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New and Emerging Treatments for Vitiligo

Carolina Rodrigues Mendonça

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Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Carolina Rodrigues Mendonça

carolinamendonca25@gmail.com

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Orientador:

Professor Doutor Tiago da Costa Ferreira Torres

Assistente Graduado do Serviço de Dermatologia da Unidade Local de Saúde de Santo António

Professor Auxiliar Convidado do Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto

Coorientadora:

Dra. Diana Catarina Coelho Bernardo Leitão

Médica Interna de Formação Específica em Dermatovenereologia do Serviço de Dermatologia da Unidade Local de Saúde de Santo António

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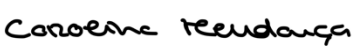
Estudante:



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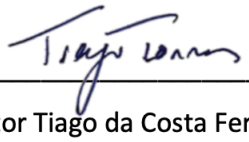

(Professor Doutor Tiago da Costa Ferreira Torres)

Coorientadora:

(Dra. Diana Catarina Coelho Bernardo Leitão)

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Resumo

O vitiligo é uma doença autoimune multifatorial caracterizada pela perda progressiva de melanócitos, resultando em manchas despigmentadas na pele dos indivíduos.

Afetando aproximadamente 0,5% a 2,0% da população mundial, origina não só alterações visíveis na pele, mas também um impacto significativo na saúde mental.

Esta doença tem origem em interações complexas entre suscetibilidade genética, fatores ambientais e desregulação do sistema imunitário. No centro da sua patogénese encontram-se os linfócitos T CD8+ autorreativos e a via JAK-STAT, que perpetuam a destruição dos melanócitos na pele dos doentes.

As terapêuticas tradicionais do vitiligo, como os corticoides, os inibidores da calcineurina e a fototerapia, oferecem frequentemente resultados limitados ou temporários, evidenciando a necessidade de opções mais eficazes e duradouras. Os avanços na compreensão da imunopatologia do vitiligo abriram caminho a novas terapias mais promissoras. Entre estas incluem-se os inibidores da Janus quinase (JAK), bloqueadores de citocinas e estratégias direcionadas às células T de memória. A mais recente aprovação pela FDA do ruxolitinib tópico constituiu um marco importantíssimo na gestão desta doença, assinalando uma nova etapa no tratamento do vitiligo. Existem ensaios clínicos em curso neste momento a explorar o potencial do afamelanotide, de inibidores da fosfodiesterase-4, de análogos das prostaglandinas e de outros imunomoduladores no tratamento desta doença.

Esta revisão bibliográfica sintetiza o panorama atual dos tratamentos em ascensão, avaliando os seus mecanismos de ação, resultados clínicos e perfis de segurança com base numa extensa análise da literatura. Embora nenhuma terapêutica se tenha ainda revelado curativa, a investigação e a inovação contínuas são essenciais para o desenvolvimento de soluções sustentáveis.

Palavras-chave: Vitiligo, Inibidores da Janus quinase, Ruxolitinib

Abstract

Vitiligo is a multifactorial autoimmune disorder marked by the progressive loss of melanocytes, resulting in depigmented patches on patients' skin.

Affecting approximately 0.5% to 2.0% of the world population, it not only causes visible skin changes but also significantly impacts mental health.

The disease arises from complex interactions between genetic susceptibility, environmental triggers, and immune dysregulation. Autoreactive CD8+ T cells and the JAK-STAT pathway are central to its pathogenesis, perpetuating melanocyte destruction.

Traditional therapies, such as corticosteroids, calcineurin inhibitors, and phototherapy, often deliver limited or temporary results, highlighting the urgent need for more effective and durable options. Advances in understanding the immunopathology of vitiligo have paved the way for promising novel therapies. These include Janus kinase (JAK) inhibitors, cytokine blockers, and strategies targeting memory T cells. The recent FDA approval of topical ruxolitinib marks a milestone, signaling a shift toward mechanism-based treatments. Ongoing clinical trials also explore the potential of afamelanotide, phosphodiesterase-4 inhibitors, prostaglandin analogs, and other immunomodulators.

This review synthesizes the current landscape of emerging treatments, assessing their mechanisms, clinical outcomes, and safety profiles based on a broad literature survey. While no single therapy has yet emerged as curative, continued research and innovation are essential to develop sustainable solutions.

Key words: Vitiligo, Janus kinase inhibitors, Ruxolitinib

List of Abbreviations

α-MSH: α-melanocyte-stimulating hormone
cAMP: adenosine monophosphate
F-VASI: Facial Vitiligo Area Scoring Index
F-VASI50: ≥50% improvement from baseline in the Facial Vitiligo Area Scoring Index
F-VASI75: ≥75% improvement from baseline in the Facial Vitiligo Area Scoring Index
F-VASI90: ≥90% improvement from baseline in the Facial Vitiligo Area Scoring Index
IFN-γ: interferon-gamma
IL-10: interleukin-10
IL-15: interleukin-15
IL-17: interleukin-17
IL-23: interleukin-23
JAK: janus kinase
MC1R: melanocortin-1 receptor
nb-UVB: narrow-band UVB
NK: natural killer
NSV: non-segmental vitiligo
ORR: overall response rate
PGF2α: prostaglandin F2α
SYK: spleen tyrosine kinase
T-VASI: Total Vitiligo Area Scoring Index
T-VASI50: ≥50% improvement from baseline in the Total Vitiligo Area Scoring Index
T-VASI75: ≥75% improvement from baseline in the Total Vitiligo Area Scoring Index
Th: T helper
TNF-α: tumor necrosis factor-alpha
TRM: resident memory T
TYK: tyrosine kinase
TYR: tyrosinase
VASI: Vitiligo Area Scoring Index

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Introduction

Vitiligo is a chronic, autoimmune skin disorder characterized by the selective destruction of melanocytes, leading to depigmented patches on the skin [1]. Affecting 0.5-2% of the world population, it is the most common cause of depigmentation. Though it does not alter life expectancy, it leads to diminished self-esteem, psychological distress, and significant social stigma, with studies showing higher rates of anxiety and depression in affected individuals [2-4].

Vitiligo lesions are typically milky white, non-scaly, and have distinct margins. This condition is classified into two primary forms: non-segmental vitiligo (NSV), the most common type, which presents as symmetrical, bilateral white patches, and segmental vitiligo, which is less common (accounting for 5–16% of cases) and generally unilateral [1].

Vitiligo is a complex disease arising from the interplay of genetic factors, cellular oxidative stress, melanocyte adhesion to the epithelium, and innate and adaptive immunity in predisposed individuals, ultimately leading to melanocyte destruction. However, the precise mechanisms linking genetic susceptibility, melanocyte auto aggression, and immune tolerance failure remain incompletely understood [5].

The diagnosis of vitiligo is typically based on the presence of acquired, well-defined, achromic, chalky-white, non-scaly macules in a characteristic distribution [6]. Although rarely required, a skin biopsy of established vitiligo lesions reveals a complete loss of melanocytes in the epidermis, while actively spreading lesions show T cell infiltration near melanocytes [4].

Cell-mediated immunity plays a central role in vitiligo, with evidence of CD8+ T-cell infiltration at lesion margins and an increased presence of autoreactive CD8+ T cells targeting melanocyte-specific antigens. Vitiligo pathogenesis involves the activation of the JAK-STAT pathway through the IFN-γ axis. IFN-γ, secreted by T cells, triggers keratinocytes to produce chemokines (CXCL9, CXCL10), which bind to T-cell receptors (CXCR3), promoting further T-cell recruitment and lesion persistence. IFN-γ binding also activates JAK proteins, leading to STAT protein phosphorylation, which regulates gene expression related to cell growth and apoptosis [3].

Relapse of vitiligo after successful repigmentation is common, with an estimated 40% risk within the first year. Interestingly, relapses typically occur in the same previously affected areas, suggesting the presence of autoimmune memory at these sites [6].

Resident memory T (TRM) cells contribute to the persistence and relapse of vitiligo by recruiting circulating T cells through cytokine release. IL-15 is crucial for TRM cell maintenance and vitiligo progression, suggesting that blocking IL-15 may provide durable remission [3, 4].

Vitiligo is fully reversible, unlike most autoimmune conditions. The disease typically spares melanocytes in hair follicles due to immune privilege, and melanocyte stem cells in the hair follicles can repopulate the epidermis, leading to repigmentation in areas with hair. However, areas without hair are much more challenging to repigment [7].

Although there is no definitive cure for vitiligo, several treatments have demonstrated favorable outcomes. Recent advancements in understanding its pathogenesis have led to new therapeutic alternatives, offering a more promising outlook for vitiligo patients [5].

Also, the expanded use of molecular-targeted therapy in skin diseases like psoriasis and systemic lupus erythematosus has significantly improved patient outcomes. Additionally, the repigmentation observed in these conditions when co-treated with vitiligo suggests potential therapeutic benefits for vitiligo. Increasingly, the role of cytokines and signaling pathways in vitiligo pathogenesis is being recognized [8].

Until recently, no FDA-approved treatments existed for repigmenting vitiligo [9]. Current therapeutic options focus on immune modulation and include topical calcineurin inhibitors, topical steroids, phototherapy, and systemic therapies such as oral steroids [10]. However, as mentioned earlier, they are not universally successful, have a high risk of relapse, and tend to lose effectiveness after discontinuation, requiring ongoing treatment [7]. These therapies are already well-established in routine clinical practice; therefore, their individual discussion was not included

in the design of this review. There remains a significant need for safe, targeted, and durable therapies, which is becoming feasible with advancements in understanding vitiligo's pathogenesis pathways [9].

In response to these challenges, various treatment approaches, including JAK inhibitors, cytokine blockers, and prostaglandin analogs, are being investigated for vitiligo treatment based on preclinical and clinical data [10].

This review examines current and emerging vitiligo treatments, highlighting recent advancements and ongoing evaluations.

New and emerging treatments in development for vitiligo

JAK Inhibitors

All members of the JAK family, including JAK1-3 and tyrosine kinase 2 (TYK2), are critically involved in the pathogenesis of vitiligo [10]. JAK1 and JAK3 are significantly overexpressed in both perilesional and lesional vitiligo skin compared to healthy controls [11]. Therefore, inhibition of the JAK-STAT pathway represents a promising therapeutic target. Elevated levels of interferon-gamma (IFN-γ) have been observed in the skin of individuals with vitiligo, which activates the transcription of the cytokines CXCL9 and CXCL10 via JAK 1/2. These cytokines are essential for the recruitment of cytotoxic T lymphocytes, responsible for melanocyte destruction. This underpins the hypothesis that JAK protein inhibition is an effective therapeutic strategy for vitiligo [3]. So far, many case reports and clinical trials have demonstrated promising results for using JAK inhibitors in treating vitiligo [12].

JAK inhibitors can be administered orally or applied topically, making them increasingly recognized as convenient and versatile treatment options [13]. Notably, response rates are comparable between the two modes of administration [14].

Ruxolitinib

Ruxolitinib, the most studied JAK1/2 inhibitor, initially used for polycythemia vera and primary myelofibrosis, is the first EMA and FDA-approved topical treatment for vitiligo patients aged 12 years or more. Ruxolitinib 1.5% topical cream received FDA approval for treating vitiligo in 2022 [2, 10, 15, 16].

Twice-daily topical administration of ruxolitinib 1.5% cream resulted in limited systemic bioavailability and achieved higher dermal concentrations of the active compound relative to oral dosing [17].

A phase II, open-label, proof-of-concept trial treated 11 patients with 1.5% ruxolitinib cream applied twice daily. After 20 weeks, participants showed overall improvement in vitiligo mean Vitiligo Area Scoring Index (VASI) of 23%, with the four patients who had facial involvement experiencing a 76% improvement in facial VASI (F-VASI). Nonfacial and acral areas exhibited minimal repigmentation, consistent with the known resistance of these regions to therapy, likely due to lower follicular density or reduced sun exposure. Erythema was the most frequent adverse event, affecting 72% of patients [18]. Additionally, an open-label extension study was conducted with eight of these patients for 32 more weeks, with three receiving adjunctive narrow-band UVB (nb-UVB) phototherapy. At week 52, a statistically significant mean improvement in the VASI score of 37.6% was observed. Facial lesions demonstrated the most pronounced response, with a

mean improvement of 92%, including one case of complete repigmentation. Enhanced repigmentation was noted, particularly among those receiving combination therapy. Notably, treatment effects were sustained up to 40 weeks after discontinuation [19].

In 2020, the results of a phase II (NCT03099304) randomized, double-blind, dose-ranging clinical trial were published. In this study, 157 patients received ruxolitinib cream at different concentrations (1.5% twice daily, 1.5% once daily, 0.5% once daily, or 0.15% once daily), along with a placebo group for 52 weeks. Significant improvement in the primary endpoint (≥50% improvement in F-VASI (F-VASI50)) was observed in patients treated with ruxolitinib 1.5% once daily. At 24 weeks, 26–50% of patients using ruxolitinib achieved F-VASI50, compared to 3% in the vehicle group. Continued improvement was observed at 52 weeks, with the 1.5% twice-daily dose yielding the highest responses (F-VASI50: 58%, F-VASI75: 52%, F-VASI90: 33%). The treatment was well tolerated, with no serious adverse events [20]. Seventy-seven patients who completed the 52-week randomized period continued to apply 1.5% ruxolitinib cream twice a day in the open-label period for another 52 weeks. Among all evaluable patients, F-VASI50, F-VASI75, and F-VASI90 were achieved by 83.6%, 65.5%, and 52.7% of patients, respectively, and ≥50% improvement from baseline in the Total Vitiligo Area Scoring Index (T-VASI50) was achieved by 58.2% of patients. Treatment with ruxolitinib cream was well tolerated over a 2-year period and resulted in substantial repigmentation of vitiligo lesions [21]. Researchers evaluated 25 patients for another 52 weeks following the 104-week phase 2 study. Among these individuals, 92% demonstrated F-VASI50, 68% achieved F-VASI75, and 48% reached F-VASI90, while T-VASI50 and T-VASI75 were observed in 60% and 20%, respectively. Notably, facial repigmentation was maintained in most patients for up to six months after treatment cessation. Participants tolerated ruxolitinib cream well throughout the three years, with fewer adverse effects, such as acne. These findings support ruxolitinib cream's long-term safety, efficacy, and durability in treating vitiligo [22].

Additionally, two phase III, randomized, double-blind, vehicle-controlled trials (TRuE-V1 and TRuE-V2) assessed the efficacy and safety of 1.5% ruxolitinib cream in patients with NSV. These two trials confirmed the superiority of 1.5% ruxolitinib cream over vehicle cream for vitiligo treatment. Six hundred seventy-four patients (330 in TRuE-V1 and 344 in TRuE-V2) were randomized to apply either ruxolitinib cream or placebo twice daily for 24 weeks. By week 24, 29.8% of patients in TRuE-V1 and 30.9% in TRuE-V2 who received ruxolitinib achieved F-VASI75, compared to 7.4% and 11.4%, respectively, in the placebo groups. Ruxolitinib also led to statistically significant improvements in key secondary endpoints, including F-VASI50, F-VASI90, and T-VASI50. The cream was generally well tolerated. Mild to moderate application-site acne and pruritus were the most observed adverse events [23].

Ritlecitinib

Ritlecitinib is a kinase inhibitor developed by Pfizer to treat conditions such as alopecia areata, vitiligo, ulcerative colitis, and Crohn’s disease. The United States and Japan first approved it in June 2023 for managing severe alopecia areata. Although ritlecitinib is not yet authorized for vitiligo treatment, several clinical studies are underway or awaiting results to evaluate its effectiveness [24].

A phase IIb, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of oral ritlecitinib for vitiligo over 48 weeks, comprising a 24-week dose-ranging phase followed by a 24-week extension phase. Participants were randomized to receive either a loading dose (100 or 200 mg daily for 4 weeks) followed by maintenance therapy (50 mg daily), a fixed dose regimen (50, 30, or 10 mg daily), or a placebo. At week 24, ritlecitinib 50 mg (with or without a loading dose) and 30 mg demonstrated statistically superior F-VASI75 score compared to placebo, with progressive improvement observed beyond week 28. Ritlecitinib was well

tolerated; side effects included nasopharyngitis, upper respiratory tract infection, and headache [25].

The phase IIb study extension trial (NCT03715829) evaluated ritlecitinib with or without nb-UVB phototherapy two days a week. Of 230 patients, 43 received ritlecitinib plus nb-UVB, while 187 received ritlecitinib alone. All patients received ritlecitinib 200 mg for 4 weeks, transitioning to 50 mg for 20 weeks. In week 24, the ritlecitinib plus nb-UVB group showed greater improvements in F-VASI and T-VASI scores than ritlecitinib alone. The most observed side effects were nasopharyngitis, urinary tract and upper tract infection, and headache. Overall, adding nb-UVB enhanced the efficacy of ritlecitinib, supporting the need for further investigation [26].

Additionally, a phase III, randomized, double-blind, placebo-controlled clinical trial (NCT06072183) is evaluating the safety and efficacy of ritlecitinib in adults with NSV. Participants are assigned to receive either 50 mg or 100 mg of ritlecitinib, or a placebo, taken once daily. The treatment duration is 52 weeks, followed by an open-label extension phase where all participants receive 100 mg of ritlecitinib daily for an additional 52 weeks. The primary objective is to assess the proportion of participants achieving significant improvement in F-VASI75 and T-VASI50 [27].

Recently, another phase III clinical trial (NCT06163326) started recruiting participants to determine the safety and effectiveness of ritlecitinib. Approximately 400 patients who were enrolled in a previous study (B7981040) will be divided into two main arms based on their prior treatment (ritlecitinib 50 mg or placebo) and will be administered oral ritlecitinib at doses of 50 mg, 100 mg, or a placebo for 52 weeks [28].

Moreover, the clinical trial NCT05583526 is also a phase III study designed to assess the effectiveness, safety, and tolerability of ritlecitinib in treating NSV. Participants were randomly assigned to receive either a 50 mg dose of ritlecitinib or a placebo, taken orally once daily over 52 weeks [29].

Tofacitinib

Approved for rheumatoid arthritis, ulcerative colitis, juvenile idiopathic arthritis, and active ankylosing spondylitis as a JAK1 and JAK3 inhibitor, tofacitinib has been showing potential as a treatment for vitiligo [30, 31].

In a non-randomized, observational clinical trial, 36 patients with refractory NSV were divided into two groups for 16 weeks. Patients in the combination group received oral tofacitinib (5 mg twice daily), nb-UVB phototherapy three times a week, and topical treatments (halometasone cream was applied to lesions on the trunk and limbs, while tacrolimus 0.1% ointment or pimecrolimus cream was used for lesions on the face and neck). In the control group, patients received the same topical treatments and nb-UVB phototherapy but did not receive tofacitinib. By the 16th week, the combination group's overall response rate (ORR) was 100%, while the ORR in the control group was only 36.84%. The VASI score also showed a significant decrease in the combination group, indicating better repigmentation than the control group. Adverse effects included mild joint pain in the thumb and hallux, burning pain or dryness in the combination group, and erythema in the control group [32].

A pilot study tested 2% topical tofacitinib cream with nb-UVB therapy in 11 patients with facial vitiligo who had not responded to previous treatments. After 3-6 months, all patients showed good to excellent repigmentation of facial lesions, suggesting a synergistic effect between the cream and phototherapy [33].

Consistently, another retrospective study reported that almost complete repigmentation of vitiligo patches was achieved in 100% of the nine patients treated with a combination of oral tofacitinib (10mg/day) and UVB therapy, compared to 77% of 58 patients who received only UVB therapy [34].

On top of that, an observational study evaluated the use of topical tofacitinib 2% cream in 16 patients with NSV, aiming to assess its efficacy and safety as a targeted JAK inhibitor therapy. The study allowed concomitant treatments, including topical corticosteroids, calcineurin inhibitors, and phototherapy. Patients applied the tofacitinib cream twice daily to affected areas, with a mean follow-up duration of 153 days. Four of the sixteen patients achieved ≥90% repigmentation, particularly in facial lesions, which responded significantly better than nonfacial sites, and five patients showed 25-75% repigmentation. Adverse effects were minimal, including transient acneiform eruptions and subtle skin contour changes in isolated cases [35].

Baricitinib

Baricitinib is a JAK1/2 inhibitor developed by Eli Lilly and Incyte and first approved by the FDA in 2018 for treating rheumatoid arthritis. Recent studies have also indicated its possible benefit in managing vitiligo [8, 36, 37].

A phase I study involving four patients with progressive vitiligo evaluated the effects of 12 weeks of oral baricitinib monotherapy (4mg daily for the first 4 weeks, followed by 2mg daily for the remaining 8 weeks). Significant repigmentation was observed in all patients, with VASI scores decreasing and repigmentation rates ranging from 59.26% to 74.17%. However, two patients experienced a recurrence of depigmentation at the 3-month follow-up [38].

Additionally, a case report described significant repigmentation in a 67-year-old man with vitiligo following eight months of oral baricitinib (4mg daily) therapy. The report also highlighted the potential role of light exposure in enhancing repigmentation [39].

A phase II clinical trial (NCT04822584) was recently completed, but the study results have not yet been submitted. The study investigated the efficacy and safety of combining baricitinib (4 mg/day) with nb-UVB phototherapy in adults with NSV. It enrolled 49 participants, who were assigned to receive either baricitinib or placebo for 36 weeks. Phototherapy was administered twice weekly for 24 weeks, starting 12 weeks after the initiation of the oral treatment [40].

Upadacitinib

Upadacitinib is an orally administered, second-generation Janus kinase inhibitor developed by AbbVie. Highly selective for JAK1, it is approved for several immunological conditions and is currently being evaluated for its potential efficacy in treating vitiligo [41, 42].

In a recent phase II clinical trial, 185 patients with NSV were randomly assigned to receive upadacitinib at doses of 6 mg, 11 mg, 22 mg, or a placebo for 24 weeks, followed by a 52-week extension. The 11 mg and 22 mg doses showed significant and sustained improvements in repigmentation compared to placebo. While adverse events were more frequent at higher doses, no new safety concerns were identified [43].

Additionally, a retrospective case series evaluated five NSV patients treated with oral upadacitinib (15 mg daily) for four months. All patients showed repigmentation, especially on the face, with four achieving F-VASI50; however, three experienced relapses after discontinuing the medication [44].

Recently, a phase III clinical trial (NCT06118411) was designed to evaluate the efficacy, safety, and tolerability of upadacitinib in treating NSV in adults and adolescents. The study plans to enroll 614 participants across two parallel replicate studies (study 1 and study 2). It includes a 48-week double-blind period A, during which participants are randomized to receive either upadacitinib 15 mg orally once daily or a placebo, followed by a 112-week open-label period B in which all participants receive upadacitinib 15 mg daily. The trial is currently ongoing [45].

Cerdulatinib (PRT062070)

Cerdulatinib (PRT062070) is a dual inhibitor of spleen tyrosine kinase (SYK) and JAK. A recent phase IIa clinical trial (NCT04103060) evaluating the safety and tolerability of a 0.37% topical gel formulation applied twice daily for treating vitiligo was recently completed; however, researchers have not yet published the results [46].

Povorcitinib

Povorcitinib, a selective JAK1 inhibitor, is currently being investigated in a phase III clinical trial (NCT06113471) to treat NSV. Researchers randomized 450 participants to receive either oral povorcitinib for 104 weeks or a placebo for the first 52 weeks, followed by povorcitinib for the remaining 52 weeks [47].

Cytokine-targeted therapies

Various monoclonal antibodies are currently being studied to treat vitiligo, targeting molecules such as IL-15, IL-17, IL-23, and TNF. These agents offer improved bioavailability, as well as enhanced affinity and specificity for their target molecules [8].

Interleukin-15 inhibitors

As an inflammatory cytokine, interleukin-15 (IL-15) is crucial in helping cytotoxic T cells survive and mature. It enhances their cytotoxicity by making them resistant to regulatory T cells. Recent research shows that levels of IL-15 are substantially higher in vitiligo patients compared with healthy individuals [48].

TEV-53408

TEV-53408 is an investigational humanized monoclonal antibody developed by Teva Pharmaceutical Industries Ltd. It functions as an IL-15 inhibitor, targeting the IL-15 cytokine involved in the activation and proliferation of natural killer (NK) cells and CD8+ T cells, which are known to play a critical role in the pathophysiology of vitiligo. By inhibiting IL-15, TEV-53408 aims to modulate immune responses implicated in autoimmune conditions.

A phase Ib open-label clinical trial (NCT06625177) is currently recruiting participants to evaluate the safety of subcutaneously administered TEV-53408. The study plans to enroll approximately 28 participants who will undergo an 84-week study period comprising a 4-week screening phase, a 24-week open-label treatment phase, a 16-week washout period, and a 40-week follow-up [49].

AMG 714

Similarly, AMG 714 is a monoclonal antibody that targets IL-15. In a recent phase IIa clinical trial (NCT04338581), 57 adults with vitiligo were randomized to AMG 714 or placebo. Participants in the experimental arm received 300mg of AMG 714 subcutaneously every two weeks for six doses over 10 weeks. Those not achieving at least 25% improvement in T-VASI by week 24 were offered nb-UVB phototherapy, a protocol also applied to the placebo group. The total duration of participation is approximately 48 weeks, including treatment and follow-up [50].

Interleukin-17 inhibitors

Biologics targeting interleukin-17 (IL-17) and interleukin-23 (IL-23) have been investigated for vitiligo management. These interleukins initially showed promise due to their success in treating related autoimmune conditions such as psoriasis. However, clinical outcomes have been inconsistent or even paradoxical [51].

Researchers have not established a direct correlation between T helper (Th) cell subsets and vitiligo severity. However, Th17 and Th22 cells have shown a positive association with the extent of affected body surface area in active vitiligo.

Although IL-17 contributes to sustaining inflammation by promoting other pro-inflammatory cytokines, its role is considered secondary in vitiligo pathogenesis [52].

Current evidence suggests that vitiligo is primarily driven by Th1-mediated immune responses, with Th17 cells potentially acting as intermediates capable of converting into Th1 cells under specific conditions. Blocking this transition could be a potential therapeutic strategy [53].

Secukinumab

Secukinumab is a monoclonal antibody that inhibits IL-17, a proinflammatory cytokine involved in inflammatory processes. It is widely used in the treatment of psoriasis [54].

Speeckaert et al. investigated this IL-17 inhibitor in a pilot trial (NCT05676333) to explore the role of the Th17 pathway in vitiligo and assess its therapeutic potential. The primary endpoint was determining whether secukinumab could induce repigmentation in patients with active NSV. Thus, 300 mg of subcutaneous secukinumab was administered at baseline, then weekly for four weeks, followed by monthly doses over seven months. Of the eight treated patients, seven experienced further depigmentation. Overall, the treatment failed to meet its primary endpoint, suggesting that IL-17 and Th17 lymphocytes do not play a central role in the immune-mediated destruction of melanocytes in vitiligo [53].

Interleukin-23 inhibitors

IL-23 serum levels are elevated in vitiligo patients and correlate with disease duration and extent, suggesting a role in promoting inflammation through Th17 cell development (55). However, in a Sudanese population, no significant differences in IL-17 or IL-23 levels were observed between patients and controls [56].

Tildrakizumab

Tildrakizumab is an IL-23 antagonist commonly used to treat plaque psoriasis. However, its impact on type 17 responses may influence pigmentation. For this reason, a phase I clinical trial (NCT04971200) was designed to explore the safety and efficacy of Tildrakizumab in adults with NSV. The trial included a single experimental group comprising 12 vitiligo patients treated with 200mg of Tildrakizumab subcutaneous injections every four weeks for six doses. The study results are still pending [57].

A prior case report demonstrated the potential efficacy of Tildrakizumab in a 63-year-old man with rapidly progressive acrofacial vitiligo. The patient received subcutaneous injections of 100 mg Tildrakizumab at weeks 0, 4, and 12. By 12 months, he exhibited a 55% reduction in VASI score and approximately 90% repigmentation in affected areas [58].

Phosphodiesterase 4 Inhibitors

Phosphodiesterase 4 (PDE-4) naturally breaks down cyclic adenosine monophosphate (cAMP) into 5'-adenosine monophosphate. Inhibiting PDE-4 raises intracellular cAMP levels, which results in a reduction of proinflammatory cytokines, such as IL-17, IL-23, tumor necrosis factor-alpha (TNF-α), and IFN-γ while enhancing the levels of anti-inflammatory cytokines like interleukin-10 (IL-10). These changes contribute to decrease proinflammatory cytokines, typically elevated in vitiligo-affected skin, and an increase in suppressive cytokines [59, 60].

Apremilast

Apremilast, a PDE-4 inhibitor developed by Amgen, is approved for treating psoriasis in several countries and is gaining attention as a possible treatment for vitiligo [61]. In a randomized, split-body pilot study, 28 patients received either nb-UVB phototherapy alone or in combination with apremilast on opposite sides of the body. After 16 weeks, the combination group showed a significantly greater likelihood of achieving grade 3 or 4 repigmentation than nb-UVB monotherapy ($P = .001$), with a more substantial reduction in VASI scores ($P = .0001$). Four adverse effects, all attributed to apremilast, were reported. These findings support the attention given to apremilast in treating generalized vitiligo [62].

A phase II clinical trial (NCT03036995) was conducted over 52 weeks and included 80 randomly assigned participants who received either oral apremilast or placebo combined with nb-UVB phototherapy. After 24 weeks of treatment, participants who achieved at least a 30% reduction in VASI score were rerandomized to continue with either apremilast or placebo combined with twice-weekly nb-UVB for an additional 24 weeks. The most frequently experienced side effects were diarrhea, abdominal pain, and headaches. At both 24 and 52 weeks, there were no statistically significant differences in VASI scores between the two treatment groups. By week 24, the mean VASI score had declined from 23.63 to 19.49 ($P = 0.011$) in the apremilast group and from 21.57 to 15.25 ($P < 0.0001$) in the placebo group. These results suggest that apremilast did not enhance the effectiveness of nb-UVB in managing vitiligo, offering no added benefit in terms of speed or extent of repigmentation when compared to placebo [63].

On the contrary, a small pilot study of 13 adults with vitiligo treated with oral apremilast did not yield similar findings. Participants received 30 mg twice daily, with follow-ups every two weeks for the first month and then monthly. More than half of the patients experienced some repigmentation, including complete repigmentation of small acral lesions, which are typically treatment-resistant. Disease progression halted in all patients, with no increase in VASI scores [64].

Likewise, a 12-week randomized controlled trial was conducted to evaluate the efficacy and safety of apremilast as an add-on therapy to standard treatments for unstable NSV. Thirty-seven patients were randomized into two groups: one received standard treatment alone, while the other received standard treatment plus apremilast (30 mg twice daily). Standard treatments included nb-UVB, topical/oral steroids, tacrolimus, and azathioprine. The study found that patients receiving apremilast experienced a faster onset of repigmentation (median: 4 weeks vs. 7 weeks) and a higher proportion of halted disease progression (93.75% vs. 66.66%). However, the difference in halting progression was not statistically significant. However, the apremilast group also experienced more adverse effects, including diarrhea and weight loss. In conclusion, add-on apremilast accelerated clinical improvement and reduced disease progression but was associated with increased side effects [(65)].

PF-07038124

PF-07038124 is a topical PDE-4 inhibitor currently being developed by Pfizer, while Crisaborole, another PDE-4 inhibitor, is already approved for treating atopic dermatitis (66). A recently completed phase II clinical trial (NCT05298033) evaluated the anti-inflammatory and pro-melanogenic effects of PF-07038124 and Crisaborole in vitiligo lesions. The study included six treatment arms: Crisaborole with nb-UVB, PF-07038124 with nb-UVB, vehicle with nb-UVB, Crisaborole with sham phototherapy, PF-07038124 with sham phototherapy, and vehicle with sham phototherapy. Thirty-two participants underwent treatment over six months. The trial aimed to assess repigmentation, with primary outcomes focused on improvements in the F-VASI score; however, the results have not yet been reported [(67)].

Afamelanotide

Afamelanotide is a synthetic analog of α-melanocyte-stimulating hormone (α-MSH). It was developed due to its higher activity and stability than the natural hormone and has since been extensively studied for its effects on pigmentation and skin health. Afamelanotide binds to the melanocortin-1 receptor (MC1R), activating downstream signaling pathways involved in melanogenesis and immunomodulation. As a result, numerous studies have been conducted to further investigate its potential role in treating vitiligo [(68)].

Building on this rationale, a phase II clinical trial evaluated the efficacy and safety of combining afamelanotide with nb-UVB phototherapy to treat NSV. Fifty-five participants were randomized to receive either nb-UVB phototherapy alone or in combination with monthly subcutaneous afamelanotide implants (16 mg) administered during months 2 to 5. Both groups received phototherapy 2-3 times weekly for 6 months. The combination group demonstrated superior repigmentation, with a mean improvement of 48.64% on the VASI score at day 168, compared to 33.26% in the monotherapy group. Both groups experienced erythema and pruritus, but the combination group also reported nausea, minor infections, and hyperpigmentation of unaffected skin. Overall, the combination of afamelanotide and nb-UVB was well tolerated and significantly more effective than phototherapy alone [(69)].

Additionally, another phase III clinical study (NCT06109649) investigated the therapeutic effectiveness and safety of combining afamelanotide with nb-UVB phototherapy versus nb-UVB treatment alone in individuals with generalized vitiligo. Around 200 participants were randomly assigned to receive either nb-UVB twice weekly by itself or alongside afamelanotide implants, which were administered every three weeks during a 20-week treatment course [(70)].

Prostaglandins analogs

Prostaglandin analogs (PGAs) are emerging as a promising therapeutic alternative for vitiligo. Melanocytes express various prostaglandin receptors, including those for PGE2 and PGF2α, suggesting that prostaglandins may play a critical role in activating melanocyte function. Considering this, several clinical trials have investigated the potential of PGAs, particularly latanoprost and bimatoprost, for treating vitiligo, aiming to evaluate their efficacy in promoting repigmentation (71).

Latanoprost

Latanoprost, a prostaglandin F2α (PGF2α) analog primarily used in the treatment of glaucoma, has also been found to stimulate melanogenesis by upregulating tyrosinase (TYR) expression. In a phase II clinical trial, the therapeutic potential of topical latanoprost 0.005% gel was evaluated for the treatment of periocular vitiligo. Thirty-one patients were randomly allocated to receive either the latanoprost formulation or a placebo, administered twice daily over 12 weeks. Those treated with latanoprost experienced markedly higher skin repigmentation (mean 45.66% vs. 2.37%). The intervention was well tolerated, with no significant side effects reported in either cohort [(72)].

In addition, a phase IV clinical trial (NCT04811326) is ongoing to evaluate the efficacy of latanoprost, nb-UVB, and their combination in the management of vitiligo. One hundred fifty patients are estimated to receive nb-UVB twice weekly, latanoprost 0.005% once weekly, or latanoprost 0.005% plus nb-UVB for 3 months. The outcomes of the study have not been disclosed [(73)].

Bimatoprost

Like latanoprost, bimatoprost has been reported to induce hyperpigmentation. Consequently, a phase II study evaluated the efficacy and safety of 0.01% bimatoprost ophthalmic solution compared to 0.1% tacrolimus ointment in 16 patients with vitiligo. Over 50% repigmentation was achieved in 20% of patients treated with bimatoprost and 10% treated with tacrolimus, although the difference was not statistically significant. The study's small sample size and short duration limit the generalizability of the results, highlighting the need for further research involving larger cohorts and more extended follow-up periods [(74)].

Discussion

In recent years, the development of small molecules for oral or topical administration has become a key focus in the search for effective vitiligo therapies. The primary objective is to combine user-friendly administration with high therapeutic efficacy, durable repigmentation, and a favorable safety profile. Given the multifactorial and complex pathophysiology of vitiligo, a broad range of investigational drugs is currently being explored, each targeting distinct molecular pathways implicated in disease progression.

JAK inhibitors have emerged as a promising class of targeted small molecules for treating chronic inflammatory diseases, including vitiligo. Following the FDA approval of topical ruxolitinib in 2022, ritlecitinib, an oral JAK inhibitor, is currently undergoing evaluation in three phase III clinical trials, highlighting the growing interest in systemic immunomodulation.

Similarly, PDE-4 inhibitors such as apremilast and PF-07038124 are being investigated in phase II trials, and they show potential as anti-inflammatory agents.
Afamelanotide, an α-MSH analog, has progressed to phase III clinical evaluation after demonstrating encouraging results in earlier trials. Cytokine inhibitors, including TEV-53408, AMG 714, Secukinumab, and Tildrakizumab, are also being tested in ongoing clinical trials, targeting specific immune pathways involved in melanocyte destruction. Additionally, prostaglandin analogs have recently gained attention for their potential repigmentation effects and have been evaluated in phase II trials.
Although emerging treatments show promise, relapse following initial repigmentation remains a concern. Long-term follow-up data are needed to better understand the durability of response and relapse rates associated with these therapies. Furthermore, several studies conducted to date involve relatively small sample sizes, limiting the generalizability of their findings, and definitive clinical guidelines for vitiligo treatment have yet to be established. These considerations highlight the importance of carefully integrating emerging therapies into clinical practice. Robust, large-scale, and long-term studies are crucial to establish these novel agents' safety, efficacy, and long-term outcomes.

Conclusion

Vitiligo is a challenging, multifactorial disease that significantly impacts patients' quality of life. While treatment options have evolved, no single therapy has emerged as entirely satisfactory. JAK inhibitors such as ruxolitinib and ritlecitinib show substantial promise, especially when combined with other therapies, and are increasingly recognized as potential first-line treatments. Additionally, cytokine-targeted therapies offer new possibilities for managing the condition.

Despite these advancements, challenges remain in achieving long-term, relapse-free repigmentation. Research into the molecular mechanisms of vitiligo, such as the role of immune cells and cytokine signaling, is critical to developing more effective, durable therapies. As new drugs emerge, comprehensive clinical trials are essential to assess these treatments' long-term safety, efficacy, and tolerability, ultimately providing patients with more effective management options for this complex and challenging disease.

Appendix

Tables

Table I: Clinical trials investigating JAK inhibitors for the treatment of Vitiligo

Treatment	Mechanism of action	Study design	Results	Adverse effects
Ruxolitinib	JAK1/2 inhibitor	Phase II [18]: 11 patients treated with 1.5% ruxolitinib cream bid for 20 weeks Phase II extension [19]: 8 of the 11 patients received 1.5% ruxolitinib cream bid for 32 more weeks, 3 of these patients received concomitant nb-UVB phototherapy Phase II (NCT03099304) [20]: 157 patients randomized into topical ruxolitinib 1.5% bid, 1.5% od, 0.5% od, 0.15% od or placebo Phase II extension [21]: 77 patients received 1.5% ruxolitinib cream bid for 52 weeks Phase II extension [22]: 25 patients received 1.5% ruxolitinib cream bid for 52 weeks Phase III (TRuE-V1) [23]: 330 patients were randomized to receive either 1.5% ruxolitinib cream bid or placebo for 24 weeks Phase III (TRuE-V2) [23]: 344 patients were randomized to receive either 1.5% ruxolitinib cream bid or placebo	Phase II [18]: mean VASI improvement of 23% and FVASI improvement of 76% Phase II extension [19]: mean VASI improvement of 37.6%. Greater repigmentation was noted in the 3 patients that received nb-UVB phototherapy Phase II (NCT03099304) [20]: 1.5% bid, 1.5% od, 0.5% od, 0.15% od at 24 weeks achieved F-VASI50 of 45%, 50%, 26% and 32%, respectively (compared to 3% in placebo) Phase II extension [21]: 83.6% patients achieved F-VASI50, 65.5% achieved F-VASI75, 52.7% achieved F-VASI90 and 58.2% achieved T-VASI50 Phase II extension [22]: 92% of patients achieved F-VASI50, 68% achieved F-VASI75, 48% achieved F-VASI90, 60% achieved T-VASI50 and 20% achieved T-VASI75 Phase III (TRuE-V1) [23]: 29.8% of patients in the ruxolitinib group achieved F-VASI75 compared to 7.4% in placebo	Phase II [18]: erythema, perifocal hyperpigmentation, and acneiform eruptions Phase II extension [19]: erythema and transient acne Phase II (NCT03099304) [20]: application site pruritus and acne Phase III (TRuE-V1 and V2)[23]: application-site acne and pruritus

			Phase III (TRuE-V2) [23]: 30.9% of patients in ruxolitinib group achieved F-VASI75 compared to 11.4% in placebo	
Ritlecitinib	JAK3/TEC inhibitor	NCT03715829 - Phase IIb [25]: 364 patients treated for 24-week dose-ranging period plus a 24-week extension period. Randomized to receive either a loading dose (100 or 200mg po od) + maintenance (50mg po od); a fixed dose (50, 30, 10mg po od), or placebo for 24 weeks. Subsequently, 187 patients received 200/50mg od for 24 weeks. NCT03715829 – phase IIb extension [26]: 24 weeks of 200mg + 50mg ritlecitinib with or without nbUVB in 230 patients NCT06072183 – phase III [27]: estimated 1450 patients randomized into 50mg, 100mg or placebo po od for 52 weeks, followed by 100mg po od for 52 weeks NCT06163326 – phase III extension [28]: 52 weeks of 50mg, 100mg or placebo in estimated 400 patients that previously received 50mg or placebo for 24 weeks NCT05583526 - phase III [29]: estimated 581 patients treated for 52 weeks, randomized into 50mg po od or placebo	NCT03715829 - Phase IIb [25]: Patients receiving 50 mg po od (with or without a loading dose) showed superior facial repigmentation compared to placebo after 24 weeks, with progressive improvement observed after extension period. NCT03715829 - phase IIb extension [26]: At week 24, patients receiving ritlecitinib + nbUVB showed a greater percent improvement in facial and total body vitiligo scores than those receiving ritlecitinib alone NCT06072183 – phase III [27]: No results yet (recruiting) NCT06163326 – phase III extension [28]: No results yet (recruiting) NCT05583526- phase III [29]: No results yet (active, not recruiting)	NCT03715829- Phase IIb [25]: Nasopharyngitis, upper respiratory tract infection and headache NCT03715829 - phase IIb extension [26]: nasopharyngitis, urinary tract and upper tract infection, and headache
Tofacitinib	JAK1/3 inhibitor	Observational study [32]: 36 patients treated for 16 weeks divided into combination group (tofacitinib 5mg po od + NB-UVB + halometasone cream + tacrolimus0.1% ointment or pimecrolimus ceam) or control	Observational study [32]: the ORR in the combination group was 100%, compared to 36.84% in the control group. The VASI score also showed a significant decrease in the combination group	Observational study [32]: mild joint pain, burning pain and dryness in

		group (NB-UVB + halometasone cream + tacrolimus 0.1% ointment or pimecrolimus cream) Pilot study [33]: 11 patients were treated with 2% topical tofacitinib and NB-UVB phototherapy for 6 months Retrospective study [34]: 58 patients received phototherapy alone and 9 patients received phototherapy plus oral tofacitinib citrate (10mg daily) for 9 months Observational study [35]: 16 patients received topical tofacitinib 2% cream bid	Pilot study [33]: all patients showed good to excellent repigmentation Retrospective study [34]: 100% of the patients in the combination group achieved almost complete repigmentation, compared to 77% in the monotherapy group Observational study [35]: 4 patients achieved >90% repigmentation, 5 achieved 25-75% repigmentation, and 4 achieved 5-15% repigmentation	the combination group and erythema in the control group Pilot study [33]: no adverse effects were observed Retrospective study [34]: no adverse effects were observed Observational study [35]: transient acneiform eruptions and subtle skin contour
Baricitinib	JAK1/2 inhibitor	Phase I [38]: 4 patients received baricitinib 4 mg/day for the first 4 weeks, then 2 mg/day for the remaining 8 weeks NCT04822584 - phase II[40] : estimated 49 patients treated for 36 weeks, randomized into 4mg po or placebo + nbUVB (for 24 weeks, starting 12 weeks after baricitinib or placebo)	Phase I[38]: Repigmentation rate ranged from 59.26% to 74.17% Case report: A 67-year-old man that received 4mg of oral baricitinib once daily for eight months showed significant repigmentation of his vitiligo lesions. NCT04822584 - phase II [40] : No results yet (completed, waiting for results)	Phase I: [38] no adverse effects were observed
Upadacitinib	JAK1 inhibitor	Phase II:[43] 185 patients treated for 52 weeks, randomized into 6mg po od, 11mg po od, 22mg po od or placebo Retrospective study [44]: five patients received 15mg daily of upadacitinib for four months	Phase II [43]: 11 and 22mg po od at 24 weeks allowed a reduction in F-VASI of 35.63% and 33.96%, respectively (compared to 14.36% in placebo)	Phase II[43]: COVID-19, headache, acne, and fatigue (22mg shows

		NCT06118411 - phase III [45]: estimated 614 patients treated with 15mg po od or placebo for 48 weeks followed by 15mg po od for 112 weeks	Retrospective study[44]: all patients showed repigmentation, with four achieving F-VASI50 NCT06118411 - phase III[45]: No results yet (active, not recruiting)	higher rates of adverse events) Retrospective study[44]: folliculitis
Cerdulatinib	JAK1/ SYK inhibitor	NCT04103060 – phase IIa [46]: estimated 33 patients treated for 6 weeks, randomized into topical 0.37% gel bid or placebo	NCT04103060 – phase IIa[46]: No results yet (completed)	
Povorcitinib	JAK1inhibitor	NCT06113471 – phase III [47]: 450 participants were randomized to receive either povorcitinib for 104 weeks or placebo for 52 weeks followed by povorcitinib for 52 weeks	NCT06113471 – phase III[47]: No results yet (active, not recruiting)	

Table II: Clinical trials investigating cytokine inhibitors for the treatment of Vitiligo

Treatment	Mechanism of action	Study design	Results	Adverse effects
TEV-53408	Monoclonal antibody (IL-15 inhibitor)	NCT06625177 – phase I [49]: estimated 28 patients received TEV-53408 via subcutaneous injection for 24 weeks	NCT06625177 – phase I [49]: No results yet (recruiting)	
AMG 714	Monoclonal antibody (IL-15 inhibitor)	NCT04338581 – phase II [50]: estimated 57 patients treated with 300mg subcutaneous every 2 weeks for 10 weeks (6 doses total) or placebo, followed by nbUVB phototherapy starting at week 24 if F-VASI <25%	NCT04338581 – phase II[50]: No results yet (active, not recruiting)	
Secukinumab	Monoclonal antibody (IL-17 inhibitor)	Pilot trial (NCT05676333)[53]: 8 patients received 300mg of subcutaneous secukinumab at baseline, then 1x/week for 4 weeks, then every 4 weeks for 7 months	Pilot trial (NCT05676333) [53]: 7 patients experienced depigmentation	Pilot trial (NCT05676333) [53]: No significant adverse events were observed
Tildrakizumab	Monoclonal antibody (IL-23 inhibitor)	NCT04971200 – phase I[57]: 12 patients received 200 mg of tildrakizumab subcutaneous injections every four weeks for a total of six doses administered as two 100 mg subcutaneous injections every 4 weeks	NCT04971200 – phase I[57]: No results yet (completed)	

Table III: Clinical trials investigating PDE-4 inhibitors for the treatment of Vitiligo

Treatment	Mechanism of action	Study design	Results	Adverse effects
Apremilast	PDE-4 inhibitor	NCT03036995 – phase II[63]: 80 patients randomized into NBUVB treatment + 30mg po bid or placebo for 24 weeks. Responders were rerandomized into NBUVB treatment combined with 30mg po bid or placebo for 24 weeks. Pilot study[64]: 13 adults treated with apremilast 30mg po od Phase II[65]: 37 patients were treated for 12 weeks with standard treatment + apremilast 30mg po bid or standard treatment alone	NCT03036995 – phase II[63]: the mean VASI score declined from 23.63 to 19.49 (P = 0.011) in the apremilast plus UVB group and from 21.57 to 15.25 (P < 0.0001) in the placebo plus UVB group, which shows no statistically difference Pilot study[64]: all patients experienced cessation of disease progression, with no increase in VASI scores. 61.5% showed partial repigmentation Phase II[65]: patients that received apremilast showed a faster onset of repigmentation (4 weeks compared to 7 weeks in the control group). The halt in progression of vitiligo and VASI score decrease were not statistically significant between groups	NCT03036995 – phase II[63]: Diarrhea, abdominal pain, and headache Pilot study[64]: headache, nausea, vomiting, abdominal pain Phase II[65]: weight loss, headache, diarrhea
PF-07038124	PDE-4 inhibitor	NCT05298033 – phase II[67]: 32 patients randomized into crisaborole 2% topical ointment bid + NBUVB phototherapy, PF-07038124 0.01% topical ointment bid + NBUVB phototherapy, vehicle ointment bid + NBUVB phototherapy, crisaborole 2% topical ointment bid + sham phototherapy, PF-07038124 0.01% topical ointment bid + vehicle ointment bid + sham phototherapy or vehicle ointment bid + sham phototherapy, for 6 months	NCT05298033 – phase II[67]: No results yet (completed)	

Table IV: Clinical trials investigating α-MSH analogs for the treatment of Vitiligo

Treatment	Mechanism of action	Study design	Results	Adverse effects
Afamelanotide	Analog of α-MSH	Phase II[69]: 55 patients were randomized into NB-UVB 2-3 times a week for 6 months + 16mg subcutaneous implants of afamelanotide from month 2 to month 5 or NB-UVB 2-3 times a week for 6 months NCT06109649 – phase III[70]: estimated 200 patients will receive either afamelanotide every 3 weeks + NB-UVB 2x/week for 20 weeks or NB-UVB 2x/week for 20 weeks	Phase II[69]: The combination group demonstrated superior repigmentation, with a mean improvement of 48.64% on the VASI score at day 168, compared to 33.26% in the monotherapy group NCT06109649 – phase III[70]: No results yet (recruiting)	Phase II[69]: Nausea, hyperpigmentation and minor infections (combination group) and erythema and pruritus (both groups)

Table V: Clinical trials investigating PGF2α analogs for the treatment of Vitiligo

Treatment	Mechanism of action	Study design	Results	Adverse effects
Latanoprost	PGF2α analog	Phase II[72]: 31 participants were randomized into latanoprost gel (0.005%) bid or placebo for 12 weeks NCT04811326 – phase IV[73]: estimated 150 patients will receive either NB-UVB twice weekly, latanoprost 0.005% once weekly, or latanoprost 0.005% plus NB-UVB, for 3 months	Phase II[72]: latanoprost demonstrated greater repigmentation (mean 45.66%) compared to 2.37% in placebo NCT04811326 – phase IV[73]: no results yet (active, not recruiting)	Phase II[72]: No significant adverse effects were reported
Bimatoprost	PGF2α analog	Phase II[74]: 16 patients were randomized into 0.01% bimatoprost ophthalmic solution bid or 0.1% tacrolimus ointment bid for 12 weeks	Phase II[74]: 20% of patients in the bimatoprost group achieves >50% repigmentation compared to 10% in the tacrolimus group, however, the difference was not statistically significant	Phase II[74]: itching and burning sensation

References

1. Ezzedine K, Eleftheriadou V, Whitton M, Geel Nv. Vitiligo. The Lancet. 2015;386(9988):74-84.
2. Mukhatayev Z, Le Poole IC. Vitiligo: advances in pathophysiology research and treatment development. Trends Mol Med. 2024;30(9):844-62.
3. Perez-Bootello J, Cova-Martin R, Naharro-Rodriguez J, Segurado-Miravalles G. Vitiligo: Pathogenesis and New and Emerging Treatments. Int J Mol Sci. 2023;24(24).
4. Ezzedine K, Tannous R, Pearson TF, Harris JE. Recent clinical and mechanistic insights into vitiligo offer new treatment options for cell-specific autoimmunity. J Clin Invest. 2025;135(2).
5. 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.
6. Bergqvist C, Ezzedine K. Vitiligo: A focus on pathogenesis and its therapeutic implications. J Dermatol. 2021;48(3):252-70.
7. Frisoli ML, Essien K, Harris JE. Vitiligo: Mechanisms of Pathogenesis and Treatment. Annu Rev Immunol. 2020;38:621-48.
8. Feng Y, Lu Y. Advances in vitiligo: Update on therapeutic targets. Front Immunol. 2022;13:986918.
9. Cunningham KN, Rosmarin D. Vitiligo Treatments: Review of Current Therapeutic Modalities and JAK Inhibitors. Am J Clin Dermatol. 2023;24(2):165-86.
10. Seong SH, Oh SH. Up-and-Coming Drugs for the Treatment of Vitiligo. Ann Dermatol. 2024;36(4):197-208.
11. Abdel Motaleb AA, Tawfik YM, El-Mokhtar MA, Elkady S, El-Gazzar AF, ElSayed SK, et al. Cutaneous JAK Expression in Vitiligo. J Cutan Med Surg. 2021;25(2):157-62.
12. Huang X, Ding X. Jak inhibitors in vitiligo: a meta analysis. Chin Med J (Engl). 2023;136(23):2897-8.
13. Huang MY, Armstrong AW. Janus-kinase inhibitors in dermatology: A review of their use in psoriasis, vitiligo, systemic lupus erythematosus, hidradenitis suppurativa, dermatomyositis, lichen planus, lichen planopilaris, sarcoidosis and graft-versus-host disease. Indian J Dermatol Venereol Leprol. 2023;90(1):30-40.
14. Phan K, Phan S, Shumack S, Gupta M. Repigmentation in vitiligo using janus kinase (JAK) inhibitors with phototherapy: systematic review and Meta-analysis. J Dermatolog Treat. 2022;33(1):173-7.
15. Kang C. Ruxolitinib Cream 1.5%: A Review in Non-Segmental Vitiligo. Drugs. 2024;84(5):579-86.
16. Samuel C, Cornman H, Kambala A, Kwatra SG. A Review on the Safety of Using JAK Inhibitors in Dermatology: Clinical and Laboratory Monitoring. Dermatol Ther (Heidelb). 2023;13(3):729-49.
17. Persaud I, Diamond S, Pan R, Burke K, Harris J, Conlin M, et al. Plasma pharmacokinetics and distribution of ruxolitinib into skin following oral and topical administration in minipigs. Int J Pharm. 2020;590:119889.
18. 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):1054-60 e1.

19. 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):1205-7 e1.
20. 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.
21. Harris JE, Pandya AG, Lebwohl M, Grimes P, Gottlieb AB, Sofen HL, et al. 27535 Safety and efficacy of ruxolitinib cream for the treatment of vitiligo: 104-week data from a phase 2 study. Journal of the American Academy of Dermatology. 2021;85(3):AB35.
22. Harris JE, Pandya AG, Lebwohl M, Hamzavi IH, Grimes P, Gottlieb AB, et al. Safety and efficacy of ruxolitinib cream for the treatment of vitiligo: A randomised controlled trial secondary analysis at 3 years. Skin Health Dis. 2024;4(6):e404.
23. 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.
24. Blair HA. Ritlecitinib: First Approval. Drugs. 2023;83(14):1315-21.
25. 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.
26. Yamaguchi Y, Peeva E, Adiri R, Ghosh P, Napatalung L, Hamzavi I, et al. Response to ritlecitinib with or without narrow-band ultraviolet B add-on therapy in patients with active nonsegmental vitiligo: Results from a phase 2b extension study. J Am Acad Dermatol. 2024.
27. A 104-Week Study of Ritlecitinib Oral Capsules in Adults With Nonsegmental Vitiligo (Active and Stable) Tranquillo 2 (Tranquillo 2): National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT06072183.
28. A 52-Week Study to Learn About the Safety and Effects of Ritlecitinib in Participants With Nonsegmental Vitiligo (Tranquillo LTE): National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT06163326.
29. A 52-Week Study of Ritlecitinib Oral Capsules in Adults and Adolescents With Nonsegmental Vitiligo (Active and Stable) Tranquillo (Tranquillo): National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT05583526.
30. 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.
31. 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.
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. 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.
34. 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.
35. 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.
36. Zhang J, Qi F, Dong J, Tan Y, Gao L, Liu F. Application of Baricitinib in Dermatology. J Inflamm Res. 2022;15:1935-41.
37. Markham A. Baricitinib: First Global Approval. Drugs. 2017;77(6):697-704.
38. Dong J, Huang X, Ma LP, Qi F, Wang SN, Zhang ZQ, et al. Baricitinib is Effective in Treating Progressing Vitiligo in vivo and in vitro. Dose Response. 2022;20(2):15593258221105370.
39. Mumford BP, Gibson A, Chong AH. Repigmentation of vitiligo with oral baricitinib. Australas J Dermatol. 2020;61(4):374-6.
40. Evaluation of Effect and Tolerance of the Association of Baricitinib and Phototherapy Versus Phototherapy in Adults With Progressive Vitiligo (BARVIT): National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT04822584.
41. Magdaleno-Tapial J, Hernandez-Bel P, Esteve-Martinez A, Penuelas-Leal R, Labrandero-Hoyos C, Sanchez-Carazo JL, et al. Upadacitinib and its role in the treatment of vitiligo: A new possible therapeutic perspective. JAAD Case Rep. 2024;46:57-8.
42. Duggan S, Keam SJ. Upadacitinib: First Approval. Drugs. 2019;79(16):1819-28.
43. Passeron T, Ezzedine K, Hamzavi I, van Geel N, Schlosser BJ, Wu X, et al. Once-daily upadacitinib versus placebo in adults with extensive non-segmental vitiligo: a phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-ranging study. EClinicalMedicine. 2024;73:102655.
44. Zhu J, Luo L, Guo Y, Wei T, Huang X, Xiao X, et al. Repigmentation in non-segmental vitiligo using the Janus kinase inhibitor upadacitinib, a retrospective case series. Arch Dermatol Res. 2024;317(1):143.
45. A Study To Assess Adverse Events and Effectiveness of Upadacitinib Oral Tablets in Adult and Adolescent Participants With Vitiligo (Viti-Up): National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT06118411.
46. Safety and Tolerability Study of Cerdulatinib Gel, 0.37% in Adults With Vitiligo: National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT04103060.
47. A Study to Evaluate Efficacy and Safety of Povorcitinib in Participants With Nonsegmental Vitiligo (STOP-V2): National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT06113471.
48. Atwa MA, Ali SMM, Youssef N, Mahmoud Marie RE. Elevated serum level of interleukin-15 in vitiligo patients and its correlation with disease severity but not activity. J Cosmet Dermatol. 2021;20(8):2640-4.
49. A Trial to Test the Safety and Efficacy of TEV-53408 in Treating Vitiligo: National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT06625177.
50. Evaluation of AMG 714 for Vitiligo (REVEAL): National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT04338581.

51. Custurone P, Di Bartolomeo L, Irrera N, Borgia F, Altavilla D, Bitto A, et al. Role of Cytokines in Vitiligo: Pathogenesis and Possible Targets for Old and New Treatments. Int J Mol Sci. 2021;22(21).
52. Kolls JK, Linden A. Interleukin-17 family members and inflammation. Immunity. 2004;21(4):467-76.
53. Speeckaert R, Mylle S, van Geel N. IL-17A is not a treatment target in progressive vitiligo. Pigment Cell Melanoma Res. 2019;32(6):842-7.
54. Blair HA. Secukinumab: A Review in Psoriatic Arthritis. Drugs. 2021;81(4):483-94.
55. Vaccaro M, Cannavo SP, Imbesi S, Cristani M, Barbuzza O, Tigano V, et al. Increased serum levels of interleukin-23 circulating in patients with non-segmental generalized vitiligo. Int J Dermatol. 2015;54(6):672-4.
56. Osman AM, Mukhtar MM, Bakheit KH, Hamdan HZ. Plasma Levels of Interleukin-17, Interleukin-23, and Transforming Growth Factor-beta in Sudanese Patients with Vitiligo: A Case-Control Study. Indian J Dermatol. 2015;60(6):635.
57. Pilot Study Assessing the Effect of Tildrakizumab in Vitiligo (TILDVIT-1227): National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT04971200.
58. Jerjen R, Moodley A, Sinclair R. Repigmentation of acrofacial vitiligo with subcutaneous tildrakizumab. Australas J Dermatol. 2020;61(4):e446-e8.
59. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. Biochem Pharmacol. 2012;83(12):1583-90.
60. Huff SB, Gottwald LD. Repigmentation of Tenacious Vitiligo on Apremilast. Case Rep Dermatol Med. 2017;2017:2386234.
61. Blair HA. Apremilast: First Pediatric Approval. Paediatr Drugs. 2025;27(1):119-24.
62. Kim HJ, Singer GK, Del Duca E, Abittan BJ, Chima MA, Kimmel G, et al. Combination of apremilast and narrowband ultraviolet B light in the treatment of generalized vitiligo in skin phototypes IV to VI: A randomized split-body pilot study. J Am Acad Dermatol. 2021;85(6):1657-60.
63. Khemis A, Fontas E, Moulin S, Montaudie H, Lacour JP, Passeron T. Apremilast in Combination with Narrowband UVB in the Treatment of Vitiligo: A 52-Week Monocentric Prospective Randomized Placebo-Controlled Study. J Invest Dermatol. 2020;140(8):1533-7 e2.
64. Majid I, Imran S, Batool S. Apremilast is effective in controlling the progression of adult vitiligo: A case series. Dermatol Ther. 2019;32(4):e12923.
65. Sharma S, Bhardwaj A, Dwivedi P, Yadav SS, Shamim MA, Singh S, et al. Apremilast Add-On Benefits Over Conventional Drugs (ABCD) in Unstable Non-segmental Vitiligo: A 12-Week Single-Center Randomized Controlled Trial. Cureus. 2023;15(4):e37180.
66. Blauvelt A, Langley RG, Gordon KB, Silverberg JI, Eyerich K, Sommer MOA, et al. Next Generation PDE4 Inhibitors that Selectively Target PDE4B/D Subtypes: A Narrative Review. Dermatol Ther (Heidelb). 2023;13(12):3031-42.
67. Study of Efficacy, Safety and Tolerability of Crisaborole and PF-07038124 With and Without NBUVB in Vitiligo: National Library of Mdicine; [Available from: https://clinicaltrials.gov/study/NCT05298033.

68. Minder EI, Barman-Aksoezen J, Schneider-Yin X. Pharmacokinetics and Pharmacodynamics of Afamelanotide and its Clinical Use in Treating Dermatologic Disorders. Clin Pharmacokinet. 2017;56(8):815-23.
69. Lim HW, Grimes PE, Agbai O, Hamzavi I, Henderson M, Haddican M, et al. Afamelanotide and narrowband UV-B phototherapy for the treatment of vitiligo: a randomized multicenter trial. JAMA Dermatol. 2015;151(1):42-50.
70. A Study to Compare the Efficacy and Safety of SCENESSE and Narrow-Band Ultraviolet (NB-UVB) Light Versus NB-UVB Light Alone in Patients with Vitiligo: National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT06109649.
71. Pourriyahi H, Hosseini NS, Nooshabadi MP, Pourriahi H, Baradaran HR, Abtahi-Naeini B, et al. Utility of prostaglandin analogues and phosphodiesterase inhibitors as promising last resorts for the treatment of vitiligo: A systematic review, from mechanisms of action to mono-, combination and comparative therapies. J Cosmet Dermatol. 2024;23(11):3466-87.
72. Nowroozpoor Dailami K, Hosseini A, Rahmatpour Rokni G, Saeedi M, Morteza-Semnani K, Sadeghi Z, et al. Efficacy of topical latanoprost in the treatment of eyelid vitiligo: A randomized, double-blind clinical trial study. Dermatol Ther. 2020;33(1):e13175.
73. Latanoprost Plus NB-UVB Versus Each Alone in Non-segmental Vitiligo: Clinical and Laboratory Evaluation: National Library of Medicine; [Available from: https://clinicaltrials.gov/study/NCT04811326.
74. Kanokrungsee S, Pruettivorawongse D, Rajatanavin N. Clinical outcomes of topical bimatoprost for nonsegmental facial vitiligo: A preliminary study. J Cosmet Dermatol. 2021;20(3):812-8.

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