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An Update on Vitiligo Target Therapy: A Semi-Structured Systematic Review

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Abstract

Background: *There is growing evidence to suggest a significant role for the adaptive immune system in disease progression and relapse. Therapies targeted the inflammatory responses of epidermal and immune system cells have been demonstrated effect in the treatment of vitiligo. However, more comparative studies are needed to inform the treatment decision making process.*

Purpose: *To discuss the new target therapies modalities which are currently being trialled or recently licenced for the treatment of vitiligo.*

Method: *A semi structured, rapid systematic review of the literature, where the findings from 11 studies was narratively discussed.*

Findings: *The reviewed medications (ruxolitinib, baritininb, tofacitinib, ritlecitinib, afamelanotide, crisaborole and apremilast) all showed reduction in the percentage of depigmented body surface area and were well tolerated. However, no head-to-head studies were identified to compare the medications to each other or to other treatment modalities used in the treatment of vitiligo, to determine superiority.*

Keywords: Ruxolitinib, Baritininb, Tofacitinib, Ritlecitinib, Afamelanotide, Crisaborole, Apremilast, Vitiligo

Background

Vitiligo is a chronic inflammatory skin condition characterized by depigmentation resulting from the loss of epidermal melanocytes [1]. The presence of white, amelanotic patches creates skin colour variation which can impact on quality of life and mental health, often leading to social isolation [2]. Traditional therapeutic options are limited to topical or systemic steroids and phototherapy, to generate melanocyte regeneration. This review focuses on specific treatment modalities that are currently being trialled in the treatment of vitiligo.

In vitiligo, epidermal melanocytes appear to respond to a form of oxidative stress that in turn initiates the innate immune cascade [3]. These cells appear to release exosomes that contain trigger antigens such as heat-shock proteins (HSP70), damage-associated molecular patterns (DAMPS), calreticulin (CRL), high-mobility group protein B1 (HMGB1). These molecules play a key role in recruiting a local innate immune response. Blocking these pathways have been shown to generate re-pigmentation in studies using animal models [4].

There is more substantial evidence showing involvement of various elements of adaptive immunity in the pathogenesis of vitiligo [5]. Cytotoxic CD8+ T cells are widely recognised as the key immune cells that target and destroy melanocytes in vitiligo. They produce active chemical cytokines such as tumour necrosis factor (TNF) and interferon gamma (IFN-γ). In response to IFN-γ, depigmented skin shows increased expression of T cell chemokine receptor (CXCR3) and its multiple ligands CXCL9, CXCL10, and CXCL11 [6]. These chemokines intensify the infiltration of CD8+

T cells in depigmented skin, contributing to disease initiation and progression. Keratinocytes within the epidermis also release MMP-9 in vitiliginous skin in response to TNF-alpha and IFN-γ; in turn the secreted MMP-9 triggers melanocyte detachment via altered cadherin expression and subsequent melanocyte apoptosis [7]. IFN-γ induces the well-studied Janus Kinase/Signal Transducer Activator of the Transcription pathway (JAK/STAT) [8]. JAK is a family of cytoplasmic tyrosine kinases that aid cytokine-mediated signal transduction. This includes 4 key types: JAK1, JAK2, JAK3 and TYK2. Once activated, the JAK system then leads to a series of gene transcriptions via the phosphorylated STAT1 in a complex cascade. By targeting any one of the JAK members, the cascade can be blocked or modulated and in turn help reverse the initiation and progression of disease. Iwanowski et al. [9] concluded that understanding the etiopathogenesis, and molecular and genetic studies, would inform the potential for new medications such as ruxolitinib, ritlecitinib and afamelanotide to be trialled as potential vitiligo treatment. Qi, Liu and Gao [10] in their review of the use of the JAK inhibitors, including ruxolitinib, baricitinib, and tofacitinib, concluded they were effective due to the involvement of IFN-g-chemokine signaling axis in the pathogenesis of vitiligo. Karagaiah et al. [11] reviewed the efficacy of biologic and targeted therapeutics in vitiligo. They concluded that while JAK inhibitors were effective and well tolerated, the addition of adjuvant phototherapy provided a superior response compared to monotherapy.

There is growing evidence to suggest a significant role for the adaptive immune system in disease progression and relapse. Targeted therapies modulating inflammatory responses of epidermal and immune cells have demonstrated benefit in the treatment of vitiligo.

Methods and Design

This paper aimed to present a discussion about the new target therapied modalities that are currently being trialled or recently licenced for the treatment of vitiligo. This was a rapid semi-structured systematic review of the literature to discuss the current state of treatment modalities of vitiligo. The search was conducted on PubMed and 11 peer reviewed articles published in the past 10 years were identified and narrative reviewed.

Citation	Title	Design
Rosmarin *et al*., 2022 [12]	Two phase 3, randomized, controlled trials of ruxolitinib cream for vitiligo.	2 phase III, double-blinded, randomized, controlled trials
Dong *et al*. 2022 [13]	Baricitinib is effective in treating progressing vitiligo in vivo and in vitro	Two part study: 1. clinical trial: single-arm, open-label. 2. in vitro study–cell culture study
Mumford *et al.* 2021 [14]	Re-pigmentation of vitiligo with oral baricitinib.	Single-arm, open-label study
Craiglow and King, 2015 [15]	Tofacitinib citrate for the treatment of vitiligo.	Case report and case study
Berbert *et al*. 2021 [16]	Topical tofacitinib: a janus kinase inhibitor for the treatment of vitiligo in an adolescent patient.	Single-patient, open-label case study
Song *et al.* 2022 [17]	Effectiveness and safety of tofacitinib combined with narrowband ultraviolet b phototherapy for patients with refractory vitiligo in real-world clinical practice.	Retrospective, observational study
Ezzedine *et al*. 2022 [18]	efficacy and safety of oral ritlecitinib for the treatment of active nonsegmental vitiligo: a randomized phase 2B clinical trial.	Randomized, double-blind, placebo-controlled trial
Lim *et al*. 2015 [19]	Afamelanotide and narrowband ultraviolet (NB-UV) phototherapy for the treatment of vitiligo.	Randomized, double-blind, placebo-controlled trial
Toh *et al*. 2020 [20]	Afamelanotide implants and narrow-band ultraviolet b phototherapy for the treatment of nonsegmental vitiligo in Asians.	Part1: randomized, double-blind, placebo-controlled trial – 8 patients. Part 2: single-arm, open-label study (13 patients)

Tam *et al*. 2021 [21]	Re-pigmentation in a patient with vitiligo on crisaborole 2% ointment.	Case Report
Majid *et al.* 2019 [22]	Apremilast is effective in controlling the progression of adult vitiligo: a case series.	Case series

Table 1: Identified studies summary.

Treatment Modalities Discussion

JAK1/JAK2 Inhibitors

Ruxolitinib is a synthetic inhibitor of the Janus Kinase family of enzymes concerned with the immune modulation, with selective inhibition of JAK1 and JAK2. First approved by the American FDA in 2011 it is available for oral and topical administration. With a plasma elimination half life of around 3 hours it is hepatically cleared, primarily metabolised by CYP3A4 so has the potential to interact with many other medications [23]. Rosmarin et al. [12] conducted a phase 3 double-blinded randomized controlled trials (RCT) of ruxolitinib cream for the treatment of patients diagnosed with non-segmental vitiligo, who were 12 to 75 years old, had minimum of 5% of their body surface area (BSA) affected by vitiligo (n=674). Patients were randomly assigned to either 1.5% ruxolitinib cream (group-1) or vehicle control (group-2) twice daily for 52 weeks. The Vitiligo Area Scoring Index (VASI) was used to measure improvement. The primary endpoint was the 75% reduction of the affected area at the end point (VASI75). The authors concluded that 39.2% of patients in group-1 achieved a VASI75 response at week 24, compared to 14.4% of patients in group-2 ($p<0.001$). The most common adverse events were mild to moderate and only experienced by patients in group-1, including application-site acne (6.3%), nasopharyngitis (5.4%), and application-site pruritus (5.4%). The study limitations were the wide range of age, the majority were female (62%), the majority were White (81%), BSA affected by vitiligo (15%, 5%-75%) and duration of vitiligo (10years, 1-40). Only 8% were Black 4% Hispanic or Latino, 4% Asian and 1% native American or Alaska native.

Baricitinib is also a synthetic orally active selective inhibitor of JAK1 and JAK2. Its elimination half life is 12.5 hours and it is mostly renally excreted. Clearance is largely independent of CYP450 enzymes. It was first licensed by the FDA in 2016 [24].

Dong et al. [13] conducted a mixed method study; an open-label trial (part-1) and an in vitro cell culture study (part-2). Participants age ranged between 25 to 40 years old and only 4 male patients were included, all participants were White. The mean body surface area (BSA) affected by vitiligo was 30% (20% -40%) and the mean duration of vitiligo was 10 years (5-15 years). The intervention group received oral baricitinib (4 mg twice daily) for 12 weeks. A reduction by 25%, 50% or 75% or greater reduction in the BSA affected by vitiligo were measured at week 12 on the Facial Vitiligo Area Scoring Index (F-VASI). The authors reported that two patients achieved a 25%, one patient achieved 50% and one patient achieved 75% reduction in the BSA affected by vitiligo at week 12. For part-2 cultured melanocytes were exposed to high-dose narrowband ultraviolet (NB-UV) irradiation then baricitinib was added, then the stained melanocytes were investigated. Baricitinib was found to significantly increase the activity of melanocytes that had been damaged by high-dose NB-UV irradiation and to increase the melanin content of the melanocytes. The main limitation of this study was the patients' sample characteristics (only males) and size (n=4). In another open-label study by Mumford et al. [14], a sample of 20 patients with non-segmental vitiligo (25-55 years old), had vitiligo affected BSA between 10-60%. The majority were female (13 patients) and White (17 patients), the mean duration of vitiligo was 10 years (5-20 years). Patients received baricitinib at a dose of 4 mg twice daily for 24 weeks. The primary endpoint was measured on the VASI 75 response at week 24, where 10 (50%) patients achieved a VASI 75 response, 12 (60%) patients achieved an F-VASI 50 response, and 15 (75%) patients achieved a VASI 25 reduction in the BSA affected by vitiligo. The main limitation of this study was the patients' sample characteristics (mainly females) and size (n=20).

Ruxolitinib and baritininb were effective in reducing the percentage of depigmented BSA and were well tolerated. However, no head-to-head studies were identified to compare them to each other or to other biologics used in the treatment of vitiligo to determine superiority.

JAK1/JAK3 Inhibitors

Tofacitinib was first approved by the FGDA in November 2012. This JAK inhibitor is selective JAK1 and JAK 3 pathways. Used orally, it is well absorbed, and has an elimination half-life of 3 hours, with extensive metabolism by CYP3A4 and CYP2C19 [25].

Craiglow and King [15] case reported a case of a single female patient (>50 years) with widespread progressive vitiligo (10% of BSA) treated with tofacitinib 5mg for 5 months. The authors concluded that the treatment was tolerated and only 5% of BSA remained depigmented at the end of the study. However, this single finding cannot be generalised.

Berbert et al. [16] investigated topical tofacitinib (0.5% cream twice daily) in one adolescent patient (15-year-old, white male), with 25% of his BSA affected by vitiligo for the past 5 years. His depigmented skin was reduced by 50% at week 12. The authors reported that tofacitinib was tolerated, but again a single case cannot be generalised. Similarly, Song et al. [17] investigated the effectiveness and safety of tofacitinib (5 mg twice daily) in combination with NB-UV phototherapy (three times per week) for patients with refractory vitiligo in real-world clinical practice. This was a retrospective, observational study (n=100), used VASI 75 response as the measured outcome at week 24. The authors concluded that 52% of patients achieved a VASI 75 response. The

most common side effects were rash, itching, and dry skin. The study main limitation was the combination therapy design which can only be applicable to patients using the same combination but not to any of the two elements alone.

Tofacitinib was effective in reducing the percentage of depigmented BSA and was well tolerated. However, there is no head-to-head studies found to compare its efficacy and safety to other biologics used in the treatment of vitiligo to determine superiority.

JAK3/TEC inhibitor

Ritlecitinib differs in having little affinity for JAK1/2 and a strong inhibitor of JAK3 and TYRK. Approved for the treatment of alopecia areata in June 2023. It has oral bioavailability of 90% and a plasma half life of only 2 hours. It undergoes extensive metabolism mainly by CYP450 enzymes [26]. Ezzedine et al. [18] conducted a double-blind, randomised placebo-controlled to investigate the efficacy and safety of oral ritlecitinib (n= 364). Patients (mean age 45 years) with non-segmental vitiligo (>20% of their BSA, mean of 30%) were randomised to once-daily oral ritlecitinib ± 4-week loading dose (200/50 mg, 100/50 mg, 30 mg, or 10 mg) or placebo for 24 weeks (dose-ranging period). Patients subsequently received ritlecitinib 200/50 mg daily in a 24-week extension period. Improvement was measured on the VASI 75. Most participants were female (60%) and White (72%). The duration of vitiligo was 10 years. Only 35% of patients achieved a VASI 75 response at week 24, for the 5 mg dose of oral ritlecitinib, 48% for the 10 mg dose of oral ritlecitinib, and 6% for placebo. There were no observed adverse effects or any dose-dependent trends, but the study was limited by its small sample size and the short duration of treatment.

Ritlecitinib was effective in reducing the percentage of depigmented BSA and was well tolerated. However, there is no head-to-head studies found to compare its efficacy and safety to other biologics used in the treatment of vitiligo to determine superiority.

Melanocortin Peptides

Afamelanotide is a synthetic structural analogue of α-melanocyte stimulating hormone (αMSH). It binds to the melanocortin-1 receptor with greater persistence than αMSH activating melanogenesis and darkening skin. Injected subcutaneously it has an elimination half life of around 30 minutes. Its metabolism and clearance are not yet fully understood [27].

Lim et al. [19], in a randomized, double-blind, placebo-controlled trial investigated afamelanotide dose of 16 mg or placebo once weekly combined with NB-UV phototherapy three times per week for 24 weeks. The response was measured using VASI. The mean age of the patients was 43 years, and the majority were female (67%) and White (75%) with mean BSA of 35% affected by vitiligo for mean duration of 10 years. Only 38% of intervention (afamelanotide and NB-UV) group patients achieved VASI 75 response compared to 15% for the placebo (combined with NB-UV) group at 24 weeks. More patients achieved a VASI 50 response at week 24 (64%) for the intervention group compared to 33% for the placebo group and 86% achieved a VASI 30 response at week 24 for the intervention group compared to 57% for the group. Afamelanotide and narrowband UV-B phototherapy combination therapy was well-tolerated. However, the combination therapy design was the study main limitation, as it findings can only be applicable to patients using the same combination but not to any of the two elements alone. While Toh et al. [20] also investigated afamelanotide, the formulation they used was an implant and NB-UV phototherapy in patients from Asians ethnicity. The authors conducted a randomised, double-blind, placebo-controlled trial (n=80). In the RCT intervention group (afamelanotide implants every 28 days x 6 doses + NB-UV twice weekly) vs. placebo implants (plus NB-UV). The mean age of the patients was 37 years; the majority were female (75%) and 92% were Asian with mean affected BSA of 30% for mean duration of 10 years of vitiligo. Combination therapy (n=18) was superior to placebo, at day 140 ($p<0.05$) and at day 196 ($p<0.05$) and the therapy had a good short-term safety profile and significant re-pigmentation effects in Asian patients with nonsegmental vitiligo. The main limitation of this study was the one ethnicity group which may make the findings not applicable to other ethnic groups.

Afamelanotide was effective in reducing the percentage of depigmented BSA and was well tolerated. However, it was not investigated alone and no head-to-head studies found to compare its efficacy and safety to other biologics used in the treatment of vitiligo to determine superiority.

PDE-4 Inhibitors

Phosphodiesterase inhibitor type 4 (PDE-4) is a key intracellular enzyme that helps degrade cyclic adenosine monophosphate (cAMP), which is a key anti-inflammatory stimulator [28]. Blocking the degradation of cAMP prevents the activation of pro-inflammatory lymphocytes (Th1 and Th-17) and increases the expression of anti-inflammatory chemokines (IL-2 and IL-10). Tam et al. [21], in a case report of one 71-year-old male patient concerned about progressive depigmentation of his forearms and dorsal aspects of his hands. The patient was prescribed topical crisaborole 2% ointment and showed evidence of re-pigmentation after 22 months without any side-effects reported. Majid et al. [22] found that apremilast was effective in controlling the progression of adult vitiligo. The authors recruited 13adults patients with vitiligo for at least 1 year and mean affected BSA of 20%. Patients were treated with apremilast 30 mg twice daily for 24 weeks and outcome measured on the VASI at baseline and at 24 weeks. The mean age of the patients was 35 years, the majority were female (70%) and White (80%). The mean affected BSA was 20% and mean duration of vitiligo was 5 years. The mean percentage of de-pigmentation decreased from 20% to 10% after 24 weeks of treatment. The main limitations of this study were the sample size and the participants characteristics, which may make the results not generalisable.

Crisaborole and apremilast were effective in reducing the percentage of depigmented BSA and were well tolerated, but no head-to-head studies were identified to compare them to each other

or to other biologics used in the treatment of vitiligo to determine superiority.

Conclusion

Current treatment modalities remain nonspecific. With a better understanding of molecular and pathogenetic patterns of vitiligo, further and/or better therapeutic targets can be identified and tested. This review highlighted the role of the JAK/STAT pathway in pathogenesis of vitiligo. There are however other possible areas to explore, especially the IFN-γ/CXCL9/10/CXCR3 cascade which could be better targeted with the emergence of newer therapies. Furthermore, other exciting areas of development include miRNA-based technologies and adoptive regulatory T-cells which may play a significant role in disease control [29]. At this point, JAK inhibitors appear the most widely studied new therapeutic modality in the current research cycle and should be considered in local treatment guidelines.

Conflict of Interest

All authors report no conflict of interest.

Authors Contributions

All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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