Predictors of Adherence to Narrowband Ultraviolet B First-month Treatment Dosage Plan

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ABSTRACT **Background:** The adherence to a narrowband ultraviolet B (NB-UVB) treatment plan is derived, in large part, from the patient's skin tolerance to the phototherapy dose. At present, the initial and first-month incremental phototherapy doses are determined prior to treatment initiation based on the patient's Fitzpatrick skin phototyping.

Objectives: To identify variables that predict adherence to NB-UVB first-month treatment dosage plan.

Methods: Charts of 1000 consecutive patients receiving NB-UVB at a hospital-based phototherapy unit were retrospectively analyzed. We included patients receiving NB-UVB for atopic dermatitis, psoriasis, vitiligo, and mycosis fungoides. The first-month NB-UVB treatment plan was determined based on the patient's Fitzpatrick phototype. Adherence to treatment was defined as receiving at least 80% of the planned first-month cumulative dose. We compared adherent vs. non-adherent patient groups for age, sex, Fitzpatrick phototype, presence of freckles, nevus count category, and type of dermatological disease.

Results: The study included 817 eligible patients, mean age 40 (2–95) years; 54% men; 32% had Fitzpatrick phototype I-II. Distribution by diagnosis was atopic dermatitis (29%), psoriasis (27%), vitiligo (23%), and mycosis fungoides (21%). Adherence to NB-UVB treatment plan was observed in 71% of patients. Adherence decreased with age, with 7% decrease per year (P = 0.03) and was higher among mycosis fungoides patients (77.3%) compared to all other diagnoses (69.8%; P = 0.02).

Conclusions: Adherence to NB-UVB treatment may be related to age and diagnosis. Fitzpatrick phototype-based first-month treatment plans should be modified accordingly.

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KEY WORDS: Fitzpatrick phototype, minimal erythemal dose, narrowband ultraviolet B (NB-UVB), phototherapy, therapy adherence

Narrowband ultraviolet B (NB-UVB) is the most common type of phototherapy [1]. The adherence to a NB-UVB treatment plan is derived, in large part, from the patient's skin tolerance to the phototherapy dose as well as short-term side effects such as burning, erythema, and pruritus [2]. Side effects during the first month of therapy may reflect excessive initial and/or incremental NB-UVB dosing relative to the patient's skin tolerance. Symptomatic side effects are observed in 8% of NB-UVB treated patients and often lead to delays in phototherapy and to dose reduction. In 2% of patients, short-term side effects lead to treatment withdrawal [3].

Sensitivity to UV exposure is considered, in large part, a constitutional phenotypic attribute of individuals. Those individuals who have fair skin color, light-colored eyes and hair, and freckles are more likely to be burned with UV exposure [4,5]. However, a significant subset of individuals responds to UV-exposure in general, and to NB-UVB in particular, not as expected from their phenotypic appearance. While individual photosensitivity could be objectively established based on the patient's minimal erythema dose (MED) [6], this testing is time-consuming and expensive. Hence, in our experience, Fitzpatrick skin phototyping is frequently used to predetermine the first-month NB-UVB treatment dosing as well as the initial and incremental doses [7]. Phototyping recall risks and misclassification bias, patient self-report of the acute skin response to initial seasonal sun-exposure, and ability to tan following repeated sun-exposures are subjective [8]. Discrepancies in NB-UVB dose planning have been shown to exist between MED- and phototype-based methods [9]. To that end, we identified demographic and clinical variables predicting adherence to the NB-UVB first-month treatment dosage plan, which was predetermined based on Fitzpatrick phototyping.

PATIENTS AND METHODS

This study was conducted in conformity with the Declaration of Helsinki Principles and was approved by the institutional ethical committee. A retrospective review of 1000 consecutive charts of patients treated with NB-UVB at a hospital-based phototherapy unit was performed. Included in the study were patients, at least 2 years of age, receiving NB-UVB therapy for atopic dermatitis, psoriasis, vitiligo, or mycosis fungoides (MF). Patients excluded from the study were those that, during the first month of treatment were non-compliant with therapy scheduling, sun

exposure limitations, or received topical and/or systemic photosensitizing medications. The retrospective patient data search used the phototherapy unit's dedicated electronic database and case inclusion starting 1 January 2000.

Demographic and clinical variables collected for the study were registered in the patient charts prior to treatment initiation, including age, sex, dermatological disease type, presence or absence of freckling, total body nevus count of nevi ≥ 2 mm in maximal diameter (low nevus count was defined as < 20 nevi), and Fitzpatrick skin phototype. The phototype was determined prior to treatment initiation using a five-tier scale, as previously described [7] and based on reported individual's erythema skin reaction to first seasonal exposure to sunlight and tanning ability after repetitive exposures.

The first month trice weekly treatment plan was standardized and predetermined according to the phototype. The initial dose varied between 0.05–0.1 J/cm^2 and the incremental dose increases similarly varied between 0.05–0.1 J/cm^2. The treatment and/or incremental dose increases were reduced or temporarily withheld intense erythema was observed by medical staff or burning sensation reported by the patient, depending on the severity of the latter. Adherence to treatment was defined as receiving at least 80% of the planned cumulative first-month NB-UVB dose.

We compared adherent vs. non-adherent patient groups for age, sex, phototype, presence of freckles, nevus count category and type of dermatological disease. Categorical variables frequency was described, and intervariable correlation was analyzed using the chi-square test. Continuous variables were examined for distribution pattern using a histogram and described as mean and interquartile range, compared using the Mann-Whitney or Kruskal-Wallis tests. All statistical tests were bi-directional and log transformation multiple linear regression analysis was performed to identify possible confounders. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

Of 1000 consecutive patient charts, 817 (81.7%) met the inclusion criteria. The mean age was 40 years (range 2–95 years), 54% were males, and 32% had Fitzpatrick skin phototype I-II [Table 1].

The most common diagnosis was atopic dermatitis (29%) and least common MF (21%). The mean age of patients with MF (57.5 years) was older than that of patients with all other diagnoses (30.1 years, $P = 0.001$). In addition, patients 60 years and older were more likely to have Fitzpatrick skin phototype I-II, while patient < 60 years of age were more likely to have photo type III-V ($P = 0.02$).

In total, 71% of patients were adherent to NB-UVB treatment. There was no significant difference in age between the adherent group (mean age 39 years) and non-adherent group (mean age 41 years, $P = 0.09$). There was no significant difference in distribution by sex, skin phototype, freckles and nevus count categories between adherent and non-adherent groups [Table 1]. Notably, while comparison across all diagnoses did

Table 1. Adherence to NB-UVB for the first month planned cumulative dose by patient demographic and clinical data

Patient characteristics		Adherence			*P*-value
		Non-adherent, n (row %)	Adherent, n (row %)	Total, n (column %)	
		234 (29)	583 (71)	817 (100)	
Sex	Female	115 (31)	257 (69)	372 (46)	
	Male	119 (27)	323 (73)	445 (54)	
Diagnosis	Atopic dermatitis	77 (32)	161 (68)	238 (29)	0.18
	Psoriasis	62 (28)	159 (72)	221 (27)	
	Vitiligo	56 (30)	130 (70)	186 (23)	
	Mycosis fungoides	39 (23)	133 (77)	172 (21)	
Fitzpatrick skin phototype	I + II	85 (32)	175 (68)	260 (32)	0.11
	III + IV	143 (26)	399 (74)	542 (66)	
	V	6 (40)	9 (60)	15 (2)	
Freckles	Yes	35 (29)	84 (71)	119 (15)	0.84
	No	199 (28)	499 (72)	698 (85)	
Nevi count	< 20	223 (30)	565 (70)	788 (97)	0.24
	≥ 20	10 (42)	14 (58)	24 (3)	

not show significant differences, subgroup analysis showed that patients with MF more frequently adherent to treatment (77%) compared to patients with all other diagnoses combined (70%, $P = 0.05$) [Table 1]. The multivariate analysis is shown in Table 2. Older patients were less adherent to treatment (odds ratio [OR] 0.99 with each additional year of age, $P = 0.03$).

In addition, patients with MF were more adherent than patients with all other diagnoses (OR 1.66, $P = 0.02$).

Table 2. Multi-variant analysis of predictors of adherence to NB-UVB after the first month planned cumulative dose

Demographic and clinical variables		Odds ratio	*P*-value
Increasing age (for each 1-year increment)		0.99	**0.03**
Male sex		1.22	0.21
Mycosis fungoides versus all other diagnosis combined		1.66	**0.02**
Fitzpatrick skin phototype (type I+ II as referent category)	III-IV	1.36	0.07
	V	0.72	0.56
Presence of freckles		0.68	0.91
Nevi count category	< 20	1.26	0.33
	≥ 20	0.64	0.37

Bold signifies significance

DISCUSSION

The efficacy of NB-UVB is strongly related to patient adherence to therapy [2,10]. Factors associated with an increase in compliance to phototherapy include younger age, higher educational level, greater disease severity and visibility, and more belief in the efficacy of treatment [11,12]. Adherence is strongly related to phototherapy tolerance, that is, the rate and severity of treatment short-term side effects such as burning, erythema, and pruritus [13], which were described in about 8% of phototherapy patients [14]. While photosensitivity can be measured objectively by performing MED testing [6], it is often empirically determined based on Fitzpatrick skin phototype estimation [7]. This subjective method is more error-prone, with some patients displaying lower than expected tolerance to phototherapy [15]. Indeed, poor correlation between Fitzpatrick skin phototype classification and MED testing has been reported [4,8].

The purpose of the present study was to identify the demographic and clinical factors that predict good adherence to the first month of NB-UVB treatment and whose dosage was predetermined based on Fitzpatrick skin phototype estimation. We analyzed adherence among patients with atopic dermatitis, psoriasis, vitiligo, and MF, which represent the most common indications for NB-UVB treatment. We found that younger age and MF are associated with higher adherence to the NB-UVB treatment plan.

Constitutional response to UV exposure may change with advancing age. After all, the skin's response to UV exposure depends on local factors, with increasing age, cumulative sun-damage, epidermis atrophies, dermal-epidermal junction flattens, number of melanocytes and Langerhans cells decreases, and skin's inflammatory response changes [16-18]. To the best of our knowledge, limited data are available on the effects of age on sensitivity to UV. Studies have demonstrated more pronounced, yet delayed, erythemal reaction to UV among the elderly. Delayed erythema and edema in response to UV exposure, were shown in a small group of older patients compared to younger ones [19]. While there was no difference in MED, dose-response curves for UVB induced erythema were significantly steeper in the younger subjects in another study [20]. Last, reaction to UV radiation was found to be slower and initially less intense in older skin. During the first 24 hours after UV irradiation, there was a slower rise in histamine and prostaglandin-E2 levels, presence of fewer sunburn cells, and less striking alterations of peri-venular mast cells and endothelial cells. However, after 72 hours from UV irradiation, these changes became more striking in older than in younger skin [19].

The increased adherence to NB-UVB therapy among MF patients is interesting since MF patients were older than participants with other diagnoses in the present study. One possible account for this observation is that patients with oncological diagnoses are more motivated to follow the treatment plan fully, even with short-term side effects, than patients with a dermatosis. Another possibility is that there may be inherent differences in the skin's response to NV-UVB among MF patients. Further research is warranted to validate our observation.

LIMITATIONS

First, the study was conducted at a single center and was designed using retrospective data collection. Second, the study included children, and their adherence and compliance with treatment may be influenced by parental decisions and motivation. In addition, skin phototyping in children is derived from parental reports, which may lead to different classification bias than with self-reported phototyping in adults. Last, seasonal and cohort effects were not investigated and may vary between diagnostic subgroups.

CONCLUSIONS

NB-UVB first-month treatment dose planning, when based on skin phototyping, should consider additional patient-related factors including age and diagnosis. Larger prospective studies are needed to validate our findings.

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Capsule

Casting a wide NET on long COVID

A substantial number of individuals who recover from COVID-19 still present with long-term sequelae. **George** and colleagues followed individuals after recovery from severe COVID-19 to identify features that distinguished those who had evidence of long-term pulmonary sequelae from those who made a full recovery. They found that a neutrophil-associated inflammatory phenotype was apparent in those who had persistent pulmonary symptoms, and evidence of neutrophil extracellular traps, or NETs, was found in the blood of these individuals. These data highlight a potential role for neutrophils in pulmonary long COVID.

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Capsule

Ex vivo model ticks all the right boxes

Lyme disease, which is caused by *Borrelia burgdorferi*, is transmitted by ticks of the genus Ixodes. Although tick saliva is generally known to be immunosuppressive, the effects of tick feeding and the accompanying tissue damage on local and systemic immunity are not well understood. **Strobl** and colleagues recruited individuals with recent tick bite history and took skin biopsies from both the site of the bite and a control area. Neutrophils, B cells, and T cells (particularly tissue-resident memory T cells) were increased at the site of the bite, whereas other immune cell populations such as Langerhans cells were decreased. Cytokine production by T cells was impaired, and innate lymphoid cells at bite sites were also decreased. The immunomodulatory effects could be replicated by injecting tick saliva, along with *Borrelia* spirochetes, into human skin explants, providing a potential model to study human-tick interactions ex vivo.

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