A Review: Vitiligo Pathogenesis and Treatment

ABSTRACT

A common skin disease called Vitiligo is characterized by loss of normal melanin in the skin which results in no white patches. The immune system targets the body's own cells and tissues in this type of disease. About 1-2% of the world population are affected by this disorder. Half of the affected individuals develop the disease before they are grown up. The current review focuses on the treatments and strategies based on therapies being developed for treating a variety of conditions. There are two types of surgical techniques available. There are three types of tissue grafts: full-thickness punch, split-thickness and suction blisters. The gold standard for the treatment of diffuse vitiligo is 7NB UVB radiation, which can be used with two recently introduced UVB sources that emit the same wavelength. This review summarizes the current knowledge. At this time the exact cause of vitiligo is still unknown, the purpose of this review is to describe the applications of various treatment used to treat vitiligo but there is no single cure. Because of its complexity, several therapeutic options are available to treat this disease.

Keywords: melanocytopenic, PUVA, NB UVB, Vitamin D analogues,Tissue grafts and cellular grafts, Xenon chloride (XeCl).

1. INTRODUCTION

The term vitiligo is derived from the Latin word vitilus, which means calf, and was first named by the Roman physician Celsus in the first century AD. Vitiligo is a widespread chronic skin condition that occurs when the cells responsible for producing pigment, known as melanocytes, are damaged or destroyed. This leads to the formation of smooth, non-scaly, chalky-white patches within the normal pigmented skin. White spots can manifest on the skin in various areas of the body. Similar patches can also be observed on the mucous membranes of the mouth and nose, the retina of the eye, and the membranous labyrinth of the inner ear. In some cases, the hair that grows in areas affected by vitiligo may change color and become white (1). The knowledge of the causes of vitiligo has greatly improved in recent times. It is now widely acknowledged as an autoimmune disorder. Metabolism and oxidative stress are closely linked to various diseases, such as cellular detaching diseases, and can be influenced by both hereditary and environmental factors [2]. The effects of vitiligo can be emotionally challenging and often have a substantial impact on daily life, so it should never be disregarded as a superficial or insignificant condition. According to a global consensus in 2011, the two primary forms of vitiligo identified were nonsegmental vitiligo (nsv) and segmental vitiligo (sv). The term "vitiligo" was selected to encompass all forms of the disease, including acrofacial, mucosal, generalized, universal, mixed, and rare variants. One of the key decisions reached by the consensus was to clearly differentiate vitiligo from other types of vitiligo, particularly considering the impact on prognosis [2]. Currently, there is a lack of comprehensive epidemiological data on vitiligo, as it is only available in certain regions worldwide, and there is no standardized method for data collection. Most research on

vitiligo is focused in Europe, South Asia, and certain regions of the United States, making it necessary to establish a centralized global resource for collecting and analyzing data on the disease's prevalence. Therefore, it is essential to have a thorough and current estimation of the prevalence of vitiligo in order to assess its impact on different populations and to gain a better understanding of its global burden (3).

2. Epidemiology

Among all the pigmentation disorders, vitiligo is the most common one. India exhibits the highest prevalence of the disease globally, with rates reaching up to 8.8%. In the United States, the prevalence of the condition is approximately 1%. Nevertheless, the most extensive epidemiological study was carried out in Denmark in 1977, revealing an incidence rate of 0.38%. According to the literature, approximately 1% of the global population is affected by vitiligo. Vitiligo affects both men and women equally, although it is often observed that women tend to report vitiligo symptoms earlier and more frequently, possibly due to societal perceptions that view vitiligo as a cosmetic issue or a stigma. The occurrence of vitiligo can happen at any point in a person's life. Nevertheless, in approximately 70% to 80% of cases, it manifests before the age of 30. Additionally, it is common for the onset of the disorder to occur before the age of 12 years, with up to 37% of patients experiencing it (4).

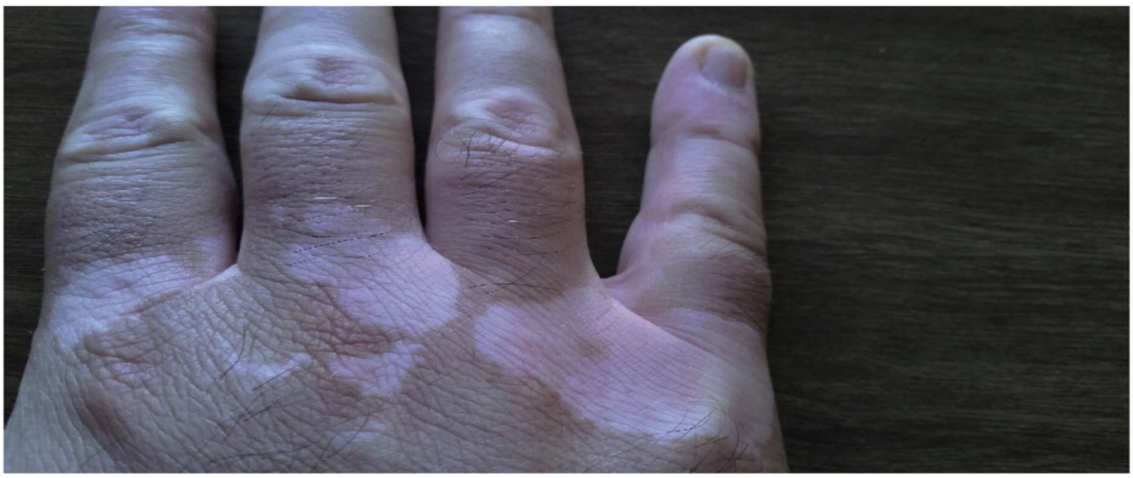

Fig. 1. Hypopigmented macules of vitiligo with sharply demarcated margins.

3. Pathogenesis

Vitiligo is a complex disorder marked by the loss of functional melanocytes. Various mechanisms have been suggested to explain the destruction of melanocytes in vitiligo, including genetic factors, autoimmune responses, oxidative stress, the production of inflammatory mediators, and mechanisms that lead to melanocyte detachment. Both the innate and adaptive immune systems appear to play a role in this process. However, none of these theories alone adequately account for the diverse phenotypes of vitiligo, and the overall impact of each mechanism remains a topic of discussion, though there is now general agreement on the autoimmune nature of the condition. The ongoing loss of melanocytes may involve multiple processes, including immune attacks and cell degeneration or detachment. The "convergence theory," also known as the "integrated theory," proposes that various

mechanisms may collaboratively act in vitiligo, leading to the destruction of melanocytes and ultimately resulting in the same clinical manifestation. Initially, it was thought that non-segmental vitiligo (NSV) and segmental vitiligo (SV) had distinct underlying pathogenic mechanisms, due to their differing clinical presentations, with the neuronal hypothesis or somatic mosaicism being favored for the segmental variant. However, recent findings indicate that both SV and NSV may share a common inflammatory pathogenesis. This process appears to be multistep, beginning with the release of proinflammatory cytokines and neuropeptides triggered by external or internal injuries, followed by vascular dilation and an immune response. Some researchers have proposed that the nervous system plays a role in the pathogenesis of vitiligo, which is termed the "neural hypothesis," based on the unilateral distribution pattern observed in SV. However, this distribution does not closely resemble that of any other skin condition, and it seldom aligns with a dermatomal pattern. Furthermore, there is insufficient evidence to substantiate this hypothesis. Additionally, melanocyte-specific T-cell infiltrations, similar to those found in NSV, have been observed in SV, further indicating that autoimmunity may also play a role in its development (5).

3. CLINICAL TYPES

1. Generalized Vitiligo: This is the most prevalent form characterized by bilateral, symmetrical depigmentation affecting the face (including periorificial regions), neck, torso, extensor surfaces, bony prominences, axillae, hands, wrists, legs, orifices, and mucosal areas.

2. Focal Vitiligo: This type presents as localized depigmented macules that do not follow a dermatomal pattern.

3. Segmental Vitiligo: This type is characterized by an asymmetrical distribution that follows dermatomal patterns.

4. Universal Vitiligo: This condition refers to the loss of pigment across the entire body surface. The most common observation in affected individuals is depigmented lesions in areas exposed to sunlight. (6).

4. Treatment

Vitiligo remains a medical problem as its pathogenesis remains unclear. Many doctors have explored creams or medications, medical imaging, camouflage therapy, surgical procedures, depigmenting agents, or a combination of the above to treat this disease. Unfortunately, when we reviewed the literature, we could not find many good studies evaluating the effectiveness of these treatments in children. In addition, most authors have to present their findings from adult literature, which is still far from good. For these reasons, when deciding when and how to treat vitiligo in this age group, various treatment methods should be recommended and the opinions of patients and parents should be taken into account (7).

Traditional treatment of vitiligo depends on the type and extent of the disease and the time of its onset. In stable non-segmental vitiligo affecting less than 10% of the body surface, it is indicated to proceed with local highly effective corticosteroids and local calcineurin

inhibitors. In cases of diffuse disease, narrowband (NB)-UVB phototherapy is recommended [8,9]. In cases of solid segmental vitiligo, it is viable to proceed both with centered topical remedies (excessive-potency corticosteroids and calcineurin inhibitors) or phototherapy and surgical therapy with autologous transplantation of wholesome melanocytes into the depigmented regions [8,9,10]. In unexpectedly revolutionary instances, systemic treatment with glucocorticoids more or much less mixed with NB-UVB is indicated [8,9,10]. As changed into noted in advance, new pathogenetic know-how has allowed the development of numerous therapies for vitiligo. The most recent ones might be reviewed here.

4.1. Afamelanotide

Afanotide is a compound of the important melanogenic molecule _-MSH, with a longer lifespan and better affinity for the target melanocortin 1 receptor (MC1R). By acting on this receptor, afanotide not only promotes melanogenesis and the conversion of eumelanin to melanosomes, but also stimulates cells such as neutrophils or lymphocytes, which can express the melanocortin 1 receptor (MC1R) and therefore also contribute to the inflammatory microenvironment altered by vitiligo lesions [11]. The drug is administered as a subcutaneous, biodegradable, controlled-release implant [12]. There are few studies on the efficacy and safety of afanotide in the treatment of vitiligo. The most important of these is the randomized controlled multicenter study conducted by Lim et al. The authors selected patients aged 18 years and above diagnosed with Fitzpatrick phototypes III to VI and covering 15% to 50% of total BSA (body area) without vitiligo [13]. Twenty-eight patients were randomized to receive combination therapy with afanotide plus narrow-band UVB phototherapy (NB-UVB) and 27 patients were randomized to receive monotherapy with NB-UVB phototherapy. Both groups received NB-UVB phototherapy for 1 month, then 16 mg afanotide every month for 4 months while the first group continued with NB-UVB phototherapy, while the second group continued with NB-UVB phototherapy alone. The study found that the combination therapy of afanotide plus phototherapy (48.64% repigmentation) was better than phototherapy alone (33.26% repigmentation) ($p < 0.05$). In particular, the combined treatment group achieved greater and faster pigmentation on the face and upper extremities (the most visible and visible part of the skin). Faster pigmentation was observed in subjects with phototypes IV-VI who received combination therapy than in those who received monotherapy, while in the case of phototype III there was no different correlation between the two groups. The treatment has few side effects, particularly erythema, nausea, and generalized skin hyperpigmentation, and is generally beneficial, although two patients had to repeat the trial because of vision loss due to hyperpigmentation [14]. A similar study was conducted a few years ago by Grimes et al. on a small group of patients. The authors present preliminary results of 1 month of NB-UVB phototherapy in 4 patients with generalized vitiligo. Afanotide 16 mg subcutaneous implants were administered for 4 months starting from the second month. The confluent areas repigmented and improved the progression of the process. Finally, another randomized controlled trial was conducted to test afanotide in combination with NB-UVB phototherapy (afanotide plus NB-UVB implant versus NB-UVB phototherapy). In 18 patients who received NB-UVB phototherapy every 2 weeks and afanotide every month for 7 months, the combination treatment outperformed placebo with a reduction in mean white area index including all scores, head and neck, hands,

upper body, and lower extremities on day 140 [16]. As mentioned above, the greater efficacy of afanotide in dark-skinned patients may be explained by the strong MC1R response in these patients. Clinuvel completed another similar study in patients with a poorer prognosis in Europe in December 2012, but the results have not yet been published or are at least not available on ClinicalTrials.gov [17]. However, another clinical trial, also conducted by Clinuvel, is ongoing to evaluate the efficacy and safety of afanotide in the treatment of facial vitiligo and is expected to conclude in August 2023 (ClinicalTrials.gov logo Symbol: NCT05210582). In conclusion, more data are needed to evaluate the efficacy and safety of afanotide. This molecule is now promising as a treatment with light therapy. In fact, only phototherapy can cause melanocyte differentiation. Afanotide can only increase the amount and extent of pigmentation in people who respond to phototherapy, but it cannot cause melanocyte differentiation and does not improve the response. In addition, more information is needed on the optimal dose and frequency of application, the long-term response to this molecule and its effects on phototypes I and II. Further studies are needed to confirm the results examined in our review and to demonstrate other potentials and limitations of this molecule [18,19].

4.2. Prostaglandins and Analogues

Prostaglandins (PG) are polyunsaturated essential fatty acids released from cell membrane phospholipids and play a role in melanin synthesis [20]. Prostaglandin F2 (PGF2_) and prostaglandin E2 (PGE2) are the main PGs: they are produced in the skin and act on keratinocytes, Langerhans cells and melanocytes, stimulating melanocyte proliferation and influencing their response to vascular stimulation. In addition, they promote the activity and expression of tyrosinase, the rate-limiting enzyme for melanin synthesis [20, 21]. In contrast, PGE2 production is reduced in patients with vitiligo due to oxidative stress, leading to melanocyte damage and glutathione depletion [22]. As a result of this treatment, patients with localized and stable vitiligo (plaques covering <5% of body surface area) may benefit from PGE2 treatment. First, in a series of 56 patients with stable vitiligo treated with PGE2 0.25 mg/g gel twice daily for 6 months, repigmentation was observed in 40 patients (71%), of whom 22 (39%) developed pigmentation, and 8 patients developed lip burning [20]. Topical bimatoprost, a prostaglandin F2-alpha (PGF2_) analog approved for the treatment of glaucoma, was suggested to be used because of the observation of hyperpigmentation in the periocular skin as a result of increased melanin production and inadequate or insufficient eyelashes. . Therefore, Kapoor et al. found an increase in melanin granules in the skin in 2 patients [23]. Enlang et al. The efficacy of 0.03% bimatoprost eye drops in the treatment of vitiligo was tested in 10 patients, the drug was used twice daily for four months. Of the 10 patients, 3 patients had 100% pigmentation, 3 patients had 75% to 99% pigmentation, and 1 patient had 50% to 75% pigmentation. The face was the most common organ response [24]. In addition, a randomized, single-blind, self-controlled study evaluated the efficacy and safety of 0.01% bimatoprost compared with 0.01% tacrolimus ointment in 16 patients with 2 or more patches of vitiligo. In safe areas, twice daily for 12 weeks. Only 10 patients completed the study. At week 12, both groups showed a decrease in vitiligo area compared to baseline ($p < 0.05$), but there was no significant difference between the two groups [25]. Another randomized, double-blind, controlled proof-of-concept study evaluated bimatoprost 0.03% monotherapy and combination therapy with mometasone compared with mometasone

plus placebo in non-episodic vitiligo or non-faced areas. Thirty-two patients were enrolled and after 20 weeks none had a 50% to 75% relapse. However, follow-up analysis using a 25% to 50% relapse rate showed that patients treated with bimatoprost alone or in combination with mometasone had better results on the neck and trunk than patients treated with mometasone Pigmentation [26]. Similarly, latanoprost, a PGF2_ analog used in the treatment of glaucoma that can induce skin pigmentation in guinea pigs, has been evaluated as a topical treatment for patients with vitiligo [27–29]. The first study compared latanoprost with placebo (Group A), topical latanoprost with narrow band ultraviolet B (NB-UVB) (Group B), and their combination with NB-UVB in the same patients. 22 patients with bilaterally symmetrical vitiligo and stable for 3 months were included in the study, and the degree and degree of recurrence were evaluated after 3 months. The study found that latanoprost was superior to placebo and compared to NBUVB alone in reducing skin pigmentation. Additionally, latanoprost combined with NB-UVB was more effective than NB-UVB alone ($p < 0.05$) [27]. Additionally, a randomized, double-blind, comparative study evaluated the effectiveness of microneedling versus 0.005% latanoprost solution combined with NB-UVB phototherapy in the treatment of vitiligo. Fifty patients with bilateral local, stable, and without vitiligo were included in this study. Both nearly identical lesions were identified and treated with microneedling (12 times, two weeks apart), followed by 0.005% latanoprost solution on one side and placebo (saline solution) on the other side. All patients then received NB-UVB treatment for 6 months. Both treatments showed a clinical improvement with an increase in pigmentation from baseline ($p < 0.001$); Greater clinical improvement was seen in patients receiving latanoprost ($p < 0.002$). Vitiligo of the face, neck, and trunk causes more pain than vitiligo of the extremities or flanks. Side effects reported with microneedle-assisted application of latanoprost were few and minor, and no patients experienced any side effects [28]. Additionally, a study of 24 patients with vitiligo evaluated the efficacy of latanoprost compared with tacrolimus in combination with NB-UVB and microneedling in the recurrence of non-segmental vitiligo. The data suggest that the activity of latanoprost in inducing repigmentation is comparable to tacrolimus [29]. In terms of ongoing studies evaluating topical prostaglandin, one clinical trial (ClinicalTrials.gov identifier: NCT05513924) randomized 40 patients with stable vitiligo to receive topical 5-fluorouracil after skin microneedling or topical latanoprost. The primary endpoint was clinical pigmentation changes in vitiligo based on an international physician assessment. In summary, topical prostaglandins represent an alternative treatment for patients with vitiligo. Current evidence suggests that they are more effective when combined with other modalities such as skin microneedling and/or NBUVB phototherapy.

4.3. Janus Kinase Inhibitors

The Janus kinase family includes JAK1, JAK2 and TYK2, which are involved in the JAK/STAT signaling mechanism. It plays an important role in mediating many extracellular signals that control growth, differentiation and cell migration functions. JAK-STAT inhibitors promote Sonic Hedgehog and Wnt signaling, which are involved in epidermal pigmentation, particularly the migration, growth and differentiation of melanocytes [30–34]. In addition, INF- has been shown to induce CXCL10 production, thereby promoting the migration of autoreactive T cells into the skin [42]. Therefore, since JAK inhibitors have been shown to block IFN signaling, they should prevent the accumulation of CD8+ T cells and

depigmentation of lesions [41, 31, 32]. Tofacitinib and ruxolitinib are two JAK inhibitors used in the treatment of rheumatoid arthritis and myelofibrosis, respectively, and there are reports of their efficacy in vitiligo [33,34]. Phan et al. also performed a content analysis of nine studies. They found that 26 (58%) out of 45 patients treated with tofacitinib and ruxolitinib had a good response (>50% pigmentation), 10 (22%) had a partial response (<50%/partial pigmentation), and 9 (20%) did not respond to treatment [35]. Vitiligo facialis showed the best response. In addition, topical tofacitinib has been shown to be effective in mouse models. It is worth noting that the treatment of white mice was completed in a short time, thus reducing the total dose. This may indicate that the use of dermal and transdermal agents may help to reduce side effects and treatment costs [36]. In the first open-label study, topical ruxolitinib was shown to be effective in facial vitiligo [37]. In a subsequent randomized study, ruxolitinib cream (1.5% twice daily, 1.5% once daily, 0.5% once daily, or 0.15% once daily) was compared with: A comparison with placebo was conducted in 157 elderly patients with vitiligo, BSA at least 3% and facial involvement at least 0.5% [38]. After 24 weeks, both patients receiving ruxolitinib 1.5% twice daily and ruxolitinib once daily experienced a final 50% improvement in facial vitiligo area score compared to placebo (45%), 50%, and 3%, respectively. The treatment was generally well tolerated, with application site pruritus and acne being the most common clinical manifestations, occurring in 3% to 19% and 3% to 18%, respectively. Ruxolitinib is currently the only JAK inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of non-segmental vitiligo in patients over 12 years of age. Baricitinib is a selective JAK1/2 inhibitor approved for the treatment of rheumatoid arthritis and atopic dermatitis [30]. It inhibits the signaling of various proinflammatory cytokines. To date, there is only 1 clinical case describing hyperpigmentation in a patient with vitiligo receiving 4 mg/day baricitinib. A phase 2 study is currently ongoing in which patients receive a combination of 4 mg/day baricitinib and phototherapy [39]. Ifidancitinib is another dual JAK1/3 inhibitor used to treat alopecia areata. It is currently in phase II clinical trials for the treatment of vitiligo [31]. Ritlecitinib is an irreversible JAK3 and tyrosine kinase inhibitor currently used in the treatment of rheumatoid arthritis. Its efficacy and safety are currently being evaluated in combination with the TYK2/JAK1 inhibitor brepocitinib in the treatment of vitiligo with phototherapy [31]. Cerdulatinib is a dual SYK/JAK kinase inhibitor whose safety and tolerability are being evaluated in a topical application for the treatment of vitiligo (0.37% cerudulinib gel BID) [31]. Delgocitinib is a JAK inhibitor that has been shown to be effective in the treatment of vitiligo in two cases reported in the literature. Particularly in both cases, better performance was observed for lesions in the neck region compared to the elbow. This may be due to differences in skin thickness, chronic disease, and sunlight exposure in the two regions [40].

5. Conclusion

Vitiligo, an autoimmune disease that targets pigment cells, represents a major research challenge for those interested in melanocyte biology and pigmentation disorders. However, more research is needed. Over the past few years, significant advances have been made in understanding the pathways and multifactorial pathogenesis of vitiligo. The current theory is that organ, neuronal and/or biochemical skin disorders cause autoimmune melanocyte destruction and patients may suffer from certain genetic alterations and polymorphisms. It

still needs to be clarified how different pathogenic mechanisms cause vitiligo subtypes. Although there is currently no cure for vitiligo, topical steroids will be the first treatment option for most patients, and a variety of medical and surgical options, including a combination of the two, have been shown to improve patients' disease status and quality of life.

6. CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest towards the publication of this article.

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8. Refrence

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