Review Article

Efficacy and Safety of Tofacitinib for Vitiligo: A Systematic Review

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ABSTRACT

The main objective of this study was to evaluate and summarize the available clinical evidence on the efficacy and safety of tofacitinib for the treatment of vitiligo. A thorough search across four databases identified 416 relevant publications. After removing duplicates using Rayyan QCRI and assessing their relevance, 204 full-text articles were reviewed, and ultimately, five studies met the criteria for inclusion were included. A total of 121 vitiligo patients were included; less than half of them 52 (43%) were males. Findings indicate that while tofacitinib alone has limited effectiveness, its combination with narrowband-ultraviolet B (NBUVB) phototherapy significantly enhances repigmentation, particularly in refractory cases, including acral lesions. Micro-focused UVB phototherapy also demonstrates high efficacy, with further improvements observed when paired with tofacitinib. However, a 16-week treatment duration may be insufficient for patients with inadequate responses to prior therapies, suggesting the need for higher doses or extended treatment periods. This makes a combination of tofacitinib and phototherapy promising as a therapeutic strategy against vitiligo, with cases resistant to all the modalities of standard therapy. As promising as these results read with significant repigmentation, full optimization of treatment duration and dosage will be imperative. These findings need to be further confirmed in future large, randomized controlled trials and long-term outcomes evaluated to definitely establish a standardized protocol for vitiligo management. These efforts will be essential to fully realize the potential of Janus kinase (JAK) inhibitors as part of a comprehensive, targeted approach to the management of vitiligo.

Keyword: Tofacitinib; JAK inhibitors; Vitiligo; Immune-mediated skin disorders; Systematic review.

Introduction

Selective melanocyte loss is a hallmark of vitiligo, a depigmenting skin condition that causes pigment dilution in the afflicted skin regions. The characteristic lesion is a chalky-white, nonscaly, amelanotic macule with distinct edges [1].

In recent years, scientists have made great progress in understanding the pathophysiology of vitiligo, and it is now clearly classified as an autoimmune disease with genetic, environmental, and metabolic origins, oxidative stress, and cell detachment [1, 2].

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Because vitiligo can have mentally devastating repercussions and significantly interfere with daily life, it should not be written off as a cosmetic or unimportant disorder [3]. According to estimates, 0.5–2% of adults and children worldwide suffer with vitiligo, the most prevalent depigmenting skin condition [4, 5]. In 1977, it was discovered that 0.38% of people on the Danish Island of Bornholm had vitiligo, according to one of the first and biggest epidemiological surveys ever documented [6]. People of different skin types and ethnic backgrounds are affected by vitiligo without any particular preference [1, 7]. But there appear to be significant regional variations [7]. One of the most challenging dermatological conditions to cure is vitiligo. One of the most important initial steps in treating vitiligo is realizing that it is more than simply a cosmetic condition and that its treatments are effective and safe [8]. Treatments that may help halt the disease, stabilize depigmented lesions, and encourage repigmentation include phototherapy, topical and systemic immunosuppressants, and surgery [9, 10]. The therapeutic decision is influenced by the subtype, severity, distribution, and activity of the disease, as well as the patient's age, phototype, impact of the quality of life, and motivation for treatment. In contrast to the face, neck, trunk, and mid-extremities, which respond well to treatment, the lips and distal extremities are more resistant [11]. Repigmentation initially appears in a perifollicular pattern or at the margins of the lesions. Treatment must be administered for at least two to three months in order to evaluate its efficacy. Ultraviolet (UV) light therapy is the most widely used treatment for vitiligo, and it has been shown to produce superior outcomes when combined with other therapies [10]. Management demands a tailored therapeutic approach in which patients are always consulted because most therapeutic options are time-consuming and require long-term follow-up. A cosmetician or skilled nurse may be able to help patients with vitiligo that affects exposed areas by offering guidance on cosmetic camouflage. Foundation-based makeup and self-tanning products with dihydroxyacetone, which imparts color that lasts for several days, are among them. By modifying immunological responses, tofacitinib, an oral Janus kinase (JAK) inhibitor, has demonstrated promise in the treatment of autoimmune conditions such as ulcerative colitis, psoriatic arthritis, and rheumatoid arthritis [2]. Due to its capacity to suppress the activity of pro-inflammatory cytokines implicated in the pathophysiology of the condition, tofacitinib may be useful in the treatment of vitiligo, according to recent clinical trials [2]. In light of this new information, a thorough evaluation is required to determine the safety and effectiveness of tofacitinib in vitiligo patients. Assessing and compiling the clinical data on tofacitinib's effectiveness and safety in treating vitiligo is the aim of this systematic review.

Methods

Search strategy: To uncover pertinent research on the safety and effectiveness of tofacitinib for the treatment of vitiligo, a systematic review was carried out using the PRISMA and GATHER criteria. The reviewers searched four electronic databases; SCOPUS, Web of Science, Cochrane, and PubMed. After removing any duplicates, we uploaded to Rayyan every abstract and title we could locate using electronic searches. After that, the study texts that met the requirements for inclusion based on the abstract or title were gathered for a thorough examination. Two reviewers independently assessed the extracted papers' suitability and looked for any discrepancies.

Study population—selection: Our review's inclusion criteria were based on the PICO (Population, Intervention, Comparison, and Outcome) factors: (i) Participants: Vitiligo patients; (ii) Treatment: Tofacitinib; (iii) Comparison: Patients who were given a placebo; (iv) Results: Safety and efficacy.

Data extraction: Two impartial reviewers used a preset and consistent technique to collect data from papers that met the inclusion criteria. The data listed below was obtained and noted: (i) Lead author; (ii) Publication year; (iii) Study design; (iv) Nation; (v) Sample size; (vi) Age; (vii) Gender; (viii) Length of disease; (ix) Intervention/dosage; and (x) Key findings.

Quality review: Since bias resulting from omitted factors is frequent in studies in this field, we used the ROBINS-I technique to assess the likelihood of bias since it enables a thorough examination of confounding. The ROBINS-I tool can be used for cohort designs where individuals exposed to different staffing levels are tracked over time and is designed to assess non-randomized studies. Each paper's risk of bias was evaluated independently by two reviewers, and any differences were settled by group discussion [12].

Results

Using the designated search approach, 416 documents in total were found (Figure 1). Following the elimination of duplicates (n = 212), the titles and abstracts of 204 trials were examined. Records excluded after the title and abstract screening were 178

full-text publications from the 204 studies. So, 26 full-text publications were examined and 1 full-text publication was eliminated for not retrieved. Finally, 25 full-text publications were examined for eligibility and 20 full-text publications were excluded. In the end, five studies were included for evidence synthesis analysis after meeting the eligibility requirements. Clinical results and sociodemographic: (Table 1) shows that, less than half of the 121 vitiligo patients in the five trials we included—52, or 43%—were men. Three of the research designs were retrospective case-series [15, 16, 18], one was a case-controls [14], and a retrospective observational study was one of them [17]. Three studies were conducted in the United States [16-18], and two in China [14, 15]. The earliest study was conducted in 2017 [16] and the latest in 2024 [14, 15]. When combined with NB-UVB therapy, oral tofacitinib at a dose of 5 mg twice daily was found to be both safe and efficacious, particularly for treating resistant cases of vitiligo, including lesions on acral regions [14]. For patients with progressive vitiligo who did not respond to conventional treatments, tofacitinib showed potential when combined with phototherapy. This combination appeared to halt disease progression and promote repigmentation, suggesting a novel therapeutic avenue [15]. JAK inhibitors, including tofacitinib, demonstrated limited efficacy as monotherapy. However, their combination with low-dose NB-UVB phototherapy or controlled sun exposure resulted in significant repigmentation, highlighting the synergy between these treatments [16]. Micro-focused UVB phototherapy emerged as one of the most effective options for vitiligo. When paired with tofacitinib, the approach further enhanced clinical outcomes, particularly in improving the rate of repigmentation, offering a promising strategy for patients [17]. Finally, a short duration of tofacitinib combined with NB-UVB phototherapy (16 weeks) was deemed insufficient for patients with inadequate responses to previous treatments. Adjustments in dosage or extending the duration of therapy were recommended to enhance therapeutic success for such cases [18]. (Table 2) shows assessment of bias across the studies highlights varying degrees of methodological rigor. Notably, Song et al. (2022) presents a predominantly low bias profile, suggesting a robust design. In contrast, Fang et al. (2021) exhibits critical biases across multiple dimensions, raising concerns about the reliability of its findings. The majority of studies demonstrated moderate bias, indicating areas for potential improvement in participant selection and outcome measurement. This variance underscores the necessity for careful scrutiny of study methodologies when interpreting results.

Discussion

The results from this study represent the bright future of JAK inhibitors, especially tofacitinib, combined with phototherapy in treating vitiligo. Although tofacitinib as a monotherapy had only limited efficacy, its combination with NB-UVB or micro-focused UVB phototherapy resulted in significant repigmentation. This further supports the concept of a dual pathogenesis in vitiligo: immune-mediated melanocyte destruction and lack of melanocyte stimulation. However, observed efficacy does vary with the duration of treatment, thus implying that longer regimens or higher dosages may be necessary for patients with refractory vitiligo. These findings support the potential of personalized therapeutic strategies in managing vitiligo. Cunningham et al. [19] stated that as understanding of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway's function in the pathophysiology of vitiligo has increased, treatment options have broadened to include the first FDA-approved cream in the United States specifically designed to restore pigmentation in vitiligo patients. Qi et al. [20] showed that vitiligo can be effectively treated with JAK inhibitors such ruxolitinib, baricitinib, and tofacitinib, confirming that the pathophysiology of the disease involves the IFN-γ-chemokine signaling pathway. Tofacitinib, both topical and oral, has demonstrated efficacy in treating immune-driven dermatological disorders, including alopecia areata, atopic dermatitis, and plaque psoriasis [21, 22]. Tofacitinib was first given orally to a female patient who had vitiligo, which affected about 10% of her body surface area. Traditional therapies, such as topical corticosteroid and tacrolimus ointments, have not helped her condition. The patient was provided oral tofacitinib citrate at a dose of 5 mg every other day, which was increased to 5 mg daily beginning in the fourth week, based on the assumed common underlying processes between vitiligo and alopecia areata. Just 5% of her body surface area was still depigmented following five months of treatment. Interestingly, no negative side effects were noted during the course of treatment [23]. Therefore, combined treatment consisting of the addition of phototherapy to a JAK inhibitor represents the most valuable current targeted strategy for this resistant group of diseases. Treatment approaches, particularly targeting acral lesions with progressive

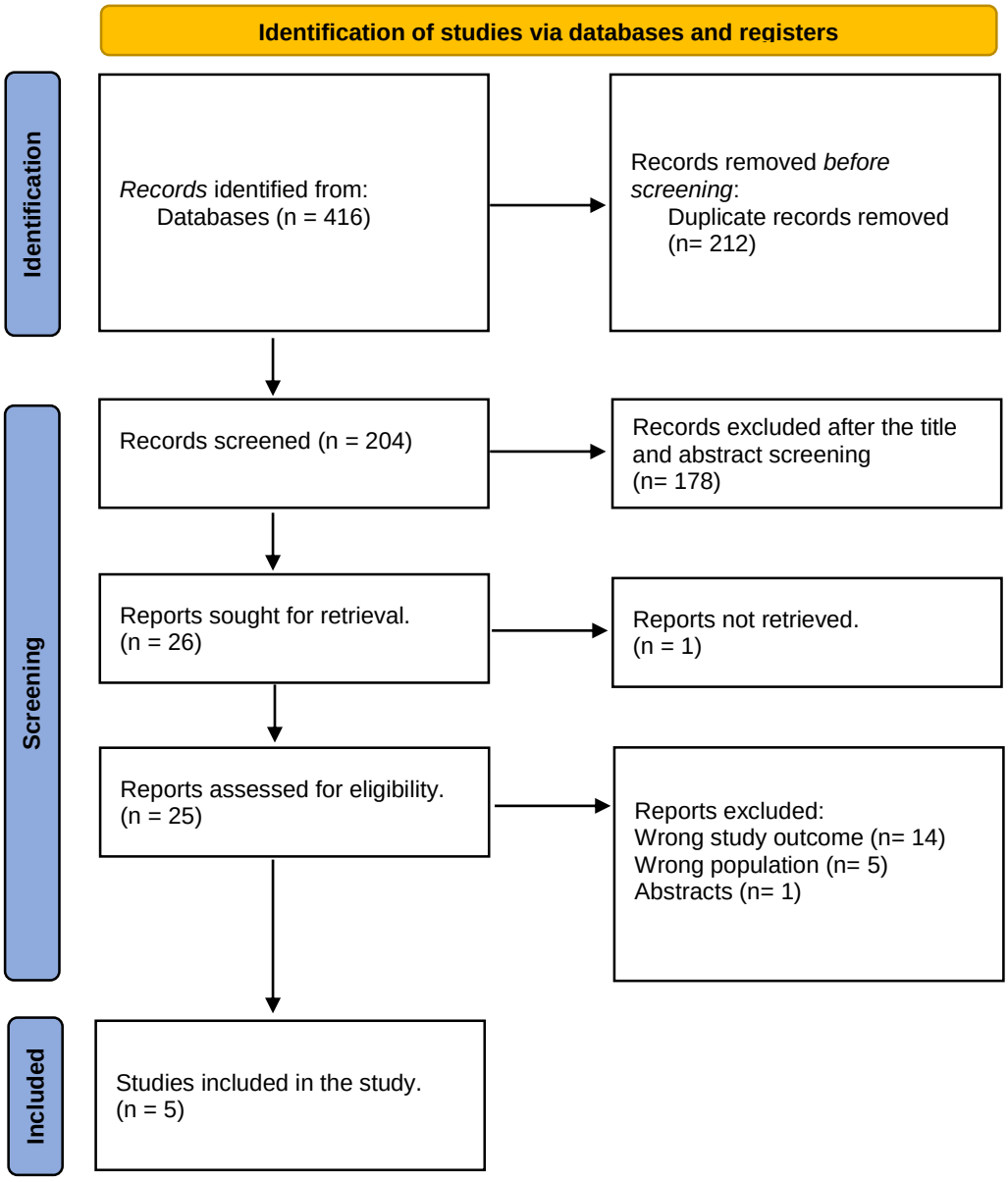

Figure 1: PRISMA flowchart [13].

Table 1: Outcome measures of the included studies.

Study ID	Study design	Country	Socio-demographics	Disease Duration (years)	Intervention	Main outcomes
Song et al., 2022 [14]	Case-control	China	Sample size: 15 Mean age: 28.2 Y Males: 12 (80%)	5.61 ± 7.43	Oral tofacitinib at 5 mg twice daily	The use of tofacitinib alongside NB-UVB* therapy proves to be both effective and safe in treating refractory vitiligo, including lesions located on acral regions.
Sun et al., 2024 [15]	Retrospective case-series	China	Sample size: 25 Age range: 12-57 Year Males: 10 (40%)	0.5-30	Oral tofacitinib at 5 mg twice daily	For patients with progressive vitiligo who do not respond to conventional treatments, tofacitinib may offer a novel therapeutic approach. When used in conjunction with phototherapy, oral tofacitinib has the potential to halt the progression of vitiligo and promote repigmentation.
Liu et al., 2017 [16]	Retrospective case-series	USA	Sample size: 10 Mean age: 28-73 Year Males: 5 (50%)	4-33	Oral tofacitinib at 5 mg twice daily	Combining JAK inhibitors with light exposure may serve as an effective targeted therapy for vitiligo. In this study, JAK inhibitors alone showed limited effectiveness; however, their use alongside low-dose NB-UVB phototherapy or sun exposure resulted in significant repigmentation.
Gianfaldoni et al., 2018 [17]	Observational retrospective study	USA	Sample size: 67 Age range: 25-61 Year Males: 23=34.4%	2-10	NM	Micro-focused UVB phototherapy is among the most effective treatment options for vitiligo. When combined with Tofacitinib citrate, this approach appears to enhance clinical outcomes, particularly in improving the rate of repigmentation.
Fang et al., 2021 [18]	Retrospective case-series	USA	Sample size: 4 Age range: 21-56 Year Males: 2 (50%)	2-10	Oral tofacitinib at 5 mg twice daily	Combining tofacitinib with NB-UVB phototherapy for 16 weeks is insufficient for patients who have not responded well to prior treatments. Increasing the dosage or extending the treatment duration may be necessary to enhance effectiveness for this group.

*Narrowband ultraviolet B

Table 2: Risk of bias assessment using ROBINS-I.

Study ID	Bias due to confounding	Bias in the selection of participants into	Bias in the classification of interventions	Bias due to deviations from the intended interval	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of reported result	Overall bias
Song et al., 2022 [14]	Low	Mod	Low	Low	Low	Mod	Low	Low
Sun et al., 2024 [15]	Mod	Mod	Mod	Low	Low	Low	Mod	Moderate
Liu et al., 2017 [16]	Mod	Mod	Low	Low	Low	Low	Mod	Moderate
Gianfaldoni et al., 2018 [17]	Mod	Mod	Mod	Low	Low	Low	Mod	Moderate
Fang et al., 2021 [18]	Crit	Crit	Low	Low	Mod	Low	Low	Critical

vitiligo disease courses, require integration, in a way which could boost results through mutual synergy for optimal repigmentation. Adjustment to therapeutic responses might mandate extended course and higher dose on failed improvement over normal periods for that particular approach [23]. Strengths and limitations: This study forms the basis for understanding synergistic effects related to the treatment of refractory vitiligo, combining JAK inhibitors with phototherapy; a gap was needed to be filled as far as treating refractory cases of vitiligo is considered. With a broad generalizability for findings that are enriched with data from diverse study designs and populations, different phototherapies- NB-UVB, micro-focused UVB-form the wider dimensions of knowing the ideal treatment combinations. However, this study has several limitations: most of the data were retrospective; small sample sizes in some studies may introduce selection bias and limit statistical power. Furthermore, the lack of standardization in treatment protocols, including dosage, frequency, and duration, complicates direct comparisons and generalizability. Lastly, lack of long-term follow-up data restricts our understanding of potential adverse effects and how long treatment effects last.

Conclusion

This study makes a combination of tofacitinib and phototherapy promising as a therapeutic strategy against vitiligo, with cases resistant to all the modalities of standard therapy. As promising as these results read with significant repigmentation, full optimization of treatment duration and dosage will be imperative. These findings need to be further confirmed in future large, randomized controlled trials and long-term outcomes evaluated to definitely establish a standardized protocol for vitiligo management. These efforts will be essential to fully realize the potential of JAK inhibitors as part of a comprehensive, targeted approach to the management of vitiligo.

Conflict of Interest

None

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