

VITILIGO AND ITS MANAGEMENT UPDATE: A REVIEW

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ABSTRACT

Vitiligo is a common, acquired, often familial melanocytopenic disorder with focal depigmentation of skin; there are several new treatments which appear to have a higher success rate than previous therapies. There are nuances in the treatment of patients with vitiligo which are not easy to list. Common therapeutic options include phototherapy with psoralens and topically applied steroids with or without PUVA. Those who have tried PUVA without success should quit and look for other treatment options like narrow band ultraviolet B (NBUVB) which has recently been reported to be effective therapy for vitiligo, the only clinical parameter that could differentiate non-responders from responders is previous exposure to PUVA.

More recently lasers, vitamin D analogues, tacrolimus and skin grafting have been shown to play some role in the treatments of patients with larger lesions. Targeted phototherapy with single wavelength laser light has proved to be effective and time-efficient therapeutic option for the management of vitiligo. Surgical techniques intend to re-pigment the skin and are an interesting therapeutic option. At this time the exact cause of vitiligo is still unknown, various treatment modalities are available but there is no single cure. The purpose of this review is to describe the different treatment modalities available currently.

KEY WORDS: Vitiligo, PUVA, Vitamin D analogues, Tacrolimus.

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INTRODUCTION

Vitiligo is a disfiguring medical disease of unknown origin that causes destruction of melanocytes in the skin, mucous membranes, eyes, and occasionally in hair bulbs. The loss of melanocytes alters both structure and function of these organs and results in the absence of pig-

ment. Melanin, the pigment that determines color of skin, hair, and eyes, is produced in cells called melanocytes. If these cells die or cannot form melanin, the skin becomes lighter or completely white. The density of melanocytes in skin is the same among different races, but skin pigmentation in ethnic groups varies because of variations in the rate of pigment production by melanocytes.

This disease is affecting about 1% of the world's population. It may appear from birth to old age but the onset is most commonly seen between the age group 10-30 years. It is rarely seen in infancy or old age. In about 30% of patients, there is familial clustering of cases. The incidence decreases with increasing age. Although vitiligo can begin on any part of the body, the first manifestations are loss of pigment most commonly on the hands, feet, arms,

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face, and lips. 40% of patients have ocular pigmentary abnormalities and 5% will note some loss of visual acuity, poor night vision, or photophobia¹.

CLINICAL TYPES

1. Generalized Vitiligo: It is the most common presentation with bilateral, symmetric depigmentation of the face (involving periorificial areas) neck, torso, extensor surfaces or bony prominences, axillae, hands, wrists, legs, orifices, or mucosal surfaces.

2. Focal Vitiligo: This type is a depigmented macule in a localized, non-dermatomal distribution.

3. Segmental Vitiligo: It occurs in a dermatomal asymmetrical distribution.

4. Universal Vitiligo: Universal vitiligo implies loss of pigment over the entire body surface area. Most common presentation in patients is usually depigmented lesions in sun-exposed areas.

ETIOLOGICAL THEORIES

1. Auto immune Theory: Anti bodies against melanocytes surface antigens exist and the extent of de-pigmentation is correlated with the incidence and the level of anti-bodies against the melanocytes. Their increased incidence of vitiligo in certain autoimmune diseases such as thyroid disease (Hashimoto's thyroiditis and Graves' disease), Addison's disease, pernicious anemia, insulin-dependent diabetes mellitus, and alopecia areata². Autoantibodies directed against these and other organ systems can also be present without clinical correlation.

2. Auto-Cytotoxicity Theory: An intermediate or metabolic product of melanin synthesis causes melanocyte destruction. A second mechanism by which auto-cytotoxicity occurs is through the inhibition of thioredoxin reductase enzyme.

3. Neural Theory: A neurochemical mediator destroys melanocytes or inhibits melanin production. Lerner³ initiated this theory on the basis of reports of patients afflicted with a nerve injury and vitiligo, with decreased or absent skin finding in denervated areas.

4. Genetic hypothesis: Melanocytes have an inherent abnormality that impedes their growth and differentiation in conditions that support normal melanocytes. Because none of these theories alone is entirely satisfactory, some have suggested a composite hypothesis.

EVALUATION OF THE PATIENT

The primary goal of the therapy should be the restoration of the melanocytes to the skin so that the repigmented skin regains its normal color and functions.

Physical Examination: For patients with fair skin, such as those with Fitzpatrick skin types I and II, detection of hypopigmented or depigmented patches of vitiligo may require the use of a Wood's lamp to delineate the areas of involvement. In patients with darker skin, a Wood's lamp examination can be helpful to assess the degree of hypopigmentation or depigmentation in individual lesions.

Laboratory Evaluation: Specific tests are required for autoimmune diseases such as adrenal insufficiency, diabetes mellitus, pernicious anemia and thyroid disease if present with vitiligo. Antinuclear antibody test, liver and renal function tests are done in case the patient is required to undergo photochemotherapy later.

Biopsy: In some situations despite all the above-mentioned tests a biopsy from the lesions is required to confirm the clinical diagnosis and to differentiate it from other hypopigmentary disorders for the management.

TREATMENT OPTIONS

A) Medical

1. Topical and systemic corticosteroids.
2. Psoralen with exposure to ultraviolet A (PUVA) radiation therapy.

3. Heliotherapy.
4. Depigmentation therapy with monobenzylether of hydroquinone.
5. Vitamin D analogues.
6. Tacrolimus

B) Surgical

1. Mini grafting, Thin split-thickness grafting and Micropigmentation.
2. Transplantation of cultured melanocytes.
3. Transplantation of non-cultured melanocytes.

C) Newer UVB/Laser Techniques

1. Narrow band UVB therapy.
2. 308-nm excimer laser.
3. Depigmentation with Q-switched ruby laser.

A) MEDICAL

1. Topical and systemic steroids

Topical corticosteroids are sometimes effective repigmenting agents. Optimal success of treatment with topical corticosteroids requires applications for 3 to 4 months or longer. Mid- or lower potency corticosteroids may be preferable to avoid the toxicity associated with long-term applications of corticosteroids. Lower potency topical corticosteroids should be considered in young children younger than 2 years of age who are not candidates for topical PUVA. Corticosteroid cream is applied to depigmented skin once daily for 3 to 4 months and the response is monitored with Wood's lamp examination at 6-week intervals. Therapy is continued if repigmentation occurs, but stopped if there is no evidence of response after 3 months. Photographs may assist in evaluating progress. Possible side effects that require discontinuation of the medication include capillary telangiectases, epidermal atrophy and striae.

2. Psoralen-UVA:

PUVA is a form of repigmentation therapy where a type of medication known as psoralen is used. This chemical makes the skin very sensitive to light. Then the skin is treated with a special type of ultraviolet light called UVA. Sometimes, when vitiligo is limited to a few small areas, psoralens can be applied to the vitiligo areas before UVA treatments. Treatment with PUVA has a 50 to 70% chance of returning color on the face, trunk, and upper arms and upper legs⁴. How PUVA therapy stimulates these inactive melanocytes is still unknown.

- a) *Oral psoralen photochemotherapy (PUVA):* Oral photochemotherapy is used for patients with more extensive vitiligo or for persons recalcitrant to topical therapy. Oral psoralens are not usually recommended for children younger than 12 years of age. Maximal repigmentation occurs with the new form of 8-methoxypsoralen (Oxsoresalen-Ultra) given in a dose of 0.2 to 0.4 mg/kg. The drug is ingested 1 to 1½ hours before UVA exposure. The usual initial UVA exposure is 1 to 2 J/cm². Subsequent treatment may be increased, usually in increments up to 1 J/cm², until moderate asymptomatic erythema is observed (a pinkness present on white skin). Treatments are given two to three times weekly, but never on two consecutive days. Darker-pigmented patients respond better to PUVA therapy because of the increased tolerance to greater cumulative UVA dosage. Children also experience repigmentation to a greater extent than adults. Vitiligo on the trunk, proximal extremities, and face respond well to PUVA therapy, although distal extremities and periorificial areas do not. Patients must wear UVA-blocking glasses from the time of exposure to psoralen same and next day. The patients are encouraged to wear appropriate clothing for sun protection and to use a sunscreen. The potential side effects include burn, erythema, pruritus, xerosis, carcino-

genicity, pigmented lesions, cataracts, and aging. It is contraindicated in pregnant or breast-feeding women, or those with a history of skin cancer, radiographic therapy, photosensitivity disorders.

b) *Topical Therapy:*

Topical psoralen photochemotherapy is often considered for patients with limited involvement (<20% of the body surface) or for children older than 5 years of age with localized patches of vitiligo. However in special circumstances, dermatologists with special expertise may use topical photochemotherapy for children younger than 5 years of age. Oxsoralen lotion is usually diluted in ethanol or hydrophilic petrolatum (Aquaphor) to a 0.01% to 0.1% concentration. The preparation is applied to the lesions 15 to 30 minutes before UVA exposure. The initial UVA dose is usually 0.12 to 0.25 J/cm² and is increased to achieve mild erythema, usually in increments of 0.12 or 0.25 J/cm² weekly according to the patient's skin type. Treatments are usually given one to three times per week, but not on two consecutive days. A broad-spectrum sunscreen to be used post treatment with other precautions as mentioned above.

3) *Heliotherapy:*

Trisoralen and sunlight (heliotherapy) is a form of photochemotherapy. Trisoralen is prescribed initially at a dose of 0.3 mg/kg with initial sun exposure up to 15 minutes, ideally at the same time each day. The drug is ingested 2 to 4 hours before exposure to sunlight. Subsequent exposures are increased in increments of 5 minutes per treatment until the skin becomes moderately erythematous. The dose and duration of sun exposure is adjusted according to the erythematous response. Treatments are given two to three times weekly, but not on two consecutive days. Patients must wear UVA-blocking glasses and follow other precautions as mentioned in the above procedures.

4) *Depigmentation:*

For some patients with extensive involvement or those with more than 50% involvement of the skin and have demonstrated therapeutic resistance to efforts at repigmentation the most practical treatment for vitiligo is to remove remaining pigment from normal skin and make the whole body an even white color. That is usually done with 20% monobenzoether or hydroquinone applied to the skin once or twice daily for one to three years. The pigment removal is permanent and irreversible, resulting in permanent photosensitivity. Whatever procedure is done, repigmentation or depigmentation one must realize that the process is about year long and demands a major commitment on the part of the patient. Possible side effects include, dermatitis, pruritus, xerosis, conjunctival corneal pigmentation may occur. Sun protection measures should be employed.

5) *Vitamin D Analogues:*

Some cases show poor clinical response to topical steroid ointments or PUVA therapy, such regimes are generally avoided in treating facial lesions due to undesirable side effects, hence such patients are treated with Vitamin D analogues i.e topical taclacitol, alpha 24(OH)₂D₃ with a good clinical response⁵.

6) *Tacrolimus:*

1% tacrolimus can be used in patients especially in children with good results, it has proved to be as effective as 0.05% clobetasol propionate to restore skin color in lesions of vitiligo, since it does not produce skin atrophy or other adverse side effects. Tacrolimus is very helpful in treating younger patients and sensitive areas such as eye-lids^{6,7,8,9}.

B) SURGICAL OPTIONS

1) *Micropigmentation or (Tattooing):*

Micropigmentation involves the tattooing of vitiliginous skin in an attempt to match the surrounding normally pigmented skin, iron oxide pigment injected into the dermis is most often utilized. An exact match of pigment is

difficult to obtain. Dark complexion cases show better results than fair complexion ones¹⁰.

2) *Dermabrasion and topical 5-fluorouracil:*

Vitiliginous skin is superficially dermabraded and 5% fluorouracil is applied twice daily under occlusion for 7 to 10 days. Complete, but darker, repigmentation may result. Undesirable effects include infection, scarring, and aggravation of vitiligo.

3) *Transplantation of in vitro-cultured epidermis:*

Melanocytes are harvested from a small fragment of pigmented skin from the patient. Blisters are formed by suction or liquid nitrogen at both donor and recipient sites, and the epidermis from the donor sites is removed. The melanocytes are isolated and grown in cell culture for 3 weeks. The melanocytes adhere to Vaseline gauze that is divided and placed over the denuded area of recipient vitiliginous skin. A variant of this technique involves injecting in vitro-cultured melanocytes into suction blisters formed at the recipient site or applying melanocytes to dermabraded skin. With the in vitro transplantation method, the repigmented site can be as large as 10 times the donor site, although continual passes with this method can yield a potentially large number of melanocytes to cover a large depigmented area. After 1 to 2 years of observation, the repigmented areas did not depigment^{11,12}. With the epidermal grafting method, there is low incidence of scarring. Epidermal grafting using tops of suction blisters has been found to be the most effective surgical procedure¹³.

4) *Transplantation of noncultured melanocytes:*

A method that resembles in vitro-cultured melanocytes, but instead noncultured melanocytes were isolated from skin samples obtained within a dermatome. The melanocytes were treated with trypsin, treated with EDTA, placed in saline solution, and injected as a suspension into blisters in the recipient site created with liquid nitrogen. There was no significant difference between these two treatments^{11,12}.

C) *NEWER UVB/ LASER TECHNIQUES*

1. *Narrow band UVB (NBUVB):*

Among the several new treatments for Vitiligo this treatment appears to have a higher success rate than previous therapies. A new device is used which can produce focused beam of narrow UVB (311nm) (microphototherapy) on vitiligo patches only, it is usually used two-three times per week with an initial dose of 100mj/cm (2), the dose is gradually increased by 10% to 20% per treatment for 20 treatments, and then by 2% to 5% until at least 50% repigmentation is observed. Photographs of the patients are taken at the beginning of the therapy and then at monthly intervals. Up till now no side effects have been reported hence this could represent the treatment of choice for Vitiligo limited to less than 30% of the skin surface^{14,15}. Repigmentation notably appears on the face, neck, lower arm, chest, back and legs while it is less on the hand, feet and ankles¹⁶.

2) *308-nm Excimer laser:*

Recently narrow-band UVB (311nm) has been successfully used for the treatment of Vitiligo patients. Targeted phototherapy with single-wavelength laser light is a treatment alternative that has proved to be time efficient and effective therapeutic option for the management of vitiligo. More recently excimer laser with wavelength of (308nm) has been tried for targeted treatments of localized vitiligo with very good results, and may represent a new treatment modality for the management of stable Vitiligo^{17,18,19}.

3) *Depigmentation with Q-switched ruby laser*

Bleaching creams which are often used in depigmentation therapy may lead to serious side effects. Q-switched (QS) ruby laser can destroy melanosomes in melanocytes and keratinocytes by selective photothermolysis. Patients with extensive Vitiligo are first tanned and then QS ruby laser is used with good results, and has proved to be an effective and safe method of removing remnants of normal pigmentation in patients with vitiligo universalis²⁰.

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