Phototherapy and Combination Therapies for Vitiligo

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KEYWORDS

• Vitiligo • Phototherapy • Narrowband ultraviolet B • Excimer

KEY POINTS

- Different forms of phototherapy for vitiligo include broadband UVB, narrowband UVB (NB-UVB), excimer light and excimer laser, and psoralen plus UVA.
- The main proposed mechanisms for induction of repigmentation in vitiligo by UV light include the induction of T-cell apoptosis, and stimulation of proliferation/migration of functional melanocytes in the perilesional skin and immature melanocytes in hair follicles.
- Optimizing NB-UVB requires consideration of different factors that affect the phototherapy protocol.
- Introducing the Vitiligo Working Group consensus to highlight possible answers to questions lacking evidence in phototherapy of vitiligo.
- Focusing on common obstacles met during phototherapy of vitiligo and how to overcome them.
- Different forms of combination therapies used with phototherapy in vitiligo and their various degrees of success.

INTRODUCTION

Vitiligo is a disease characterized by disappearance of melanocytes from the skin. It can negatively influence the physical appearance of affected individuals, and may profoundly affect a person's psychosocial function and quality of life.[1–4] Therefore, vitiligo should not be considered as merely a condition that affects a patient's appearance, but needs to be actively treated in patients who seek medical help. Phototherapy has been used as the main treatment modality for patients with vitiligo. Different forms of phototherapy for vitiligo include broadband UVB (BB-UVB), narrowband UVB (NB-UVB), excimer light and excimer laser, and psoralen plus UVA (PUVA).

PHOTOTHERAPY OF VITILIGO FROM EARLY AGES TO MODERN MEDICINE

Historically, phototherapy was first used to treat vitiligo more than 3500 years ago in ancient Egypt and India, when ancient healers used ingestion or topical application of plant extracts (*Ammi majus*

Conflicts of Interest: None declared.
Funding Sources: None.
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Dermatol Clin 35 (2017) 171–192
http://dx.doi.org/10.1016/j.det.2016.11.008

Linnaeus in Egypt and *Psoralea corylifolia Linnaeus* in India) in combination with sunlight for the treatment of "leucoderma."[5]

Since the middle of the last century, PUVA or photochemotherapy had been the most popular form of phototherapy for patients with vitiligo.[6] However, in recent years, it has been gradually superseded by NB-UVB, which has been shown by various studies to have greater efficacy and fewer adverse effects than PUVA.

NARROW BAND ULTRAVIOLET B: THE WINNING HORSE

NB-UVB phototherapy is characterized by polychromatic light with a peak emission wavelength of 311 to 313 nm. In 1997, Westerhof and Nieuweboer-Krobotova[7] first reported the efficacy of NB-UVB phototherapy compared with topical PUVA for the treatment of vitiligo. They found that after 4 months of treatment, 67% of patients receiving NB-UVB phototherapy twice a week developed significant repigmentation, whereas only 46% of patients undergoing topical PUVA twice a week developed repigmentation. Since then, several other studies also have shown that NB-UVB is effective for the treatment of vitiligo both in adults and children.[8–18]

Various studies also have demonstrated that NB-UVB has superior efficacy compared with oral PUVA in the treatment of vitiligo.[19–22] In a double-blind randomized study, 25 patients with generalized vitiligo received twice-weekly NB-UVB phototherapy and 25 patients were treated with twice-weekly oral PUVA. It was found that 64% of patients in the NB-UVB group achieved more than 50% overall repigmentation, compared with 36% of patients in the oral PUVA group.[19] The efficacy of NB-UVB phototherapy in the treatment of vitiligo is summarized in (**Table 1**).

Because most studies have demonstrated that NB-UVB has superior efficacy compared with other forms of phototherapy, NB-UVB is now considered as the first-line treatment modality for generalized vitiligo.[36,55,56] Apart from its efficacy, NB-UVB has a better safety profile compared with PUVA, mainly due to absence of adverse effects related to psoralen.[57]

HOW DOES IT WORK?

The underlying mechanism for the repigmentation effects of NB-UVB phototherapy in vitiligo has not been completely defined, although several different mechanisms have been proposed.[58,59] Vitiligo is characterized by 2 stages: the active stage in which there is ongoing destruction of melanocytes by immune cells, and the stable stage in which the depigmented skin lesions remain constant over time.

In the active stage of vitiligo, the main mechanism of NB-UVB phototherapy may be explained by its immunomodulatory actions. NB-UVB may stimulate epidermal expression of interleukin-10, which induces differentiation of T-regulatory lymphocytes that can inhibit the activity of autoreactive T lymphocytes.[40] NB-UVB irradiation also has been shown to induce apoptosis of T cells in psoriatic skin lesions,[41] and a similar mechanism may occur in vitiligo.

In the stable stage of vitiligo, the major repigmentation effect of NB-UVB may be due to stimulation of functional melanocytes in the perilesional skin or immature melanocytes in hair follicles. This effect has been described as "biostimulation." In vitiligo lesional skin, there is a selective loss of active melanocytes in the epidermis, while the inactive/immature melanocytes in hair follicles are spared. UV radiation promotes the proliferation and migration of melanocytes located in the perilesional skin, and enhances activation and functional development of immature melanocytes in the outer root sheath of hair follicles.[60] The upward migration of melanocytes from the outer root sheath to the epidermis leads to the commonly observed formation of perifollicular pigmentation islands. Previously, we and others have shown that NB-UVB irradiation increased the expression of endothelin-1 and basic fibroblast growth factor by keratinocytes, which in turn may promote melanocyte proliferation.[42,61,62] Moreover, we demonstrated that NB-UVB irradiation may induce phosphorylated focal adhesion kinase (FAK) expression and matrix metalloproteinase (MMP)-2 activity in melanocytes, leading to increased melanocyte migration.[42] Therefore, NB-UVB phototherapy may promote vitiligo repigmentation directly by increasing melanocyte mobility and indirectly by inducing melanocyte-related growth factors from keratinocytes (**Fig. 1**). Furthermore, it is known that vitiligo lesions are characterized by increased oxidative stress, and treatment with NB-UVB had been found to reduce oxidative stress in patients with vitiligo.[63] Due to the differences in the mechanisms of action between active-stage and stable-stage vitiligo, we propose that higher fluence of NB-UVB may be required for stabilization of active disease and lower doses for repigmentation (biostimulation).

ADVERSE EFFECTS

Patients treated with NB-UVB phototherapy may experience various acute side effects, including