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Phototherapy: The vitiligo management pillar

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Abstract Phototherapy has been the mainstay of vitiligo therapy for several decades. A variety of wavelengths and modalities are available, but narrowband ultraviolet B remains the safest and most commonly used treatment. Acting on multiple steps in vitiligo pathogenesis, narrowband ultraviolet B is one of the few therapies that can effectively induce stabilization and stimulate repigmentation. Achievement of optimal results involves using a combination of appropriate treatment protocols, careful patient selection, and patient education to set expectations. Individual patient characteristics, including disease activity, vitiligo phenotype, lesion location, and skin phototype, should all be considered, along with combination therapies.

Introduction

Phototherapy has been the pillar of vitiligo treatment whether for stabilization or stimulation of repigmentation. Despite the emergence of different therapeutic tools, phototherapy remains significant.

Limitations, related to absence of melanocyte reservoir, anatomic distribution, and duration of the lesions, might make this exceptional tool sometimes less effective. Phototherapy is still required with or resumed after surgical or medical correction in cases having such limitations.

The beginning of phototherapy for vitiligo

The use of phototherapy for vitiligo in the form of photochemotherapy was known as early as 1500 BCE. Early forms of treatment included application or ingestion of plant-derived products from *Psoralea corylifolia* (used in India) and *Ammi majus Linnaeus* (used in Egypt), followed by sun exposure.[1] Further study revealed the active ingredients to be psoralen derivatives.

In 1948, Abdel Monem El Mofty introduced the use of purified 8-methoxypsoralen (8-MOP)[2] with solar or artificial ultraviolet (UV) light in the treatment of vitiligo.[3] Investigators studied topical combined with oral preparations of psoralens and found notable repigmentation in areas treated topically and then exposed to ultraviolet radiation.[4] Intradermal injections of psoralens, however, were ineffective.

These findings led to further study of psoralens photochemotherapy in the 1950s by Thomas B. Fitzpatrick.[5] His group determined that the artificial wavelength ultraviolet A (320–400 nm) was the most effective for activating 8-MOP.[6] The subsequent development of artificial sources that enabled the efficient delivery of these photons to the skin heralded the emergence of the modern psoralens and ultraviolet A (PUVA).

Consequently, the efficacy of PUVA was studied initially in the treatment of vitiligo and then for psoriasis and other skin diseases. Initial investigations in 26 vitiligo patients found that treatment with 8-MOP or trioxsalen followed by exposure to

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artificial sources of UVA led to equivalent repigmentation compared with oral psoralens followed by natural sunlight exposure.[7] Histochemical studies on four patients treated with 8-MOP PUVA confirmed induction of hypertrophic melanocytes perifollicularly within islands of repigmentation, as well as in the peripheral repigmenting margins of skin lesions.[8]

Topical 8-MOP and PUVA was also studied, revealing that low-dose concentrations were as effective as higher dose topical preparations with fewer side effects.[9] Limitations to the use of topical psoralens include phototoxicity and the potential long-term risk of skin malignancy; an additional limitation of systemic psoralens is significant gastrointestinal side effects. These have limited the current use of PUVA in vitiligo.[10–14]

Narrowband UVB: The modern era

In 1981, the TL-01 lamp (311 nm) was first introduced for the treatment of psoriasis.[15] By 1997, narrowband UVB (NBUVB) was under investigation for the treatment of vitiligo given the lower toxicity and improved tolerability of NBUVB compared with PUVA.[16–18]

Initial studies in children with vitiligo revealed that twice weekly treatment sessions for up to 1 year led to more than 75% overall repigmentation in 53% of patients and in stabilization of the disease in 80%.[19] Another early retrospective study, using thrice weekly treatments starting at 280 mJ/cm^2 with 15% dose increments at each subsequent treatment, indicated that five out of seven vitiligo patients achieved more than 75% repigmentation.[20] Further investigations with thrice weekly long-term regimen found similarly high rates of repigmentation with long-term therapy. The main patterns of repigmentation associated with NBUVB are perifollicular pigmentation[21] followed by diffuse repigmentation.[18]

Compared with PUVA in a retrospective review, patients treated with NBUVB had higher rates of marked to complete repigmentation (41.9% versus 23.6% in PUVA-treated patients).[22] NBUVB-treated participants also had more stable repigmentation and better color match. NBUVB is better tolerated than PUVA and has the advantages of being able to be used in children and pregnant or lactating women.[22–24] Side effects of NBUVB include possible phototoxic reactions, koebnerization, reactivation of herpes simplex virus, and pruritus. Also, darkening of normal-appearing surrounding skin may temporarily accentuate the appearance of vitiliginous lesions, and patients should be counseled appropriately. Proper dosing lamp calibration and close follow-up can often minimize many of these side effects.[25]

The mechanisms by which NBUVB induces repigmentation are incompletely understood (Figure 1)[26]. *In vitro* testing has found that NBUVB irradiation can stimulate melanocyte proliferation as well as migration.[27–39] Another report described melanocyte proliferation that was stimulated by supernatant of NBUVB-irradiated keratinocytes, an effect that seemed to be mediated via endothelin 1.[38] NBUVB has also been found to directly stimulate hair follicle–derived neural crest stem cells to differentiate into melanocyte lineage.[35,40] NBUVB appears to be more cytotoxic to lymphocytes in the epidermis and papillary dermis compared with broadband UVB. If vitiligo is considered as an immune-mediated process, this may party explain its efficacy.[41]

Monochromatic excimer light (308 nm)

Monochromatic excimer light was first described for the treatment of psoriasis in 1997, and the first case of successful use of the excimer laser for the treatment of vitiligo was reported 4 years later.[42] Additional studies have found that twice weekly treatments with monochromatic excimer light (MEL) for up to 60 treatments starting at 100 mJ/cm^2 with increments of 10% to 25% led to higher rates of repigmentation on the face compared with acral and axillary lesions.[43] The initial repigmentation with twice weekly treatments can be seen as early as after eight treatments in 95% of patients, with the vast majority of patients achieving good to excellent repigmentation, including some who were NBUVB nonresponders.[44] The main advantage of the MEL lamp is the ability to irradiate larger body surface areas compared with laser-treated areas.[45] Both devices have been found to be comparable[46] or even superior to NBUVB.[45,47] Benefits of MEL include less frequent treatments needed and lower total treatment duration, which often increases patient compliance.[44,46] Both MEL laser and lamp are FDA approved for treating vitiligo.[48]

Combination therapies

Although NBUVB is the cornerstone of vitiligo treatment, combinations with medical or surgical therapies may enhance the anticipated results.[49] Such combinations are often most useful in patients with recalcitrant lesions or with lesions in special sites. Topical immunomodulators can be used simultaneously with phototherapy to achieve better response. The greatest benefit has been found with topical corticosteroids[50] or calcineurin inhibitors.[51] One randomized controlled trial reported significantly higher repigmentation rates for head and neck lesions treated with hydrocortisone 17-butyrate cream in addition to MEL.[52] In a randomized trial with the addition of tacrolimus 0.1% to MEL therapy, there were better rates of repigmentation and a higher percentage of patients achieved more than 75% repigmentation than with use of MEL alone.[53] Vitamin D analogues,[54] which, in addition to immune modulation, stimulate melanocyte proliferation (via stem cell factor) and migration (via matrix metalloproteinase [MMP]-9) and increase melanin synthesis,[55] have unfortunately not been found to provide additional benefit in patients undergoing phototherapy. Afamelanotide, a synthetic analogue of the naturally occurring α-melanocyte–stimulating hormone, stimulates melanogenesis and protects against UV-induced damage.[56] It