

# Parametric Modeling of Narrowband UV-B Phototherapy for Vitiligo Using a Novel Quantitative Tool

## *The Vitiligo Area Scoring Index*

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**Background:** There is currently no quantitative tool for evaluating vitiligo treatment response using parametric methods.

**Objective:** To develop and apply a simple clinical tool, the Vitiligo Area Scoring Index (VASI), to model the response of vitiligo to narrowband UV-B (NB-UV-B) phototherapy using parametric tests.

**Design:** Prospective, randomized, controlled, bilateral left-right comparison trial.

**Setting:** North American tertiary care, university-affiliated phototherapy center.

**Patients:** Patients older than 18 years with stable vitiligo involving at least 5% of their total body surface in a symmetric distribution.

**Intervention:** Treatment with NB-UV-B was given 3 times a week to half of the body on all patients for either 60 treatments or 6 months. The contralateral side served as a no-treatment control.

**Main Outcome Measure:** Repigmentation was assessed using the VASI, which was based on a composite estimate of the overall area of vitiligo patches at baseline and the degree of macular repigmentation within these

patches over time. The VASI was validated separately against physician and patient global assessments. The overall reductions in VASI for NB-UV-B and control groups were modeled by multilevel regression with random effects and compared parametrically.

**Results:** The VASI scoring correlated well with both patient and physician global assessments ( $P = .05$  and  $P < .001$ , respectively, using ordinal logistic regression). The extent of repigmentation after 6 months on the treated side was 42.9% (95% confidence interval, 26.7%-59.0%) vs 3.3% (95% confidence interval -19.3% to 30.0%) on the untreated side ( $P < .001$ ). A significant difference between control and NB-UV-B groups was apparent within the first 2 months of therapy. The legs, trunk, and arms were much more likely to repigment than the feet and hands.

**Conclusions:** The VASI is a quantitative clinical tool that can be used to evaluate vitiligo parametrically. Patients treated with NB-UV-B can be expected to achieve approximately 42.9% repigmentation of their vitiligo after 6 months of treatment, with the greatest response being achieved over the trunk and nonacral portions of the extremities.

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**T**HERE ARE SEVERAL AVAILABLE treatments for vitiligo but only limited data to actually guide the practical management of patients with vitiligo. Based on the currently available literature, it is difficult to compare the efficacy of different treatment modalities not only because measurement of repigmentation is not standardized, but also because most published studies have been uncontrolled. The rather slow response of vitiligo to treatment represents yet another impediment to conducting appropriate clinical trials for this condition.

Many vitiligo treatments have typically been analyzed using nominal binary scales in which the proportion of treated patients who either do or do not achieve a specified degree of repigmentation is reported and compared by non-parametric statistical approaches. The degree of repigmentation that defines success has often been set somewhat arbitrarily at 50% to 75% repigmentation based largely on the global impression of the overall response.<sup>1,2</sup> There is currently no validated quantitative scale that allows vitiligo to be characterized parametrically.

The primary advantage of using quantitative scales for evaluating vitiligo is that

they provide direct estimates of the expected quantitative responses that patients might expect to achieve. In contrast, nominal and nonparametric methods can only estimate the proportion of patients who achieve a certain arbitrarily set level of response. Quantitative methods provide data that are generally more intuitive and meaningful to patients and physicians, while at the same time being more sensitive for detecting significant subtle treatment effects. In addition, a quantitative method for measuring vitiligo severity would allow more studies to be compared across a range of data sets. A recent meta-analysis of treatment options for vitiligo used odds ratios to compare studies that define treatment success as 75% repigmentation.<sup>2</sup> Studies that did not use the 75% repigmentation threshold were not included in the analysis. A simple quantitative technique could standardize vitiligo outcome measurements and allow more studies to be included in meta-analyses.

Current analyses of narrowband UV-B (NB-UV-B) therapy for vitiligo have several limitations, including the above-mentioned lack of a quantitative scale to measure response. Deficiencies also include the paucity of rigorous controlled studies, lack of detailed statistical analyses, and inconsistent periods of follow-up. Westerhof et al<sup>3</sup> evaluated NB-UV-B therapy in a nonrandomized trial where patients received treatment with either topical psoralen UV-A (PUVA) or NB-UV-B. Sixty-three percent of patients receiving NB-UV-B achieved some degree of pigmentation, while 46% of patients achieved an equivalent end point with topical PUVA. Comparisons were made for only a 4-month period, and differences between the 2 groups were not compared statistically. Moreover, the results in this and other studies<sup>2,3</sup> were reported in terms of ordinal categories as opposed to quantitative scales. Thus, there remains a paucity of data to confirm the efficacy of NB-UV-B in comparison with no-treatment controls. While there are several case series documenting that NB-UV-B is well tolerated and induces repigmentation, these studies do not provide direct data on either the actual quantitative degree of response or the rate of repigmentation.<sup>4</sup>

The goals of the present study were to develop and validate a simple quantitative scale to measure the response of patients with vitiligo using a randomized, controlled, left-right study of NB-UV-B phototherapy. Specifically, we sought to develop a relatively simple method analogous to the Psoriasis Area Severity Index (PASI) used for psoriasis<sup>5,6</sup> to measure repigmentation and to validate this method against global assessments by patients and investigators.<sup>7</sup> We call this tool the *Vitiligo Area Scoring Index*, or VASI. The second aim of this study was to model the effect of NB-UV-B treatment on vitiligo in terms of overall response, rate of response, and differential body site repigmentation and to compare these findings with a no-treatment control. Finally we have described our exact NB-UV-B dosage guidelines in detail; these have typically not been specified in previous studies.

## METHODS

This was a prospective, randomized, parallel, right-left bilateral study involving NB-UV-B exposure to half the body (trunk and

extremities) and no light exposure to the other half as a control. The University of British Columbia Clinical Research Ethics Board approved this study. Patients were enrolled and treated at a tertiary care university teaching hospital-affiliated phototherapy center. For each patient, one side of the body was randomly assigned to receive NB-UV-B, and no light was given to the contralateral side. Enrolled patients were required to have symmetric involvement with greater than 5% total body surface involvement. All patients were older than 18 years, had no significant medical problems, and were not being treated with photosensitizers. They did not receive topical or systemic treatment for their vitiligo for 2 weeks prior to the initiation of NB-UV-B phototherapy nor for the duration of their participation in the study.

## ASSIGNMENT OF LIGHT SOURCE

For each patient, we determined by coin toss which side of the body would receive NB-UV-B treatment, and the contralateral side received no active treatment. During treatments, protective "half-body" garments impervious to UV light (data not shown) were used to cover the untreated side (Proshield Hazmasters; Burnaby, British Columbia). The genitals were covered with opaque fabric, and the eyes were protected with UV safety glasses during all exposures. For those patients with facial vitiligo, the entire face was treated with NB-UV-B at the patient's request in an all-or-none fashion. Data for these treatments were analyzed separately from the rest of the body.

## PHOTOTHERAPY PROTOCOL

Prior to the initiation of therapy, phototesting was performed on depigmented skin to determine the minimal erythral dose (MED), which was defined as the minimum dose of light that caused barely perceptible visible erythema. A UV phototherapy unit (National Biologic Systems, Twinsburg, Ohio) with 48 NB-UV-B fluorescent lamps (Philips TL-01, Amsterdam, the Netherlands) was used with an average irradiance of 3.1 mW/cm<sup>2</sup> as measured by a UV-B light meter (National Biologic Systems).

The starting treatment fluences were based on the MEDs as determined by initial phototesting of 1-cm<sup>2</sup> areas of depigmented skin with 100, 200, and 300 mJ/cm<sup>2</sup> of NB-UV-B in each patient. Patients were then treated with 70% of the MED to half of their bodies. Subsequent doses were increased by 10% increments until repigmentation was clinically evident. At that point, the dose was held constant.

However, if persistent erythema lasting more than 24 hours developed, indicating a phototoxic effect, further treatment was delayed until this resolved. Treatments were then reinitiated using the last previous dose, and 1 of 2 possible scenarios evolved for subsequent dose increments: (1) the dose was increased by 5% increments until either the skin repigmented or signs and symptoms of phototoxicity redeveloped; or (2) the dose was decreased by 25% if the patient was developing persistent signs of phototoxicity. In the second case, attempts were periodically made to reincrease the dose gradually by 5% increments until either repigmentation or a mild phototoxic effect was observed. Experienced phototherapy nurses made decisions on dose changes in consultation with a dermatologist.

Unilateral phototherapy was given 3 times a week for 6 months or 60 cumulative treatments, whichever came first. Patients were never treated for 3 consecutive days.

## OUTCOMES

Efficacy was assessed in 2 separate ways. The first involved structured monthly estimation of body surface area vitiligo involve-

ment using the VASI. The body was divided into 5 separate and mutually exclusive regions: hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. The axillary and inguinal regions were included with the upper and lower extremities, respectively, while the buttocks were included with the lower extremities. The face and neck areas were assessed and treated for vitiligo if requested by the patient, but these areas were not included in the overall evaluation.

One hand unit, which encompasses the palm plus the volar surface of all the digits, is approximately 1% of the total body surface area<sup>8</sup> and was used as a guide to estimate the baseline percentage of vitiligo involvement of each body region. To eliminate variations in hand size, we defined a hand unit to be the volar hand, including fingers, of one of us (I.H.).

At each follow-up assessment, any macular repigmentation was noted, and the extent of residual depigmentation within each affected patch that had been present at baseline was estimated to the nearest of 1 of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100% (**Figure 1**). Any new depigmented patches that developed during the study were also estimated using the hand unit method and were included in the VASI calculation.

For the second measurement method, total body photographs were taken at baseline and at each monthly follow-up visit as an aid to the global clinical scoring. The photographs were taken under conditions that were standardized for lighting, position, exposure time, and focal length using a Nikon F80 camera with a 60-mm macro lens (Nikon Canada; Mississauga, Ontario). These 35-mm slides were used by investigators for global assessments, which were done halfway through and at the end of the study. They were not used to derive the VASI, which was instead determined by direct clinical examination.

For each body region, the VASI was determined by the product of the area of vitiligo in hand units (which was set at 1% per unit) and the extent of depigmentation within each hand unit-measured patch (possible values of 0, 10%, 25%, 50%, 75%, 90%, or 100%). The total body VASI was then calculated using the following formula by considering the contributions of all body regions (possible range, 0-100):

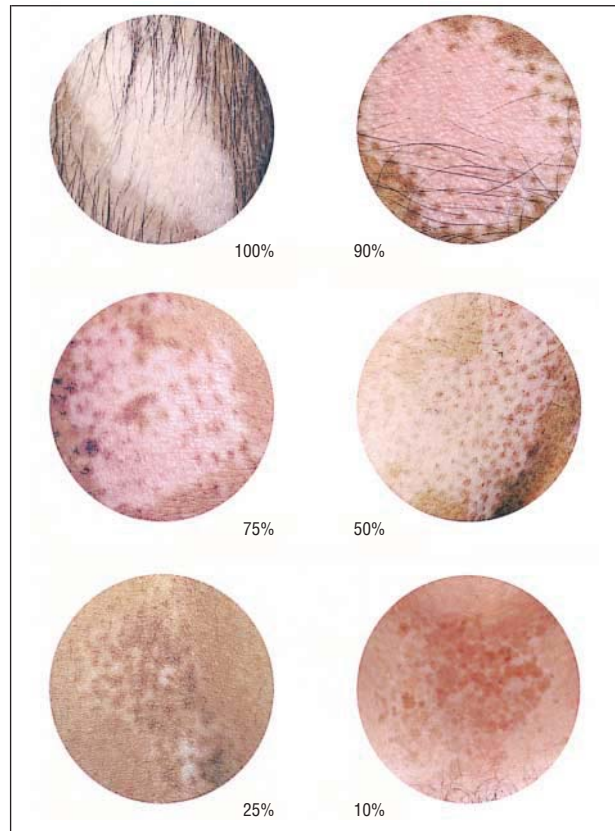
$$\text{VASI} = \sum_{\text{All Body Sites}} [\text{Hand Units}] \times [\text{Residual Depigmentation}]$$

To compare the VASI system with ordinal scales analogous to those used in previous studies,<sup>2</sup> we performed global assessments. At the completion of the study, each patient and one of us (I.H.) separately graded the treated sides on a 6-point ordinal scale based on a global estimate of the change in vitiligo as follows: complete improvement (100%), very much improved (76%-99%), much improved (51%-75%), improved (26%-50%), minimal change (1%-25%), no change.

#### DATA ANALYSIS AND STATISTICS

Based on a 1-sample, 2-tailed *t* test, a minimum of 17 patients were needed to detect a 50% difference in repigmentation (ie, 50% difference in VASI) between the control and the treated sides at  $\alpha = .05$  and 80% power. For this calculation, a total mean baseline body surface involvement (ie, VASI) of 20% and a 7% SD for the difference between the 2 body sides were assumed. After allowing for a possible attrition rate of 15%, we determined that 20 patients were required; 22 patients were actually recruited.

Validation of the VASI was done by ordinal logistic regression to compare the VASI against patient and physician global assessments separately. The efficacy of NB-UV-B treat-



**Figure 1.** Standardized assessments for estimating the degree of pigmentation to derive the Vitiligo Area Scoring Index. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeds the depigmented area; and at 10%, only specks of depigmentation are present.

ment of vitiligo was assessed by comparing the VASI scores of the treated and control sides using multilevel random-effects regression modeling software (MLn; Centre for Multilevel Modelling, Institute of Education, University of London, London, England).<sup>9</sup> Multilevel statistical modeling provides a practical means to include all repeated measures (ie, VASI) from all patients in a hierarchical analysis that accounts for data clustering on a per-patient basis according to time and NB-UV-B exposure. A further advantage of this model is that the effects of any irregularities in the times of VASI measurement (ie, missed or delayed monthly follow-up visits) are directly adjusted for by the model.

For this study, the model regressed VASI scores according to time and treatment number within the NB-UV-B and non-treated control sides. The regression model was tested linearly and quadratically for time. Vitiligo responses were also analyzed separately by body region using this model. The effects of patient age, sex, skin type, and ethnic origin on overall repigmentation were each tested as covariates in this model. Finally, repigmentation was also regressed according to the duration of vitiligo, baseline extent of vitiligo, and a history of prior vitiligo therapy with either UV light or corticosteroids.

In addition, the response of the face was compared with that of the body for patients who had treatment of all body regions to see if improvement of the face correlated to the amount of improvement on the rest of the body. Except for the multilevel random-effects model previously described, all statistical analyses were performed using SPSS 10.0 for Windows (SPSS Inc, Chicago, Ill) and JMP In 4.0 (SAS Institute Inc, Cary, NC).

## RESULTS

Twenty-two patients were recruited and treated from July 2000 to February 2001, and all were included in the analysis. The mean subject age was 47 years; mean duration of vitiligo, 24 years; mean extent of vitiligo, 15.7%; and the man-woman ratio was 9:13 (**Table 1**). Fifteen patients were white, 6 were Indo-Pakistani, and 1 was of Chinese descent. The Fitzpatrick skin type distribution was as follows: 9 patients had type II skin; 5 had type III; 1 type IV; and 7 type V. Eight patients had previously used topical corticosteroids and 11 had undergone UV phototherapy without success.

During the study, no patients developed any new patches of vitiligo, nor did any patient develop complete repigmentation on either side of the body

**Table 1. Demographic Features of Patients With Vitiligo\***

Age, mean (SD) [range], y	47 (12.7) [23-77]
Duration of disease, mean (SD) [range], y	24 (16.3) [4-51]
Extent of vitiligo (VASI), mean (SD) [range], %	15.7 (8.9) [4-35.7]
Sex	
Men	9
Women	13
Ethnicity	
White	15
Indo-Pakistani	6
Chinese	1
Fitzpatrick skin type	
II	9
III	5
IV	1
V	7
Previous UV therapy	11
Previous topical steroid use	8

Abbreviation: VASI, Vitiligo Area Scoring Index.

\*Except as otherwise noted, data are number of patients.

(**Figure 2**). Any macular pigmentation that developed typically appeared within the first 4 to 8 weeks of treatment. The average total NB-UV-B light dose was 17.3 J/cm<sup>2</sup> (range, 5.6-30.7 J/cm<sup>2</sup>). Adverse effects were limited to hyperpigmentation of newly repigmented skin and mild phototoxic effects. One patient dropped out of the study because of the hyperpigmentation. The hyperpigmentation resolved within the 6-month study period in all patients who developed this reaction.

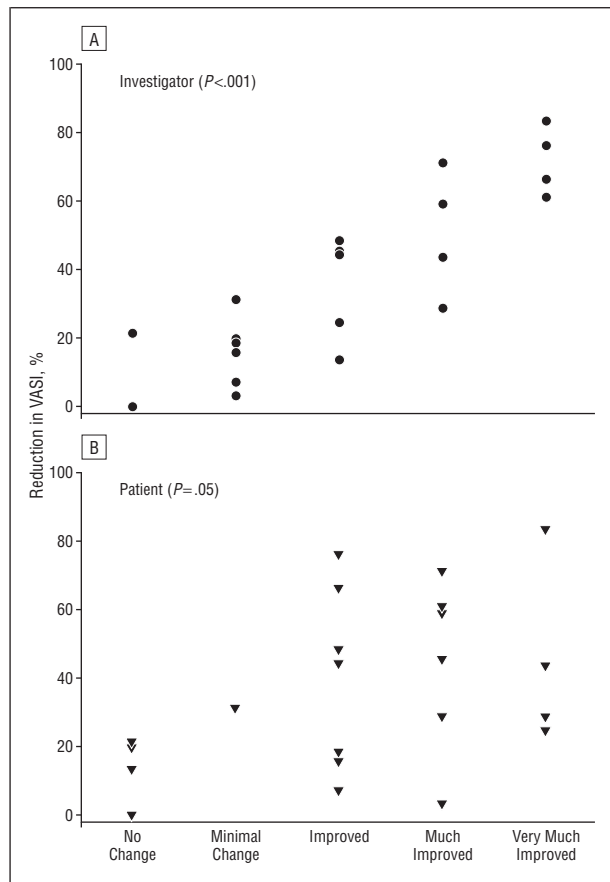
By the end of therapy, the percentage reduction in VASI for each patient was evaluated and correlated with global assessments of the NB-UV-B treated sides. By ordinal logistic regression, there was a stronger correlation between the VASI and the investigator global assessment ( $P < .001$ ) than between the VASI and the patient global assessment ( $P = .05$ ), although both were statistically significant (**Figure 3**).

Using multilevel random effects modeling, we found the mean improvement due to NB-UV-B treatment to be 42.9% (95% confidence interval, 26.7%-59%) vs 3.3% (95% confidence interval, -19.3% to 30.0%) on the control side after 6 months of treatments (**Figure 4A**). The effect of NB-UV-B on vitiligo repigmentation was highly significant ( $P < .001$ ). A significant difference between NB-UV-B and control became evident by 2 months of treatment ( $P = .05$ ). The overall improvement due to NB-UV-B followed a quadratic relationship over time ( $P = .05$ ). In addition to time, repigmentation was also modeled according to the number of treatment sessions with the same overall results (data not shown).

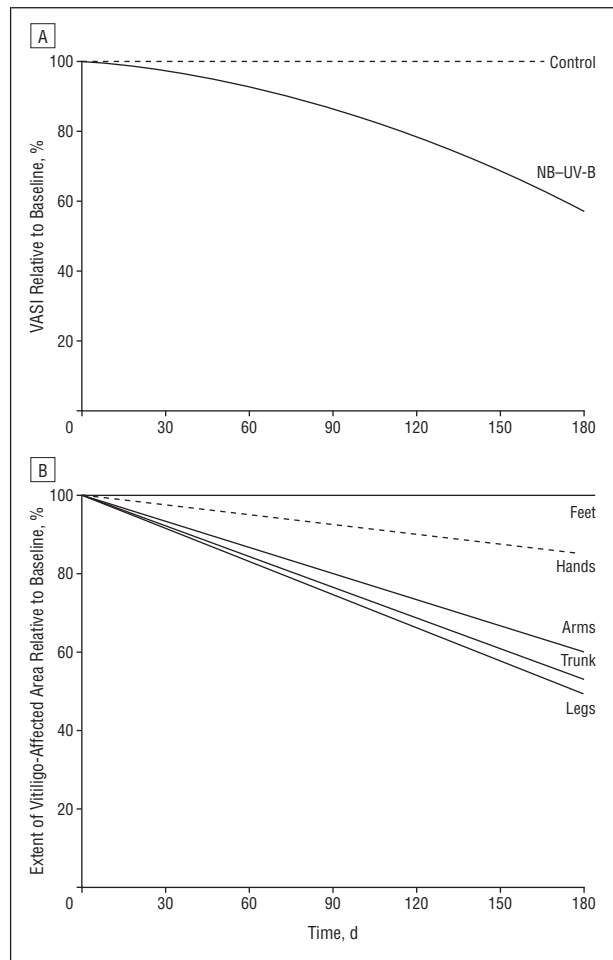
There was significant variability in the responses of different body sites to NB-UV-B. The lower extremities had the best response, and the feet the worst. These results are illustrated in **Figure 4B** and summarized in **Table 2**. Patient demographic characteristics, including age, sex, skin type, and ethnic origin, were not significantly predictive of outcome, nor was duration of vitiligo or prior vitiligo treatment with either steroids or UV



**Figure 2.** A, Patient with symmetric vitiligo before treatment. B, The same patient after 6 months of narrowband (NB) UV-B treatment of the left leg and no treatment of the right shows 90% improvement on the treated leg.



**Figure 3.** Validation of the Vitiligo Area Scoring Index (VASI) against investigator (A) and patient (B) global scoring. Ordinal global categories were graded according to overall estimated degree of repigmentation as follows: complete improvement (100%), very much improved (76%-99%), much improved (51%-75%), improved (26%-50%), minimal change (1%-25%), no change. *P* values were calculated using ordinal logistic regression.



**Figure 4.** A, Relative reduction in Vitiligo Area Scoring Index (VASI) by time. B, Relative improvement in vitiligo by body region for all patients. NB indicates narrowband.

phototherapy. The baseline extent of vitiligo did not correlate with responsiveness to NB-UV-B ( $P = .20$ ).

The face was evaluated with the VASI system, but not all patients desired facial treatment. Of the 8 patients who had their faces treated, 3 had greater than 75% repigmentation, 3 had 10% to 50% repigmentation, and 2 patients had no repigmentation. There was no correlation between the response of the face and the effect of NB-UV-B on the body, but these findings were most likely owing to the small subgroup of patients who received treatment to their face. Since the whole face was treated in an all-or-none fashion, there was no control. Anecdotally, patients who developed any degree of facial repigmentation were especially pleased with that response.

#### COMMENT

When a new therapy is developed for a condition, initial expectations are high, only to be tempered once the technology is more widely used in practice. Vitiligo rarely responds completely to treatment, so any treatment must be evaluated according to the degree of repigmentation that can be expected, regional variation by body site, and the range and frequency of adverse events.<sup>10</sup> To quan-

**Table 2. Odds Ratios for the Response of Vitiligo to Narrowband UV-B Phototherapy According to Body Region**

Comparison	Odds Ratio	<i>P</i> Value (Corrected)
Legs vs hands	17.9	.04
Trunk vs hands	14.8	.003
Arms vs hands	9.5	.001
Feet vs hands	0.05	.01

tify the impact of NB-UV-B on vitiligo, it is important to have a simple tool with reproducible results, which the VASI has proven to achieve. In addition, the controlled nature of the present trial provides the clinician with reliable data.

In 1998, Njoo et al<sup>2</sup> found 11 published randomized controlled trials on the treatment of vitiligo. Since that time, at least 4 additional controlled trials have appeared in the literature.<sup>7,11-13</sup> In all trials to date, the methods for assessing efficacy vary widely and often cannot be easily used to compare different treatments. The methods range from planimetry to binary scales of repigmentation vs no repigmentation. There are no randomized controlled trials looking at the response of vitiligo to NB-

UV-B treatment. The VASI methodology used in the present study may serve to improve some of these deficiencies by establishing a quantitative method to standardize outcome measurements in vitiligo as well as to test the effects of NB-UV-B on vitiligo in a controlled trial.

Another advantage of using quantitative scales is that they can more easily capture sequential trends in response by time or treatment number. Although such data for vitiligo are currently unavailable, they are nevertheless important because at the present time patients with vitiligo are asked to commit to treatment for a year or more based largely on knowing only the probability of achieving a certain specific degree of repigmentation at the end of therapy without any actual data on the expected rate of response over time. Finally, although investigators have reported their clinical impressions with respect to the differential response of vitiligo to phototherapy based on body sites, there are almost no data that quantify these differences in repigmentation according to specific body regions.<sup>2</sup> Our data allow clinicians to estimate for patients the likely degree of repigmentation, the response according to body site, and the number of treatments required for a specific effect.

The VASI provides a sensitive method for detecting treatment responses, as evidenced by our demonstration of a significant difference between NB-UV-B and control within 2 months of treatment. If our study had used a nonparametric method to evaluate response and chosen the usual 75% repigmentation threshold as representing treatment success, our trial would have shown a nonsignificant result ( $P = .50$  by the McNemar test) instead of the highly significant difference that we found using the VASI ( $P < .001$ ). Also, the VASI provides information over a range of time points rather than an arbitrarily set end point.

We confirmed a wide variation in response of vitiligo to NB-UV-B according to body site. The differential response might be due to the regional variation in the density of hair follicles, which have been shown to be reservoirs for melanocytes in patients with vitiligo.<sup>14,15</sup> This might explain why areas with a lower density of hair follicles such as the feet and hands have a lower response rate. However, others have shown that there are variations in melanocyte density within the epidermis that do not explain completely the anatomic variation in response.<sup>1</sup>

There are several limitations of the present study. First, it was not possible to blind this study because of the unilateral tanning induced by NB-UV-B. Also, the study period was limited to 6 months because we expected that patients who did not respond to treatment by that time would stop treatment and that those who achieved clear-cut unilateral repigmentation would not be willing to continue treatment to one side only beyond 6 months.

It could be argued that the VASI has a subjective component to it because it involves the physician deciding the amount of pigmentation and the area of involvement. A more objective technique might involve the use of standardized grids to measure areas marked out on the skin as is done with the ADASI score.<sup>16</sup> In addition, studies have used digital technology to quantify the extent of depigmentation.<sup>13,17</sup> However, these techniques are te-

dious and difficult to perform in studies with large numbers of patients. The PASI has become the gold standard to assess treatment response in patients with psoriasis because of its ease and reproducibility. This is despite the subjective decisions involved in rendering the score. Despite its limitations, it has allowed different treatments to be compared both historically and concurrently. The VASI is easy to perform and although there are other objective measures of response, they cannot be performed in the clinic without the aid of expensive, well-trained, and well-equipped support staff. These objective techniques also lack the validation that the VASI now has.

Any outcome scale that measures response in vitiligo should be validated against patient perceptions, which has been done with the VASI. The correlation with the VASI is lower for patient assessment than for physician assessment but is still statistically significant. The difference may be owing to a wider variation in what patients perceive to represent improvement. It could also be owing to the patients' heightened concern over exposed areas vs normally clothing-covered areas. For example, a patient whose skin repigments completely on the chest might still not be happy with treatment if it did not improve the vitiligo on his hands. It is important for other investigators to evaluate the validity of this technique, but we believe it is a quick and reliable tool, which can be applied to any setting and treatment.

Ultimately, NB-UV-B phototherapy for vitiligo works to a limited extent, and we have been able to quantify the degree to which it can repigment the skin. However, it is a long and arduous treatment process, and we hope that our data will prove useful in helping patients make an informed decision. Unfortunately, better treatments are still needed. Timed surgery and the grafting of autologous cultured melanocytes hold promise but may not be available in many parts of the world owing to their cost and regulatory issues.<sup>18</sup> In addition, the excimer laser has been suggested as a treatment of vitiligo,<sup>19</sup> but this is an expensive treatment modality, and its efficacy should be evaluated in a rigorous controlled fashion before it is used in widespread clinical practice. Until other treatments become available, NB-UV-B is likely to be the treatment of choice for widespread vitiligo because of its favorable response-to-adverse effect profile and low cost. However, patients should be educated on what to expect. Worldwide, patients with vitiligo are still limited in what they can expect from even the most advanced treatments. We hope that the VASI will help patients and physicians develop a common language to express the response of vitiligo to treatment as well as further define the effects of NB-UV-B on depigmented skin.

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## News and Notes

The 25th Symposium of the International Society of Dermatopathology will be held in Lisbon, Portugal, September 16-18, 2004, under the patronage of the International Society of Dermatopathology and the Portuguese Society of Dermatology and Venereology. Scientific Committee: L. Cerroni, O. Sanguenza, H. Kutzner, L. Requena, E. Vale, L. Almeida. The preliminary program is presented on [www.intsocdermpath.org](http://www.intsocdermpath.org) or [www.mundiconvenius.pt](http://www.mundiconvenius.pt). For further information, contact: MUNDICONVENIUS, Rua do Embaixador, 13-2º, 1300-215, Lisboa, Portugal; phone: ++351 213649498; fax: ++351 213649523; e-mail: [saudade\\_leitao@mundiconvenius.pt](mailto:saudade_leitao@mundiconvenius.pt).