Review Article

Developments on Janus Kinase Inhibitors and Biologics as Prospective Treatment Strategies for Vitiligo

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Abstract: A selective loss of melanocytes characterises vitiligo, the most common skin depigmenting disorder that significantly impairs its patients' quality of life. Comprehending the pathogenesis of this autoimmune disease and creating effective treatment strategies to achieve remission are challenging due to the complex interplay between genetic and non-genetic factors that propel its advancement. The current standard of care consists of topical and oral corticosteroids, phototherapy, and calcineurin inhibitors. These treatments are vague, ineffective, and may cause unexpected side effects. Therefore, a deeper comprehension of the pathophysiology of vitiligo is critically needed to support the development of targeted treatment advancements. This study aims to provide a comprehensive overview of current studies on biologics and Januse Kinase (JAK) inhibitors used in individuals with vitiligo. JAK inhibitors have shown promising results with regard to their effectiveness and tolerability. However, the outcomes of biologics therapy have been less predictable. But more in vitro research and thorough clinical trials involving a larger population are required to provide a deeper understanding of which specific pathways to target for a more successful treatment of vitiligo.

Keywords: vitiligo, pathophysiology, treatment strategies, janus kinase inhibitors, biologics

1. INTRODUCTION

One feature of vitiligo, an acquired chronic skin disorder, is patchy depigmentation, which is caused by the selective loss of melanocytes [1]. It affects around 1% of the world's population worldwide and is the main cause of depigmentation. While it can manifest at any age, the range of 10 to 30 years old is the most common. Regarding gender, race, or skin type, there are no discernible variations in its incidence [2]. This condition is classified into two primary categories: nonsegmental vitiligo (NSV) and segmental vitiligo (SV) [3, 4]. Variable-sized depigmented macules that gradually spread throughout the body are the hallmark of NSV. Acrofacial, mucosal, universal, and generalised are some of its subtypes. On the other hand, SV starts earlier and develops more quickly, but it is more time- and space-limited. Depigmentation often occurs over a period of 6–24 months and has a mostly unilateral distribution pattern. Mixed vitiligo (MV), which often starts with SV and proceeds to bilateral NSV patches a few months later, is characterised by the coexistence of SV and NSV [5]. Hereditary predisposition, oxidative stress caused by disruption of the melanocyte redox balance, autoimmune responses, and autoimmune diseases are some of the components of the multifactorial aetiology of vitiligo [6–8]. Due to its intricate pathophysiology, vitiligo can be difficult to treat in dermatology. Stabilising depigmented lesions, encouraging repigmentation, and halting the immune system's impact on melanocytes would be the
optimal therapeutic approaches. Currently, the only conventional treatments for vitiligo that are accessible are generic immunosuppressants, such as oral and topical corticosteroids, calcineurin inhibitors, phototherapy, and surgical techniques [9, 10]. Long-term therapeutic benefit of phototherapy with narrowband ultraviolet B (NB-UVB) is limited, despite the fact that it is a well-tolerated method that activates melanocyte precursors to generate a strong stimulus for skin repigmentation. Recent studies into the molecular processes underlying this skin disorder have raised the prospect of more targeted and effective treatments. This article provides an update on state-of-the-art molecular targeted therapy for vitiligo.

2. LITERATURE REVIEW

JAK1, JAK2, JAK3, and TYK2 are the four intracellular tyrosine kinases that make up the Janus kinases (JAKs) family. The JAK–STAT system's signaling pathway controls T-cell-mediated inflammation and immune cell activation in response to various cytokines. IFNγ, a key player in the development of vitiligo, requires the JAK–STAT pathway to function. This cytokine phosphorylates STAT by activating the associated JAKs in response to its specific receptor attachment. Next, the nucleus is reached by the phosphorylated STAT molecules, which regulate the expression of the CXCL9 and CXCL10 genes. The targeted destruction of melanocytes by autoreactive CD8+ T lymphocytes, facilitated by these chemokines, leads to skin depigmentation. Craiglow and colleagues conducted the first research showing the efficacious use of tofacitinib in a woman in her 50s with widespread, progressive vitiligo [11]. The initial dosage of oral tofacitinib was 5 mg every other day; however, after three weeks, the dosage was raised to 5 mg daily. Following two months of therapy, there were noticeable indications of partial repigmentation on the face and upper limbs. After five months, the other affected areas had only half healed from their significant repigmentation, but the hands and forehead had almost completely healed. Approximately 5% of the body's surface area remained depigmented. The patient had a good tolerance to tofacitinib and did not have any unfavorable side effects during the course of treatment. No anomalies in serum creatinine, lipids, hepatic function, or complete blood cell count were found during laboratory monitoring. Song et al. evaluated the safety and efficacy of tofacitinib in conjunction with NB-UVB phototherapy in a clinical trial involving 15 refractory individuals with nonsegmental vitiligo [12]. They discovered that individuals getting tofacitinib 5 mg twice day in addition to topical medicines and phototherapy had a significantly higher response rate and repigmentation level than the control group of 19 patients receiving these treatments. Furthermore, they stated that after 16 weeks, the combination group's total response rate was 100%, compared to the control group's 36.84%. These results imply that a safe and efficient alternative treatment for patients with active/stable nonsegmental refractory vitiligo might involve the combination of tofacitinib with NB-UVB phototherapy. Serious adverse events were only experienced by one patient. In a multicenter observational retrospective study, Gianfaldoni et al. evaluated the safety and efficacy of NB-UVB microphototherapy in 67 patients with stable or active forms of localized vitiligo, either on its own or in combination with tofacitinib (10 mg/die) [13]. A previous study found that, despite not having any adverse effects, the nine individuals receiving tofacitinib had a higher rate of repigmentation than the control group. A 30-year-old woman with vitiligo and rheumatoid arthritis who was taking tofacitinib at a dose of 5 mg twice a day showed notable improvement, according to Scheinberg et al. After four months of uninterrupted treatment, hypopigmentation almost totally decreased [14]. Furthermore, two vitiligo patients with extensive facial involvement experienced fast repigmentation after receiving tofacitinib plus low-dose NB-UVB treatment. These results support the hypothesis that melanocytes require photoactivation to be stimulated, while tofacitinib inhibits the
autoimmune response [15]. Liu et al. provided retrospective evidence for this idea in a trial that included 10 vitiligo patients treated with tofacitinib at a daily dosage ranging from 5 to 10 mg, either once or twice daily, during an average duration of 9.9 months [16]. In the 5/10 individuals who saw a response to treatment, repigmentation did, in fact, only occur in sun-exposed areas of the skin or in patients receiving concomitant NB-UVB phototherapy. As a result, a 43-year-old female patient using tofacitinib 5 mg twice a day for extensive vitiligo and rheumatoid arthritis displayed preferential repigmentation over sun-exposed skin area [17]. These findings are in contrast to a study by Fang et al. that included four patients and revealed that a 16-week course of NB-UVB therapy combined low-dose tofacitinib was insufficient to treat resistant vitiligo, with just one patient exhibiting a noticeable repigmentation [18]. Fortunately, more positive results from a subsequent study by the same researchers using three patients treated with low-dose tofacitinib in combination with 308 nm excimer light were found [19].

Furthermore, a clinical example of a 40-year-old female patient with vitiligo and rheumatoid arthritis who was treated with tofacitinib for two years at a dose of 5 mg twice a day without being exposed to UV radiation was provided by Konniński and colleagues. The hands and cheeks had several regminated islands after eight months of treatment, which showed a marked improvement in the macules and patches. Over the course of the following two years, there was complete repigmentation in the forehead and perialabial macules, but only partial repigmentation in the upper chest and posterior region of the neck [20]. Following oral therapy with tofacitinib, two other patients showed satisfactory outcomes: a 44-year-old White man with atopic dermatitis, alopecia areata, and a 3-year history of nonsegmental multifocal vitiligo; the 30-year-old patient also had concurrent alopecia areata, vitiligo, plaque, and inverse psoriasis [21, 22]. The efficacy of tofacitinib in treating vitiligo was also evaluated as a topical formulation to reduce systemic side effects [23–26]. In a research by McKesey et al., 11 vitiligo patients who received NB-UVB therapy and tofacitinib 2% cream twice a day for three and a half months demonstrated significant repigmentation of their facial vitiligo lesions [26]. Excellent improvements were also seen by young patients with a long history of refractory early-onset extensive vitiligo [23, 25]. JAK/STAT signaling-related inflammatory dermatoses are already treated in dermatology with the tiny medication baricitinib, which primarily targets the JAK1 and JAK2 subtypes. Mumford et al. initially reported the effectiveness of baricitinib in a 67-year-old Caucasian male patient with vitiligo on his hands and forearms who was not improving with tofacitinib treatment [33]. The patient almost fully recovered from repigmentation after switching to baricitinib 4 mg daily for 8 months, with no adverse effects. Four patients with progressive nonsegmental vitiligo were treated with baricitinib, and Dong et al. reported on the drug’s effectiveness and tolerability. However, at the three-month follow-up, two people had depigmentation [26]. The scientists also examined the in vitro mechanism of baricitinib in cultures of melanocytes exposed to high UVB radiation levels, with the aim of simulating injured melanocytes. They discovered that baricitinib upregulates the genes TYR and TRP-1, which are related to melanogenesis, and may also restore tyrosinase activity and melanin production in UV-damaged melanocytes. Two individuals with vitiligo showed promising results when NB-UVB phototherapy was coupled with baricitinib. Upadacitinib, an oral JAK inhibitor that selectively inhibits JAK1 and stops the activation of many pro-inflammatory mediators, was studied by Su and colleagues. In vitiligo patients who had not reacted to systemic steroids, calcineurin inhibitors, or phototherapy as prior therapies, they assessed the safety and efficacy of upadacitinib 15 mg. Repigmentation did not significantly correlate with age, sex, length of disease, or Fitzpatrick skin type. Pang et al. reported on a 16-year-old boy who had rapidly progressed from vitiligo over the preceding four months and had suffered from atopic dermatitis since childhood. Upadacitinib treatment resulted in considerable improvements in both illnesses, including improved
repigmentation in sun-exposed areas [27]. Contemporary studies have illuminated the etiology and maintenance of vitiligo, demonstrating the pivotal role that cytokines implicated in cell-mediated immunity play in the depigmentation process. Individuals suffering with vitiligo have irregular immunological reactions and changes in cytokine concentrations, suggesting that targeting pro-inflammatory mediators like TNFα and ILs-12, 23, and –17 could be a feasible treatment strategy. Nonetheless, there are reports in the literature of vitiligo caused by biological drugs. A case report from Burlando's group described a 32-year-old man with developing psoriasis and stable patches of vitiligo in the perioral and subaxillary areas. A monoclonal antibody called uzekinumab targets IL-12 as well as IL-23. The psoriasis cleared up after therapy, but the pre-existing lesions did not go away, and a new hypopigmented lesion developed next to the cleared lesions. Over the following three months, this lesion kept getting bigger.

Conversely, Elkady and colleagues reported good results on vitiligo patches in a patient who also had alopecia areata, vitiligo, and psoriasis at the same time. Alghamdi's group investigated the safety and efficacy of anti-TNFα medications in six vitiligo patients (two treated with etanercept, two with adalimumab, and two with infliximab). One patient receiving infliximab showed worsening after treatment, but no other patient showed signs of repigmentation. Several trials have demonstrated the ineffectiveness of anti-TNFα treatment. However, Kim's team observed improvement in two vitiligo patients who were resistant to treatment while using the anti-TNFα drug etanercept [34–37]. Furthermore, they looked at tissue TNFα levels and their relationship to vitiligo disease activity. This suggests that TNFα may be a valuable biomarker for anticipating the response of nonsegmental vitiligo patients who are resistant to anti-TNFα therapy. Furthermore, when using etanercept, Campanati et al. noted a little improvement in vitiligo lesions. In addition, a 24-year-old male patient with extensive vitiligo and ankylosing spondylitis experienced significant repigmentation after receiving infliximab treatment for six months [38]. Secukinumab is an anti-IL17 drug that was used to treat vitiligo patients; nevertheless, there were also noticed conflicting results. A sixty-three-year-old man with psoriasis who had developed vitiligo while on adalimumab therapy showed nearly complete repigmentation following a year of secukinumab treatment. Additionally, a one-year-old boy with generalized pustular psoriasis responded well to secukinumab combined with topical steroids after receiving acitretin for three weeks. The face and trunk gradually began to repigment after secukinumab was given for the fifth and twelfth times, respectively, however there was no appreciable change in the scalp. Conversely, in a single-arm pilot research with seven out of eight patients receiving secukinumab for active nonsegmental vitiligo, there was an additional skin depigmentation [39]. Additionally, five patients with active disseminated vitiligo who received a single intravenous infusion of rituximab—a monoclonal antibody against CD20—showed varying results, according to Argüelles and associates. During the six-month follow-up, vitiligo improved in four patients while remaining unchanged in one. A sixty-three-year-old man with deteriorating vitiligo saw 90% repigmentation of his acrofacial vitiligo after receiving treatment for a year with the anti-IL23 monoclonal antibody tildrakizumab.

While JAK inhibitors, in particular tofacitinib and ruxolitinib, have shown promising results, larger sample sizes and longer follow-up periods are required for future studies. These studies are necessary in order to thoroughly assess the therapy medications' long-term safety and efficacy. It is also crucial to carefully investigate the role that cytokines such as TNFa, IL17, and IL23 play in the pathophysiology of vitiligo in order to shed light on the potential application of biologics in the treatment of vitiligo.

3-CONCLUSION
JAK inhibitors have demonstrated encouraging outcomes in vitiligo treatment in a number of small studies and cases. JAK inhibitors have been applied topically as well as orally, frequently in conjunction with phototherapy. However, there has been little and conflicting data on the benefits of biologics for vitiligo, with few positive cases documented.

REFERENCES


