement. VASI score declined from 4.68 to 3.95 at 5 months
Joshipura et al (2018) ⁷⁹	Tofacitinib 5 mg PO BID	12 weeks	None	CR	1	43 y F: RA, vitiligo	GV	Preferential repigmentation over sun-exposed areas
Gianfaldoni et al (2018) ⁸⁰	A, Phototherapy alone vs B, tofacitinib 10 mg PO daily + phototherapy	NR	UVB microphototherapy	ORS	67	A, 58 B, 9 total: 7 F, 2 M (vitiligo, RA)	GV	Group B (tofacitinib + phototherapy) had superior repigmentation rates vs Group A (phototherapy alone), 92% and 77%, respectively.
Liu et al (2017) ⁸¹	Tofacitinib 5-10 mg PO daily or BID	Average 9.9 months	UVB in some patients	CS	10	Vitiligo	8 GV, 2 acral	5/10 patients achieved repigmentation at sites of sun exposure or UVB, with a mean decrease in BSA of 5.4%
Kim et al (2018) ⁸²	Tofacitinib 5 mg PO BID	3 months	NB-UVB twice weekly	CS	2	Vitiligo: 30 y F, 50 y M	NR	Rapid, near complete repigmentation of facial lesions
Oral Ruxolitinib/JAK 1,2								
Harris et al (2016) ⁸³	Ruxolitinib 20 mg PO BID	20 weeks	None	CR	1	35 y M: vitiligo, AA	NR	Improvement of facial pigmentation (0.8% to 51%). Repigmentation regressed 12 wks after discontinuation
Topical Ruxolitinib/JAK 1,2								
Rothstein, et al (2017) ⁸⁴	Topical ruxolitinib 1.5% cream BID	20 weeks	None	OL	12	≥ 1% BSA of NSV	NSV	VASI score improved by 23%. Significant repigmentation (76%) in facial vitiligo in 4 patients
Joshipura et al (2018) ⁷⁹	Topical ruxolitinib 1.5% cream BID	NR	None	CR	1	49 y M: vitiligo	GV	Significant repigmentation on sun-exposed facial skin.
Joshipura et al (2018) ⁸⁵	Topical ruxolitinib 1.5% cream BID	32 weeks	Optional NB-UVB (3/8)	OL	8	Vitiligo	NR	Response in 5/8 patients. Mean VASI score improvement of 92% facial and 12.6% upper extremity.

Abbreviations: AA, alopecia areata; AD, atopic dermatitis; BID, twice daily; BSA, body surface area; CR, case report; CS, case series; F, female; GV, generalized vitiligo; M, male; NB-UVB, narrowband ultraviolet B; NSV, nonsegmental vitiligo; NR, not reported; OL, open-label; ORS, observational retrospective study; PO, per os/by mouth; VASI, Vitiligo Area Scoring Index; y, years.

vitiligo.⁸⁵ A multicentre, observational, retrospective study supports the above findings, as patients treated with UVB microphototherapy plus oral tofacitinib (10 mg per day) had better repigmentation rates compared to phototherapy alone.⁸⁰ Another retrospective case series of 10 patients treated with oral tofacitinib showed 5 patients achieved repigmentation at sites of sun exposure or UVB phototherapy.⁸¹ Only 1 of the 5 patients who did not experience repigmentation reported significant sun exposure, and the others avoided sunlight.⁸¹ This study also performed suction blister sampling, which found that tofacitinib treatment effectively decreased T cell numbers and chemokine proteins (a measure of IFN- γ signalling) in skin.⁸¹ Lastly, Kim et al⁸² reported rapid repigmentation in 2 vitiligo patients with significant facial involvement treated with combination oral tofacitinib and low-dose NB-UVB. Interestingly, 1 patient in the case series was able to achieve repigmentation despite previous depigmentation with monobenzy ether of hydroquinone.⁸² Together, these reports suggest that substantial repigmentation in vitiligo using JAK inhibitors may require photoactivation to stimulate melanocyte seeding of the epidermis.

Reported Adverse Events

Oral tofacitinib treatment was well tolerated with only a few reports of mild adverse effects such as upper respiratory tract infections, diarrhea, weight gain, and arthralgia.^{78,81} One study found mild elevations in lipid levels typical of this medication.⁸¹ Mild adverse events were also observed with topical ruxolitinib treatment including erythema of the affected area, a rim of hyperpigmentation surrounding vitiligo patches, and worsening of facial acne.^{84,85} None of the adverse events described above required treatment interruption. There were no serious adverse events reported.

Future Directions

To further explore the efficacy and safety of JAK inhibitor use in vitiligo, there are phase II clinical trials underway: an open-label pilot study of the safety, tolerability, and efficacy of a topical JAK 1/3 inhibitor, ATI-50002, applied twice daily in individuals with facial NSV (NCT03468855, $n = 24$)⁸⁹ and a randomized, double-blind, dose-ranging study of topical ruxolitinib vs vehicle in individuals with vitiligo (NCT03099304, $n = 150$).⁹⁰ The results of 1 completed phase II, open-label, clinical trial of topical ruxolitinib 1.5% cream twice daily in patients with vitiligo has been submitted, although results are not yet publicly available (NCT02809976, $n = 12$).⁹¹ Currently, there is 1 registered phase IIb clinical trial involving 2 next-generation JAK inhibitors, PF-06651600 (JAK3 inhibitor) and PF-06700841 (TYK2 inhibitor), to evaluate the efficacy and safety profile of these agents in active NSV patients in combination with phototherapy (NCT03715829).⁹²

Future research should investigate the ideal JAK target (ie, broad or selective inhibitors) and recommended dose to achieve optimal efficacy with minimal side effects. Durability of repigmentation will have to be further explored, as current studies found that repigmentation is not maintained after discontinuation of JAK inhibitors.^{77,83} Combination therapy with phototherapy should also be explored. Large-scale, long-term, randomized, controlled trials are needed to answer these questions in addition to further characterizing any safety risks in this population.

Conclusions

Vitiligo is a common acquired depigmenting disorder. Many patients face significant social stigma that is worse in some countries and cultures, and can be psychologically devastating and significantly affect QoL. The mechanism responsible for the destruction of melanocytes in vitiligo lesions remains unclear. Classically, several interventions have been used to treat vitiligo including topical and oral pharmacologic interventions, phototherapy, and surgical techniques. Treatment options that provide both substantial repigmentation and target the pathophysiology of disease continue to be lacking. Recently, JAK inhibitors have been explored as a promising new treatment option in vitiligo. The JAK-STAT pathway is an attractive therapeutic target because IFN- γ -dependent cytokines are dependent on it for signalling in the pathogenesis of this disease. A few case reports, open-label, and observational retrospective studies of JAK inhibitors in vitiligo have been reported to date and demonstrate a favorable risk-benefit profile in this population. Further studies of JAK inhibitors in vitiligo are required to confirm efficacy, establish safety, and investigate durability of repigmentation. Formal clinical trials are ongoing and will provide more definitive conclusions.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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