Symposium - Vitiligo

Ultraviolet-based therapy for vitiligo: What's new?

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ABSTRACT

Vitiligo is an ancient disease in which depigmented and hypopigmented macules appear on the skin. It is a disfiguring condition that may lead to severe psychological trauma. Among the many treatment modalities available for use in vitiligo, those using light therapy, and in particular ultraviolet (UV) light, are some of the most effective treatments. UV-based therapy includes phototherapy (narrowband UVB), photochemotherapy (psoralens with UVA), and targeted phototherapy (excimer laser and excimer lamp). It is important for any practitioner of UV-based therapy to understand the efficacy of each treatment type, as well as their respective adverse effects. In order to take full advantage of UV-based therapy, location, dosing, and photoadaptation must also be taken into account. This review discusses the various UV-based therapeutic options, adjuvant therapies, optimal dosing guidelines, appropriate patient selection, future treatment options, and recommendations based upon the current evidence and the authors' experience with vitiligo.

Key words: Adjuvant therapy, dosing, phototherapy, photochemotherapy, vitiligo

INTRODUCTION

For many years, among dermatologic diseases, dyschromic conditions such as vitiligo are often sidelined due to their apparent lack of symptomatology or functional deficit. However, vitiligo can be a distressing and potentially disfiguring condition, especially to those patients with darker skin phototypes. It has a prevalence of approximately 1% in the worldwide population, with specific studies finding prevalences of 1.13% in Surat, India,[1] and 0.46% in Kolkata, India.[2] Clinically, vitiligo lesions appear as hypopigmented and depigmented macules and patches. It can cause social anxiety and have serious repercussions on the personal lives of many patients.[3] The etiology of vitiligo is thought to be multifactorial; genetics, autoimmunity, and other auto-cytotoxic components are all thought to play a role in the pathophysiology to varying degrees.[4] There are many misconceptions concerning vitiligo in the lay population, such as confusion with leprosy or other contagious disease.[5]

When considering treatments for vitiligo, there are many factors which must be considered. Pigmentation must be color matched to the surrounding skin to avoid the appearance of hyperpigmented or hypopigmented areas. Time to repigmentation and stability of repigmentation are also important parameters, as a faster repigmentation rate followed by recurrence of lesions is not as clinically useful as a slow but stable repigmentation. Because most studies are done on clinically stable vitiligo lesions, treatments that stabilize progressive vitiligo have not been well evaluated. Side effect profiles of the treatment modalities are also very important, especially in patients with darker skin types. Iatrogenically induced dyspigmentation can cause further distress to the already distressing lesions of vitiligo.

A key aspect in clinical research that is deficient in vitiligo is a lack of a uniform scoring index. Many researchers use clinical measures, such as subjectively

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/0378-6323.90945

How to cite this article: Hamzavi IH, Lim HW, Syed ZU. Ultraviolet-based therapy for vitiligo: What's new?. Indian J Dermatol Venereol Leprol 2012;78:42-8.

Received: January, 2011. **Accepted:** April, 2011. **Source of Support:** Nil. **Conflict of Interest:** None declared.

assessed 50% repigmentation as a metric for determining the lesion resolution.[6] Although it is often convenient and efficient to use quick clinical estimates of repigmentation, the lack of objectivity and large interobserver variability makes it virtually impossible to compare the studies for different treatments. There have been some recent attempts at developing more objective, parametric measures for vitiligo repigmentation which have shown some promise.[7] Such metrics offer a much more standardized method of scoring individual vitiligo lesions and can make it much easier to compare studies with each other. These include the Vitiligo Area Scoring Index (VASI),[7] the Vitiligo European Task Force score,[8] and the digital image analysis-based methods.[9]

There are now multiple treatment modalities for vitiligo, ranging from topical corticosteroids, topical calcineurin inhibitors, ultraviolet (UV)-based therapy (narrowband [NB] UVB, targeted phototherapy, and psoralen and UVA photochemotherapy), to surgical treatments (punch grafting, suction blister grafting, melanocyte keratinocyte transplantation). This article will focus on UV-based therapy and give practical treatment guidelines for practitioners treating vitiligo patients.

OPTIONS FOR ULTRAVIOLET-BASED THERAPY

UV-based therapy has been a mainstay of therapy for vitiligo for many decades. The earliest form is psoralen and UVA (PUVA) photochemotherapy. Currently, the most commonly used form is NB-UVB and for limited areas, targeted phototherapy (excimer laser or excimer lamp).

PSORALEN AND ULTRAVIOLET A

The use of UV-based therapy in the treatment of vitiligo is not a new concept. Ancient Egyptian and Indian writings mention the application of the *Ammi majus*[10] and *Psoralea corylifolia*[11] plants upon pale macules, which were then exposed to sunlight. The active components of these plants were later determined to be 8-methoxypsoralen, 5-methoxypsoralen, and 8-isoamyleneoxypsoralen.[12] Modern photochemotherapy began with El-Mofty[13] in 1948, with the purification of topical and oral psoralens. Once it was determined that psoralens were optimally activated with UVA at 360 nm,[14,15] investigators began using fluorescent black lights in combination with psoralens, and PUVA therapy came into existence.[16]

PUVA was shown to be an effective repigmentation strategy for vitiligo by many earlier studies.[14,17] However, it has several limitations. Administration of psoralens can cause nausea, and rarely, vomiting. UVA administration needs to be done within 1 to 2 hours after ingestion of psoralens, and ocular and skin photoprotection needs to be done once psoralens are administered. Because of deeper penetration of UVA compared to UVB, inappropriate administration of PUVA can result in severe and painful blisters. Chronic treatment (>400 sessions), as used for psoriasis, can induce lentigines and photocarcinogenesis.[18] Furthermore, it was noted to be only moderately effective for vitiligo, and has been reported to have poor color match, at least at the end of the treatment course.[19]

Dosing schedules for PUVA follow a relatively similar course in most prospective studies. Initial doses range from 0.25 to 2 J/cm^2, with increases of 0.2 to 0.5 J/cm^2 each session until erythema develops or a maximum dose is reached (one study cited a maximum of 6 J/cm^2).[20-23] One study used a 20% increase instead of a fixed increase, but otherwise followed the same endpoint.[24] Treatments were done two to three times a week.

NARROWBAND ULTRAVIOLET B

NB-UVB lamps have a sharp emission peak at 311 to 313 nm. Therefore, NB-UVB is easier to administer than PUVA, and lacks many of the side effects of the latter. The efficacy of NB-UVB has been shown in several studies. A study in 2004 compared the use of NB-UVB three times a week with unirradiated control for the treatment of symmetrically distributed vitiligo. Each patient was treated on one half of their body with NB-UVB, while their other half was left unexposed. After a total of 60 treatments (or 6 months), there was a 42% improvement in VASI scores on the side treated with NB-UVB, compared to just 3% on the control side.[7] In addition, it was noted that the legs responded best to the treatment, followed by the trunks, arms, hands, and feet. The face was treated in an all-or-none fashion and assessed but not included in the final analysis due to lack of control data.

Yones *et al.*[6] compared twice weekly NB-UVB to

PUVA therapy in two groups of patients with vitiligo; patients were treated until complete resolution of vitiligo took place, or no improvement after 32 sessions, or intolerance to treatment, or a completion of 200 sessions. The median number of treatments for the NB-UVB and PUVA groups was 97 and 47, respectively. The investigators showed that NB-UVB treatment resulted in greater than 50% repigmentation in 64% of patients, while PUVA resulted in a similar degree of pigmentation in only 36% of patients. In addition, the color match for NB-UVB was noted to be superior to PUVA.[6] Another study by Bhatnagar *et al.*[22] compared the mean repigmentation for therapy-resistant sites (hands and feet) in patients exposed to NB-UVB *vs* PUVA; it showed that after approximately 6 months of treatment (thrice weekly), a 68% of repigmentation was possible using NB-UVB *vs* 54% using PUVA.[22]

Although NB-UVB has notably fewer adverse effects when compared to PUVA therapy, it has been known to cause phototoxic reactions and tanning.[25] There are little long-term data on the use of UVB in the treatment of vitiligo, but one potential adverse effect could be an increased chance of non-melanoma skin cancer (NMSC) in vitiliginous skin receiving NB-UVB. A retrospective review of 477 vitiligo patients in 2009 showed a small non-statistically significant increase in the incidence of NMSC in vitiligo patients.[26] However, all patients with reported NMSC were of skin types I and II, and had the NMSC on sun-exposed areas. The increased incidence was not correlating with NB-UVB treatment.

Although there are little to no comparisons of the dosing regimens for NB-UVB in the literature, the typical dosing regimen for NB-UVB prospective studies involve an initial dose of 150 to 250 mJ/cm^2, with an increase in dose at each visit of 10 to 20%.[22-24,27-31] Some studies base their initial dose on skin type,[32] while others choose a starting dose at 70% of the minimal erythema dose (MED) of the patient.[7] Treatment occurs two to three times a week, with a maximum dose that varies from 300 to 3 J/cm^2, or until there is perceptible erythema, whichever comes first.

TARGETED PHOTOTHERAPY

In addition to NB-UVB, monochromatic and near-monochromatic UV light sources have been used as a treatment for vitiligo as well. The xenon-chloride excimer laser is a 308 nm high-intensity light source with proven efficacy for vitiligo. Two studies compared the efficacy of excimer laser to NB-UVB, and found that excimer laser caused more significant and quicker repigmentation.[33,34] None of these studies were controlled for body site, and none used a standardized scoring method. Excimer laser has also been compared with excimer lamp, a nearly monochromatic light source. The excimer lamp treats a larger area since it is a light source, as opposed to a laser source, and therefore can be more efficient in supplying the required dose. The excimer lamp was found to give equivalent pigmentation as compared with excimer laser. The excimer lamp showed increased erythema, which was hypothesized to be caused by a difference in the photobiological response to the lamp *vs* the laser. The repigmentation rate was between 25 and 50% over the entire body, and between 50 and 75% for vitiligo lesions not located at bony prominences or extremities. These scores were equivalent for both light sources.[35]

As with any treatment, UV radiation is not without adverse effects. Excimer laser has been found to be very well tolerated with mild to severe erythema being the most common adverse effect; blisters and pruritus are reported very rarely.[36]

Dosing for targeted phototherapy (excimer laser and lamp) may start with a fixed dose, in studies varying from 5.5 to 100 mJ/cm^2, and increasing by 10 to 30% at each treatment.[37-39] Dosing may also be based on the patient's MED, in which case the initial dose is 70% of the MED.[40] The doses are increased until erythema develops, at which point the dose is kept constant.

ADJUVANT THERAPY

To evaluate if response to NB-UVB can be enhanced, a number of adjuvant therapies have been studied. Vitamin D analogs such as calcipotriol (also called calcipotriene) have been used, with mixed results in terms of efficacy. In 2004, a study reported improvement in patients using calcipotriol when combined with NB-UVB.[41] Conversely, in 2005 another study showed that there was no statistically significant benefit in adding topical calcipotriol to NB-UVB treatment regimen.[42]

Topical calcineurin inhibitors such as a pimecrolimus and tacrolimus, which have been shown to be effective

as monotherapy, have also been evaluated as possible adjuvant therapies in combination with NB-UVB. Compared with NB-UVB alone, NB-UVB plus twice daily use of pimecrolimus cream has been shown to cause better repigmentation of lesions on the face, but not in other areas of the body.[29] Tacrolimus ointment has been shown to increase the repigmentation rate when used twice daily in combination with excimer laser on typically UV-resistant areas (bony prominences and extremities).[43] However, when used in combination with NB-UVB, one study found that it did not cause a statistically significant increase in repigmentation.[44]

Topical hydrocortisone butyrate has been shown to have some benefit in conjunction with excimer laser, as shown by a study in 2008, in which 43% of patients receiving topical hydrocortisone showed greater than 75% repigmentation as compared to 16% of patients who received excimer alone.[45]

Topical antioxidants such as pseudocatalase have also been suggested for use as adjuvant therapy for vitiligo, but a recent randomized controlled study showed no significant increase in repigmentation when using topical pseudocatalase cream in conjunction with NB-UVB.[31] Oral antioxidants have also been studied, with mixed results. Multiple studies have investigated the use of vitamins E, C, B12, and folic acid, and most have either shown statistically insignificant improvements when compared to UV therapy alone or no improvement at all.[46-48] One study compared the use of a combination of antioxidants containing vitamins C and E, alpha lipoic acid, polyunsaturated fatty acids, and cysteine monohydrate, and found it to give significantly increased repigmentation when used in conjunction with NB-UVB when compared towing NB-UVB alone.[49]

Plant immunomodulators, such as *Polypodium leucomotos*, were originally used as a method of protecting against the phototoxic characteristics of UV therapy.[50] They have since then been shown to have some benefit when used in the head and neck area in combination with NB-UVB.[51] One study compared the efficacy of topical human placental extract as an adjuvant to NB-UVB and found a statistically insignificant response on the side of the body using the extract.[52]

The use of oral corticosteroids as a treatment for vitiligo has been a controversial subject, with few controlled studies comparing their efficacy. One such study by Rath *et al.*[22] compared four treatment groups of patients with progressive vitiligo: oral minipulse steroid (OMP) alone, OMP with PUVA, OMP with NB-UVB, and OMP with broadband-UVB. The results showed that OMP was not useful on its own, but had some value as an adjuvant therapy for PUVA and NB-UVB.[23] This is an area of investigation which could be improved by better measures to assess vitiligo stability.

OPTIMAL DOSING

Correctly dosing a UV-based therapy regimen is one of the most important aspects of correctly treating patients with vitiligo. In particular, how patients' skin reacts and adapts to UV can have profound consequences on incrementally increasing the dose. Photoadaptation refers to the phenomenon by which increasing doses of radiation (in this case, UV radiation) after initial treatment are required to cause the same level of effect on the skin. In order to test this, MED testing is often done, which requires incremental doses of UVB to be irradiated on small areas of the skin until erythema is noted. These results can be assessed clinically by inspection, or spectroscopically using a colorimeter or other color-measuring device.

A study of photoadaptation in vitiliginous skin in 2009 showed that approximately two-thirds of patients receiving NB-UVB therapy for vitiligo were shown to be photoadapters, i.e., the MED after treatments was higher than before, with a mean change of 49%. The other third of the patients were noted to be non-photoadapters, as their MED levels either stayed the same or even decreased by a small amount. In the same study, Hexsel *et al.*[53] measured the rate of repair of UVB-induced DNA damage in both vitiliginous and normal skin. Cyclobutane pyrimidine dimer (CPD) levels per megabase of DNA were measured over a 24-hour period, and it was found that vitiliginous skin had 40 to 45% more CPD/megabases of DNA as compared to normal skin, indicating a greater degree of UVB-induced DNA damage on the vitiliginous skin. However, the rate of clearance of CPD/megabases of DNA (a measure of DNA repair) was equivalent between normal and vitiliginous skin, indicating a normal DNA repair mechanism in vitiliginous skin.[53] This study indicates that in order to allow DNA repair to take place, thereby minimizing the long-term side effects of UV exposure, patients with vitiligo should

be treated on a 48-hour dosing schedule, and that 24-hour dosing schedules should be avoided. Based on these two studies, dose increments for patients with vitiligo are only justified in those who are known to photoadapt. Photoadaptation can be assessed after 6 to 9 treatments by repeat MED testing, and comparing the results with the initial MED test.

PATIENT SELECTION

In addition to correct dosing, selecting the appropriate patient for UV-based therapy is important for optimal outcome. In a study of prognostic factors for NB-UVB, Nicaloudiou *et al.*[54] determined several factors for good patient response to phototherapy. Darker skin types generally did better than lighter skin types; patients who showed some response after 1 month were more likely to have better long-term repigmentation rates; and facial lesions responded the best, except for perioral lesions.[54] Although this study gives very relevant information to the practitioner, it was an uncontrolled, non-randomized study. In previously published work, one of the authors anecdotally found that lesions on the head and neck repigmented as well or better than lesions on the rest of the body, and any degree of repigmentation in the face led to patients being pleased with the response.[7] Although these results were not rigorously analyzed, this is confirmed by the experience of the other author.

Yang *et al.*[55] noted that the perifollicular pattern is the most common morphology of repigmentation using both NB-UVB and excimer laser, and that marginal repigmentation around a lesion is associated with better repigmentation.[55] Parsad *et al.*[56] studied various repigmentation patterns to various treatment modalities, and placed them into one of the four categories: perifollicular, diffuse, marginal, and combined. The perifollicular pattern was the most common and was associated with PUVA therapy.[56] This same pattern is most often seen with other forms of UV-based therapy, such as NB-UVB and excimer laser.[55] Diffuse repigmentation, which was associated with topical corticosteroids, appeared to be the fastest pattern but was also the least stable. Marginal repigmentation appeared to be associated with combination PUVA therapy with topical corticosteroids and/or vitamin D analogs, and was noted to have the most stable effect.[56] In the authors' experience, marginal repigmentation is also frequently observed with topical calcineurin inhibitors treatment.

RECOMMENDATIONS

Based on the currently available evidence, it is important for practitioners to select the appropriate patient for UV-based therapy. Stable vitiliginous lesions are usually more responsive, as are lesions in nonacral areas. The patient must be able to commit to at least two months of twice to thrice weekly treatment in order to determine response, which would include being able to detect the non-photoadaptive patient. If the patient does not show any response after 30 twice or thrice weekly treatments, it is unlikely that further treatment will yield any significant response. This should be communicated to the patient at the onset of the treatment course to appropriately manage the expectation of the patient.

Regarding dosing schedules, the evidence in the literature supports the dosing based either on skin type or MED testing. In our institution, we assume all vitiliginous skin to be of skin phototype I, and dose as such. Treatment in all modalities is typically done two to three times a week. For PUVA therapy, dosing is started at 0.25 J/cm^2 and increased to 0.25 to 0.50 J/cm^2 up to a maximum of 8 J/cm^2 or until moderate erythema develops. The initial dose for NB-UVB is usually based on the skin phototype (once again, the assumption is that vitiliginous skin is type I), in which case the starting dose would be 150 mJ/cm^2. However, if MED testing is done, the preference is to use a starting dose of 70% of the MED. This is increased by a factor of 10 to 15% at each treatment as tolerated or up to a maximum of either 3 J/cm^2 on the body or 1 J/cm^2 on the face. The protocol for excimer laser is almost equivalent to NB-UVB in that it is started at 150 mJ/cm^2 and increased by 15% up to a maximum dose of 3 J/cm^2 for the body and 1 J/cm^2 for the face. In all types of UV therapy, if mild erythema develops without tenderness, the increase in the next dose is lowered by 5-15%. If moderate to severe erythema develops, or there is a blistering reaction, and treatment resumes at the last tolerated dose once symptoms resolve.

Among the UV-based therapies, NB-UVB is the most cost effective one. Excimer laser and excimer lamp, although more expensive, give faster pigmentation, and are most appropriate for patients with limited disease, given the treatment times needed for larger areas. Adjuvant therapy, because of the additional cost involved, should also be discussed with the patient at the onset as a potential option. Based on the current

evidence, topical calcineurin inhibitors and topical corticosteroids may be effective adjuvants, with the former being favored by our group because of the well-known long-term side effects of topical corticosteroids.

FUTURE DIRECTIONS

Although UV is the mainstay of current treatment of vitiligo, there are other wavelengths of light which may be considered. Longer wavelengths of light in the visible light range penetrate deeper into the skin, and therefore may produce a reaction at a deeper level than what UV light is capable of producing. In a study published in 2010, Mahmoud *et al.* compared the reaction of skin following irradiation with UVA1 (340-400 nm) and broadband visible light. The study was performed in normal individuals with skin types IV to VI. The melanin and oxyhemoglobin values were measured through the use of diffuse reflectance spectroscopy. The investigators showed that melanin value increased in a dose-dependent manner following UVA1 or visible light exposure. However, the pigmentation produced from visible light was much more prolonged compared with that induced by UVA1. Visible light exposure also induced brisk, prominent but transient erythema, observed clinically and detected by spectroscopy as increased oxyhemoglobin; no such changes were noted following UVA1.[57]

Yu *et al.*[58] showed that visible light produced by a helium neon laser (633 nm) was able to induce melanocyte migration and proliferation.[58] This study was followed up by Lan *et al.*[59] who were able to use the same low-level laser light source to cause repigmentation in segmental type vitiligo.[59]

Further research is needed to elucidate the mechanisms of visible light reactions within the skin. Of particular interest to vitiligo researchers is the action spectrum of melanogenesis, which has never been determined for visible light. This must coincide with basic science research into the immunomodulation and melanocyte repopulation that occurs with visible light or UV radiation. From these principles, we may determine new, undiscovered treatment modalities for vitiligo that may be beneficial for patients.

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