Dermatology Practical & Conceptual

Treatment Advances in Vitiligo: An Updated Review

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ABSTRACT

Introduction: Vitiligo is a common disorder of depigmentation caused by the progressive destruction of melanocytes that affects the skin, hair, and mucous membranes, clinically presenting as depigmented macules and leukotrichia. This condition, affecting millions of people worldwide, has a significant psychosocial burden on patients' quality of life, particularly in relation to skin colour. The etiopathogenesis of this disorder is obscure, but multiple factors contribute to the loss of melanocytes in the skin, like oxidative stress, inflammation, genetics, and autoimmunity. The treatment of vitiligo has been challenging over the past years, but recent developments in understanding the etiopathogenesis of the disease have paved the way for the development of more effective and promising therapeutic treatment options.

Objective: The aim of this review was to provide an overview of the underlying mechanisms and highlight the latest advances in the treatment of vitiligo.

Methodology: This review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Metanalyses) guidelines. A comprehensive search of the literature was carried out through the PubMed electronic database from inception to 31 December 2023 using the following search terms "vitiligo" AND "JAK inhibitors", "vitiligo" AND "prostaglandin", "vitiligo" AND "afamelanotide", "vitiligo" AND "antioxidants", "vitiligo" AND "vitamin D3", "vitiligo" AND "statins", "vitiligo" AND "TNF-alpha", "vitiligo" AND "interleukin", "vitiligo" AND "light therapy". Two independent reviewers screened titles, abstracts, and full texts to select papers dealing with vitiligo and its treatment.

Conclusion: The advent of treatment modalities like Janus kinase inhibitors, prostaglandin analogues, antioxidants, TNF-α inhibitors, targeted phototherapy, and excimer lasers has revolutionized the therapeutic possibilities, offering a ray of hope to the individuals suffering from this devastating condition.

Introduction

Vitiligo is a chronic autoimmune hypomelanotic disorder presenting as well-defined hypopigmented macules on the skin and mucous membranes along with leukotrichia. It is caused by the destruction of melanocytes in the epidermis, which makes the skin appear white. It is quite a common disease, affecting nearly 1% of people across the globe [1]. It can affect anyone, irrespective of age, sex, geographical location, ethnicity, or skin color. It may cause the patient significant psychosocial distress due to the stigma associated with the disease and may result in social isolation and low self-esteem [2]. Vitiligo is broadly classified into three groups (Figure 1) [3].

Etiopathogenesis

The etiopathogenesis of vitiligo is complex and is not fully elucidated. Genetics, autoimmunity, oxidative stress, and neurological dysfunction are some of the theories and pathogenetic mechanisms that have been put forward. However, none of these can explain the different types of vitiligo that have been seen [4]. This has led to the development of the convergence theory, which states that there are several mechanisms contributing to the loss of melanocytes; among these, autoimmunity and oxidative stress theories are regarded as the major ones in the pathogenesis of vitiligo (Figure 2) [5]. The etiopathogenesis of this disease is summarized below (Table 1) [6-17].

Methodology

This review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Metanalyses) guidelines. A comprehensive search of the literature was carried out through the PubMed electronic database from inception to 31 December 2023 using the following search terms "vitiligo" AND "JAK inhibitors", "vitiligo" AND "prostaglandin", "vitiligo" AND "afamelanotide", "vitiligo" AND "antioxidants", "vitiligo" AND "vitamin D3", "vitiligo" AND "statins", "vitiligo" AND "TNF-alpha", "vitiligo" AND "interleukin", "vitiligo" AND "light therapy". A manual search was also performed by analyzing the reference sections of all relevant studies or reviews on the topic. Titles, abstracts, and full texts were screened by two independent reviewers to select papers dealing with vitiligo and its treatment. Inclusion criteria were (i) articles discussing vitiligo treatment, (ii) all types of articles, and (iii) no sample size limitation. Exclusion criteria were (i) non-English articles, (ii) irrelevant review articles, personal opinions/editorials and duplicates, and (iii) articles published before the year 2010 (Figure 3).

Treatment

Vitiligo treatment is difficult and frequently distressing for patients. Since it impairs one's quality of life (QOL), treatment must be swift and aggressive. The goal of vitiligo treatment is to limit disease development, induce pigmentation, and retain repigmentation, thereby minimizing the psychological stress.

Janus Kinase Inhibitors

Janus kinases (JAK) like JAK1, JAK2, and TYK2 (tyrosine kinase 2) are a class of cytoplasmic tyrosine kinases that contribute to cytokine-mediated signal transduction via the JAK/STAT (JAK/signal transducer and activating protein) pathway. The cell surface receptor for interferon-γ is composed of two subunits, IFNGR1 and IFNGR2, which belong to JAK1 and JAK2, respectively. Once interferon- γ binds to its

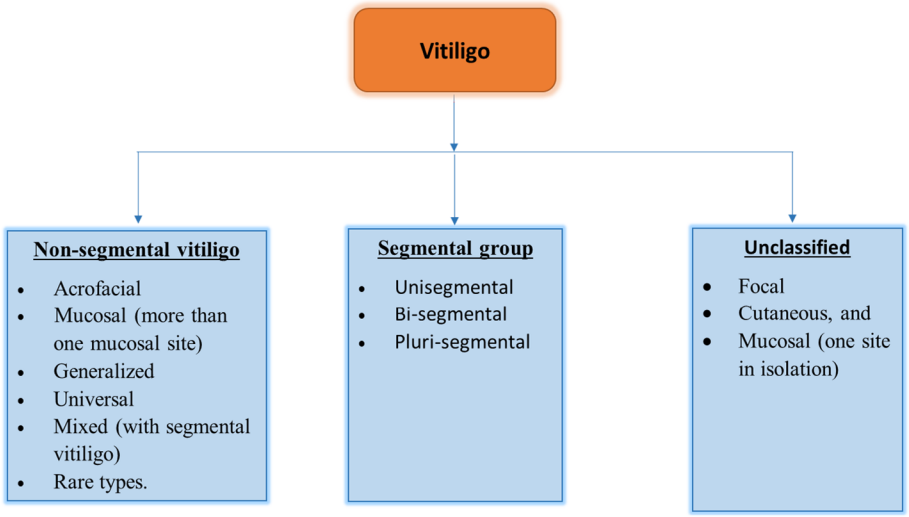

Figure 1. Classification of vitiligo.

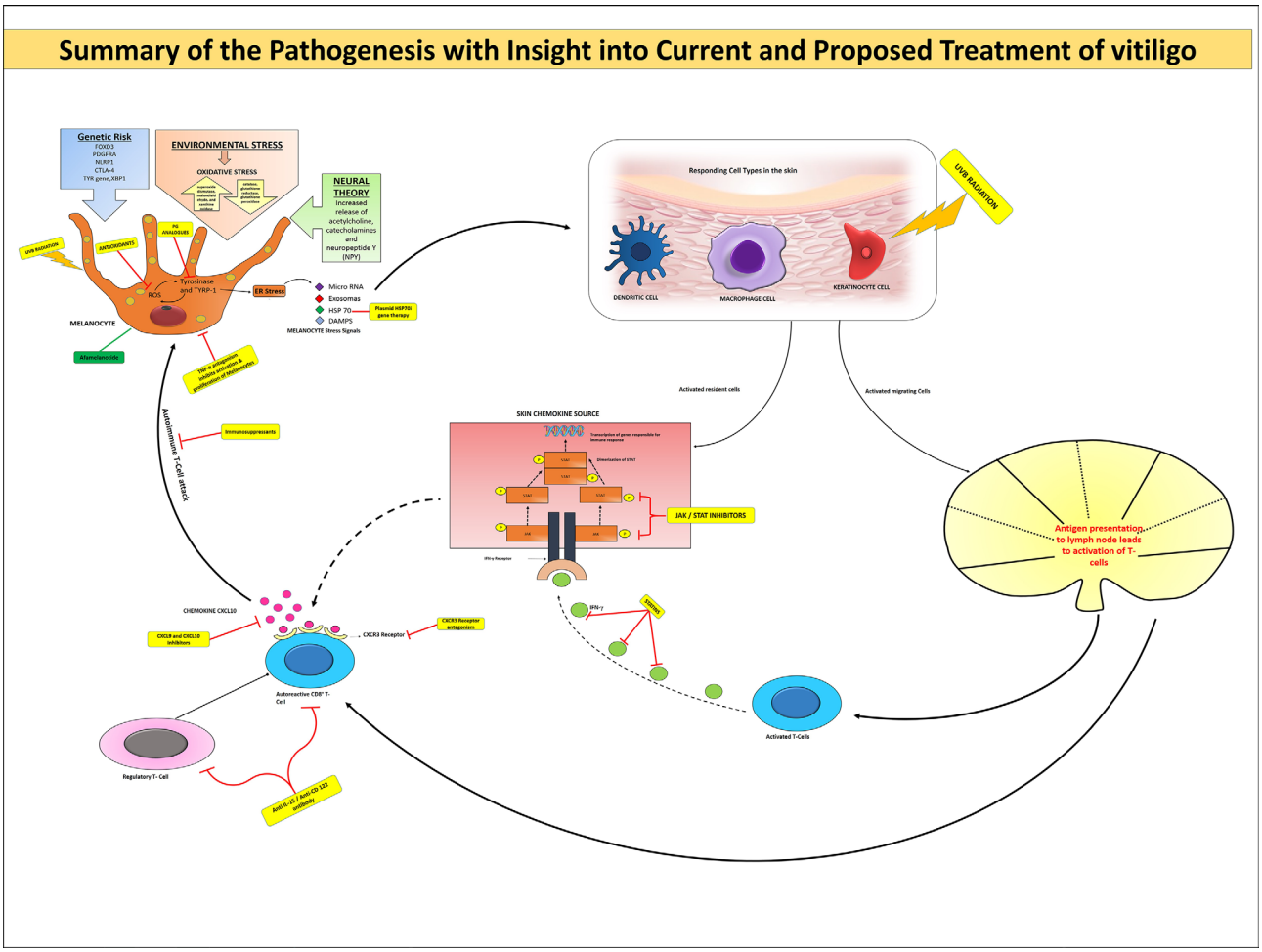

Figure 2. Schematic diagram of the pathogenesis with insight into current and proposed treatment of vitiligo.

Table 1. Summary of the Main Pathogenetic Mechanisms in Vitiligo.

Genetics	• Many genetic loci have been identified like NLRP1 (NLR family pyrin domain containing 1), PDGFRA (Platelet-Derived Growth Factor Receptor α), PTPN22 (Protein Tyrosinase Phosphatase Non-Receptor Type 22), FOXD3 (Forkhead Box D3), XBP1 (X-box binding protein 1), CTLA-4 (cytotoxic T-lymphocyte antigen 4), • Vitiligo has a significant association with other autoimmune disorders like type 1 diabetes mellitus, autoimmune thyroiditis, pernicious anemia, Addison's disease, systemic lupus erythematosus, and alopecia areata. • Familial vitiligo is associated with polymorphism in HLA-DRB1/DQA1.
Autoimmunity	• Melanocytes communicate stress to antigen-presenting cells through exosomes, extracellular vesicles with micro-RNAs, heat shock protein 70 (Hsp 70), and DAMPs (damage-associated molecular patterns). • There is production of interferon-γ leading to the activation of CXC chemokine ligands (CXCL9, CXCL10, and CXCL11) and attracting more CD8+T cells towards vitiliginous sites. • Dysfunction of regulatory T cells (Tregs) and CD8+ tissue-resident memory T cells (Trm) is also seen.
Oxidative stress hypothesis	• There is excessive production of oxidative stress markers and reduction in antioxidants. • Components of UPR (unfolded protein response) like encoding X-box protein 1 (XBP1) causes the release of immune mediators like IL-6/8, which halt T regulatory cells (Tregs). • Significant reduction in nuclear factor erythroid 2-related factor (Nrf2) and mTORC1 (mammalian target of rapamycin complex 1) causes significant oxidative stress to melanocytes.
Neural hypothesis	• Different neurochemical substances released from nerve endings in the skin kill melanocytes and damage cells. • Increased levels of norepinephrine in plasma and catecholamine catabolites in urine are observed. • There is an increase in neuropeptide Y (NPY) in vitiligo-lesional and peri-lesional skin.

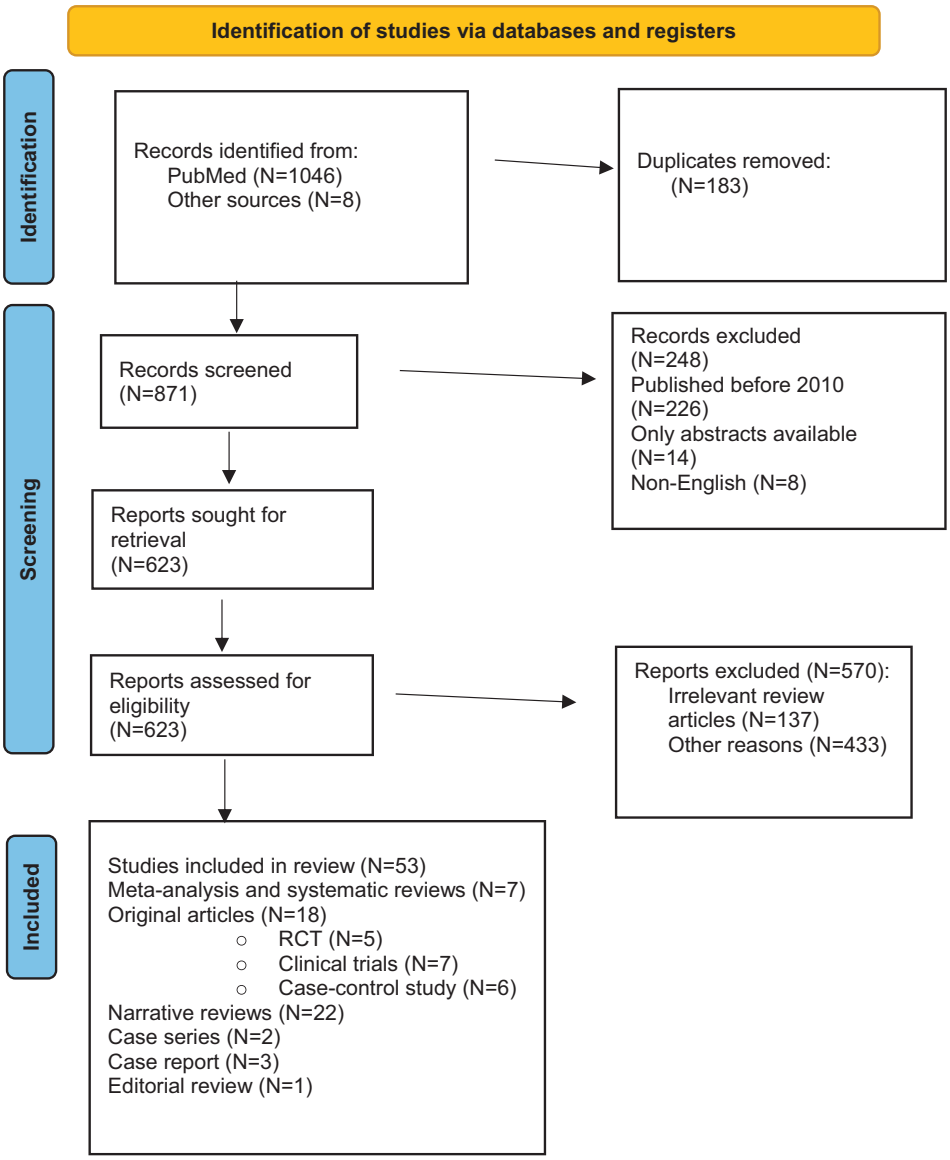

Figure 3. Metodology of the study.

receptor, there is activation and phosphorylation of STAT1, leading to transcription of IFN-γ-stimulated genes [18]. Therefore, inhibition of the JAK1/JAK2 pathway can block IFN-γ signaling, which makes Janus kinase inhibitors an attractive treatment option for the management of vitiligo.

Topical

Ruxolitinib 1.5% cream, a JAK 1 and 2 inhibitor, is the first JAK inhibitor approved by the FDA for the treatment of non-segmental vitiligo (NSV) in patients aged more than 12 years [19]. It is a chimeric antibody that targets CD20 cells, which are pre- and mature B lymphocytes. It also inhibits CD4+ T cells and CD8+ cytotoxic and CD8+ antigen-specific T cell responses as well as human dendritic cells. Hamzavi et al. tested ruxolitinib cream on 157 adults in a phase II study. After 24 weeks, the cream repigmented facial and total body vitiligo lesions, improving until week 52. Ruxolitinib cream also clinically repigmented all body parts, including acral areas, which are notoriously difficult to treat. Milder side effects were observed, like acne at the site of application and pruritus [20].

Ruxolitinib cream has been used in combination with narrow-band UVB (NB-UVB) phototherapy for 52 weeks in an open-label phase II study, with significant repigmentation of lesions, particularly on the face and body [21]. However, more studies are needed on a large number of patients to further evaluate its efficacy and safety.

Currently, studies are underway on the safety and tolerability of cerdulatinib gel 0.37% BID, a dual JAK and spleen tryrosine kinase (Syk) inhibitor, in the treatment of vitiligo [22].

Oral JAK inhibitors

Baricitinib, a selective JAK1/2 inhibitor that primarily interferes with the transduction of pro-inflammatory cytokines, has been recently approved for the management of atopic

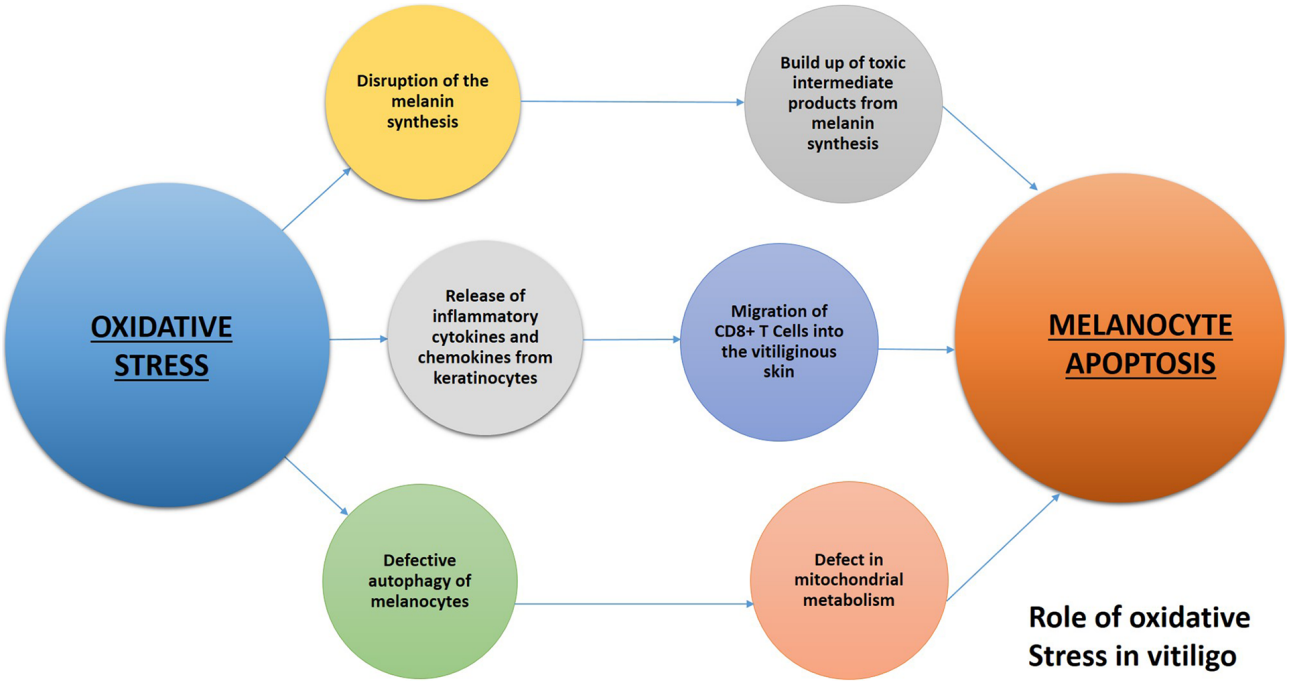

Figure 4. Role of oxidative stress in vitiligo.

dermatitis and rheumatoid arthritis [23]. Currently, there is only a single clinical case report documenting its use in individuals with vitiligo, who were given 4 mg of baricitinib daily. The effectiveness of 4 mg of baricitinib in combination with phototherapy is being studied in various clinical trials [24].

Ritlecitinib is another JAK3 inhibitor that is used in the treatment of active NSV. The efficacy and safety of ritlecitinib 50 mg (with or without loading dose) were studied by Khaled Ezzedine et al. in a randomized phase IIb clinical trial in which ritlecitinib substantially outperformed placebo in achieving centrally read F-VASI75 at 24 weeks. Furthermore, during the extension period, accelerated improvement was seen after 28 weeks, and ritlecitinib was well tolerated for up to 48 weeks [25].

Delgocitinib has shown its effectiveness in the management of vitiligo in only two reported cases to date, where response was more for the cervical lesions in comparison to the elbows. This could be attributed to differences in skin thickness, disease duration, and sun exposure at these two sites [26].

Ifidancitinib is a JAK1/3 inhibitor that has been used to treat alopecia areata. Its efficacy in the treatment of vitiligo is being explored in a phase II clinical trial, but more data are needed for its safety of use in vitiligo [22].

An interesting 52-week phase IIb trial on povorcitinib (a JAK-1 inhibitor) for extensive NSV with a total body surface area >8% and facial involvement >0.5% was performed. Patients showed significant repigmentation after receiving povorcitinib once daily for 24 weeks as compared to placebo, which continued through 36 weeks during the extension period. No serious treatment-related adverse events were reported [27].

Prostaglandin Analogues

Prostaglandins can enhance the expression of the enzyme tyrosinase, which regulates the rate of melanin production in the skin [28]. In vitiligo, there occurs a decreased synthesis of prostaglandins like prostaglandin E2 (PGE2) and prostaglandin F2 (PGF2α) in the skin in response to oxidative stress [29]. PGF2 is a well-known oxidative stress marker, and its levels are seen increase in the skin of vitiligo patients. The ability of topical bimatoprost, an analogue of PGF2, to cause increased melanogenesis and peri-ocular skin hyperpigmentation in glaucoma patients is being utilized to treat vitiligo [29,30]

Various analogues of PGF2α, like topical bimatoprost and latanoprost, have been proven effective in treating vitiligo when used with other modalities like topical corticosteroids, narrow-band phototherapy, and microneedling [30]. Presently, the efficacy of topical latanoprost 0.005% ophthalmic solution and 5-fluorouracil in vitiligo is being studied in an ongoing clinical trial (NCT05513924).

Hormone Analogue

Afamelanotide

Afamelanotide is an α-melanocyte-stimulating hormone (α-MSH) analogue that binds to the melanocortin 1 receptor (MC1R) present on melanocytes and that causes melanogenesis by increasing the uptake of eumelanin by melanosomes. Since the MC1R receptor is also present on many inflammatory cells, such as neutrophils and lymphocytes, afamelanotide has been shown to possess some anti-inflammatory properties as well. It is used as a biodegradable, sustained-release implant administered subcutaneously to patients with vitiligo [31].

Numerous clinical trials have been done regarding the efficacy and safety of afamelanotide in the treatment of vitiligo. Lim et al. conducted a randomized comparative study on patients with non-segmental vitiligo having 15% to 50% of total BSA involvement, where the use of afamelanotide in combination with narrow-band UVB phototherapy showed more effectiveness in treating vitiligo than phototherapy alone, with a faster rate of repigmentation over face and upper extremities. Side effects observed were erythema and nausea [32]. The safety of afamelanotide use on the face in vitiligo patients is being studied in various experimental trials (NCT05210582).

Antioxidants

Antioxidants play a significant role in the pathogenesis of vitiligo (Figure 4). Various antioxidants have been studied for the effective treatment of this condition.

Pseudocatalase/Superoxide Dismutase

In vitiligo, there is an accumulation of free radicals like H_2O_2 in melanocytes, which are lethal to enzymes such as tyrosinase and catalase [33]. The catalase enzyme is responsible for reducing H_2O_2 and preventing oxidative stress in melanocytes. Alshiyab et al. performed a study on pediatric vitiligo patients to evaluate the efficacy of pseudocatalase gel in combination with topical tacrolimus 0.1% versus topical tacrolimus 0.1% alone. No significant difference in the percentages of repigmentation was observed [34]. Nevertheless, information regarding pseudocatalase's safety profile and adverse effects is scarce.

Ginkgo Biloba Extract

Ginkgo biloba (GB) extract inhibits H_2O_2-induced apoptosis and the release of heat shock protein 70 (HSP70), therefore preventing oxidative damage to melanocytes [35]. In addition, it reduces inflammation by blocking the activity of the cyclooxygenase enzyme, proinflammatory interleukins like IL-8, and vascular endothelial growth factor (VEGF) [36].

A clinical trial on vitiligo patients showed that supplementing ginkgo biloba at a dose of 40 mg three times a day might induce repigmentation of facial lesions in vitiligo. In another study conducted by Szczurko et al., it was seen that 60 mg of ginkgo biloba twice daily also reduced the severity of disease in vitiligo patients. GB may interact with antiplatelets and anticoagulants and increase the risk of bleeding. Hence, the hazards of ginkgo biloba may outweigh its benefits [37].

Alpha Lipoic Acid

Alpha lipoic acid is a lipoxygenase inhibitor. It promotes the synthesis of glutathione enzymes and scavenges free radicals like hydroxyl radicles, thus preventing oxidative damage in vitiligo [37]. It is synthesized in the liver and is present in green leafy vegetables like broccoli and spinach in small amounts [38]. As it is important for the recycling of the antioxidant vitamins C and E, it has been used with these vitamins along with NB-UVB phototherapy to halt disease progression. Yan Sun assessed the safety and effectiveness of oral ALA and NB-UVB phototherapy and suggested that the use of alpha-lipoic acid did not provide any advantage when combined with phototherapy [39].

Polypodium Leucotomos

Polypodium leucotomos (PL) is a fern native to Central America. It can be used in the treatment of vitiligo, as it prevents the peroxidation of membrane lipids in keratinocytes and fibroblasts. It also prevents the oxidation of the glutathione enzyme and directly absorbs many reactive oxygen species (ROS) like peroxide ions, hydroxyl ions, and superoxide ions. By stimulating the production of inflammatory cytokines like IL-10, it produces a shift in cytokine profile from Type 1 to Type 2 T lymphocytes [40]. According to research by Pacifico et al., patients with diffuse vitiligo may experience faster repigmentation at lower cumulative doses with PL and NB-UVB phototherapy treatments [41].

Selenium

Selenium is an important component of more than 30 selenoproteins in the human body, which makes it an essential trace element. It is required for the proper functioning of the glutathione peroxidase (GPx) isoenzyme. It can be a key player in redox regulation through cascading enzyme systems and protecting melanocytes from the damaging effects of free radicals. Studies have shown elevated serum selenium levels in vitiligo patients. Dai et al. conducted a systematic review to evaluate the correlation between selenium levels and vitiligo. Overall, no significant difference was seen in selenium levels between vitiligo patients and controls. However, a subgroup study showed decreased selenium levels in the Asian population in comparison to Caucasians and healthy individuals. It was concluded that selenium levels vary in different races, and its supplementation might prove beneficial in the treatment of vitiligo in the Asian population [42].

Vitamin D3 Analogues

Vitamin D has a role in differentiation, maturation of keratinocytes, and maintenance of the integrity of the epidermal barrier. Additionally, it has immunomodulatory effects by suppressing overactive immunological responses, which can lead to the loss of melanocytes in vitiligo. It increases the melanin synthesis within melanocytes and may aid in the repigmentation process in vitiligo [43]. Moreover, vitamin D affects the release of several cytokines and growth factors that promote melanocyte survival and proliferation. Topical vitamin D analogues like calcipotriol and tacalcitol are commonly used as second-line therapy for the treatment of vitiligo [44]. A comparative randomized study was conducted in

three groups of patients to evaluate the efficacy and safety of topical calcipotriol and betamethasone ointment. Group A applied topical calcipotriol ointment only; Group B used topical betamethasone dipropionate ointment; Group C applied both ointments twice daily for three months. The combination of vitamin D analogues, calcipotriol, and betamethasone steroids proved superior in efficacy over individual preparations [45]. To enhance the rates of repigmentation in patients with vitiligo, vitamin D analogues have been used in combination with phototherapy. Liu X et al. performed a systematic review and meta-analysis to establish the efficacy and safety of the combined use of narrow-band ultraviolet B phototherapy (NB-UVB) and vitamin D analogues. It was found that adding topical calcipotriol or tacalcitol to phototherapy may help treat vitiligo better, with tacalcitol having a stronger effect than calcipotriol [46].

Vitamin D analogues have been used in combination with microneedling as well. Maha Wafic et al. evaluated the effectiveness of topical vitamin D (cholecalciferol) and microneedling in 25 patients with stable vitiligo. Fifty-two percent of the patients showed a good-to-excellent response to microneedling plus topical cholecalciferol, in contrast to 40% of patients treated with microneedling alone [47,48].

Statins

Statins are the drugs that lower plasma lipids. It has been reported that in individuals with active vitiligo, the dose-dependent action of simvastatin significantly inhibits the INF-γ-dependent MHC-II expressions, which in turn inhibit activated T lymphocytes [49]. Various studies showed significant improvement in the vitiligo disease activity (VIDA) score and lipid profile in patients who received 80 mg of simvastatin daily. Thus, simvastatin has shown a potentially beneficial role in vitiligo patients with dyslipidemia and reduces cardiovascular morbidity [50].

TNF-α Inhibitors

TNF-α is an anti-inflammatory mediator that induces B cell activation, inhibits melanogenesis, promotes apoptosis in melanocytes, and increases autoantibody production in vitiligo [51]. Recent studies have shown a significantly higher expression of TNF-α in vitiligo, especially in the lesional skin. It is postulated that TNF-α prevents repigmentation since it dose-dependently inhibits tyrosinase activity and suppresses melanocyte proliferation. It has been also observed that TNF-α may hinder the development of melanocyte stem cells and facilitate melanocyte death, hence impeding repigmentation in skin affected by vitiligo [52]. Thus, inhibition of TNF-α may play a pivotal role in the treatment of vitiligo. In a pilot study, the TNF-α inhibitor etanercept was administered for 16 weeks to four individuals who had vitiligo. All these patients achieved disease stabilization during the treatment period, but post-treatment follow-up was not documented. Ironically, some people taking TNF-α inhibitors for ailments other than vitiligo have reported worsening of their vitiligo or the development of de novo vitiligo. This paradox may be explained by the multifactorial pathophysiology of vitiligo, which includes upregulation of ICAM-1 molecules on melanocytes and other cytokines like IFN γ, which attract more cytotoxic T cells to the lesional skin [53].

Drugs Targeting Interleukins

Interleukin-17, produced by T helper 17 (Th17) cells, is a pro-inflammatory cytokine that may stimulate the monocytes to release other inflammatory cytokines like IL-1, IL-6, and TNF-alpha, leading to the persistence of the inflammatory cascade [54]. IL-17 levels have been found to positively correlate with the activity of disease in vitiligo [55]. Treatment with NB-UVB phototherapy has been found to decrease both the serum IL-17 levels and Th17 cells in the skin of vitiliginous patients, suggesting that the Th17 pathway has a role in the induction as well as the progression of the disease [56]. In a pilot study done by Speeckaert et al. on eight patients with active non-segmental vitiligo, secukinumab 300 mg was given at 0, 1, 2, 3, 4, followed by once every 4 weeks thereafter. Out of these eight patients, seven showed no progression of disease, whereas in one patient, there was mild repigmentation in skin lesions after seven months of treatment with secukunimab [57].

Interleukin 23 is believed to play a significant role in the etiopathogenesis of vitiligo. With the help of TGFβ and IL-6, IL-23 stimulates the differentiation of Th17 cells and the recruitment of more neutrophils to the epidermis [58]. Thus, blocking it may have a role in the treatment of this disease. In few studies, ustekinumab has been found to successfully induce stabilization and repigmentation of vitiligo after 16 weeks of continuous use. Also, one study has reported that it produces significant hair repigmentation in patients as well. All these results have been attributed to its ability to inhibit interleukin-16, which acts as an anti-melanogenic cytokine [59].

Light Therapy

Phototherapy, a major therapeutic option for the treatment of vitiligo, has been used over the decades. Narrow-band phototherapy (NB-UVB) is quite effective and relatively safe, making it a first-line treatment option for vitiligo. NB-UVB causes T cells to undergo apoptosis, downregulates the inflammatory signaling pathway, and causes upregulation of regulatory T cells. Furthermore, NBUVB reduces antigen presentation by depleting epidermal Langerhans cells [60]. In stable vitiligo, it promotes melanocyte proliferation and their migration from the outer root sheath of the hair follicle to the epidermis of the skin, which causes islands of repigmentation with a speckled

appearance [61]. In addition, it also upregulates the tyrosinase enzyme and increases the synthesis of melanin. According to the Global Vitiligo Foundation recommendations, phototherapy is to be given 2–3 times a week, starting at a dose of 200 mJ/cm^2, with subsequent increments of 10% to 20% if no erythema occurs. After 12 months of therapy, more than 75% repigmentation is generally expected to occur. Patients should be informed of the long-term nature of phototherapy at the outset only for better compliance and effective results [62].

The excimer laser (ExLs) offers a suitable option for vitiligo patients who have limited skin involvement. It has a wavelength of 308 nm, which is produced by combining xenon and chlorine gases. It has certain advantages, like accessibility to hard-to-reach areas, a lower cumulative dose, and limited exposure of UVB to target areas [63]. It has certain adverse effects like erythema, blistering, hypo and hyperpigmentation of the skin, and pruritus. However, these are localized to the treatment area only in comparison to the whole body in NBUVB phototherapy. ExLs costs more than alternative phototherapy equipment.

Another device that has been widely used to induce repigmentation in vitiligo is monochromatic excimer light lamps (ExLp). It emits a wavelength of 308 nm. Compared to excimer lasers, it gives faster repigmentation as it has a broader field of treatment [64]. It is far less expensive than other laser devices available on the market. Many studies have been done to compare the efficacy of NBUVB, ExLs, and ExLp in treating vitiligo [65]. According to recent meta-analyses, the excimer treatment has a better degree of repigmentation and a quicker result than NB-UVB [66].

Future Directions

Vitiligo is a disease that has been known to mankind for years; however, recent advancements in the etiopathogenesis of the disease could lead to more precise, efficient, and secure treatment for those who experience this debilitating condition. The management of vitiligo with IL-15 inhibitors or IL-15 receptor blocking agents appears alluring due to its significant contribution to the promotion of tissue-resident lymphocytes (Trm) and the persistence of the lesions [67]. The role of CXCL9 and CXCL10 chemokines in vitiligo has been defined to induce cytotoxic T cell production and migration to the basal layer of the epidermis, where they target melanocytes, cause their apoptosis, and decrease melanin production [68]. Since there is a significant role of CD8+ T lymphocytes in the production of vitiligo, it may be worthwhile to investigate and test therapeutics that block the CXCL9 and CXCL10 chemokines and their receptor, CXCR3, involved in the IFN-γ signaling pathway [69]. As mentioned earlier, damage-associated molecular patterns (DAMPs) have a role in autoantigen recognition, regulation of immune responses, and induction of melanocyte apoptosis. The primary DAMP molecule, i.e., heat shock protein (HSP70i), plays a central role in the pathogenesis of vitiligo [9]. By blocking HSP70i, there could be downregulation of the Th-1 lymphocytes in active vitiliginous lesions. Another potential target among DAMPS is the high-mobility group box protein B1 (HMGB1) whose levels have been found to be increased in the serum of the patients [70]. It may be worthwhile to investigate thoroughly the role of HMGB1 in causing toxicity to melanocytes to enhance our knowledge of vitiligo and develop newer therapeutic options (Table 2).

Table 2. Future Drug Targets in Vitiligo.

Drug class	Treatments	Mechanism	Treatment goal
Anti IL-15 biologics	Anti IL-15 antibody Anti-CD 122 antibody	Blocking of interleukin 15 signaling	Immunosuppression and Trm cell elimination
Phosphodiesterase 4 inhibitor	Apremilast Roflumilast	Inhibition of PDE-4, increasing CAMP and decreasing expression of inflammatory mediators	Immunosuppression
Plasmid HSP70i gene therapy	HSP70iQ435A	HSP70i in mutant form may inhibit endogenous HSP70i-induced immune system activation	Blocks endogenous innate immune activation
Agonists of Wnt signaling pathway	SKL2001	Stimulation of melanoblast proliferation and migration production of more melanocytes	Melanocyte regeneration
Tricholoroacetic acid	70% TCA along with microneedling	TCA-induced necrosis stimulates the proliferation of melanocytes through synthesis of melanocortins and their precursor molecule- Proopiomelanocortin (POMC)	Release of growth factors and inflammatory mediators
Platelet-rich plasma	Used in conjunction with laser, phototherapy, and surgical treatments	Restores normal cellular function and promotes growth and maturation of keratinocytes and melanocytes in skin	Epidermal repigmentation

Conclusion

Vitiligo is a debilitating disease that affects an individual's health, psychosocial well-being, and quality of life. Since the pathogenesis of vitiligo is complex, with multiple pathways that are intricately involved, using combination therapies for its treatment rather than targeting a single pathway can be suggested. Use of biologicals along with other novel drugs may prove beneficial to target the complex cytokine network involved in this disease. In the pursuit of conquering vitiligo, understanding it at a molecular, cellular, and systemic level is crucial to developing effective therapeutic strategies.

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