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Vitiligo: Pathogenesis, clinical presentations and types of treatment

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Abstract
Vitiligo is an autoimmune disorder characterised by the loss of melanocytes, leading to depigmented patches on the skin. Its pathogenesis involves both intrinsic melanocyte defects and immune responses targeting melanocytes. A key factor in vitiligo is an imbalance of cytokines, favoring pro-inflammatory responses (Th1/Th17) over anti-inflammatory ones (Th2/Treg). Elevated cytokine levels such as IL-1, IL-6, and TNF-α contribute to melanocyte destruction. Cytotoxic CD8+ T cells are also included in this process. Additionally, regulatory T cells (Tregs), which typically help maintain tolerance to melanocytes, are reduced in vitiligo patients, further promoting autoimmune reactions. These findings suggest that cytokine-targeted therapies could offer new treatment options for vitiligo.

Keywords: Vitiligo, Pathogenesis, cytokine, Treatment

Introduction
Vitiligo is a primary acquired condition marked by distinct, milky chalk-white or white macules on the mucous membranes or skin, produced by the depletion of functional melanocytes in the affected regions. The pathophysiology of vitiligo involve inherent abnormalities in melanocytes that trigger cellular stress responses, as well as autoimmune processes that target melanocytes, including both cell-mediated and humoral immunity [1]. Cytokines play a crucial function as mediators of humoral and cellular immune responses. The disproportion between anti- and pro-inflammatory cytokines, favouring a Th1/Th17 responses over a Th2/Treg responses, has been suggested as a potential underlying cause of vitiligo. There is substantial evidence supporting the involvement of CD8 type 1 T lymphocytes in the eradication of melanocytes. Numerous studies have demonstrated increased levels of pro-inflammatory cytokines, like IL-1, IL-6, and TNF-α, in patients with vitiligo [2].
The cytotoxic T cells infiltration in perilesional lesions is a defining feature of vitiligo. Increasing data indicates that cytokines play a significant part in the depigmentation process and exhibit a cytokine imbalance in the skin of vitiligo individuals, indicating their critical involvement in autoimmune aetiology. Systemic biological treatments employed for the management of psoriasis and other autoimmune disorders by cytokine targeting suggest that a comparable approach may be beneficial for vitiligo [3].

Vitiligo
Vitiligo is a depigmenting skin condition marked by the selective loss of melanocytes, resulting in pigment dilution in the impacted skin regions. The defining lesion is an entirely amelanotic, chalky-white, non-scaly, macule with well-defined margins [4]. Vitiligo is the predominant depigmentation disease, with a worldwide frequency estimates between 0.5% and 2%. Research indicates that prevalence escalates with age, rising from 0.5% in children under one year to 1% in those aged 1 to 5 years, and further raising to 2.1% in children aged 5 to 12 years [5]. The precise aetiology of vitiligo remains unidentified [6]. The condition is multifactorial, with numerous theories proposed, such as the autoimmune theory, reactive oxygen species (ROS) theory, genetic theory, zinc-α2-glycoprotein deficiency theory, intrinsic theory, viral theory, molecular and cellular alterations theory, melanocytorrhage

theory and neurohormonal theory [7].

Both the cellular and humoral components of the immune system have been demonstrated to contribute to the pathogenesis of vitiligo [8]. The activation of an autoimmune-mediated T-cell response resulting in an absence of tolerance to melanocyte antigens has been documented in vitiligo instances; however, the precise mechanism remains incompletely elucidated [9].

Cytokines play essential roles in the developing, regulation, and differentiation of immune cells, consequently contributing to autoimmunity. Cytokines serve as essential mediators for cellular networking and communication. Furthermore, keratinocytes may synthesise and secrete pro-inflammatory cytokines, including IL-6, IL-1α, and TNF-α, that subsequently enhance the adhesion molecules expression on the membrane of melanocytes, like ICAM-1, so facilitating additional recruitment of lymphocyte. An imbalance of systemic and epidermal cytokines between Th1 and Th2 types, as well as anti- and pro-inflammatory cytokines, is seen in vitiligo. An imbalance of anti- and pro-inflammatory cytokines is routinely seen among individuals with GV who additionally present with other autoimmune comorbidities [10].

Among the different cytokines, IFN-γ, a pro-inflammatory cytokine, was shown to promote death in melanocytes and is higher in vitiligo individuals, causing depigmentation in animal models of vitiligo via the IFN-γ-CXCL10 axis. Likewise, TNF-α was demonstrated to provoke CD8+ T cell-mediated death of melanocytes and is higher in the lesional skin and serum of individuals with vitiligo [11].

Furthermore, the involvement of cytokines IL-17, IL-6, IL-1α, and IL-8 in the breakdown of melanocytes in vitiligo is becoming increasingly evident, with some cytokines demonstrating their mechanisms via TNF-α; hence, additional investigation into their mechanisms of action is necessary. Additionally, it is emerging that the interaction across numerous components that result in the creation of ER stress, to resolve the ER stress UPR responses, is triggered by melanocytes, resulting in the imbalance of cytokines [11].

The main lymphocytes implicated in promoting the autoimmune responses in vitiligo are circulating CD4+ T helper cell subsets, Th17 and Th1. Effector CD4+ T helper cell and not suppressor CD4+ T helper cell are the immunological lever of the activity of the disease in vitiligo since the latter might induce loss of self-tolerance to melanocytes [9]. The concept that depigmentation may develop in the lack of regulatory T cells (Treg) has been demonstrated. There is a reduced expression of the skin homing chemokine ligand 22 (CCL22) in vitiligo skin, as well as a decreased amount of Treg cells in non-lesional, perilesional, and lesional vitiligo skins. This was discovered by immunohistochemistry. It is possible that this will shed light on the failure of circulating Treg cells and their decreased skin homing due to the loss of functionality that could extend reactivity versus melanocytes in vitiligo [12].

Clinical presentation

Vitiligo often manifests as finely defined, macules and patches of completely amelanotic (milk-white) skin that are enclosed by skin that is not affected. Lesions may exhibit round, oval, or entirely irregular shapes, with diameters varying from millimetres to several centimetres. In individuals with dark or black skin, the difference between skin that has lesions and skin that is normal is striking. It is common for the lesions to be asymptomatic. Pruritus was documented in few instances [13].

Lesions may manifest anywhere on the body and are typically symmetrical. Common locations include the facial area, nipples, axillary regions, dorsal surfaces of the hands, anogenital area, elbows, shins, knees, and dorsal surfaces of the foot. The illness appears to preferentially affect areas exposed to recurrent friction, trauma, or pressure [14]. Leukotrichia might be linked to vitiligo lesions. Vitiligo often manifests on the scalp as localised areas of white hair, known as poliosis. Dispersed white hairs or complete depigmentation of all the hair of the scalp may additionally manifest [15].

A. Topical therapies

- **Topical Corticosteroids**
  Topical corticosteroids (TCS) are often used as the primary therapy for localized vitiligo due to their ease of application and convenience for patients. Some experts advocate for daily treatment for a duration of 2-3 months, whilst others propose a discontinuous regimen with once-daily administration for 15 days each month over a span of 6 months [16].
- **Calcineurin inhibitors**
  Topical pimecrolimus (1%) and tacrolimus (0.03% or 0.1%) are commonly utilised off-label to treat vitiligo. These calcineurin inhibitors promote melanocyte growth and decrease TNF-α levels, aiding in repigmentation by lowering pro-inflammatory cytokines and stimulating the proliferation of the melanocytes and melanoblasts [17]. They have a higher preference over TCS for treating limited vitiligo on the face or areas prone to skin thinning, such as the genitals, and are typically administered bi-daily for a minimum duration of six months [18].
- **5-Fluorouracil**
  It was hypothesised that 5-FU may facilitate repigmentation through direct melanocytes stimulation and a rise in melanosome quantity within keratinocytes [19]. Additionally, it may provoke the C4 and D4 inflammatory leukotrienes release, additionally, in order to increase the synthesis of enzymes that are metalloproteinases, thereby creating a conducive environment for the migration of melanocytes [20].
- **Basic fibroblast growth factor-derived peptide**
  Basic fibroblast growth factor (bFGF) and its derived peptides have been utilized topically in the treatment of vitiligo, with inconsistent outcomes [21]. It is applied topically at night and thereafter exposing to sunlight for 10 mins in the morning. It is safe for usage in both children and adults and has a minimal negative effect profile [21].
- **Vitamin D3 analogue**
  It is utilised topically and may be utilised in conjunction with phototherapy. A maximum weekly dosage of 100 g of the fixed combination of betamethasone 0.05% and calcipotriene 0.005% may be securely applied to 30% of the body surface area (BSA) for a maximal length of 4-weeks for ointment and 8-weeks for solution and cream. Topical vitamin D3 analogues are secure for children as well as adults, with a low incidence of adverse effects, with only infrequent complaints of mild discomfort. [22].

- **Prostaglandin F2 alpha analogue**
  Topical 0.03% bimatoprost combined with phototherapy demonstrated a more rapid and extensive repigmentation than only phototherapy [23]. It has been shown that the prostaglandin F2-alpha analogue latanoprost is effective in promoting repigmentation of vitiligo patches that are located on the eyelids. [24, 25]
- **Pseudocatalase**
  Pseudocatalase has been utilised as a topical treatment bi-daily in conjunction with phototherapy bi-weekly. This regimen results in satisfactory clinical pigmentations on the hands and face, however, not on the fingers. Limited data exists regarding the safety and adverse reaction profile of pseudocatalase [26].
- **Topical Janus kinase (JAK) inhibitors**
  Recently, The Food and Drug Administration (FDA) has sanctioned Opzelura (ruxolitinib) cream for the management of NSV in both adults and pediatric individuals who are 12 years old or older. Opzelura is the first FDA-approved pharmacological intervention for promoting repigmentation in individuals with vitiligo [27].

B. Systemic therapies

- **Oral corticosteroids**
  Oral mini-pulse treatment (OMP) employs modest dosages of corticosteroids (e.g., 2.5-10 mg dexamethasone on two consecutive days per week) to halt the development of the disease. It has been seen to halt disease development in 88% of individuals following 18.2 weeks of therapy [28].
- **Methotrexate (MTX)**
  The MTX dose ranged from 7.5 to 25.0 mg weekly, accompanied with folic acid supplements. The outcomes varied from the cessation of vitiligo activity to considerable repigmentation [29].
  The adverse impacts of MTX include hepatotoxicity, idiosyncratic lung toxicity, pancytopenia, vomiting, nausea, and diarrhoea [30].
- **Azathioprine**
  Azathioprine is an immunosuppressive agent that obstructs the synthesis of DNA in immune effector cells [20]. Research carried out by Madarkar *et al*. [31], examined the efficiency of azathioprine 50 mg administered bi-daily against betamethasone 5 mg given on two consecutive days each week for a 6-months duration in the treatment of vitiligo. Significant enhancements were seen in both groups, and the authors propose that both medications exhibit comparable efficacy in treating vitiligo.
  Cyclosporine has been previously identified as a possible immunomodulator and immunosuppressant useful in the treatment of active vitiligo [32]. Cyclosporine has been found to have faster onset of action for arrest of disease progression in comparison to OMP in individuals of active vitiligo [33].
- **Systemic Janus kinase inhibitor therapy**
  Research indicates that the IFN-γ-CXCL10 axis might serve as a viable target for vitiligo treatment, leading to the development of a novel category of targeted immunotherapies, namely JAK inhibitors [33, 34]. Notable repigmentation has been shown after therapy with two oral JAK inhibitors, tofacitinib[35] and ruxolitinib[36]. Tofacitinib (JAK3 and JAK1 inhibitor) and ruxolitinib (JAK2 and JAK1 inhibitor) interfere with IFN -γ signaling, which reduce CXCL10 expression, blocking the activity of vitiligo [36, 37].
- **Levamisole**
  Levamisole inhibits heightened B-cell activity. It is administered orally at a dosage of 150 mg over two consecutive days for the treatment of vitiligo. This medication has demonstrated efficacy in managing the condition and facilitating spontaneous repigmentation. Potential side effects may include nausea, vomiting, diarrhoea, anorexia, fatigue, and dizziness [38].
- **Antioxidants**
  According to the findings of certain research, the administration of oral antioxidants (such as polypodium leucotomos, vitamin C, and vitamin E) in conjunction with NB-UVB results in an increase in the rates of repigmentation; hence, oral antioxidants may be recommended for individuals receiving phototherapy [39, 40].
- **Alpha-Melanocyte-stimulating hormone**
  Alpha-Melanocyte-stimulating hormone (α-MSH) is an endogenous hormone that promotes melanogenesis [41]. Afamelanotide, which is a synthetic version of αMSH, has been given approval by the European Medicines Agency for the purpose of alleviating photosensitivity for individuals with erythropoietic protoporphyria, perhaps enhancing the effectiveness of phototherapy for vitiligo [42, 43].

C. Phototherapy

Narrowband UV-B is frequently employed and has emerged as the preferred modality of phototherapy for both children and adults. Wavelengths ranging from 311 to 312 nm are often used [44].

Psoralen photochemotherapy employ psoralens in conjunction with UVA radiation. Psoralens might be administered orally or topically, subsequently requiring being exposed to UVA radiation, either from artificial sources or from natural sunlight. One of the adverse consequences is an increased chance of developing cancer of the skin, in addition to phototoxicity and nausea [44].

Laser Therapy

Low-level laser treatment (LLLT) is a kind of laser phototherapy that employs low-power, continuous, or pulsed emissions within the wavelength range of 600-1,100 nm. It is accessible as a helium-neon (He-Ne) laser or a ruby laser [30]. The He-Ne laser was used in the treatment of vitiligo, promoting melanocyte proliferation via increased production of α2β1 integrin, upregulating phosphorylated cyclic-AMP response element binding protein (CREB), and reducing mobility while enhancing attachment to type IV collagen. It is additionally posited to restore the impaired sympathetic nerves and enhance cutaneous circulation [45].

Erbium-doped yttrium aluminum garnet (Er:YAG) laser: ER:YAG laser and dermabrasion increase melanocyte stem cells, promote the drugs absorption, and facilitate the autoinoculation of melanocytes from the margins; nevertheless, they induce wounds that need an extended healing period [46].

Fractional carbon dioxide (CO2) laser
Fractionated lasers constitute a method for skin resurfacing grounded in the principle of fractional photothermolysis, as proposed by Manstein *et al*. [47]. Because fractionated lasers don't ablate the whole epidermis, they are able to preserve the integrity of the skin in between coagulated necrotic columns. This results in the formation of tiny therapeutic zones that improve the penetration of agents that are administered inside, thereby improving efficacy [48].

D. Microneedling
Micro-needling combined with tacrolimus has shown to be an efficient and secure treatment for vitiligo [49]. A research assessing the efficacy of combining tacrolimus with microneedling against tacrolimus monotherapy for vitiligo treatments revealed that the combination therapy yielded superior outcomes. Repigmentation over 75 percent had been demonstrated in 50 percent of individuals in the combined regimen group, in contrast to 29.2 percent in the tacrolimus monotherapy group [50].

E. Dermabrasion
Dermabrasion is a cost-effective and widely used technique for preparing recipient sites, with precise bleeding being the desired therapeutic outcome. A limitation of manual dermabrasion is its time-consuming nature, which leads to fast user fatigue, and its difficulty in application on extensive or concave areas like the eyelids, axilla, neck, and glans penis. Motorised dermabrasion offers a quick option; nonetheless, it need expertise because to the challenges in depth control [51].

F. Surgery
Surgical interventions have shown improved repigmentation rates for people with vitiligo. These surgical procedures are employed for individuals with persistent vitiligo persisting for one year who have not responded to medicinal interventions. Surgical interventions might involve tissue grafts and cellular grafts, while non-grafting treatments encompass therapeutic wounding, using cryotherapy, ablative lasers, or dermabrasion to stimulate the pro-pigmenting cytokine cascade and promote melanoblast migration [20].

G. Cosmetic: Camouflage
Camouflage might be a beneficial alternative. A diverse array of cosmetic goods, comprising self-tanners and cover creams, is accessible. Due to variations in skin type, afflicted areas, and personal preferences, subjects often need referrals for specialised guidance in camouflaging their vitiligo, thereby alleviating the everyday effects of the condition and associated social stress. Exercise caution about permanent tattoos and camouflage, since vitiligo may develop over time. This may result in unsatisfactory outcomes [52].

H. Depigmentation
In individuals who have severe vitiligo (body surface area exceeding 50 to 60%) or it is possible to investigate the possibility of depigmentation of the remaining pigmented areas in cases with disfiguring resistant vitiligo on the hands or face [53]. There is a wide range of depigmentation methods available, which includes bleaching creams (for example, monobenzone ethyl ester), laser treatment, and cryotherapy. Monobenzone ethyl ester necessitates an extended duration of treatments, sometimes requiring a period of 5 to 12 months to get adequate depigmentation. Multiple treatments are necessary for cryotherapy and laser [54].

I. Selective sunscreen
Repigmentation of vitiligo lesions is almost unattainable without ultraviolet radiation, whether by natural means or phototherapy devices, lamps, or lasers. Patients with vitiligo ought to be instructed to consistently expose their affected skin to sunlight until the lesions become pink, following which the use of a high-SPF broad-spectrum sunscreen is recommended to avoid sunburn [55].

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