An Overview about Treatment Modalities of Vitiligo

Khaled Mohamed Gharib [1], Yasmeen Ahmed Fahmi El Sharkawi *[1], Nagia Ahmed Elmegrab[2] Al Shimaa Mohamed Ibrahim[1]

Abstract

Background: Vitiligo is the most common depigmentation disorder where the selective destruction of functioning melanocytes causes depigmentation of the skin, hair and mucosal surfaces. It affects approximately 0.5% to 1% of the population, with an average age of onset at about 24 years, its prevalence appears to be equal between men and women and there is no difference in the rate of occurrence according to skin type or race. The term leucoderma is applied to depigmented patches of known etiology as that following burns, contact with chemicals like phenol or following an inflammatory skin disease. As opposed to vitiligo, it doesn't progress after the cause is removed. Skin repigmentation is the main goal of therapy regardless of its types; however, spontaneous repigmentation is occurring in about 1%–25% of patients.

Key Words: Treatment Modalities, vitiligo

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Introduction

Vitiligo was among the first skin disorders to be recognized and described in a formal medical context, It is an autoimmune disease in which destruction of skin melanocytes results in patches of white skin and hair, The loss of melanin is in the skin but partly also in mucous membranes**,** Several mechanisms have been implicated to explain melanocyte disappearance, including genetic predisposition, environmental triggers (such as friction), metabolic alteration and altered inflammatory and immune responses **(1).**

It affects ~1% of the world's population without any significant difference in prevalence due to sex, ethnicity, or geographic region **(2).**

The term leucoderma is applied to depigmented patches of known etiology as those following burns, contact with chemicals like phenol or following an inflammatory skin disease. As opposed to vitiligo, it doesn't progress after the cause is removed **(3).**

Factors such as poor nutrition, emotional stress, autoimmunity, trauma, drugs, infections, sepsis, and exposure to the sun, chemicals, allergens, occupations, systemic illness, diet and toxins are often considered to trigger it **(4).**

Corresponding author: Yasmeen Ahmed Fahmi El Sharkawi
[1] Dermatology, Venereology & Andrology Department, Faculty of Medicine, Zagazig University, Egypt
[2] Pharmaceutics Department, Faculty of Medicine, Zagazig University, Egypt
[1*]E-mail: Yasmeenfahmi1992@gmail.com

Generalized vitiligo is characterized by asymptomatic well-circumscribed milky-white macules involving both sides of the body with usually a symmetrical pattern **(5).**

Vitiligo is typically diagnosed by the clinical presentation. The classical clinical presentation of vitiligo vulgaris is hypo- or depigmented, discrete or coalescing, macules or patches, with convex borders that are surrounded by normal skin **(6).**

The symptoms of vitiligo vulgaris are mainly related to the embarrassment they cause due to cosmetic disfigurement. The lesions are typically asymptomatic. However, a rare variant, inflammatory vitiligo, can be itchy **(7).**

Vitiligo primarily destroys the pigment-producing cells, melanocytes, located in the epidermis between the hair follicles (interfollicular epidermis). However, the disease commonly spares melanocytes residing within the hair follicle because of immune privilege at this site, like other privileged sites that contain melanocytes, such as the brain, eye, and inner ear. Hair follicles also contain melanocyte stem cells that can repopulate the epidermis of vitiligo lesions with functional, newly differentiated melanocytes that possess the capacity to restore normal pigmentation. Thus, clinical repigmentation of vitiligo lesions typically appears in a punctate, perifollicular pattern, and areas of vitiligo lesions containing no hair or white hairs where autoimmunity has not spared the follicular melanocyte populations do not repigment **(8).**

There are 3 aims for optimal treatment of vitiligo:

1) Halting disease progression.
2) Repigmentation by stimulation of melanocyte differentiation and proliferation.
3) Prevention of relapses

(9).

Skin repigmentation is the main goal of therapy regardless of its types; however, spontaneous repigmentation is occurring in about 1%–25% of patients **(10).**

I- Topical Therapy:

A) topical corticosteroid:

Topical corticosteroids are the first-line therapy and more effective for small vitiligo lesions and should not use more than 4 months due to the risk of skin atrophy. Alternate day or weekend approach, several weeks off corticosteroid use ("corticosteroid holidays") should be encouraged **(11).**

B) Calcineurin inhibitors:

Topical calcineurin inhibitors such as tacrolimus are effective as topical corticosteroids without risk of skin atrophy. twice daily topical calcineurin inhibitors for head and neck lesions as a first-line approach **(12).**

C) Basic fibroblast growth factor (bFGF) derived peptide:

bFGF is a decapeptide used topically in vitiligo for recalcitrant disease. Side effects are rare, common ones being dry skin, burning and skin irritation **(13).**

D) Prostaglandin F2 alpha analogue (PGF2α):

Latanoprost and bimatoprost are PGF2α analogues. PGF2α, however, exerts its effect indirectly through induction of COX-2. Bimatoprost ophthalmic solution 0.03% can be used as one drop for 2 cm^2 body surface area twice a day. The side effects are minimal, periorbital hyperpigmentation being a rare side effect. It may be a promising treatment option for recalcitrant disease with increased efficacy when combined with phototherapy **(14).**

E) Topical Methotrexate (MTX):

Recently, a topical formula of MTX was used in a case report with significant improvement in repigmentation of the vitiligo lesion **(15).**

II- Physical therapy:

Physical modalities of treatment in vitiligo include the use of phototherapy and lasers.

A) Ultraviolet Light (phototherapy):

Phototherapy is often used as first line of treatment in extensive vitiligo. It may be used in the form of UVA with psoralens (PUVA), UVB therapy or as targeted phototherapy **(16).**

B) Laser therapy:

- **The 308-nm monochromatic excimer laser (MEL):** It is one of targeted photothepy in which only the lesional skin is targeted. As uninvolved skin is not exposed, it remains protected and rapid therapeutic response can be achieved by delivering higher energies without adverse effects **(17).**
- **Low-level laser therapy (LLLT)** is a form of laser phototherapy that uses low power, continuous or pulsed emission of wavelength 600-1100nm. It is available as **helium-neon (He-Ne) laser or Ruby laser.** It is a relatively newer modality of treatment with not much data regarding its safety in pregnancy and children. **Lotti et al., (18).** evaluated **UVA 1 laser** of non-responder vitiligo patients and stated that UVA1 laser with monochromatic emission at 355 nm, could be an applicable therapeutic option in patients with vitiligo, also for the ones who did not respond to the more

conventional phototherapies **(18).**

- Another study evaluated the use of **fraxelherbium laser**, topical latanoprost and successive irradiation with UVA - 1 laser and demonstrated that this combination seems to provide good clinical results in term of repigmentation rate, without side effects **(18).**

III- systemic Therapy:

- **Oral steroids:** Oral steroids may help stabilize rapidly progressive disease. The regimen consists of low-dose betamethasone or dexamethasone for 3 to 6 months on 2 consecutive days **(19).**
- **Vitamin D3 analogue**: Calcipotriol and tacalcitolare vitamin D analogues modulate calcium homeostasis by acting on 1, 25 dihydroxy vitamin D3 receptors on melanocytes. They are used as a second line therapy in vitiligo **(20).**
- **Psoralens**: Psoralens, derived from the plant Psoraleacorylifolia, have been used for the treatment of vitiligo for a long time **(21).**
- **Levamisole**: Levamisole is an isomer of tetramisole. Although it is commonly used as an antihelminthic, it does have a wide range of immunomodulatory properties **(22).**
- **Afamelanotide**: Afamelanotide is an alpha melanocyte stimulating hormone agonist analogue, a regulatory protein that regulates melanogenesis and melanocyte proliferation. Afamelanotide is delivered as a subcutaneous implant, which roughly lasts for about 2 months **(13).**
- **Statin**s: Statins are competitive inhibitors of 3-hydroxy-3-methylyglutaryl-coenzyme A reductase that reduce low-density lipoprotein-C levels and are proposed to exert anti-inflammatory, antioxidant and immunomodulatory properties; thus, they (Atorvastatin and Simvastatin) are being tried in the treatment of several immunological disorders like vitiligo, alone or in combination with NBUVB **(23).**
- **Minocycline**: Minocycline is an antibiotic with immuno-modulatory, anti-inflammatory, and free radical scavenging properties. Its efficacy has been reported in vitiligo at a daily dose of 100 mg orally **(13).**
- **Cyclosporine**: Cyclosporine is an oral calcineurin inhibitory with a predominant immunomodulatory action **(24).**
- **Cyclophosphamide:** It has the suppressive action on lymphocytes and antibody production so recently used as an off-label drug in vitiligo **(25).**
- **Azathioprine:** Azathioprine is used as an immunosuppressant. It is a corticosteroid-sparing agent, and thus reduces the toxicity and side effects associated with prolong use of corticosteroids **(26).**
- **Zinc:** Vitiligo patients have decreased intracellular zinc, with leads to oxidative damage and apoptosis of melanocytes **(25).**
- **Biologicals**: Rituximab is a chimeric monoclonal antibody against CD20 protein on the surface of B cells. Its use in vitiligo is off label **(27).**
- **Vitamin B12 and Folic Acid:** Vitiligo is associated with decreased serum levels of vitamin B12 and folic acid. Vitamin B12 and folic acid supplementation may act via decreasing homocysteine levels. Homocysteine has been noted to be elevated in vitiligo patients **(28).**
- **Antioxidant Vitamins:** Antioxidants, notably vitamin E, have an important role in the skin to scavenge ROS, prevent membrane oxidation, and reduce UVB-induced skin damage **(29).**
- **Methotrexate**: Methotrexate is an antimetabolite and anti-folate drug that is tested in many autoimmune diseases. It helps in decreasing the number of T cells producing TNFa and thus may help in the treatment of vitiligo **(30).**

A prospective randomized open label study showed oral methotrexate 10mg weekly dose to be comparable to corticosteroid oral mini pulse (total weekly dose of 5 mg dexamethasone) after 6 months of treatment and was well tolerated. Sun exposed lesions responded the most and lesions on palms, soles and mucosa responded poorly to methotrexate. Blood parameters need to be closely monitored, as methotrexate is known to cause myelosuppression and hepatotoxicity **(31).**

IV- Surgical Modalities in Management of Vitiligo:

A therapeutic option to patients with SV and those with NSV with stable disease after at least a year of documented nonresponse to medical interventions and absence of Koebner's phenomenon. The purpose of the transplantation is to transfer to the vitiliginous skin a reservoir of healthy melanocytes for proliferation and migration into areas of depigmentation **(32).**

The surgical techniques that are mentioned in the European guidelines include:

- ***Tissue grafts*** (full-thickness punch, split-thickness and suction blister grafts).
- ***Cellular grafts*** (autologous melanocyte cultures and noncultured epidermal cellular grafts) **(33).**
- Other techniques include cultured epidermal suspensions **(34)**.

- Hair follicle transplantation **(35).**

V- *Alternative Treatment Options*:

- **Platelet-rich plasma (PRP)**: It is an autologous preparation of platelets in concentrated plasma which contains various growth factors. It is hypothesized that these growth factors promote melanocyte stimulation **(36).**
- **Fluorouracil (5-FU)**: Several studies have shown the efficacy of 5-FU in the treatment of vitiligo using different methods of application, such as after skin ablation by laser combined with phototherapy after dermabrasion **(37).**

VI- *Camouflage*:

In mild cases, vitiligo patches can be hidden with makeup or other cosmetic camouflage solutions. If the affected person is pale skinned, the patches can be made less visible by avoiding tanning of the affected skin **(38).**

VII- *Depigmentation*:

In cases of extensive vitiligo, the option to depigment the unaffected skin with topical drugs like monobenzone, hydroquinone or mequinol (4-methoxy phenol, a derivative agent from hydroquinone which inhibits the synthesis of melanin by polymerization of the oxidation of tyrosine) may be considered to give the skin an even colour. The removal of all the skin pigment with monobenzone is permanent and vigorous. Sun-safety must be adhered to for life to avoid severe sunburn and melanomas. Depigmentation takes about a year to complete **(39; 40).**

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