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Vitiligo: Highlights on Pathogenesis, Clinical Presentation and Treatment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Vitiligo is a common acquired skin depigmentation that affects people of all races, but is significantly more disfiguring in black individuals. The exact cause of vitiligo is unknown. It is believed that an autoimmune process targeting melanocytes mediates its pathogenesis. In accordance with this hypothesis, histopathological examinations of vitiliginous skin have revealed the absence of melanocytes.

Multiple autoantibodies against melanocyte antigens, including various enzymes and other substances, have been detected in the sera of some vitiligo patients. Twenty to thirty percent of patients were reported to have a family history of the disease, suggesting that genetic factors play a role. Despite this, a substantial proportion of vitiligo sufferers have neither a family history of vitiligo nor a history of other autoimmune diseases. As a result, numerous alternative hypotheses have been proposed to explain the underlying causes of this disorder, such as a weak defence against the toxic effects of free radicals and exposure to industrial pollutants.

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The most frequently prescribed treatments for vitiligo are systemic and topical phototherapy, immunomodulators such as corticosteroids, calcineurin inhibitors, and vitamin D analogues, as well as cosmetics that can camouflage the condition and improve quality of life. Other forms of treatment include surgical grafting and depigmenting procedures.

Keywords: Vitiligo; melanocytes; autoimmunity; clinical presentation; topical phototherapy.

1. INTRODUCTION

"Vitiligo is a pigmentary disorder of the skin characterised by macules and patches of depigmentation that are circumscribed. It is a progressive disorder characterised by the selective destruction of some or all melanocytes in the affected skin. Although vitiligo may be more noticeable in patients with darker skin, it has no racial or ethnic preference". [1] It is the most prevalent pigmentary disorder, occurring worldwide with an incidence rate between 0.2% and 2%, regardless of age, race [2], ethnicity, or skin colour. [3] Both genders are affected equally [2]. A female preponderance for vitiligo has been reported in some studies [2,4] but it is not statistically significant, and the discrepancy has been attributed to an increase in female patients reporting cosmetic concerns. [2] "It typically begins in childhood or early adulthood, with a peak onset between the ages of 10 and 30, but it can occur at any age" [2].

2. VITILIGO PATHOGENESIS

- **Pathogenesis of non-segmental vitiligo**

"The pathogenesis of vitiligo is multifactorial and polygenic. It has both genetic and non-genetic influences. Although numerous hypotheses have been proposed regarding the pathogenesis of vitiligo, its exact cause remains unknown. In accordance with generally accepted principles, vitiligo skin lacks functional melanocytes and loses histochemically identifiable melanocytes due to their destruction. However, the destruction is likely a gradual process that results in a decline of melanocytes. Regarding the destruction of melanocytes, the following theories exist: autoimmune mechanisms, cytotoxic mechanisms, neural mechanisms, oxidant-antioxidant mechanisms, intrinsic melanocyte defects, biochemical, and viral theories" [5].

2.1 Autoimmune and Cytotoxic Hypotheses

The dysfunction or destruction of melanocytes is caused by abnormal immune surveillance. The autoimmunity theory proposes that the destruction of vitiligo melanocytes is due to alterations in humoral and cellular immunity. [6,7] Given that nonsegmental vitiligo (NSV) is more frequently associated with autoimmune conditions than segmental vitiligo, this theory is relevant (SV). Therefore, diagnosing NSV in a patient with a family history of autoimmune disease may necessitate a more comprehensive evaluation. "Certain disorders, such as Hashimoto thyroiditis, Graves' disease, Addison disease, diabetes mellitus, alopecia areata, pernicious anaemia, inflammatory bowel disease, psoriasis, and autoimmune polyglandular syndrome, have been linked to vitiligo for these reasons" [9].

The role of humoral immunity: "Antibodies to melanocytes that are uncommon in healthy individuals have been discovered in the sera of vitiligo patients. These antibodies appear to be related to the severity of the disease, being present in more than 90 percent of patients with extensive depigmentation and in 50 percent of those with minimal lesions. The tenth characteristic of these antibodies is that they belong to the IgG class. IgG and C3 deposits have been observed sporadically in the basal membrane zone of lesional skin, which correlates with the observation that IgG binding to cultured melanocytes increases with disease activity and extent. In addition, research has shown that IgA levels of antipigment cell membrane antibodies correlate with disease activity, indicating a close relationship with anti-melanocyte IgA antibody levels" [6,11].

"IgG anti-melanocyte antibodies may also play a role in the stimulation and inappropriate expression of human leukocyte antigen (HLA-DR) and induction of intercellular adhesive molecule1 (ICAM-1) on melanocytes, as well as an increase in IL-8 production. Thus, major histocompatibility complex II (MHC II) molecules expressed in melanocytes can present antigens to CD4+ cells, enabling an immune response, and ICAM-1 may play a crucial role in immunological and inflammatory responses that result in melanocytotoxicity" [12].

"A few specific antigens have been identified through the use of various techniques, including tyrosinase (a melanocytic enzyme), tyrosinase-related protein (TRP) 1, 2, and Melan A/MART 1 Melan-A (melanocyte antigen) /MART1 (melanoma antigen recognised by T cells 1). Antibodies have been shown to target the melanocyte transcriptor factor (SOX10) and the melanine-concentrating hormone receptor 1 (MCHR1) with varying frequency in vitiligo patients" [11,13].

The role of cell-mediated immunity: Biopsies of vitiligo patients' skin have revealed that perilesional areas are rich in inflammatory cells. This perilesional infiltration is composed of CD8+ and CD4+ T cells, with a frequently augmented CD8+/CD4+ ratio. [14] Their cytokine secretion profile is predominantly Type-1-like, with secretion of tumour necrosis factor- (TNF-) and interferon (IFN-). IFN- enhances T-cell trafficking to the skin in particular by increasing ICAM-1 expression. The expression of the cutaneous lymphocyte-association antigen by CD8+ cells, a skin-homing receptor that could recruit T cells from peripheral circulation to affected skin, is another significant finding. High frequencies of Melan A/MART 1-specific CD8+ T cells have been detected in the perilesional skin and peripheral blood; these cytotoxic T cells demonstrated in vitro anti-melanocyte cytotoxic activity and skin-homing capacity, which appears to correlate with disease extension and severity. [17] It is established that depigmentation can advance in the absence of regulatory T cells (Treg). Immunohistochemistry has revealed decreased numbers of Treg cells in non-lesional, perilesional, and lesional vitiligo skins, as well as decreased expression of the skin homing chemokine ligand 22 (CCL22) in vitiligo skin. This may explain the failure of circulating Treg cells and their reduced skin homing due to the loss of functionality, which may perpetuate the vitiligo-associated reactivity against melanocytes [18].

The role of cytokines in vitiligo: "The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway plays crucial roles in orchestrating the immune system, particularly cytokine receptors, and can modulate T helper cell polarisation. This pathway is controlled by a variety of regulator proteins, such as suppressors of cytokine signalling, protein inhibitors of activated STATs, and protein tyrosine phosphatases that determine the initiation, duration, and termination of signalling cascades. In T helper cells, dysregulation of the JAK-STAT pathway may result in a variety of immune disorders. Ongoing research identifies additional regulators of the JAK-STAT pathway and develops innovative therapeutic strategies" [19].

2.2 Neural Hypothesis

A neurochemical mediator inhibits melanin production or destroys melanocytes. This hypothesis proposes that melanocytic apoptosis can be explained by an altered response of pigment cells derived from the neural crest to exposure to neuropeptides, catecholamines, or catecholamine metabolites, in conjunction with a generalised increase in the sympathoadrenal system. [21] "The presence of the unilateral pattern of distribution in SV forms, the symmetrical, bilateral distribution of lesions in NSV forms, and the loss of pigmentation in areas with transverse myelitis or diabetic neuropathy generated the neural mechanism hypothesis". [21] Neurochemical mediators such as norepinephrine and acetylcholine that are secreted by nerve endings are toxic to melanocytes. [22] Patients with vitiligo have abnormal neuropeptide levels in their perilesional skin and blood. [23] The neuropeptide Y released by exogenous stimuli, such as trauma (e.g. Koebner phenomenon), or endogenous stimuli, such as stress, alters the balance of neuropeptides in vitiliginous skin [16,24].

2.3 Oxidant-antioxidant and Melano-cytorrhagy Mechanisms

Cytotoxic precursors to melanin synthesis, such as dopa and dopachrome, accumulate in melanocytes and induce melanocyte death (self-destruction). Koebner phenomenon could be one of the adhesion defects of melanocytes associated with inadequate E-cadherin expression. In vitiligo, a change in E cadherin expression level prior to the development of depigmentation is associated with a loss of melanocyte adhesion during oxidation or melanocyte stress (melanocytorrhagy theory). A study compared "the immunohistochemical expression of Discoidin Domain Receptor-1 (DDR1, which is the main protein that adheres melanocytes to the epidermal basal layer) in lesional and non-lesional skin of vitiligo patients to controls in order to determine its potential role in the pathogenesis of vitiligo. Expression of DDR1 was significantly reduced in lesional vitiligo skin compared to non-lesional skin. In addition, both lesional and non-lesional DDR1 expression was reduced in vitiligo skin compared

to controls. Therefore, reduced DDR1 expression may be implicated in the impaired melanocyte adhesion process that contributes to the pathogenesis of vitiligo. In vitiligo, there is an increase in multiple oxidative stress markers and a breakdown of the antioxidative mechanism, which leads to immune-mediated melanocyte destruction" [28].

2.4 Intrinsic Defect of Melanocytes

"Melanocytes have an inherent abnormality that inhibits their growth and differentiation in environments that support normal melanocyte growth and differentiation. Depending on the progression of the disease, melanocytes in the same patient may be affected to varying degrees. They exhibit various abnormalities, such as abnormal rough endoplasmic reticulum or deficiency of unidentified melanocyte growth factors such as bFGF, as well as a reduction in the number of melanocytes expressing the c-kit receptor in lesional skin. Melanocytes require constant keratinocyte-derived c-kit stimulation for their maintenance [31]; therefore, weak expression of keratinocyte-derived factors, such as SCF, may result in passive melanocyte death and may explain the Koebner phenomenon" [32].

2.5 Biochemical Hypothesis

ROS are small reactive molecules that play essential roles in the regulation of numerous cellular functions, chemical and biological processes. Under environmental stress, a dramatic increase in ROS levels can result in oxidative stress, leading to cellular damage or triggering various diseases, such as neurological disorders, cardiovascular diseases, or various forms of inflammation and cancer [33].

"Mitochondria appear to be the primary inducers of reactive oxygen species, and vitiligo patients have altered mitochondrial function. Membrane lipids and cellular proteins are compromised by oxidative stress. Additionally, the synthesis and recycling of biopterin are altered, resulting in increased oxidative stress and cell damage. ROS overproduction triggers the unfolded protein response and induces melanocytes to release exosomes containing melanocyte-specific antigens, microRNAs, heat shock proteins, and damage-associated molecular patterns (DAMPs). These exosomes transport vitiligo-target antigens to nearby dendritic cells and stimulate their maturation into effective antigen-presenting cells. This is followed by the activation of T helper 17 cells by cytokines and chemokines and the dysfunction of T regulatory cells. Lesions of vitiligo contain CD8+ T cells that produce multiple cytokines, including IFN-. The activation of the JAK-STAT pathway and skin secretion of CXC chemokine ligand 9 (CXCL9) and CXC chemokine ligand 10 (CXCL10) by IFN- binding to its receptor. CXCL9 promotes the bulk recruitment of melanocyte-specific CD8+ T cells to the skin via the cognate receptor chemokine receptor type 3 (CXCR3), whereas CXCL10 promotes their localization within the epidermis and their effector function, which increases inflammation via a positive feedback loop" [34].

2.6 Viral Hypothesis

Hepatitis C virus (HCV) is a virus that is both hepatotropic and lymphotropic. This agent can stimulate the onset of a variety of autoimmune diseases. Vitiligo is strongly associated with chronic HCV infection and autoimmune hepatitis. This relationship between HCV infection and vitiligo, in which it is believed that autoimmune mechanisms play a role, has not yet been clarified. [35] Akcan et al. [36] reported a low seropositivity for hepatitis B virus in vitiliginous patients. A previous or concurrent infection with cytomegalovirus may contribute to the etiopathogenesis or progression of vitiligo. [36, 37] "In addition, other viruses, such as Epstein-Barr virus, hepatitis E virus, herpes virus, and human immunodeficiency virus, have also been linked to vitiligo" [37,38].

2.7 Zinc-α2-Glycoprotein Deficiency Hypothesis

Bagherani et al. [39] and Yaghoobi et al. [40] identified for the first time a possible association between Zinc-2-Glycoprotein (ZAG) and vitiligo [39,40]. "It was hypothesised that the pathogenesis of vitiligo could be attributed to a decrease in ZAG, as ZAG is a keratinocyte-derived factor that influences melanocyte proliferation and dendrity. Therefore, ZAG could be considered a marker of cell maturation and differentiation" [41]. In addition, a chronic detachment of melanocytes is essential to the pathogenesis of vitiligo. In the absence of ZAG, melanocyte adhesions to the other cells in the epidermis will be impaired. It has been suggested [40,42] that zinc can precipitate ZAG. Thus, zinc's efficacy in treating vitiligo is dependent on its ability to precipitate circulating ZAG at the vitiligo site [40,43].

2.8 Integrated Theory (Conversion Theory)

Despite the attractiveness of each of the aforementioned hypotheses, it is likely that vitiligo results from the combination of these pathogenic mechanisms. The majority of experts concur that vitiligo may be a syndrome with a multifactorial aetiology, as opposed to a single entity [44].

- **Pathogenesis of segmental vitiligo:**

Previously, the pathogenesis of SV was attributed to the "neurological theory" [45] Recent studies have shown, however, that SV is more closely associated with cutaneous mosaicism than with neural or dermatomal distribution. [46] Somatic mutations in melanocytes may result in intrinsic abnormalities that activate the stress and autoimmune pathways involved in the pathogenesis of vitiligo. Similarly to the NSV, melanocyte-specific T cells have been found infiltrating the SV, confirming this further. However, identification of such somatic mutations in SV melanocytes is an area requiring additional study [47].

3. VITILIGO CLINICAL PRESENTATION

3.1 Physical Examination

Almost always, a clinical diagnosis of vitiligo is made through physical examination. Vitiligo is characterised by the appearance of depigmented macules or patches surrounded by areas of healthy skin. These macules are chalky or milk-white in colour, with well-defined borders. Lesions may have a variety of shapes, including round, oval, and linear. The edges could be convex. The size of lesions has a tendency to increase centrifugally and at an unpredictable rate over time. A lesion's size could range between millimetres and centimetres. Lesions on individuals with lighter skin tones may not be visible without a Wood lamp. Face, neck, forearms, feet, dorsum of hands, fingers, and scalp are the most frequently affected areas by vitiligo. Lesions that occur on the face may exhibit a preference for periocular or perioral distribution. When vitiligo is widespread or generalised, lesions may also appear around the genital region, areola, and nasopharynx (GV). In addition, lesions can form in areas frequently exposed to trauma, such as bony prominences, elbows, and knees. The Koebner phenomenon is the development of vitiligo at sites of trauma, such as a burn, abrasion, or a cut. Twenty percent to sixty percent of vitiligo patients may develop koebnerization. On the body, vitiliginous macules may cause hair to lose its colour. This condition is known as leukotrichia, and it may indicate an unfavourable prognosis for regimentation therapy. The spontaneous regimentation of depigmented hair is extremely uncommon [49].

3.2 Clinical Classifications of Vitiligo

Vitiligo Global Issues Consensus distinguished SV from all other types of vitiligo, and the term vitiligo was defined to include all types of NSV. Mixed vitiligo, which occurs when SV and NSV coexist in the same patient, is a subtype of NSV (Table 1). Distinguishing SV from other forms of vitiligo was one of the most important decisions reached by the consensus, primarily due to its implications for prognosis [50].

i. Segmental vitiligo

Segmental vitiligo (SV) is distinguished by the presence of dermatomal or quasi-dermatomal macules that do not cross the midline. In terms of clinical characteristics, natural history, and therapeutic response, it differs from NSV. Unlike NSV, which predominantly affects adults, SV typically manifests during childhood. In SV, lesions grow rapidly in a limited area for a brief period of time and then stabilise, whereas the course of NSV is highly variable, with phases of progression, remission, and stability. [51] SV responds poorly to medical treatment, and surgical procedures are the preferred method of treatment. The distribution pattern of SV lesions is a defining characteristic of the virus. SV patterns are classified as dermatomal or quasidermatomal, blaschkoid, or acupuncture line-following [52,53].

ii. Non-segmental vitiligo

Non-segmental vitiligo (NSV) is an umbrella term for all forms of vitiligo that cannot be classified as segmental vitiligo (SV). Importantly, NSV is more strongly associated than SV with autoimmunity or inflammation markers, such as halo nevi and thyroid antibodies [54].

Table 1. Classification of vitiligo [50]

Type of vitiligo	Subtypes
NSV	Focal[1] Mucosal Acrofacial Generalized Universal Rare variants of vitiligo (leukoderma punctata, hypochromic vitiligo, follicular vitiligo)
SV	Focal[1] Unisegmental Bi- or multisegmental
Mixed (NSV + SV)	Concomitant occurrence of SV and NSV According to severity of SV
Unclassified	Focal at onset, multifocal asymmetrical nonsegmental, mucosal (one site),

[1] Can evolve into segmental (SV) or nonsegmental vitiligo (NSV).

Examples of NSV include the following:

- Focal vitiligo is defined as a small, isolated, depigmented lesion without an obvious distribution pattern that has not evolved over a one- to two-year period. It can develop into either SV or NSV. Mucosal vitiligo refers to a depigmented lesion consisting of a single or multiple mucosal sites on the buccal or genital mucosa. If more than one mucosal site is involved, the condition is classified as NSV. A single mucosal vitiligo lesion, however, is classified as unclassified vitiligo. Typically, acrofacial vitiligo affects the face and distal extremities. Involvement of fingers and facial periorificial sites, i.e. perioral and periorbital regions, is characteristic. This form can develop into a widespread or universal disease. Acro-facial vitiligo is typically resistant to treatment. [55] Generalized vitiligo (GV): macules or patches of depigmentation are bilateral, nearly symmetrical, and occur randomly over the entire body surface. It affects regions susceptible to friction, pressure, and/or trauma. It can begin in childhood or adolescence. Universal vitiligo is defined as the total or nearly total loss of body pigmentation. Recent descriptions of rare variants of vitiligo include hypochromic or minor vitiligo (observed in dark patients with partial facial and torso depigmentation), follicular vitiligo (involving depigmentation of hair without affecting the surrounding skin, at least initially), and dotted vitiligo (involving damage by dotted spots that can affect any skin area). The macules range in size from 1 to 1.5 mm, and if they do not coexist with vitiligo macules, they should be classified as "dotted leukoderma or leukoderma punctata" [34,56].

iii. Mixed vitiligo

Due to the coexistence of SV and NSV, it is believed that mixed vitiligo is a superimposed segmental manifestation of a widespread polygenic disorder. In this instance, SV typically precedes NSV by one to two years, and it is typically more resistant to treatment. Leukotrichia and the presence of halo nevi at the onset of vitiligo may be potential risk factors for the development of mixed vitiligo. Halo nevus or Sutton nevus is the loss of pigmentation surrounding an existing nevus, resulting in the appearance of a halo. The presence of numerous halo nevi is suggestive of an autoimmune response against pigment-producing cells, which in turn increases the likelihood of developing vitiligo [55,57,58].

3.3 Clinical Variants

Trichrome vitiligo is a clinical variant characterised by the presence of a narrow to broad intermediate colour zone between a vitiligo macule and the surrounding normal pigmented skin. Hann et al. [59] highlighted its clinical and histopathological characteristics and concluded that it may be an unstable form of vitiligo.

Cockade like vitiligo is a variant of trichrome vitiligo. A cockade is an oval-shaped emblem with distinct colours that is typically worn on a hat. Quadrichrome vitiligo is a subtype of vitiligo characterised by the appearance of a fourth colour (dark brown) at sites of perifollicular repigmentation in darker skin phenotypes. It is distinguished by a macular perifollicular or marginal pigmentation, which indicates repigmenting disease. Penta-chrome vitiligo is a rare form of vitiligo characterised by the sequential appearance of white, tan, brown, and blue-gray hyperpigmentation on top of normal skin. Those with darker skin phenotypes are more likely to develop this disorder. [62] Marginal inflammatory vitiligo: This extremely rare form of vitiligo is characterised by a raised, erythematous border in a vitiligo macule in addition to recurrent itching and/or burning. These changes could be brought about by aggressive treatment. It typically refers to vitiligo macules that can develop at the site of postinflammatory hypermelanosis. Ivkar et al. reported the appearance of extensive blue vitiligo in a patient with acquired immunodeficiency syndrome who simultaneously developed vitiligo and postinflammatory hyperpigmentation [64].

Halo nevus: It is a benign skin condition characterised by a central melanocytic nevus and a halo of depigmentation. It is caused by the body's immune response to the nevus, which can destroy the melanocytes in the surrounding skin, resulting in the appearance of a depigmented halo. There is an increase in the number of halo nevi in vitiligo patients. It is more prevalent in children and young adults of both sexes, particularly on the trunk, and less prevalent on the face, neck, and extremities [65].

3.4 Assessment of Vitiligo Activity

3.4.1 Vitiligo signs of activity score (VSAS)

The following clinical manifestations of vitiligo activity have been reported: In addition to itching, confetti-like lesions, Koebner's phenomenon, tri- and hypochromic areas (including poorly defined borders), inflammatory borders/areas, the presence of new lesions, the extension of old lesions, and the presence of new lesions are also indicative of atopic dermatitis. [66] This compels the vitiligo community to develop consensus-based definitions and a reliable scoring system (VSAS) to evaluate these clinical signs, as well as to design optimal trials to investigate their true predictive value. The VSAS global score ranges from 0 to 15 based on the presence of at least one visible clinical sign in each of 15 predefined areas [67].

Subscores can be generated by assigning a similar score (between 0 and 15) to each clinical sign individually. The grading reflects the following estimations of the intensity of each clinical sign within a specific area: [67]

a. c-VSAS (confetti-like lesions): This is the estimated number of depigmentations resembling confetti surrounding a representative lesion (grade one, 10; grade two, 10–50; grade three, > 50).

b. k-VSAS (Koebner phenomenon): This represents the presence (estimated number of signs) per delineated area: grade one, 1, grade two, 2–5, and grade three, > 5.

c. h-VSAS (hypochromic areas/borders): This is the presence (estimated number of signs) per demarcated area: grade one, 1; grade two, 2–5; grade three, > 5.

These grades correspond to "somewhat present" (grade one), "present" (grade two), and "very present" (grade three) (grade three). In addition to the grading per area, one 'global grade' (total body grade) per sign can be determined, which can be regarded as the grade that is most apparent on average for a particular sign [67] [Fig. 1, 2] [67].

3.4.2 Vitiligo disease activity score (VIDA)

The VIDA score was proposed by Njoo et al. [68] as an additional method for developing objective case selection criteria. It is a six-point scale that measures the disease's activity or progression based on the formation of new vitiligo lesions or the enlargement of pre-existing lesions over a time period ranging from less than six weeks to one year. It is proposed that vitiligo surgery should only be considered for patients with VIDA scores of -1 or 0 [68].

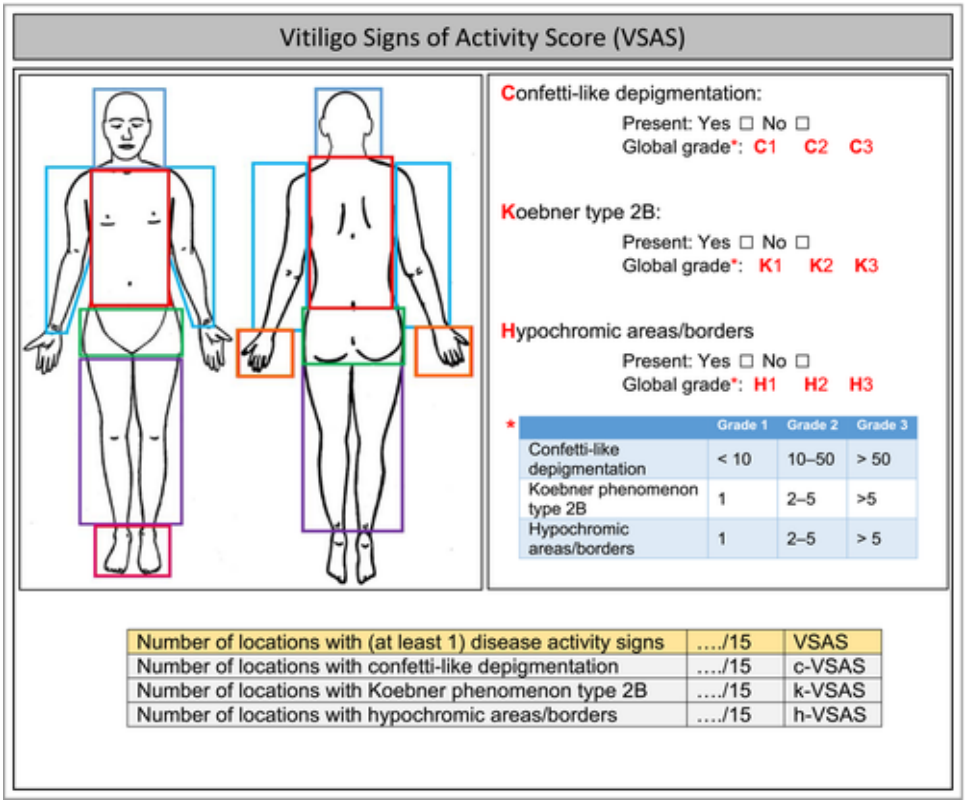

Fig. 1. Vitiligo Signs of Activity Score (VSAS) [67]

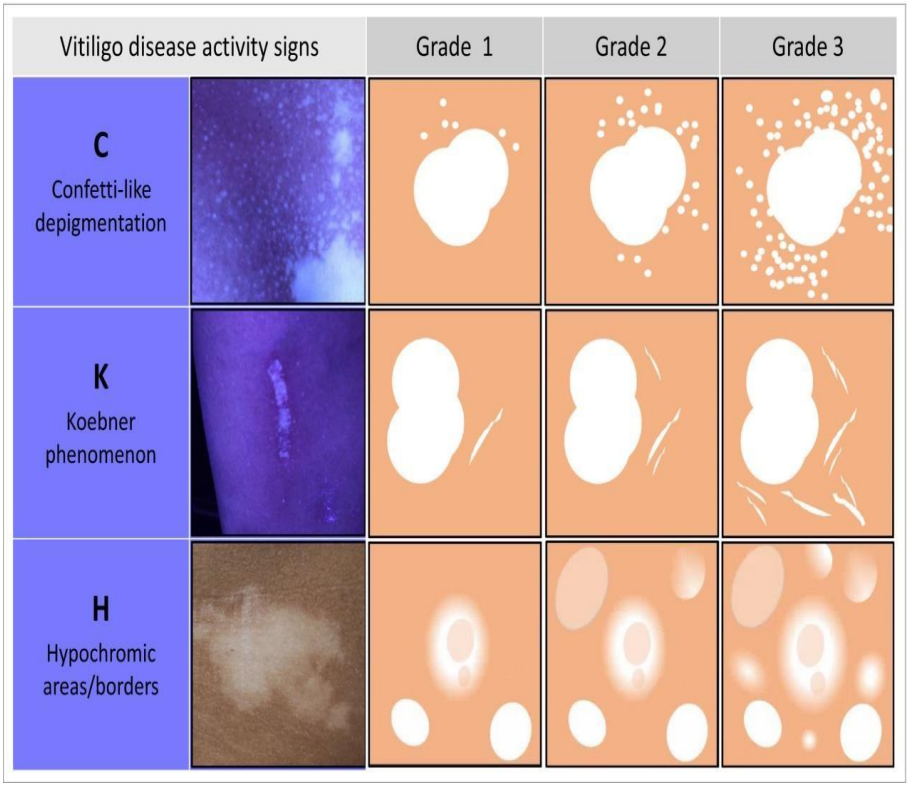

Fig. 2. Grading each sign (grade 1–3) in the Vitiligo Signs of Activity Score (VSAS). The clinical photographs represent an example of each sign [67]

3.4.3 Vitiligo area severity index (VASI)

Calculating the percentage of vitiligo involvement in terms of hand units. One hand unit (consisting of the palm and volar surfaces of all digits) is nearly equivalent to one percent of the total body surface area. The pigmentation level is estimated to the nearest of the following percentages:

- 100% - no pigment is present, complete depigmentation.
- 90% - specks of pigment can be seen.
- 75% - depigmented area more than the pigmented area.
- 50% -both pigmented and depigmented areas are equal.
- 25% - pigmented area more than the depigmented area.
- 10% - only specks of depigmentation can be seen [69,70].

The vitiligo area severity index (VASI) for each body area is calculated by multiplying the area of vitiligo in hand units by the degree of depigmentation present in each hand unit patch. VASI of the entire body = All body areas [Hand Units] [Depigmentation Residue [69].

3.4.4 Wood's light

It can be used for allowing the precise evaluation of the lesion's limits and characteristics, as well as for analysing possible subclinical lesions that are not evidenced by the phenomenon of reflection, but only by its fluorescence. For example, this case of vitiligo is more evident under Wood's lamp (detection of subclinical lesions) [71] [Fig. 3] [71].

Dermoscopy: Under dermoscopy, the preservation or loss of perifollicular pigment is a key indicator [72].

a. Dermoscopic features of unstable vitiligo:

Lesions characterised by perifollicular pigmentation, starburst, comet tail, salt-and-pepper, or trichrome patterns are more likely to be progressive or unstable in vitiligo lesions with irregular margins [73] [Fig. 4, 5] [73].

In clinically unaffected areas, dermoscopy reveals white, amorphous macules measuring around one millimetre in diameter. This characteristic, known as "tapioca sago," can be observed in the perilesional skin of active vitiligo patients; Jha et al. first described "tapioca sago." [72 73][Fig. 6] [73].

b. Dermoscopic features of stable vitiligo:

Perifollicular hypopigmentation, on the other hand, is characteristic of stable or remitting vitiligo. [Fig. 4] [73] Leukotrichia may also be detected in vitiligo that is stable and is associated with treatment resistance. Patients whose vitiligo is repigmenting as a result of treatment will demonstrate perilesional hyperpigmentation, intralesional or perilesional erythema, and telangiectasias [72].

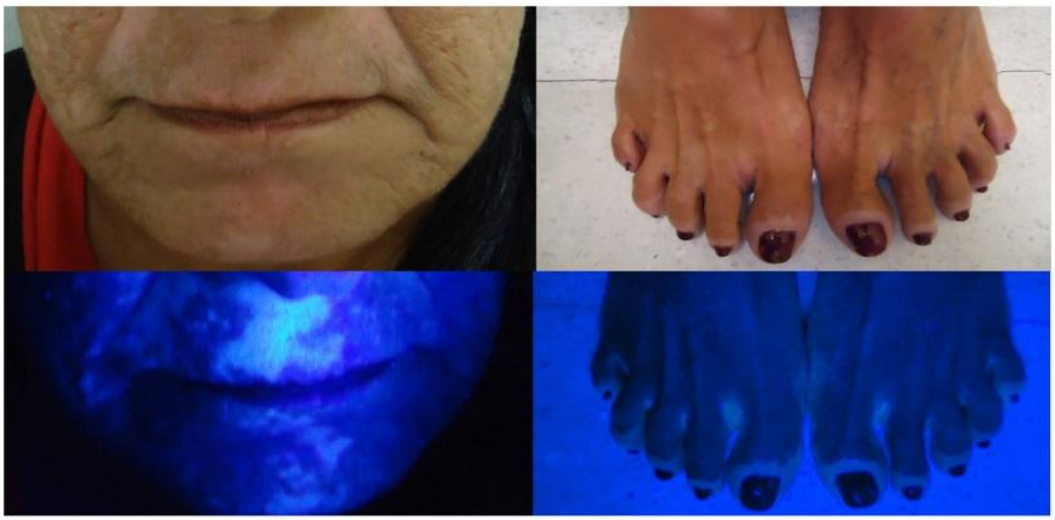

Fig. 3. Vitiligo lesions better evidenced under Wood's lamp than under visible light [71]

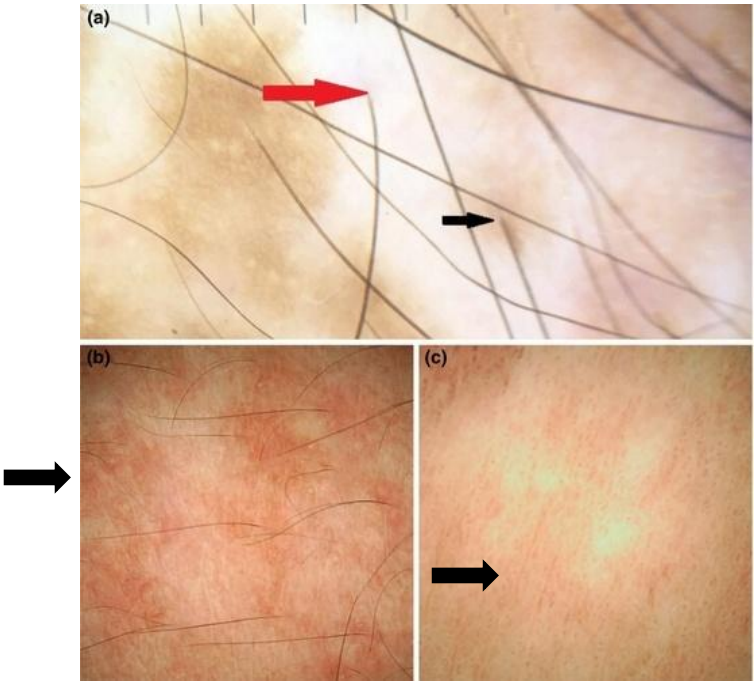

Fig. 4. Dermoscopic image from a vitiligo lesion (polarized ×10) showing (a) perifollicular pigmentation (black arrow) and perifollicular depigmentation (red arrow), and altered pigment network: (b) reduced pigment network, and (c) absent pigment network [73]

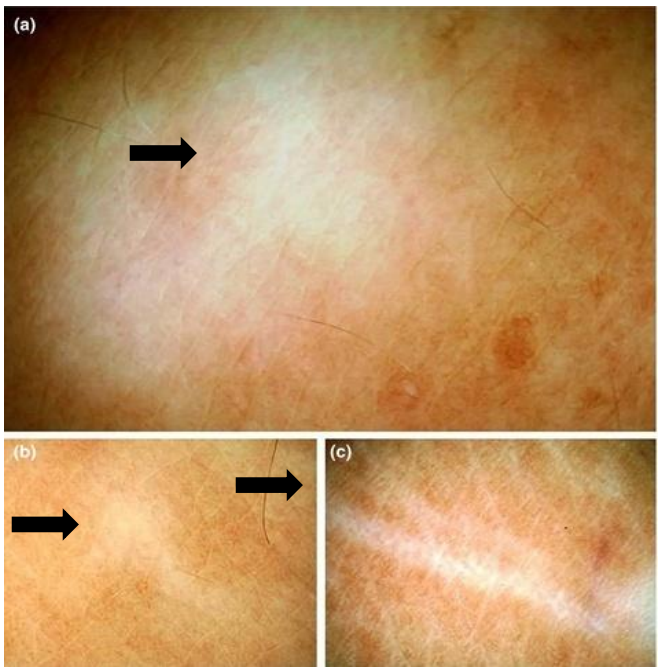

Fig. 5. Dermoscopic image (polarized ×10) from an active vitiligo lesion displaying (a) starburst pattern, (b) comet tail, and (c) micro-Koebner's phenomenon with a morphology distinct from comet tail [73]

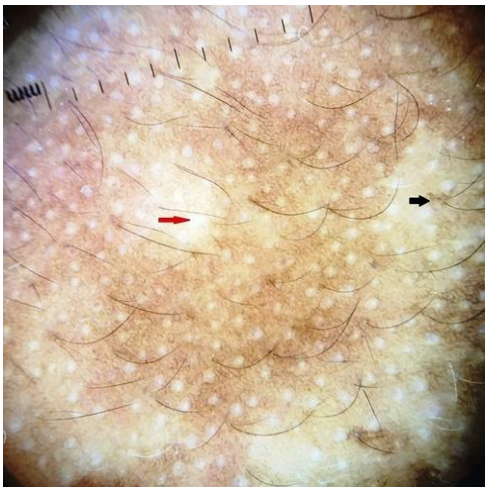

Fig 6. Dermoscopic image (polarized ×10) from the margin of an active vitiligo lesion showing tapioca sago appearance denoting white structureless areas less than 1 mm diameter in the clinically normal-looking perilesional skin. Areas of active vitiligo (red arrow) with relative preservation of perifollicular pigmentation (black arrow) are also appreciable [73]

3.6 Reflectance Confocal Microscopy (RCM)

In vivo RCM is a tool for repetitive imaging in real-time that provides non-invasive images with histological-like resolution. Active stage of vitiligo was characterised by apparent melanin loss in lesional skin, loss or disappearance of the bright dermal papillary rings normally seen at the level of the dermo-epidermal junction, unclear border between lesional and non-lesional skin, and dense infiltration of refractile inflammatory cells within the papillary dermis at the edge of vitiligo lesions. [74] In addition, research confirmed that highly refractile inflammatory cells within the papillary dermis at the edge of a vitiligo lesion may be a good indicator of the stability [75].

Stable vitiligo was characterised by a complete loss of melanin in lesional skin, a distinct border between lesional and normal skin, and the absence of inflammatory cell infiltration at the lesion margin [74].

3.7 Histopathological evaluation and immunohistochemical examination

Microscopic examination of lesional skin (H&E) reveals a total absence of functional melanocytes as well as loss of epidermal pigmentation, epidermal thinning, and dermal papillae flattening. At the margin of active vitiliginous lesions, superficial perifollicular and perivascular lymphocytic infiltrates may be observed, consistent with a cell-mediated process that damages melanocytes. Keratinocytes and melanocytes have been shown to undergo degeneration in both border lesions and adjacent skin. Active vitiligo lesions are typically characterised by epidermal spongiosis, basal vacuolar degeneration, and an increase in dermal melanophages. The loss of pigment and melanocytes in the epidermis is demonstrated by immunohistochemistry and Fontana-Masson staining [76].

Histochemical and immunohistochemical analysis confirm the presence of an increased number of CD8+ T lymphocytes at the periphery of vitiligo lesions. Given that CD8+ T cell-mediated melanocyte destruction is hypothesised to play a role in the pathogenesis of vitiligo, determining the status of lymphocyte infiltration by RCM could be advantageous for assessing vitiligo activity [77].

3.8 Test Grafting

The stability of the disease process in vitiligo is the most important factor in achieving a successful surgical outcome. Stability is defined as the absence of both new lesions and the spread of existing lesions for a limited time. However, there is no consensus on the exact period of stability, which, according to different authors, ranges from four months to two years. [78,79] Other methods of demonstrating stability, such as test grafting and VIDA scoring, have been proposed as the stability history provided by patients may not be entirely reliable. Falabella

et al. [80] proposed the test graft method, which consists of placing 6 to 8 punch grafts within a vitiliginous lesion and observing repigmentation over the subsequent twelve weeks. Repigmentation that extends beyond 1 mm from the edge of the test graft indicates a positive test and is considered an indicator of stability. However, its utility has been questioned because it has been observed that the minigraft test is positive even when the disease is unstable or active, and because the test may only confirm the stability of the lesion tested and not necessarily the disease process in the patient [80].

4. VITILIGO ASSOCIATIONS

In addition to the skin, pigment cells are found in the uveal tract, retinal pigment epithelium, leptomeninges, and inner ear. Therefore, it is not surprising that the process that destroys melanocytes in the skin can also affect diverse tissues including the eye, the ear, and the central nervous system. Vitiligo is commonly associated with autoimmune disorders, with thyroid abnormalities being the most prevalent. Vitiligo typically occurs before thyroid dysfunction. It may be prudent to screen for thyroid dysfunction and antibody levels in paediatric patients with vitiligo, given the high prevalence of thyroid dysfunction in NSV patients. Multiple autoimmune syndrome is the combination of at least three autoimmune diseases in the same patient (MAS). Approximately 25% of patients with autoimmune diseases are susceptible to developing additional autoimmune diseases. Multiple autoimmune syndrome can be divided into three groups based on the frequency of their interrelationships: type 1, type 2, and type 3. Myasthenia gravis, thymoma, polymyositis, and giant cell myocarditis are included in Type 1 MAS. Type 2 MAS is characterised by the presence of Sjogren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, scleroderma, and autoimmune thyroid disease. Autoimmune thyroid disease, myasthenia gravis and/or thymoma, Sjogren's syndrome, pernicious anaemia, idiopathic thrombopenic purpura, Addison's disease, type 1 diabetes mellitus, vitiligo, autoimmune hemolytic anaemia, systemic lupus erythematosus, and dermatitis herpetiformis comprise Type 3 MAS. The development of MAS has been linked to genetic, infectious, immunologic, and psychological factors. [83] Patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy can have vitiligo (APECED). In this genetic syndrome, endocrine cells are destroyed by autoantibodies. APECED is a rare autosomal recessive disease caused by mutations in the gene encoding the immune system regulator (AIRE gene). The disease's clinical spectrum includes a variety of autoimmune endocrine and non-endocrine manifestations, which may result in acute metabolic alterations and eventually life-threatening events. At least two components of the classic triad, including chronic mucocoutaneous candidiasis, chronic hypoparathyroidism, and Addison's disease, define the clinical diagnosis. Hypergonadotropic hypogonadism, alopecia, vitiligo, autoimmune hepatitis, Type 1 diabetes, and gastrointestinal dysfunction are additional common symptoms of the disease. APECED typically starts during childhood. Depigmentation resembling vitiligo can occur in patients with malignant melanoma,[86] which is thought to be the result of a T-cell–mediated reaction to antigenic melanoma cells and cross-reactivity to healthy melanocytes. The majority of patients with melanoma or vitiligo develop antibodies to antigens present on both melanocytes and melanoma cells. These results provide support for the hypothesis that the clinical connection between the two diseases is due to immune responses to antigens shared by normal and malignant pigment cells. Patients with melanoma may exhibit halo nevus, hypopigmentation, or depigmentation. The depigmentation or hypopigmentation spreads from the trunk to other parts of the body via centrifugal force. It is believed that active vitiligo in melanoma patients may indicate a better prognosis, as melanoma patients with vitiligo have longer survival rates than expected [87].

5. VITILIGO TREATMENT & MANAGEMENT

5.1 Approach Considerations

Individualized therapy is required, and patients must be aware of the risks associated with treatment. There is no single treatment for vitiligo that reliably produces excellent results in all patients, and the response to treatment is highly variable. [88,89] Several factors influence the choice of therapy, including the subtype of the disorder, its severity, distribution, and activity, as well as the patient's age, phototype, impact on quality of life, and motivation for therapy. Lips and distal extremities are more resistant to treatment than the face, neck, mid-extremities,

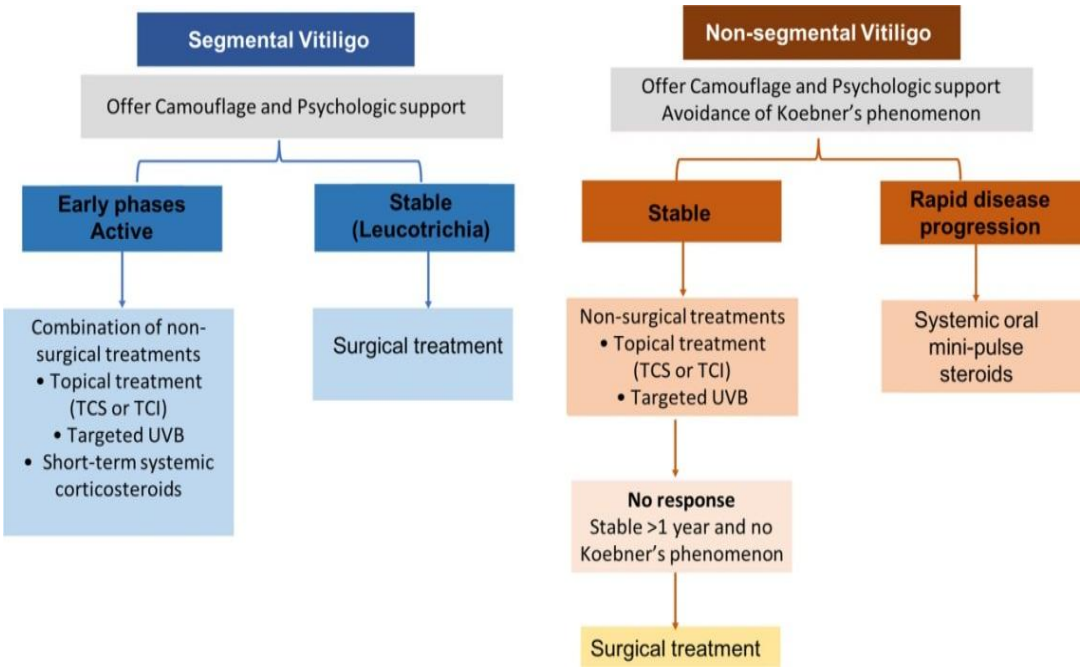

Fig. 7. Therapeutic algorithm of vitiligo. TCS, topical corticosteroid; TCI, topical calcineurin inhibitor; UVB, ultraviolet B. [34]

and trunk. SV and an age of onset younger than fourteen years have been linked to a more resistant disorder. During treatment, pigment cells emerge and multiply from the pilosebaceous unit, spare epidermal melanocytes, and migrate up to two to four millimetres from the lesion's border. The European Dermatology Forum Vitiligo Subcommittee has established guidelines for the management and treatment of vitiligo. These recommendations are based on the best available evidence and expert opinion. Options for treatment were ranked from first- to fourth-line. Primitive treatments are topical treatments (corticosteroids and calcineurin inhibitors). Second-line treatments include phototherapy (NB-UVB and psoralen and UVA [PUVA]) and systemic steroid therapy. Third-line therapies involve surgical grafting, while fourth-line therapies involve depigmenting agents. [93] [Fig. 7] [34].

5.2 Medical Treatment

5.2.1 Topical treatment

As a first-line treatment for localised vitiligo, topical corticosteroid (TCS) preparations are frequently chosen due to their patient-friendliness, anti-inflammatory, and immunomodulatory effects. Some authors recommend daily administration for 2–3 months, while others propose a discontinuous regimen (once-daily application for 15 days per month for 6 months). Topical tacrolimus ointment (0.03 percent or 0.1 percent) and pimecrolimus cream are effective treatments for vitiligo, especially when the head and neck are affected. These may be utilised in tandem with TCS. According to studies, combining topical calcineurin inhibitors (TCI) with laser therapy or NB-UVB may improve treatment outcomes. Vitamin D analogues, specifically calcipotriol and tacalcitol, have been applied topically to treat vitiligo. They target the local immune response and act on the activation of specific T cells. These vitamin D3 compounds affect melanocyte maturation and differentiation in addition to upregulating melanogenesis via specific ligand receptor-activated pathways (eg, endothelin receptor and c-kit). While the role of calcipotriol in the treatment of vitiligo remains unclear, it is more likely to serve as a supplementary therapy than as a monotherapy. [97,98] 5-Fluorouracil (5-FU) is a chemotherapeutic agent that has been approved for the topical treatment of several dermatological conditions. It is used to treat a variety of malignant tumours. Localized hyperpigmentation, a side effect of 5-FU's use in cancer treatment, has sparked interest in the drug's potential to induce repigmentation in vitiligo patches. Latanoprost is a topical

prostaglandin analogue, more specifically a prostaglandin F2 analogue. It causes iris, eyelash, and periocular skin hyperpigmentation. [101] In the past decade, it has been reported that topical latanoprost is effective in repigmenting vitiligo lesions [101,102] and that its effect is enhanced when combined with NB-UVB phototherapy [102,103].

Janus kinase (JAK) inhibitors applied topically may provide a novel treatment option for vitiligo. The topical 1.5 percent ruxolitinib twice daily demonstrated promising results. The Food and Drug Administration (FDA) recently approved opzelura (ruxolitinib) cream for the treatment of NSV in adults and children older than 12 years. Opzelura is the first FDA-approved pharmaceutical treatment for vitiligo patients' repigmentation [104].

5.2.2 Systemic treatment

Systemic corticosteroids are the first-line treatment for rapidly progressing vitiligo. It not only slows the progression of the disease, but also promotes repigmentation by allowing normal melanocytes to migrate from the periphery or perifollicular region of lesions. [105,106] Oral mini-pulse (OMP) therapy refers to the administration of cyclical pulsed dose corticosteroids in significantly lower doses than typical pulsed therapy (administration at suprapharmacological doses for 2 days per week to reduce adverse effects). Betamethasone and dexamethasone are the two most frequently utilised corticosteroids. Long-term use of steroids can cause striae, atrophy, tachyphylaxis, telangiectasias, acneiform eruptions (topical), hyperglycemia, hypertension, osteoporosis, Cushing's syndrome, and suppression of the hypothalamic-pituitary axis (systemic). Methotrexate, azathioprine, and cyclosporine have been reported as potential immunosuppressants and immunomodulators for treating active vitiligo [106,107,108]. In patients with active vitiligo, cyclosporine has been found to have a quicker onset of action in halting disease progression than OMP. Recent studies suggest that the IFN—CXCL10 axis may be an effective treatment target for vitiligo, which has led to the development of a new class of targeted immunotherapies, the JAK inhibitors. There have been reports of significant repigmentation following treatment with two oral JAK inhibitors, tofacitinib [113] and ruxolitinib [112]. Tofacitinib (JAK1 and JAK3 inhibitor) and ruxolitinib (JAK2 inhibitor) inhibit IFN- signalling, thereby reducing CXCL10 expression and inhibiting vitiligo activity [113,114].

Afamelanotide is a long-lasting synthetic analogue of alpha-melanocyte stimulating hormone (-MSH) and an emerging treatment for vitiligo.

Lim et al. [115] Afamelanotide activates melanocyte proliferation and melanogenesis by binding to the melanocortin-1 receptor. Afamelanotide is administered as an implant placed subcutaneously. When combined with NB-UVB, a 7- to 10-day release implant of 16 mg afamelanotide produced faster repigmentation of facial and upper extremity lesions than NB-UVB alone. Hyperpigmentation of normal skin, nausea, and abdominal pain are adverse reactions [115,116].

It has been demonstrated that oral administration of a single or multiple antioxidants can slow the progression of vitiligo and promote repigmentation.

Pseudocatalase, vitamin E, vitamin C, ubiquinone, lipoic acid, Polypodium leucotomos, catalase superoxide dismutase, and ginkgo biloba have all been used with or without phototherapy [107].

5.3 Phototherapy

A majority of patients with early or localised disease respond favourably to phototherapy-induced repigmentation [117]. Prolonged phototherapy courses should be encouraged, as a treatment period of at least six months may be required to accurately evaluate the phototherapy's efficacy. Notably, phototherapy causes the normal skin surrounding the lesion to tan, making the lesion more visible. Before beginning treatment, it is necessary to carefully counsel the patient regarding his or her expectations and anticipated outcomes, as this may be cosmetically unacceptable for some individuals. Narrowband UV-B (NB-UVB) is the phototherapy of choice for adults and children with graft-versus-host disease (GV). Typically, wavelengths between 311-312 nm are utilised. The frequency of treatment is 1-2 times per week. PUVA, also known as Psoralen photochemotherapy, has been largely replaced by NB-UVB, which is highly effective and has fewer side effects. Literature reviews from 2017 indicate that NB-UVB therapy has a better response rate than PUVA therapy. Additionally,

NB-UVB has shorter treatment times, no drug costs, no nausea, and no need for subsequent photoprotection. The excimer laser emits monochromatic rays at 308 nm for the treatment of limited, stable vitiligo patches. This new treatment for vitiligo is effective, harmless, and well-tolerated. Nevertheless, therapy is costly. Localized vitiligo lesions are typically treated twice weekly for 24 to 48 sessions. Monochromatic excimer light (MEL) has been combined with both topical tacrolimus and short-term systemic corticosteroids for repigmentation-resistant SV. Studies indicate that the repigmentation response to SV is enhanced when excimer laser treatment is administered at an earlier disease stage. In addition, the use of khellin 4% ointment in conjunction with MEL at 308 nm has been investigated and may be a viable treatment option for vitiligo. The 308-nm excimer lamp stimulates melanocyte proliferation and induces apoptosis in T cells. Khellin is a furanochromone that shares a similar chemical structure to psoralens. Narrowband UV-B (NB-UVB) phototherapy, topical tacrolimus, or topical calcipotriol in combination with fractional CO2 laser could be used effectively and safely to treat vitiligo. It was discovered that the fractional CO2 laser and NB-UVB combination was more effective. Furthermore, fractional CO2 laser can be combined with topical 5-FU to achieve repigmentation of greater than fifty percent in fifty percent of patients with fewer side effects [122].

5.4 Office Techniques

Microneedling is recommended for the treatment of resistant localised stable vitiligo either as an exclusive therapy [123] or in combination with NB-UVB phototherapy [124] or topical therapeutic agents such as triamcinolone acetonide, [125] latanoprost,[126] tacrolimus,[103,127] 5-fluorouracil [127] or trichloroacetic acid. It induces processes similar to wound healing, including the production of cytokines and growth factors that are advantageous to repigmentation. Additionally, it facilitates drug permeation through the skin, which may increase their activity [129].

Platelet Rich Plasma (PRP) contains growth factors such as platelet derived growth factor, TGF-, epidermal growth factor, vascular endothelial growth factor, insulin growth factor, and bFGF that are stored in the alpha granules of the platelets, as well as numerous plasma proteins including fibrin, fibronectin, and vitronectin. These growth factors contribute to the regeneration and repair of tissues. PRP may stimulate the proliferation of keratinocytes and fibroblasts, resulting in an increased interaction with melanocytes that stabilises melanocytes. [130] Ibrahim et al. [130] concluded that a combination of intradermal PRP and NB-UVB phototherapy can be considered as an efficient, simple, safe, and cost-effective treatment modality for vitiligo. As the use of intradermal PRP could also reduce the duration of UVB exposure, resulting in a lower cumulative dose and increased patient compliance [131].

5.5 Surgical Procedures

After at least a year of documented non-response to medical interventions and the absence of Koebner's phenomenon, surgical methods may be offered as a treatment option to patients with SV and NSV who have stable disease. The goal of the transplantation is to transfer a reservoir of healthy melanocytes to the vitiliginous skin for proliferation and migration into areas of depigmentation. [132] Although surgery is usually recommended for all types of stable vitiligo, only a small percentage of vitiligo patients are suitable. The best indications are stable SV or focal vitiligo, particularly when SV is marked by leukotrichia [133].

According to the type of graft, vitiligo surgery could be divided into tissue grafts and cellular grafts [134]:

a. Tissue grafts

- Split-thickness skin grafting (STSG): grafting of donor skin as thin as 0.1–0.2 mm, which can be obtained using a hand dermostome or shaving blade fixed in a straight hemostat. Then, grafts are placed on the recipient sites. Obtaining grafts with uniform thickness requires special skills and dexterity. STSG is not appropriate for vitiligenous lesions on the palms, soles, or skin folds. This technique offers immediate results and the highest average success rate. Suction epidermal grafting: Epidermal grafts can be obtained via vacuum suction, typically at a pressure of 150 mm Hg. The recipient site can be prepared 24 hours prior to grafting by suction, freezing, or dermabrasion. The depigmented blister roof is discarded, and donor epidermal grafts are applied to the vitiliginous areas. Small donor grafts are inserted into the incision of recipient sites and held in place with a pressure dressing

during punch minigrafting. The graft heals quickly and begins to repigment within four to six weeks. A small amount of pebbling remains, but it is minimal, and the aesthetic result is excellent [136].

b. Cellular grafts

- Cultured epidermis with melanocytes or suspensions of cultured melanocytes: Liquid nitrogen, superficial dermabrasion, thermosurgery, or CO2 lasers are used to remove depigmented skin; very thin sheets of cultured epidermis are grafted or suspensions are applied to the depigmented surface. After removing the achromic epidermis, an epidermal suspension containing melanocytes and keratinocytes that was previously prepared by trypsinization of normally pigmented donor skin is applied to the bare area and immediately covered with nonadherent dressings. Using noncultured epidermal cellular grafts can result in repigmentation of greater than 75%, particularly in SV, piebaldism, and halo nevi. Color mismatches are potentially problematic, and GV did not repigment adequately. Techniques for grafting non-cultured, non-trypsinized melanocytes and keratinocytes, as follows:

✓ **Jodhpur technique:** Using a dermabrader micromotor, the epidermis was removed superficially until it appeared wet and shiny. Then, an antibiotic ointment was applied, and dermabrasion was continued until the whitish region of the upper dermis was reached. Collecting the paste-like substance (ointment with entangled epidermal particles) and applying it to the dermabraded recipient site. Complete repigmentation occurred 16 to 20 weeks after the procedure, beginning 8 to 12 weeks after the procedure. In fifty percent of patients, the repigmentation rate was greater than seventy-five percent [140].

✓ **Tanta technique:** Using dermabrasion, epidermal cells were harvested from the donor site, then prepared, homogenised with autologous plasma gel, and applied to the abraded recipient, followed by 16 NB-UVB sessions after complete healing. Complete repigmentation occurred 14-16 weeks after NB-UVB sessions, with repigmentation beginning 4-8 weeks after treatment. 65 percent of patients experienced repigmentation rates greater than 75 percent [141].

6. DEPIGMENTATION THERAPY

If vitiligo is widespread and attempts at repigmentation fail to produce satisfactory results, depigmentation may be attempted on patients who have been meticulously selected. Consider the long-term social and emotional consequences of depigmentation. Depigmentation should not be attempted unless the patient is fully aware of the treatment's irreversible nature. Consultation with a mental health professional has been suggested in order to discuss potential social consequences of depigmentation. A 20% monobenzylether of hydroquinone (MBEH) cream is applied twice daily for three to twelve months. Burning or itching could potentially occur. Possible allergic contact dermatitis. [143] Mild toxicity has been attributed to MBEH; however, no research has been conducted on the safety of applying the drug to large skin surfaces to induce widespread depigmentation. Therefore, it is recommended that depigmentation therapy be limited to the lesions that cause the patient the most discomfort, such as those on the face and hands. Micropigmentation is an additional option. Tattooing can be used to repigment depigmented skin on individuals with dark skin. It is difficult to match colours, the colour tends to fade, and the treatment may cause the emergence of new lesions. Alternately, skin can be dyed with dihydroxyacetone preparations, although the colour match is frequently inadequate [145].

7. CONCLUSION

Vitiligo is considered the most commonly seen depigmenting dermatological disease and continues to be one of the most challenging issues. It is a multifactorial skin disorder with a very complex pathogenesis. Despite considerable progress has been made in our understanding of vitiligo, its cause and pathogenesis remain unclear. Uncertainties remain about what essentially causes the destruction of melanocytes, and further studies are needed to completely elucidate its pathogenesis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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