

Narrowband ultraviolet B phototherapy and 308-nm excimer laser in the treatment of vitiligo: A review

Electra Nicolaidou, MD, PhD, Christina Antoniou, MD, PhD, Alexander Stratigos, MD, PhD,
and Andreas D. Katsambas, MD, PhD
Athens, Greece

Vitiligo is a common and chronic disease with a great impact on patients' quality of life. Phototherapy with narrowband ultraviolet B radiation and excimer laser are two treatment modalities that are used increasingly for the management of the disease with variable results. In this article, we review the efficacy, adverse effects, and possible mechanisms of action of narrowband ultraviolet B and excimer laser in the management of vitiligo. Available data concerning the follow-up of treated patients and some criteria for the selection of patients with a greater chance to respond satisfactorily to treatment are also presented. (J Am Acad Dermatol 2009;60:470-7.)

Vitiligo is a disease characterized by destruction of melanocytes that occurs mainly in the skin and results in the appearance of well-circumscribed white macules. The exact pathophysiologic mechanism that leads to the destruction of melanocytes is still elusive, but recent research underlies the important role of CD8⁺ T lymphocytes in vitiligo pathogenesis.¹

Vitiligo is common and affects 0.1% to 2% of the general population. For many patients with vitiligo, the disfigurement caused by the disease has a great impact on their quality of life.²

Currently, we have several therapeutic modalities that we can use for the treatment of vitiligo. However, it is still very difficult to compare the efficacy of different treatment modalities and the results of different studies on the same treatment because: (1) most published studies are uncontrolled; and (2) there is not a generally accepted biometric tool to assess disease severity and response to treatment. As a result, we have no meta-analyses for vitiligo treatments. Most treatments until now have been assessed using nominal binary scales in which the percentage of treated patients who achieve a specified degree of repigmentation (usually > 75%) is presented and compared by nonparametric statistical methods.

Abbreviations used:

IL:	interleukin
NB:	narrowband
PUVA:	psoralen plus ultraviolet A
UV:	ultraviolet
VASI:	Vitiligo Area Scoring Index
VETF:	Vitiligo European Task Force

To overcome this limitation, Hamzavi et al³ introduced in 2004 a quantitative clinical tool that would allow the parametrical evaluation of vitiligo. This tool has been called Vitiligo Area Scoring Index (VASI). To calculate the VASI score, the body is divided into 5 regions and, for each region, the VASI score is determined by the product of the area of vitiligo in hand units and the extent of depigmentation within each hand unit. The VASI has not yet been used in studies assessing the response of vitiligo to treatment.

Three years after the introduction of VASI, the Vitiligo European Task Force (VETF) proposed, for the assessment of vitiligo treatment outcomes, a system that combined analysis of extent, stage of disease, and disease progression.⁴ The VETF mentioned in this report that the VASI could be used in combination with their scale in future studies. They also emphasized the need for: (1) a global index for staging and spreading of vitiligo; (2) experiments with automated devices to assess extent more accurately; (3) setting up a teaching tool for scoring vitiligo; and (4) setting up an international conference on classifying, staging, and scoring vitiligo.

Psoralen plus ultraviolet (UV) A (PUVA) photochemotherapy and topical corticosteroids have been, for a long time, the mainstay of treatment of

From the First Department of Dermatology, University of Athens School of Medicine, "Andreas Sygros" Hospital.

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Reprint requests: Andreas D. Katsambas, MD, PhD, 35 Skoufa Str, GR-10673 Athens, Greece. E-mail: katsabas@internet.gr.

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generalized and focal vitiligo, respectively.⁵ In 1997, however, a first report appeared by Westerhof and Nieuweboer-Krobotova⁶ on the use of narrowband (NB) UVB phototherapy for the treatment of vitiligo. NB-UVB light source emits polychromatic light, but the 311- to 313-nm wavelength range predominates in its emission spectrum. NB-UVB was introduced approximately 10 years before the above report for the treatment of psoriasis, after the observation that wavelengths around 311 nm provoked less erythema and, at the same time, were most effective for complete clearance of psoriasis lesions.⁷ Based on the report by Westerhof and Nieuweboer-Krobotova,⁶ the guidelines for the treatment of vitiligo⁸ that were published in 1999—and have not been revised yet—proposed NB-UVB as first-choice therapy for generalized vitiligo in adults and as alternative therapy, after class-III corticosteroids, for vitiligo in children. In the following years, several studies assessed the efficacy of NB-UVB alone^{3,9-18} or in combination with other agents¹⁹⁻³¹ in the treatment of vitiligo with variable results. A number of studies³²⁻³⁵ have also compared the efficacy of NB-UVB with that of PUVA in patients with vitiligo and have reported comparable or slightly better efficacy for NB-UVB.

It was not until 2001 that the 308-nm xenon-chloride excimer laser appeared in the literature of vitiligo therapies.³⁶ The 308-nm excimer laser emits a monochromatic light of 308 nm and induces photobiological effects similar to NB-UVB. Several studies³⁷⁻⁵⁰ have shown response of vitiligo patches to excimer laser and it has been approved by the US Food and Drug Administration for the treatment of both vitiligo and psoriasis. Excimer laser permits the selective treatment of only lesional skin and ensures no unnecessary treatment of healthy skin. Thus, the patient receives less radiation. Furthermore, the unsightly tanning of all perilesional skin is avoided and perilesional tanning is usually limited to small areas around the lesion that have received the laser pulse during treatment. On the other hand, this selectivity makes the treatment of extensive vitiligo very time-consuming and may not prevent the occurrence of new lesions on untreated body sites. Finally, another drawback of laser treatment, compared with NB-UVB, is its high cost.

NB-UVB and 308-nm excimer laser are two treatment options for vitiligo that combine both high efficacy and minimal side effects and they are going to be used increasingly in the coming years for the management of the disease. In this review, we will present the available data regarding their efficacy, adverse effects, and mechanism of action.

NB-UVB Efficacy

There is no universally accepted protocol for NB-UVB, so treatment protocols differ from study to study. Sessions are performed twice or thrice weekly, on nonconsecutive days (Table I). The initial dose ranges from 100 to 280 mJ/cm². The dose is subsequently increased in most studies by 10% to 20% per session. In many studies, the dose is stabilized when mild erythema develops. Generally, after the first few sessions, the rate of increase in UVB dose is individualized for each patient.

Overall response of vitiligo to NB-UVB has been variable (Table I). More than 75% repigmentation (which is considered cosmetically acceptable repigmentation) has been achieved by 12.5%¹⁵ to 75%¹³ of treated patients, after approximately 1 year of treatment. The best results have been reported in two studies from the same center in India, with 71.4%¹⁴ and 75%¹³ of patients achieving cosmetically acceptable repigmentation. Two studies from the same center in the Netherlands, also, have reported high rates (53%⁹ and 63%⁶) of cosmetically acceptable repigmentation. The lowest response rates have been reported in Asian patients: 33% and 12.5% in studies from Thailand¹¹ and Taiwan,¹⁵ respectively.

The above variability of response to treatment could be attributed to several factors. One of them is the skin phototype of the study participants. All patients in the studies from India had a skin phototype IV or V, and the two Dutch studies included a high percentage of patients with skin phototypes III to V. In our series,¹⁸ 64.2% of patients had skin phototypes III to V and a multivariate analysis showed a statistically significant odds ratio of 6.68 for these patients to achieve a cosmetically acceptable repigmentation on the face, compared with patients with skin phototypes I to II. However, this tendency was not observed in nonfacial skin. Other studies have reported no correlation between response to treatment and skin phototype,^{3,9,11,16} but some had included patients with skin phototypes III to V (no lighter ones)^{9,11} whereas another³ analyzed response to treatment of nonfacial skin, where we did not find an association either. Based on these data, we believe that patients with skin phototypes III to V have a greater chance to achieve cosmetically acceptable repigmentation on their face, compared with patients with skin phototypes I to II.

Another factor that can influence the response to treatment is the location of lesions. Several studies^{6,9,13,14,16} report better response rates (without statistical confirmation) for facial lesions compared with lesions on the rest of the body. In our series¹⁸

Table I. Studies reporting the efficacy of narrowband ultraviolet B monotherapy in patients with vitiligo (studies on >10 patients are included)

Authors	Study design	No. of patients who completed treatment	No. of sessions/wk	Length of treatment	Response to treatment
Westerhof and Nieuweboer-Krobotova ⁶	Open trial	51	2	1 y	>75% Repigmentation: 63% of patients
Njoo et al ⁹	Open trial	51 Children	2	Up to 1 y	>75% Repigmentation: 53% of patients (72% of treated facial lesions)
Natta et al ¹¹	Retrospective study	60	2	5 mo-2 y	>75% Repigmentation: 33% of patients
Yashar et al ¹²	Retrospective study	71	2-3	Not mentioned	>66% Repigmentation: 39% of patients after 62 ± 26 sessions
Hamzavi et al ³	Prospective, randomized, controlled, left-right comparison trial	22	3	6 mo	43% Mean repigmentation vs 3.3% of untreated controls (<i>P</i> < .001) (facial lesions were not included)
Kanwar and Dogra ¹³	Open trial	20 Children	3	Up to 1 y	>75% Repigmentation: 75% of patients
Kanwar et al ¹⁴	Open trial	14	3	1 y	>75% Repigmentation: 71.4% of patients
Chen et al ¹⁵	Retrospective study	72	2-3	Up to 1 y	>75% Repigmentation: 12.5% of patients
Brazzelli et al ¹⁶	Open trial	10 Children	2-3	6 mo	>75% Repigmentation: 50% of patients
Anbar et al ¹⁷	Open trial	97: NS 13: S	2	8 mo	>75% Repigmentation (NS): 48% of patients (76.3% of patients with facial lesions) >75% Repigmentation (S): 0%
Nicolaidou et al ¹⁸	Open trial	70 (61 With lesions on face, 68 with lesions on body)	2	Up to 1.5 y	>75% Repigmentation: 34.4% of patients with facial lesions, 7.4% of patients with lesions on body

NS, Nonsegmental; S, segmental.

and in the study by Anbar et al,¹⁷ a statistically significant difference was documented. Lesions on acral sites (hands and feet) always show minimal response^{3,6,9,11,13-18} and in one study¹⁷ this observation was statistically confirmed. The reason behind this anatomic variation in response to treatment is unclear, but it may be related to the regional variation in the density of hair follicles, which have been shown to be reservoirs for melanocytes.⁵¹

There seems to be no association between response to treatment and patients' sex,^{3,9,18} age,^{3,9,15,18} positive family history of vitiligo,^{9,18} and body surface area affected.^{9,18} The association between response to treatment and duration of vitiligo is unclear: some studies report such an association,^{14,16,17} whereas others do not.^{3,9,18}

An earlier response to treatment has been correlated to a higher level of posttreatment repigmentation.^{15,18} Chen et al¹⁵ showed that a shorter period

before initial repigmentation correlated with a higher percentage of final repigmentation. In our series,¹⁸ patients who responded after just 1 month of treatment achieved a higher repigmentation level, compared with those who responded later. If this finding is confirmed, it would be possible to identify patients with a greater chance of achieving satisfactory final repigmentation early in the course of treatment.

In some patients with skin phototypes IV and V, the newly repigmented skin may be darker than the patient's native skin color. This hyperpigmentation resolves after a couple of months, providing a good cosmetic result.^{10,18}

Follow-up data of patients after termination of NB-UVB are limited. In our series,¹⁸ we followed up 25 patients for up to 4 years after stopping phototherapy. Relapse was observed in 44% of them within 1 year after treatment cessation. In 14.3% of patients, no new vitiligo lesions appeared

within the repigmented areas 4 years after treatment. Sitek et al⁵² followed up 11 patients with more than 75% overall repigmentation after a course of NB-UVB and reported that 45% of patients were in full remission 2 years after the end of treatment. Natta et al¹¹ followed up 9 patients for up to 2 years and reported 25% and 43% relapse rates in 1 year and 18 months, respectively, whereas in the series by Kanwar et al,¹⁴ 4 of the 8 patients they followed up relapsed within 3 months. Patients who relapse usually respond to a second course of treatment.

Adverse effects

Acute adverse effects during NB-UVB are not frequent; include only erythema, pruritus, and xerosis; and usually resolve after topical applications of emollients.

Chronic adverse effects of NB-UVB include photoaging⁵³ and photocarcinogenesis.

NB-UVB has been shown to induce DNA damage in cell cultures,⁵⁴ and in human skin and animal models,⁵⁵ a mechanism that leads to carcinogenesis. However, a recent study⁵⁶ did not provide evidence for an increased skin cancer risk in patients with psoriasis treated with either broadband- or NB-UVB. In another study,⁵⁷ no increased risk for melanomas or squamous cell carcinomas was detected in patients receiving NB-UVB for diseases other than vitiligo, but an increased risk was evident for basal cell carcinomas. No data are available so far regarding carcinogenesis in patients with vitiligo treated with NB-UVB, but because the development of skin cancer in patients with vitiligo seems to be rare,⁵⁸ it is rational to expect that patients with vitiligo will not have an increased risk compared with other patients receiving NB-UVB. Until more data are available, NB-UVB is considered less carcinogenic than PUVA,⁵⁹ but still it should be used cautiously and patients receiving long-term therapy should be followed up regularly.

Combination therapy

Several investigators have combined NB-UVB with other agents to enhance its efficacy in patients with vitiligo. Most of these studies have combined NB-UVB with vitamin D₃ analogues.²²⁻²⁷ Topical tacrolimus ointment,^{28,29} vitamins,²¹ topical pseudocatalase mousse,²⁰ *Polypodium leucotomus* extract,³⁰ and antioxidants³¹ have also been used.

Topical vitamin D analogues. Calcipotriene (calcipotriol), a synthetic vitamin D₃ analogue, has been used in the treatment of vitiligo as monotherapy and in combination with NB-UVB and PUVA. Its exact mechanism of action is not clear, but several observations support a connection between calcium metabolism and vitiligo.⁶⁰⁻⁶² The immunomodulatory

effects of vitamin D₃ analogues may also contribute to their action against vitiligo.⁶³

Both calcipotriene and its vehicle have been reported to have a photoprotective effect.^{64,65} Therefore, they should not be applied immediately before irradiation. They may be applied at any time up to 2 hours before or immediately after irradiation.

Five studies²²⁻²⁶ have compared so far the combination of NB-UVB plus topical calcipotriene with NB-UVB monotherapy. Among them, only one²⁶ has reported a statistically significantly better response for patients who received the combination treatment. Significantly higher repigmentation scores have also been demonstrated for the combination of NB-UVB with the vitamin D₃ analogue tacalcitol.²⁷ Until more data are available, no definite conclusion can be reached regarding the synergistic effect of NB-UVB and topical vitamin D₃ analogues.

Topical tacrolimus. Tacrolimus is a macrolide immunosuppressant capable of inhibiting the activation and maturation of T cells by blocking the transcription of several cytokines, including interleukin (IL)-2, IL-3, IL-4, IL-5, tumor necrosis factor α , and interferon-gamma. It also enhances T-cell apoptosis in vitro.⁶⁶ After several reports that topical application of 0.1% tacrolimus ointment can provoke repigmentation in vitiligo patches,^{67,68} Mehrabi and Pandya²⁸ compared NB-UVB plus 0.1% tacrolimus ointment with NB-UVB plus placebo in a randomized, double-blind trial that included 8 patients. They found that the combination was not more efficacious than NB-UVB alone. In another open-labeled study, Fai et al²⁹ combined once daily application of tacrolimus ointment with twice per week NB-UVB for 16 weeks in 110 patients. The treatment resulted in more than 75% repigmentation on 40% of facial lesions and 23% of lesions on trunk and limbs. However, this study was not controlled and so the conclusions we can reach on the superiority of the combination treatment over NB-UVB monotherapy are limited. Furthermore, because there are concerns about the carcinogenicity of topical tacrolimus when combined with exposure to sunlight, patients treated with topical tacrolimus are currently advised in the package insert of the drug against exposure to natural or artificial sunlight. Clearly, more data are needed to clarify both the issue of topical tacrolimus plus exposure to sunlight and the efficacy of combining NB-UVB plus topical tacrolimus in patients with vitiligo.

Other agents. After a report by Schallreuter et al¹⁹ that topical application of pseudocatalase (Mn/EDTA-bicarbonate complex) and calcium in combination with low-dose broadband UVB resulted in complete repigmentation in the face and back of

the hands in 90% of patients, Patel et al²⁰ used a novel pseudocatalase and calcium chloride-containing mousse preparation combined with suberythemogenic doses of NB-UVB. They found no clear evidence of the efficacy of the regime.

Tjioe et al²¹ combined NB-UVB plus folic acid and vitamin B12 and found that the combination was not more effective than NB-UVB treatment alone.

Because oxidative stress has been implicated in the pathogenesis of vitiligo, two very recent randomized, double-blind, placebo-controlled studies have examined the combination of NB-UVB with agents that have antioxidative properties. In the first,³⁰ NB-UVB was combined with oral administration of *Polypodium leucotomus* extract, which is known to have antioxidative and immunomodulating properties. In the combination treatment group, a trend toward an increased repigmentation in the head and neck area was observed, which nearly reached statistical significance. In the second study,³¹ the treatment group received for 2 months before and 6 months during the NB-UVB treatment a balanced antioxidant pool containing α -lipoic acid, vitamins C and E, and polyunsaturated fatty acids. The antioxidant treatment increased the percentage of patients achieving more than 75% repigmentation from 18% (with placebo) to 47% ($P < .05$).

Mechanism of action

The mechanism of action of NB-UVB on patients with vitiligo has not been completely elucidated. In patients with vitiligo, the active melanocytes in the epidermis are destroyed, whereas the inactive (dopa-negative) melanocytes in the outer root sheaths of hair follicles are not affected.⁵¹ Repigmentation is supposed to be initiated by activation, proliferation, and migration of these melanocytes upward along the surface of the outer root sheath to the nearby epidermis, where they form perifollicular pigmentation islands.⁵¹ It has recently been demonstrated⁶⁹ that NB-UVB could stimulate a significant increase in the release of basic fibroblast growth factor and endothelin-1 from keratinocytes, both of which induced melanocyte proliferation. Furthermore, melanocyte migration can be enhanced by NB-UVB through stimulation of the expression of phosphorylated focal adhesion kinase (p125^{FAK}) on melanocytes and through increased expression of matrix metalloproteinase-2 activity from melanocytes.⁶⁹

The immunosuppressive action of NB-UVB may also contribute to the treatment of vitiligo. As mentioned above, T lymphocytes seem to participate in the pathogenesis of the disease¹ and so the induction of T-lymphocyte apoptosis by NB-UVB⁷⁰ may play a pivotal role in repigmentation of vitiligo lesions.

308-nm EXCIMER LASER

Efficacy

After the first case report by Baltas et al,³⁶ several studies have assessed the efficacy of 308-nm excimer laser in vitiligo (Table II).³⁷⁻⁵⁰ Sessions are performed 2 to 3 times a week for a period of 4 to 36 weeks. Repigmentation occurs faster with the thrice weekly treatment, but the ultimate rate of repigmentation seems to depend on the total numbers on sessions and not on their frequency.⁴⁸ Repigmentation greater than 75% is usually reported for 15% to 50% of treated lesions.

Location of lesions seems to be the best predictor of response: lesions on the face,^{37,38,40-42,44-46} neck,^{38,40,41,45-46} and trunk^{40-42,44} respond to a greater extent than lesions on extremities. Lesions on hands and feet tend to have the least favorable prognosis.^{38,39,41-42,45} However, only in the studies by Ostovari et al⁴¹ and Hofer et al⁴⁵ was statistical analysis performed for the confirmation of the above observations. In these studies, a statistically significantly better response was observed in the UV-sensitive areas (face, neck, back, breast, and arm) compared with UV-resistant areas (knees, elbows, wrists, hands, ankles, and feet). Furthermore, in the study by Ostovari et al,⁴¹ although all UV-sensitive areas responded more or less in the same way, among UV-resistant areas, knees, elbows, and wrists responded significantly better than hands, ankles, and feet.

Two studies^{43,50} reported a better outcome in patients with darker skin (type III-VI vs I-II), but no statistical analysis was performed for the confirmation of this observation.

Side effects

The sessions are generally well tolerated and side effects are minimal. Mild to severe erythema is usually reported, whereas blisters and pruritus are observed occasionally.

Combination therapy

In accordance with NB-UVB, topical tacrolimus^{40,43} and calcipotriol⁵⁰ have also been assessed for a possible synergistic effect with excimer laser in the treatment of vitiligo.

Topical tacrolimus. Two prospective, randomized, intraindividual studies^{40,43} have evaluated the possible synergistic action of 308-nm excimer laser and tacrolimus.

The first study by Passeron et al⁴⁰ compared the efficacy of the 308-nm excimer laser combined with twice daily topical application of 0.1% tacrolimus ointment with excimer laser monotherapy. Two sessions per week were performed for a total of 24

Table II. Studies reporting the efficacy of excimer laser in patients with vitiligo

Authors	No. of patients who completed treatment	No. of treated patches	No. of sessions/wk	Length of treatment, wk	Patches with > 75% repigmentation
Spencer et al ³⁷	6	11	3	4	18%
Taneja et al ³⁸	15	18	2	30	33% (100% On face)
Choi et al ³⁹	50	108	2	15	15.7% (33% On face and neck, 0% on extremities and bony prominences)
Ostovari et al ⁴¹	31	52	2	12	27% (57% On face, neck, trunk, 16% on bony prominences and extremities)
Esposito et al ⁴²	24	Not mentioned	2	36	29%
Hong et al ⁴⁴	8	23 Laser 23 NB-UVB	2	10	0%
Hofer et al ⁴⁵	24	80	3	6-10	25% (Face, trunk, arm, leg), 2% (elbow, wrist, back of hand and foot, knee)
Hadi et al ⁴⁶	97	221	2	15	51%
Passeron et al ⁴⁰	14	20 Laser alone 23 laser plus tacrolimus	2	12	20% Laser alone 70% laser plus tacrolimus
Kawalek et al ⁴³	6	10 Laser plus placebo 10 laser plus tacrolimus	3	8-10	20% Laser plus placebo 50% laser plus tacrolimus

NB, Narrowband; UV, ultraviolet.

sessions. In UV-sensitive areas, a repigmentation rate of 75% or more was achieved in 77% of lesions treated with the combination therapy versus 57% of lesions treated by laser monotherapy. However, in UV-resistant areas, the above percentages became 60% and 0%, respectively ($P < .002$). Thus, combination therapy was clearly superior to laser monotherapy in UV-resistant areas.

Comparable results were also reported by Kawalek et al.⁴³ In their study, they performed 3 sessions per week and used placebo cream. Of patches, 50% receiving combination therapy with tacrolimus achieved 75% repigmentation versus 20% of patches treated with laser and placebo cream.

Short-term side effects were generally unaffected by the addition of tacrolimus except for stinging⁴⁰ and moderate lesional and perilesional hyperpigmentation, which subsided within 3 weeks.⁴³

Topical calcipotriol. In a very recent pilot study of 9 patients, Goldinger et al⁵⁰ reported that the addition of topical calcipotriol to excimer laser did not enhance the efficacy of the laser treatment alone.

Mechanism of action

The mechanism of action of excimer laser in vitiligo is not known. One could speculate a similar mechanism of action with NB-UVB. However, there are several differences between NB-UVB and excimer laser that have to be taken into account. NB-UVB sources emit a polychromatic, continuous,

incoherent light, whereas excimer laser emits a monochromatic and coherent beam of light in short impulses with much higher intensity. Excimer laser has already been found to be a more potent inductor of T-cell apoptosis than NB-UVB.⁷¹ Other differences in the mechanism of action between NB-UVB and excimer laser cannot be ruled out.

Conclusions

NB-UVB and excimer laser can induce repigmentation in many patients with vitiligo, but both the rate and the duration of the induced repigmentation are variable. Certain patients, such as those with skin that tans easily, and certain areas, such as the face, seem to respond more favorably. Patients should be informed about the variability of the expected results and should participate in the decision on whether to start treatment or not. According to our hospital-based experience, patients are rarely discouraged by treatment limitations. Most of them are willing to start a treatment that can offer them a chance of improvement and they appreciate the induced repigmentation, even when it is not the best possible.

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