Received: 27 August 2021 | Revised: 3 January 2022 | Accepted: 10 January 2022

DOI: 10.1111/jocd.14770

JCD Journal of Cosmetic Dermatology WILEY

REVIEW ARTICLE

Biologic and targeted therapeutics in vitiligo

Priyanka Karagaiah MD[1] | Robert A. Schwartz MD[2] | Torello Lotti MD[3,4] | Uwe Wollina MD[5] | Stephan Grabbe MD[6] | Mohamad Goldust MD[6]

[1]Department of Dermatology, Bangalore Medical College and Research Institute, Bangalore, India

[2]Department of Dermatology, Rutgers New Jersey Medical School, Newark, New Jersey, USA

[3]Department of Dermatology, University of Studies Guglielmo Marconi, Rome, Italy

[4]Department of Dermatology and Communicable Diseases, First Medical State University of Moscow I. M. Sechenev Ministry of Health, Moscow, Russia

[5]Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Academic Teaching Hospital of the Technical University of Dresden, Dresden, Germany

[6]Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Correspondence
Mohamad Goldust MD, Department of Dermatology, University Medical Center Mainz, Mainz, Germany.
Email: mgoldust@uni-mainz.de

Abstract

Background: Vitiligo is a long-standing progressive autoimmune disease with depigmented macules/patches with significant psychological morbidity to the patients. From being one of the most poorly understood diseases in the past, there has been a rampant advance in determining the molecular and genetic factors influencing the disease process. More light has been shed on the complex intracellular environment and interplay between innate and adaptive immunity. Numerous cytokines and signaling pathways have been associated with disease pathogenesis in the recent past.

Objective: The aim of this review the efficacy of biologic and targeted therapeutics in vitiligo.

Methods: A detailed literature search was conducted on databases like PubMed, COCHRANE Central, EMBASE and Google Scholar using keywords—"biologics," "vitiligo," "treatment," "repigmentation," "JAK inhibitors,", "TNF-α inhibitors," and "IL17/23 inhibitors," Relevant studies and review articles in English were analyzed in detail and report was written. This article aimed at a comprehensive review of all the biologicals and newer targeted therapeutics tried in vitiligo and their efficacy with an insight into the potential complications arising as a result of the therapy.

Results: Most conventional vitiligo treatment modalities are restricted to generalized nonspecific immunosuppressants like topical and oral corticosteroids, calcineurin inhibitors, phototherapy, and surgical modalities. There have been reports and studies on the usage of biologicals in treating vitiligo. JAK inhibitors have shown good efficacy in vitiligo; however, it lacks substantial evidence in the form of randomized control trials. Similarly, the use of targeted therapeutics in treating vitiligo is substantiated by limited evidence and requires more randomized trials for further evidence.

Conclusion: JAK inhibitors have shown promising results and good tolerability; Adjuvant phototherapy can achieve a superior response compared to monotherapy. Though TNF-α has been tried in a few cases, it is best used if vitiligo is present in association with other chronic autoimmune diseases for which it is indicated. More in vitro studies and clinical research are required to understand the pathogenesis clearly, and therapy has to be targeted at specific pathways for a better approach toward vitiligo.

Treatment aimed at induction and differentiation of melanocytes may be added to achieve faster repigmentation.

KEYWORDS
biological, JAK inhibitors, treatment, vitiligo

1 | INTRODUCTION

Vitiligo is an autoimmune disorder caused by persistent destruction of mature melanocytes by the ongoing inflammation in the skin and presents as sharply demarcated, circumscribed achromic macules, and patches.[1] The overall prevalence of vitiligo in the world ranges between 0.5% and 2%.[1] The peak occurrence is between 1st and 3rd decade of life; however, it can appear anytime in the course of life. The prevalence is most probably the same in both sexes and all races are equally afflicted by vitiligo.[1] It is a multifactorial disease with an intricate interplay between genetic and nongenetic factors.

2 | ETIOPATHOGENESIS OF VITILIGO

A plethora of theories have been put forward to explain the destruction of melanocytes in vitiligo, however, no single mechanism has fully been implicated in disease causation. Moreover, the melanocyte loss accruing in vitiligo may result from different pathogenetic mechanisms acting together ("convergence" or "integrated" pathway).[1]

2.1 | Genetic factors

The complex interaction of genetic and nongenetic factors forms the crux of the aetiopathogenesis of vitiligo. The genetic model of etiopathogenesis of vitiligo is complex and involves many genes encoding both adaptive and innate immune responses and also, shares gene complexes with various other autoimmune diseases. Genome-Wide Association Studies have discovered a large pool of susceptibility codons encoding components of both innate and adaptive immune systems. It includes TRIF, NLRP1, CASP7, C1QTNF6 genes of innate immunity and FOXP3, HLA, PTPN22, CCR6, and IL2R genes for adaptive immunity.[2]

Vitiligo associated with autoimmune syndromes are associated with polymorphisms in HLA-A2, −DR4, −DR7, and −DQB1*0303.[3] Replication studies showed association of generalized vitiligo with HLA class I and class II genes, C1QTNF6, GZMB, UBASH3A, and less consistent association with RERE, PTPN22, IL2RA, and TYR.[4] TYR gene encodes for tyrosinase enzyme, which although not associated with immunity, is a susceptible target for immune-mediated destruction. TYR peptide is presented to the autoreactive cytotoxic T cells by HLA-A*0201 facilitating the loss of immune tolerance toward tyrosinase and thereby, mediating auto reactive destruction of melanocytes.[4] Single nucleotide polymorphisms in the NALP1 gene, a regulator of innate immunity has been implicated recently. Not only was NALP1 associated with specific variants of vitiligo but also with other autoimmune and autoinflammatory diseases.[3]

Autoimmune susceptibility (AIS1) loci associated with vitiligo have been located on chromosome 1p31.3–p32.2, AIS2, and AIS3.[4] AIS1 and AIS2 linkages were associated with familial vitiligo, whereas AIS3 was associated with the non-autoimmune family subgroup. Systemic lupus erythematosus vitiligo-related gene (SLEV1) was linked with generalized vitiligo with the concurrent autoimmune syndrome.[3]

2.2 | Oxidative stress

Intrinsic defect in the oxidative stress mitigating mechanism of native melanocytes is one of the key inciting factors of autoimmune melanocyte destruction. Elevated superoxide dismutase and decreased catalase and glutathione peroxidase are the markers of oxidative stress and are often found in the perilesional skin. An increased superoxide dismutase activity results in raised H_2O_2 levels.[3]

Glutathione peroxidase is a major erythrocyte antioxidant, a key component in balancing the oxidative environment in the body. Superoxide dismutase binds to superoxide molecules and inactivates them by converting O_2^- to O_2 and H_2O_2. Thereafter, H_2O_2 is converted to O_2 and H_2O by the catalase enzyme. H_2O_2 accumulated due to imbalance in these pathways leads to microenvironmental changes in the mitochondria and subsequently leads to apoptosis of the melanocytes.[3]

Alterations in the markers of redox reaction like malondialdehyde, selenium, vitamins, glutathione peroxidase, superoxide dismutase, and catalase can be used to assess stress in vitiligo.[3]

Studies have put forth a new theory called the haptenation theory; here genetic polymorphism allows tyrosinase to bind to substrates like noradrenaline, tri-iodothyronine, and estrogen, making them a hapten, which further can convert the tyrosinase into a neoantigen target for uptake by the dendritic T cells.[3] Dysregulated Nrf2 pathway has recently been implicated in the susceptibility of melanocytes to cellular oxidative stress. The Nrf2-ARE is one of the major reactive oxygen species scavenging pathways that induce heme oxygenase-1 (HO-1), a potent antioxidant and thereby, prevent oxidative damage.[5]

2.3 | Effector mechanism

The elevated levels of H_2O_2 in the skin mediate the production of proinflammatory cytokines like IL-1β, IL6, and IL-8 indirectly by activating the calreticulin pathway.[6]

Inducible heat shock protein 70 (HSP70i) acts as a link between innate and humoral immune mechanisms. HSP70i is involved indirectly in the recruitment and maturation of antigen-presenting dendritic cells specific to melanocytes through cytokines like IL-6, IL-12, IL-1β, and Tumour necrosis factor-alpha (TNF-α).[6] Thus, in vitro modification and reintroduction of Hsp70iQ435A needs to be explored as a treatment modality in vitiligo. This may prove to be a novel therapeutic option in treating vitiligo by inhibiting this pathway and may also bring about repigmentation.[6]

IFN-γ is a key cytokine in the pathogenesis of vitiligo. Cytotoxic CD8 T lymphocytes are the last leg of effectors involved in the destruction of melanocytes. JAK-STAT intracellular signaling mediated up-regulation of CXCR3 receptors and CXCL 10 chemokines bring about the recruitment of CD8 T lymphocytes in the keratinocytes. This signaling is mediated by the key cytokine IFN-γ. Extracellular binding of IFN-γ activates JAK, a transmembrane protein kinase that undergoes self-phosphorylation. This leads to the binding of STAT proteins along the inner side of the cellular membrane to form a dimer unit following which a series of intracellular signaling enables the nuclear transcription of CXCL 10 and CXCL 9. These chemokines play a key role in the recruitment of cytotoxic T lymphocytes.[7]

Interleukin-15 (IL-15) plays a key role in the formation of T_{RM} cells. IL-15 receptor of T_{RM} cells expresses CD122 subunit, essential for binding of IL-15. Meanwhile, the CD215 subunit required to display the bound cytokine is upregulated by keratinocytes and there is subsequent activation of T cells.[8]

HMG-CoA reductase inhibitors like statins have been reported to inhibit STAT1 function in some in vitro studies. Recent animal studies have highlighted the role of systemic simvastatin in disease stabilization and repigmentation in vitiligo.[9]

FoxP3, a marker of Tregs (T cell regulatory cells) has been recently viewed as a marker for vitiligo. It normally functions as a downregulator of T cells and an upregulator of CTLA-4 and CD25 like immunosuppressive molecules. FoxP3+ Treg cells and Tregs homing receptors like CCL22 are significantly reduced in lesional skin specimens in vitiligo.[10] This serves as a rationale for exploration of Tregs transfer, Tregs enhancers like rapamycin, regulation of expression of FoxP3 by vitamin D therapy, and topical CCL22 as new modalities in treating vitiligo.[10]

Immune checkpoints like PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) are known to modulate T cell functions in response to inflammatory triggers. Studies on immune checkpoint inhibitors as a possible treatment for melanoma showed depigmented vitiligo-like patches occurring as a side effect of the therapy. This demonstrates the possibility of the occurrence of vitiligo due to dysregulation of immune checkpoints.[11] Selective activation of these immune checkpoints may prove useful in restoring immune tolerance and cytokine balance and therefore help in treating vitiligo.[11]

Moreover, the loss of melanocytes in vitiligo may also be the result of different pathogenetic mechanisms working together ("convergence" or "integrated" pathway).[1]

Vitiligo treatment largely comprises of general, off-label, nontargeted immunosuppressants with modest efficacy and compounded by the problem of recurrence after stopping treatment. The psychological burden caused by cosmetic disfigurement is of greatest concern to the treating doctors as well as the patients' families. Thus, there is a demand for a better understanding of the pathogenesis and development of newer targeted treatment options for vitiligo. In this respect, biologicals are being explored in the treatment of vitiligo. This review is thus aimed at shedding light on using different biological and targeted therapeutics and their efficacy in treating vitiligo.

2.3.1 | JAK inhibitors

JAK signaling by cytokines is an important target to be considered in treating vitiligo. At present, tofacitinib and ruxolitinib are being tested in various clinical trials for treating vitiligo (Table 1). Ruxolitinib is a selective Jak1/2 inhibitor with little or no affinity toward Jak 3 receptor. Tofacitinib on the other hand is an inhibitor of Jak3 and Jak1 receptors and to a lesser extent Jak2 receptor. It has minimal effect on Tyk2.[7]

Tofacitinib acts by blocking γc cytokines like IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, all of which act via Jak3 signaling. Jak1 inhibition would result in the blocking of IL-6 and IL-11, as well as the type II cytokine receptor family like (IFN)-α/β, IFN-γ, and IL-10. By inhibiting Jak1 and Jak2 receptors, tofacitinib also interferes with the differentiation of IFN-γ producing Th1 cells. Ruxolitinib by blocking JAK 1 and 2 receptors may inhibit many of the cytokines inhibited by tofacitinib.[7]

2.4 | Tofacitinib

It was the first JAK 1/3 inhibitor used in the treatment of generalized progressive vitiligo with almost complete reappearance of pigment on the hands and the face after 5 months of oral therapy.[12] In a similar case study, a 44-year-old male patient with atopic dermatitis, vitiligo, and alopecia areata was treated with oral tofacitinib 5 mg BD for 6 months with a minimal decrease in VASI from 4.68 at baseline to 3.95 at 5 months.[13] In a multicentric retrospective observational study, 58

out of the 67 patients received micro focussed narrow band UV-B (NBUVB) and nine patients with coexisting rheumatoid arthritis (RA) were treated with tab tofacitinib 10 mg/day orally as an adjuvant to NBUVB. Patients treated with tofacitinib reported an overall repigmentation of 92% as compared to a mean of 77% repigmentation in the NBUVB group.[14] In a retrospective case series of

TABLE 1 JAK inhibitors in vitiligo

Authors	Type of report	No of patients	Type/site of vitiligo	Formulation and dosage/ adjuvant treatment	Duration	Results
Tofacitinib						
Craiglow et al[12]	CR	1 50 y, F	Acral, facial and trunk	Tofacitinib PO 5 mg alternate days ×3 weeks, followed by 5 mg daily	5 months	Complete pigmentation of forehead, partial pigmentation of other areas reduction in % of depigmented area from 10% to 5% BSA
Vu et al[13]	CR	1 44 y, M	NSV with concomitant atopic dermatitis and alopecia areata	Tofacitinib 5 mg PO BID	6 months	Minimal improvement of VASI from 4.68 at baseline to 3.95 at 5 months
Gianfaldoni et al[14]	ORS	67 A) 58 vs B) 9	GV (vitiligo) vs (vitiligo, rheumatoid arthritis)	A)Micro focussed NBUVB once /3 weeks ×12 weeks vs B) Tofacitinib 10 mg PO daily + micro focussed NBUVB	3 months	42 patients in group A had good results with a mean of 77% repigmentation All the patients in group B had near-complete repigmentation with a mean 92% repigmentation
Liu et al[15]	CS	10	8 GV, 2 acral	Tofacitinib 5–10 mg PO daily or BID UVB in 2 patients	Average 9.9 months	3 patients responded with repigmentation in sun-exposed areas, whereas minimal or no response in sun protected areas. In patients with adjuvant UVB therapy complete repigmentation in 1 patient and partial improvement in another was noted
McKesey et al[16]	OL Pilot trail	11	Facial	2% tofacitinib cream BID + (NB-UVB) thrice weekly	3 ± 1 months.	Good to excellent repigmentation in all patients with 0.80 (range 0.1–2.25) at baseline to 0.23 (range 0.03–0.75) at follow-up. A mean improvement of 70% noted
Ruxolitinib						
Rothstein et al[19]	OL proof-of-concept trial	12	NSV	Topical ruxolitinib 1.5% cream BID	20 weeks	9 patients completed the study. 4 patients with facial vitiligo showed mean improvement of 76% in VASI. Overall improvement of 23% noted in all patients. Acral areas responded poorly
Joshipura et al[20]	OL	8	Not reported	Topical ruxolitinib 1.5% cream BID +optional NB-UVB (3/8)	32 weeks	5/8 responded to treatment. 92% improvement in mean VASI score in facial areas and 12.6% in upper extremities
Harris et al[21]	CR	1 35 y, M	Vitiligo with alopecia areata	Ruxolitinib 20 mg PO BID	20 weeks	Improvement of 51% seen in facial lesions. Pigmentation worsened after stopping treatment

Note: Abbreviations: BID, twice daily; BSA, body surface area; CR, case report; CS, case series; F, female; GV, generalized vitiligo; M, male; NB-UVB, narrowband ultraviolet B; NSV, nonsegmental vitiligo; OL, open-label; ORS, observational retrospective study; PO, per os/by mouth; VASI, Vitiligo Area Scoring Index; y, years.

ten patients treated with 5–10 mg BD dose of oral tofacitinib, only five patients with daily exposure to either, sun or NBUVB at a low dose responded with some repigmentation.[15]

In a pilot study, 11 subjects with vitiligo of the face were treated with topical application of 2% tofacitinib along with NBUVB for 3 ± 1 months and showed a mean improvement of 70% in VASI score. It was also found to be cost-effective in patients affected with limited body surface area.[16]

Common side effects are diarrhea and upper respiratory tract infections.[13] Mild elevation of lipid levels, arthralgia, and weight gain were noticed in patients.[15] In most patients oral tofacitinib was tolerated well.

Other adverse effects that have been noted in randomized trials in psoriasis include herpes zoster, reactivation of herpes simplex, urinary tract infections, and activation of latent tuberculosis.[17] Other serious life-threatening infections like *Pneumocystis jirovecii* pneumonia, non-tuberculosis mycobacterial pneumonia, legionellosis, and BK virus encephalopathy have been rarely reported following tofacitinib therapy.[18]

Laboratory abnormalities like reversible, dose-dependent decline in hemoglobin levels, RBC count, absolute neutrophil counts, and absolute lymphocyte count, enzyme elevations; dose-dependent increase in SGPT, SGOT, CPK, dyslipidemia; dose-dependent elevation in HDL, LDL, and total cholesterol levels, TG levels are common.[17] Rare occurrences of malignancies like melanoma, non-melanoma skin cancer, cancers of the prostate, lungs, breast, pancreas, lymphomas, and EBV-induced lymphoproliferative disorders have been reported.[18] Gastrointestinal perforations can occur rarely especially in patients with diverticulitis, on concomitant NSAIDs or corticosteroids.[18] However, it further warrants meticulous randomized trials to assess the side effects of JAK inhibitors.

Hepatic metabolism is primarily mediated by CYP3A4 with a minor contribution from CYP2C19 enzymes. Pharmacokinetics of tofacitinib may be changed by other medications affecting CYP such as strong CYP3A4 inhibitors (e.g., ketoconazole) or with strong CYP2C19 inhibitors (e.g., fluconazole). Reduced metabolism leading to raised serum tofacitinib necessitates dosage reduction, for example, from 5 mg BD or 11 mg XR (extended-release) OD to 5 mg OD.[18]

2.5 | Ruxolitinib

A 20-week study of twice-daily topical ruxolitinib 1.5% cream was done in 11 patients with at least 1% body surface area affected by vitiligo with a daily maximum of 3.75 g of cream or 10% body surface area (BSA). A mean improvement of 27% was noted in 9 patients who completed the study and facial vitiligo responded best (mean improvement of 76% in VASI) compared to truncal or acral vitiligo.[19] In a 32-week open-label trial, patients were treated with topical application of 1.5% ruxolitinib cream with additional NBUVB in a few who opted for it. Five out of 8 patients completed the trial. Patients with facial vitiligo showed an overall improvement of 92% in VASI scoring and truncal lesions showed a moderate response. Three patients who had opted for NBUVB showed a mean improvement of 37.6% ±31.2% in VASI. In 5 patients who had completed the study, the response was maintained at 6 months post-treatment.[20]

Side effects were limited to mild erythema, worsening of pre-existing acne, transient acneiform eruptions, and a rim of hyperpigmentation around the vitiligo patches with topical ruxolitinib treatment.[19,20]

In a case report, oral ruxolitinib 20 mg BD was tried in a 35-year-old male patient with concomitant alopecia areata and vitiligo for 20 weeks. Facial lesions improved temporarily, only to recur at 12 weeks post-treatment.[21]

Many authors believed that JAK inhibitors respond better in patients with facial vitiligo and in the upper extremities. Patients with sufficient sun exposure or concurrent NBUVB had excellent repigmentation.[14-16,19] JAK inhibitors halt the disease activity, whereas low dose light therapy either in the form of sunlight or NBUVB is necessary to stimulate the melanocytes to achieve repigmentation.[18]

2.6 | Role of JAK inhibitors in the wake of COVID-19 pandemic

A meta-analysis showed significantly reduced odds of mortality and ICU admission in those who received Janus kinase-inhibitor for COVID 19 pneumonia compared to the standard treatment group. The group also showed significantly increased odds of hospital discharge. This suggests the potential of the use of JAK inhibitors in Covid 19 coinfection with good safety.[22]

However, JAK inhibitors are known to inhibit various cytokines including Type I interferons which form a part of innate immunity and provide protective immunity against viral replication. This stands true for SARS-CoV-19 as well. A consensus study by Bastard et al showed that autoantibodies against Type 1 interferons were capable of neutralizing the ability of interferons to inhibit viral replication in vitro and could lead to severe pneumonia.[23] This necessitates caution while using JAK inhibitors during the COVID-19 pandemic.

Usage of JAK inhibitors is also associated with the problem of thromboembolic episodes which might aggravate the SARS-CoV-19-induced microvascular coagulopathy.[24]

Hence, JAK inhibitors have to be used with utmost caution in vitiligo patients especially those with COVID pneumonia considering the risk-benefit ratio.

2.6.1 | STAT inhibitors

Statins, HMG-CoA reductase inhibitors, a group of commonly used drugs to lower cholesterol was reported to have an inhibitory action on STAT1 molecules in an in vitro study (Table 2). Simvastatin, a member of the statin family was reported to have a halting effect on disease progression and to have repigmenting properties in a mouse model study.[25]

TABLE 2 Statin in vitiligo

Authors	Type of report	No of patients	Type/Site of vitiligo	Formulation and dosage/adjuvant treatment	Duration	Results
Noel et al[25]	CR	1	Facial and acral	Simvastatin PO 80 mg daily	6 months	Moderate repigmentation of the vitiligo patches noted
Vanderweil[26]	DB- RCT	15	Nonsegmental	Simvastatin PO 40 mg daily for 1 month,then 80 mg daily for 5 months	6 months	Mean increase of 26% in the VASI score of study group compared to 0% change in the placebo group

Note: Abbreviations: CR, case report; DB- RCT, double-blinded randomized control trial; PO, per os/by mouth; VASI, Vitiligo Area Scoring Index.

Repigmentation following oral simvastatin was 1st reported in a 55-year-old male patient with long-standing vitiligo, being treated for uncontrolled hypertension.[26]

In a phase-II clinical trial with oral simvastatin for vitiligo, authors noticed an average worsening of disease, with a 26% increase in the mean VASI (95% confidence interval, 45:97%) in the treatment group, while the placebo group had 0% change in the mean VASI (95% confidence interval, 5:5%). The study did not support the use of oral simvastatin for the treatment of vitiligo. The disparity in results when compared with the mouse model may be a result of dosing limitations in human beings because of potential toxicity, which is not a concern in mice.[27]

The side effects of simvastatin were limited to occasional myalgia, diarrhea, mild, transient transaminitis, and mild elevation of creatine phosphokinase, none requiring dose modifications. Vertigo and headache are very common and may be severe enough to necessitate withdrawal of treatment.[27]

There are two ongoing clinical trials using atorvastatin with NBUVB[28] and topical simvastatin and atorvastatin[29] in vitiligo to overcome the problem of systemic toxicity with high dose oral statins.

2.6.2 | TNF-a inhibitors

An imbalance in the local cytokine setting facilitates the destruction of melanocytes by cytotoxic T cells (Table 3). An abundance of pro-inflammatory cytokines such as TNF-a has been mentioned in vitiligo-affected skin in comparison to non-lesional skin.[30]

Patients with active vitiligo were found to have increased TNF-α levels, particularly in the lesional skin and hence was believed to contribute to the destruction of melanocytes in vitiligo.[30] There was a positive correlation between tissue levels of TNF-a and vitiligo disease activity.

TNF-α inhibits proliferation of melanocyte and its tyrosinase activity in a dose-dependent manner and is thus expected to interpose with repigmentation.[31] Studies found that TNF-α was also capable of inhibiting the differentiation of melanocyte stem cells and promoting melanocyte apoptosis, further inhibiting repigmentation in vitiliginous skin.[32]

In a pilot study with six patients with widespread, progressive vitiligo, etanercept, infliximab, or adalimumab were given to two patients each as per recommended guidelines for psoriasis. Digital photography was used to assess vitiligo lesions at 2 and 6 months following cessation of treatment. None of the patients achieved repigmentation, although one patient under infliximab experienced further disease progression. But, 5 patients developed no new lesions during the therapy or through 6 months follow-up.[32]

In another pilot trial, four patients with progressive vitiligo were treated with etanercept for a duration of 16 weeks. Disease stabilization was achieved by all the patients during the course of treatment, but post-treatment follow-up was not documented.[33] In another small pilot study, 2 patients with recalcitrant progressive vitiligo were treated with adjuvant etanercept along with ongoing treatment modalities for more than a year. Both patients showed disease stabilization and repigmentation.[34]

Paradoxically, there are reports of worsening vitiligo or emergence of de novo vitiligo in patients receiving TNF-α inhibitors for conditions other than vitiligo. In one such report, a 57-year-old male patient with ankylosing spondylitis with stable vitiligo of 20 years duration developed rapid progression of lesions following adalimumab therapy. Disease progression stopped and partial repigmentation was seen after stopping the treatment.[35]

In a case series of eight patients being treated with TNF-α inhibitors (7 adalimumab and 1 infliximab) for conditions other than vitiligo, patients developed new-onset hypopigmentation after a mean duration of 17.4 ± 15.8 months.[36]

Multiple other case reports have recorded de novo vitiligo in patients treated with TNF-α inhibitors for other dermatological, rheumatological, or gastrointestinal conditions. Most patients in case reports were treated with adalimumab.[37]

This paradox could be explained by the fact that the pathogenesis of vitiligo is multifactorial, in that it involves many other cytokines like IFN γ[38] and increased expression of ICAM 1 on the melanocytes, facilitating recruitment of cytotoxic T lymphocytes.[39]

Adverse events include infections, sepsis, and latent tuberculosis reactivation, malignancies such as lymphoma, other hematologic disorders such as anemia and pancytopenia, demyelinating disorders/neuropathy, worsening of congestive heart failure, the occurrence

TABLE 3 Tumour necrosis factor-alpha inhibitors in vitiligo

Authors	Type of report	No of patients	Type/Site of vitiligo	Formulation and dosage/Adjuvant treatment	Duration	Results
TNF α Inhibitors in treatment of vitiligo						
Alghamdi KM et al[31]	Pilot study	6	GV progressive	Infliximab ($n = 2$): 5 mg/kg IV at 0, 2, 6 weeks and then every 8 weeks. Etanercept ($n = 2$): 50 mg SC twice weekly Adalimumab ($n = 2$): 80 mg SC at week 0, 40 mg SC at week 1, then 40 mg SC every 2weeks		One patient on infliximab worsened with the progression of depigmented patches and occurrence of new patches. Other 5 patients attained stability which was maintained at 6 months post-treatment but did not attain the primary target of attaining >50% repigmentation.
Rigopoulos et al[32]	Pilot study	4 (24–34y)M	Progressive	Etanercept 50 mg SC once/week for 12 weeks, then 25 mg once/week for 4 weeks	16 weeks	Stabilized
Kim et al[33]	Pilot study	2 42/F, 46/F	Progressive	Etanercept 50 mg twice/week, then 50 mg once/week for ≥1 year with continued NB-UVB and topical calcineurin inhibitors		Disease stabilization and repigmentation
TNF α Inhibitors in treatment of chronic autoimmune diseases with concomitant vitiligo						

Abbreviations: CR, case report; CS, case series; F, female; GV, generalized vitiligo; IV, intravenously; M, male; SC, subcutaneously.

of autoantibodies and autoimmunity, and infusion/injection-related hypersensitivity reactions.[40]

2.6.3 | *IL 17/23 inhibitors*

Many studies in the recent past have shown the possible role of Th 17 cells and IL17 in the pathogenesis of vitiligo (Table 4). Studies revealed an increased level of Th17 cells and IL 17 in the affected skin and serum of patients with vitiligo, which showed a positive correlation with the disease activity.[41] There have also been reports of decreased frequency of IL17 and Th17 cells in the skin and serum following treatment with NBUVB, suggesting a possible role of the Th17 pathway in the initiation and progression of the disorder.[42]

IL23 is a proinflammatory cytokine belonging to a family of IL 12 cytokines and acts synergistically with Th17 cells and IL17 in the pathogenesis of a large number of chronic autoinflammatory diseases like rheumatoid arthritis, Crohn's, and multiple sclerosis. Thus, IL23/Th17 axis acts as a potential target of therapy in these cases.[43] Recent reports have shown expanded serum IL 23 levels in patients with nonsegmental vitiligo and a positive correlation with the disease duration and activity.[44]

In an isolated case report, a 37-year-old woman with psoriasis involving 10% of BSA and concomitant vitiligo and alopecia areata with unsatisfactory response to etanercept in the past was treated with IL23 inhibitor, ustekinumab 90 mg subcutaneous injections at 0 and 4 weeks and every 8 weeks subsequently. Psoriasis lesions cleared completely by the end of 16 weeks. At 20 weeks, there was complete hair growth at the sites of alopecia areata and vitiligo lesions had improved with some amount of repigmentation.[45]

In another similar case report, ixekizumab, an inhibitor of IL17A was tried in a 40-year-old female with coexisting vitiligo and psoriasis. The psoriatic lesions responded with complete clearance at 59 weeks, whereas the vitiligo lesions showed no response and in fact, the progression continued with the appearance of new depigmented patches in previously uninvolved areas. Thus, the authors were of the opinion that targeting the IL17/Th17 axis may not be effective in treating vitiligo.[46]

In another pilot trial, 8 patients with active vitiligo were treated with secukinumab 300 mg at weeks 0, 1, 2, 3, 4, and subsequently every 4 weeks for 7 months and followed up for an additional 2 months post-treatment. Photographic assessment using UV photography was done at each visit and biomarkers were assessed at regular intervals. Seven out of eight patients showed signs of further progression and only 1 patient showed limited depigmentation. Biomarkers of vitiligo like CXCL9, CXCL10, sCD25, sCD27, and BAFF showed no significant changes over time. sCD25 inversely correlated with baseline Th17 cells, which was surprising as sCD25 is a biomarker of active vitiligo. The percentage of Th17 cells was negatively correlated to the percentage of Th1 cells and positively linked with Th2, Th9, and Th22 lymphocytes. These findings were not in agreement with previous reports where the

TABLE 4 Biologics other than tumour necrosis factor alpha inhibitors in vitiligo

Authors	Type of report	No of patients	Type site of vitiligo	Formulation and dosage/Adjuvant treatment	Duration	Results
Elkady et al[44]	CR	1, 37/F	Generalized vitiligo with psoriasis and alopecia areata	Ustekinumab 90 mg SC at 0 and 4 weeks and then at every 8 weeks	20 weeks	Psoriasis improved at 16 weeks. alopecia areata and vitiligo improved at 20 weeks
Katz et al[45]	CR	1 40/F	Vitiligo with psoriasis	Ixekizumab dose unknown	59 weeks	Psoriasis responded. No response in vitiligo lesions
Speeckaert et al[46]	Pilot study	8	Active nonsegmental vitiligo	Secukinumab 300 mg at weeks 0, 1, 2, 3, 4, and subsequently every 4 weeks	7 months	7 patients showed no signs of progression. 1 patient showed mild repigmentation

Abbreviations: CR, case report; F, female; SC, subcutaneously.

Th17 pathway was correlated with active disease. In contrast, there was a positive correlation of Th17.1 lymphocytes with Th1 cells ($p < 0.001$).

In a further study with a larger cohort, it was found that there was a shift in Th1/Th17.1/Th17 balance toward Th1 differentiation instead of Th17 pathway in active non-segmental vitiligo. High circulating IL17 levels in patients with active non-segmental vitiligo were reported previously. The increased levels were attributed to elevated intermediary phenotype with the characteristics of both Th1 and Th17, like the Th17.1 lymphocytes. Th17.1 cells can produce both IL-17 and IFN-γ and are capable of polarising toward the Th1 phenotype in a skewed Th1 environment. Thus, the study concluded that IL17 inhibition offered no benefit in treating active vitiligo.[47]

2.7 | Immune checkpoint modulators

T cell responses to inflammation are modulated by molecules known as immune checkpoints comprising of PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) among many others. The use of immune checkpoint inhibitors in melanoma patients has shed light on the probability of dysregulation in immune checkpoints playing a role in the pathogenesis of vitiligo.[48] It is believed that selective activation of these surface molecules could restore tolerance in patients with vitiligo.[11]

On this basis, abatacept, a fusion protein that is approved by the FDA in the management of moderate to severe RA, was tried in the management of vitiligo.[49] Abatacept has IgG1 linked to the extracellular domain of CTLA-4 by the Fc region of the immunoglobulin.[49]

2.8 | Future therapeutic prospects

Currently, preclinical trials are being conducted to assess the role of PD-1 ligand in the treatment of psoriasis.[50] This could also serve as an option in the management of vitiligo in the future given its role in the regulation of immunity.

Studies have shown that activation of the mTORC1 pathway by Rapamycin has a protective action against H_2O_2-induced loss of dendrites in melanocytes. α-MSH can also block TNFα mediated activation of NF-κB and has a protective effect on dermal melanocytes. The authors are of the opinion that modulation of mTORC1 and NF-κB pathway may offer a better prospect for vitiligo clinical management.[51]

The anti-CD122 antibody has been shown to reverse vitiligo in mice models by inhibiting Il-15 mediated T_{RM} formation and production of interferon γ and depletes T_{RM} from lesional skin with long-term treatment.[8] However, they have to be used with caution as they are key regulators of adaptive immunity and inhibiting IL15 pathways may have safety concerns.

3 | CONCLUSION

Vitiligo has been a challenge, in terms of understanding the pathogenesis or achieving a satisfactory remission. The treatment modalities in vitiligo have mostly been nonspecific and generalized like topical immunosuppressants, phototherapy, surgical methods with modest efficacy, and potential adverse effects. Owing to a better understanding of the pathophysiology, there has been an emergence of newer specific targeted therapies aimed at limiting disease progression and achieving repigmentation with a good safety profile. JAK inhibitors have so far been the only class with promising results and good tolerability; although like any immunosuppressant, it comes with the risk of activation of latent infections and a few systemic side effects. Patient selection by adequate screening and routine baseline investigations can alleviate the chances of potential side effects. Adjuvant phototherapy can achieve a superior response compared to monotherapy. Though TNF-α has been tried in a few cases, it is best used if vitiligo is present in association with other chronic autoimmune diseases for which it is indicated. Also, the risk of worsening or emergence of de novo vitiligo must be borne in mind and the risk explained to patients before starting the therapy. IL17 inhibitors have been futile in attaining desired response. More in vitro studies and clinical research is required to understand the pathogenesis clearly and therapy has to be targeted at specific pathways for a better approach toward vitiligo. Treatment aimed at induction and differentiation of melanocytes may be added to achieve faster repigmentation.

ACKNOWLEDGMENT

Open access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

Priyanka Karagaiah: Writing and revising the manuscript; Robert A. Schwaertz: Review and revising the manuscript; Uwe Wollina: Review and revising the manuscript; Stephan Grabbe: Review and revising the manuscript; Mohamad Goldust: Conception, writing, review, and revising the manuscript.

ETHICAL APPROVAL

This was a review article and open access no ethic committee approval was warranted.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Uwe Wollina https://orcid.org/0000-0001-5933-2913
Mohamad Goldust https://orcid.org/0000-0002-8646-1179

REFERENCES

1. Krüger C, Schallreuter K. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. *Int J Dermatol*. 2012;51(10):1206-1212. doi:10.1111/j.1365-4632.2011.05377.x
2. Shen C, Gao J, Sheng Y, et al. Genetic susceptibility to vitiligo: GWAS approaches for identifying vitiligo susceptibility genes and loci. *Front Genet*. 2016;7: doi:10.3389/fgene.2016.00003
3. Kumaran M, Arora A. Pathogenesis of vitiligo: an update. *Pigment Int*. 2017;4(2):65. doi:10.4103/2349-5847.219673
4. Jin Y, Birlea S, Fain P, et al. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. *N Engl J Med*. 2010;362(18):1686-1697. doi:10.1056/nejmoa0908547
5. Jian Z, Tang L, Yi X, et al. Aspirin induces Nrf2-mediated transcriptional activation of haem oxygenase-1 in protection of human melanocytes from H 2 O 2 -induced oxidative stress. *J Cell Mol Med*. 2016;20(7):1307-1318. doi:10.1111/jcmm.12812
6. Mosenson J, Zloza A, Nieland J, et al. Mutant HSP70 reverses autoimmune depigmentation in vitiligo. *Sci Transl Med*. 2013;5(174):174ra28. doi:10.1126/scitranslmed.3005127
7. Schwartz D, Bonelli M, Gadina M, O'Shea J. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol*. 2015;12(1):25-36. doi:10.1038/nrrheum.2015.167
8. Richmond J, Strassner J, Zapata L, et al. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. *Sci Transl Med*. 2018;10(450). doi:10.1126/scitranslmed.aam7710
9. Agarwal P, Rashighi M, Essien K, et al. Simvastatin prevents and reverses depigmentation in a mouse model of vitiligo. *J Investig Dermatol*. 2015;135(4):1080-1088. doi:10.1038/jid.2014.529
10. Abdallah M, Lotfi R, Othman W, Galal R. Assessment of tissue FoxP3+, CD4+and CD8+T-cells in active and stable nonsegmental vitiligo. *Int J Dermatol*. 2014;53(8):940-946. doi:10.1111/ijd.12160
11. Speeckaert R, van Geel N. Targeting CTLA-4, PD-L1 and IDO to modulate immune responses in vitiligo. *Exp Dermatol*. 2016;26(7):630-634. doi:10.1111/exd.13069
12. Craiglow B, King B. Tofacitinib citrate for the treatment of vitiligo. *JAMA Dermatol*. 2015;151(10):1110. doi:10.1001/jamadermatol.2015.1520
13. 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):942-944. doi:10.1111/ced.13290
14. Gianfaldoni S, Tchernev G, Wollina U, 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):46-48. doi:10.3889/oamjms.2018.042
15. Liu L, Strassner J, Refat M, Harris J, King B. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J Am Acad Dermatol*. 2017;77(4):675-682.e1. doi:10.1016/j.jaad.2017.05.043
16. McKesey J, Pandya A. A pilot study of 2% tofacitinib cream with narrowband ultraviolet B for the treatment of facial vitiligo. *J Am Acad Dermatol*. 2019;81(2):646-648. doi:10.1016/j.jaad.2019.04.032
17. Papp K, Bissonnette R, Gooderham M, et al. Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: a Phase 2b randomized clinical trial. *BMC Dermatol*. 2016;16(1). doi:10.1186/s12895-016-0051-4
18. Accessdata.fda.gov.https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf Published 2022 Accessed January 3, 2022
19. Rothstein B. Topical JAK inhibitor ruxolitinib for vitiligo treatment. *Skin J Cutaneous Med*. 2018;2:S110-S111. doi:10.25251/skin.2.supp.102
20. 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):1205-1207.e1. doi:10.1016/j.jaad.2018.02.023
21. Harris JE. Vitiligo and alopecia areata: apples and oranges? *Exp Dermatol*. 2013;22(12):785-789. doi:10.1111/exd.12264
22. Goker Bagca B, Biray AC. The potential of JAK/STAT pathway inhibition by ruxolitinib in the treatment of COVID-19. *Cytokine Growth Factor Rev*. 2020;54:51-61. doi:10.1016/j.cytogfr.2020.06.013
23. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020;370(6515):eabd4585. doi:10.1126/science.abd4585
24. Spinelli F, Conti F, Gadina M. HiJAKing SARS-CoV-2? The potential role of JAK inhibitors in the management of COVID-19. *Sci Immunol*. 2020;5(47). doi:10.1126/sciimmunol.abc5367
25. Agarwal P, Rashighi M, Essien K, et al. Simvastatin prevents and reverses depigmentation in a mouse model of vitiligo. *J Investig Dermatol*. 2015;135(4):1080-1088. doi:10.1038/jid.2014.529
26. Noël M, Gagné C, Bergeron J, Jobin J, Poirier P. Positive pleiotropic effects of HMG-CoA reductase inhibitor on vitiligo. *Lipids Health Dis*. 2004;3:7. doi:10.1186/1476-511X-3-7
27. Vanderweil SG, Amano S, Ko WC, et al. A double-blind, placebo-controlled, phase-II clinical trial to evaluate oral simvastatin as a treatment for vitiligo. *J Am Acad Dermatol*. 2017;76(1):150-151.e3. doi:10.1016/j.jaad.2016.06.015
28. Atorvastatin in Active Vitiligo - Full Text View - ClinicalTrials.gov. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02432534 Published 2022 Accessed January 3, 2022
29. Niezgoda A, Winnicki A, Kosmalski T, Kowaliszyn B, Krysiński J, Czajkowski R. The evaluation of vitiligous lesions repigmentation after the administration of atorvastatin calcium salt and simvastatin-acid sodium salt in patients with active vitiligo (EVRAAS), a pilot study: study protocol for a randomized controlled trial. *Trials*. 2019;20(1):78. doi:10.1186/s13063-018-3168-4
30. Moretti S, Spallanzani A, Amato L, et al. New insights into the pathogenesis of vitiligo: imbalance of epidermal cytokines at sites of lesions. *Pigment Cell Res*. 2002;15(2):87-92. doi:10.1034/j.1600-0749.2002.1o049.x
31. Swope V, Abdel-Malek Z, Kassem L, Nordlund J. Interleukins 1α and 6 and tumor necrosis factor-α are paracrine inhibitors of human melanocyte proliferation and melanogenesis. *J Investig Dermatol*. 1991;96(2):180-185. doi:10.1111/1523-1747.ep12460991
32. Alghamdi KM, Khurrum H, Taieb A, Ezzedine K. Treatment of generalized vitiligo with anti-TNF-a agents. *J Drugs Dermatol*. 2012;11:534-539.
33. Rigopoulos D, Gregoriou S, Larios G, Moustou E, Belayeva-Karatza E, Kalogeromitros D. Etanercept in the treatment of vitiligo. *Dermatology*. 2007;215(1):84-85. doi:10.1159/000102044
34. Kim N, Jeon S, Lee H, Lee A. Impaired PI3K/Akt activation-mediated NF-κB inactivation under elevated TNF-α is more vulnerable to apoptosis in vitiliginous keratinocytes. *J Investig Dermatol*. 2007;127(11):2612-2617. doi:10.1038/sj.jid.5700900
35. Exarchou S, Voulgari P, Markatseli T, Zioga A, Drosos A. Immune-mediated skin lesions in patients treated with anti-tumour necrosis factor alpha inhibitors. *Scand J Rheumatol*. 2009;38(5):328-331. doi:10.1080/03009740902922612
36. Bonnet N, Guis S, Koeppel MC, et al. Evénements cutanéomuqueux au cours des traitements par anti-TNF alpha : étude observationnelle prospective de 41 cas [Cutaneous events during anti-TNF alpha therapy: a prospective observational study of 41 cases]. *Ann Dermatol Venereol*. 2010;137(1):12-20. doi:10.1016/j.annder.2009.12.003
37. Hernández M, Sanmartí R, Cañete J, et al. Cutaneous adverse events during treatment of chronic inflammatory rheumatic conditions with tumor necrosis factor antagonists: study using the Spanish registry of adverse events of biological therapies in rheumatic diseases. *Arthritis Care Res (Hoboken)*. 2013;65(12):2024-2031. doi:10.1002/acr.22096
38. Webb KC, Tung R, Winterfield LS, et al. Tumour necrosis factor-α inhibition can stabilize disease in progressive vitiligo. *Br J Dermatol*. 2015;173(3):641-650. doi:10.1111/bjd.14016
39. Ohmori Y, Schreiber R, Hamilton T. Synergy between interferon-γ and tumor necrosis factor-α in transcriptional activation is mediated by cooperation between signal transducer and activator of transcription 1 and nuclear factor κB. *J Biol Chem*. 1997;272(23):14899-14907. doi:10.1074/jbc.272.23.14899
40. Antoni C, Braun J. Side effects of anti-TNF therapy: current knowledge. *Clin Exp Rheumatol*. 2002;20:S152-S157.
41. Bassiouny D, Shaker O. Role of interleukin-17 in the pathogenesis of vitiligo. *Clin Exp Dermatol*. 2010;36(3):292-297. doi:10.1111/j.1365-2230.2010.03972.x
42. Hegazy R, Fawzy M, Gawdat H, Samir N, Rashed L. T helper 17 and Tregs: a novel proposed mechanism for NB-UVB in vitiligo. *Exp Dermatol*. 2014;23(4):283-286. doi:10.1111/exd.12369
43. Toussirot E. The IL23/Th17 pathway as a therapeutic target in chronic inflammatory diseases. *Inflamm Allergy-Drug Targets*. 2012;11(2):159-168. doi:10.2174/187152812800392805
44. Vaccaro M, Cannavò S, Imbesi S, et al. Increased serum levels of interleukin-23 circulating in patients with non-segmental generalized vitiligo. *Int J Dermatol*. 2014;54(6):672-674. doi:10.1111/ijd.12392
45. Elkady A, Bonomo L, Amir Y, Vekaria A, Guttman-Yassky E. Effective use of ustekinumab in a patient with concomitant psoriasis, vitiligo, and alopecia areata. *JAAD Case Rep*. 2017;3(6):477-479. doi:10.1016/j.jdcr.2017.07.009
46. Katz K, Rupley K, Sink J, Shuley A, Gottlieb A. Interleukin-17 inhibition in a patient with psoriasis and concurrent vitiligo. *J Psoriasis Psoriatic Arthritis*. 2018;3(4):126-130. doi:10.1177/2475530318788943
47. Speeckaert R, Mylle S, Geel N. IL-17A is not a treatment target in progressive vitiligo. *Pigment Cell Melanoma Res*. 2019;32(6):842-847. doi:10.1111/pcmr.12789
48. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors. *Am J Clin Dermatol*. 2017;19(3):345-361. doi:10.1007/s40257-017-0336-3
49. Open-label Pilot Study of Abatacept for the Treatment of Vitiligo. Available from: https://clinicaltrials.gov/ct2/show/NCT02281058 NLM Identifier: NCT02281058 Published 2022 Accessed January 3, 2022.
50. http://www.genexine.com/m31.php Published, 2022 Accessed January 3, 2022.
51. Wan J, Lin F, Zhang W, et al. Novel approaches to vitiligo treatment via modulation of mTOR and NF-κB pathways in human skin melanocytes. *Int J Biol Sci*. 2017;13(3):391-400. doi:10.7150/ijbs.17318

How to cite this article: Karagaiah P, Schwartz RA, Lotti T, Wollina U, Grabbe S, Goldust M. Biologic and targeted therapeutics in vitiligo. *J Cosmet Dermatol*. 2023;22:64–73. doi:10.1111/jocd.14770