

A UVB phototherapy protocol with very low dose increments as a treatment of atopic dermatitis

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From 1991 to 1992, 15 patients with atopic dermatitis were treated with a new UVB treatment regimen guided by skin reflectance measurements. The new treatment was characterized by very low dose increments from start to end of therapy. The median cumulative dose increment during therapy was only 20%. The severity of the disease, the efficacy of the treatment, the occurrence of adverse effects and the cumulative UVB dose were obtained from the case records. This data were compared in an open study with the data obtained from 17 patients with atopic dermatitis who were treated from 1988 to 1991 at the department with a standard UVB treatment regimen with stepwise dose increments. There was no difference in the severity of the disease at the beginning of the therapy between the two groups. The skin reflectance-guided low-dose UVB therapy was not significantly faster (3.5 weeks) than the regimen with stepwise dose increments (4.5 weeks). The cumulative UV exposure was four times lower with the new treatment regimen (34 standard erythema doses) compared with the old regimen (161 standard erythema doses), $P < 0.001$. The healing score was significantly higher with the new treatment regimen compared with the old, $P < 0.05$. This study indicates that skin reflectance-guided UVB phototherapy may enable the dermatologist to lower the cumulative UVB exposure significantly without losing effect.

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Ultraviolet B (UVB) radiation (280–320 nm) is commonly used in the treatment of atopic dermatitis (AD) (1, 2). UVB is an effective treatment, but conventional UVB therapy with increasing exposure doses is connected with adverse effects, which have limited its use. With conventional UVB therapy, the increasing exposure doses during the second and third week of treatment often induce xerosis and inflammation, which may aggravate the disease by increasing pruritus (3, 4). This UVB-induced inflammation often necessitates prolonged treatment, and sometimes UVB therapy has to be abandoned.

The department wanted to develop a new concept for UVB phototherapy of AD. We wanted to use the known anti-inflammatory effects of low-dose UVB (5), but to avoid erythema and inflam-

mation induced by erythemogenic UVB doses. The initial dose decided upon was equivalent to the highest dose in a test for minimal erythema dose (MED) that does not elicit any sign of erythema in the skin. Our intention was to keep the subsequent exposures at almost the same level and to allow only minimal dose increments. If the treatment course was effective, then the cumulative UVB dose for clearance would be much lower compared with conventional therapy. This would reduce the potential long-term adverse effects of UVB treatment.

Skin reflectance measurement is a fast non-invasive technique that can quantify both skin pigmentation and erythema (6–9). There exists a positive correlation between skin pigmentation and the erythema response to UVB (8, 9). This knowledge

has been used to develop an instrument that measures skin reflectance, processes the measurement and calculates the UVB exposure dose according to skin pigmentation. This instrument (UV-Optimize, Matic, Copenhagen, Denmark) makes it possible to initiate the UVB therapy at a certain predetermined suberythemogenic dose level in all patients. Since the skin pigmentation of the patients varies, so does the initial UVB dose.

Previous studies have shown that repeated exposure to suberythemogenic UVB doses only minimally stimulates melanogenesis (10–12). Therefore the instrument measures almost the same degree of pigmentation, and consequently the daily UVB dose does not increase much during a treatment course. Therefore the skin reflectance-guided UVB treatment is an almost constant low dose therapy, in contrast to conventional therapy, which has stepwise dose increments. With lower dose increments during therapy the UV-induced adverse effects, such as xerosis and inflammation, may be avoided.

In 1991 the department changed from a UVB regimen with stepwise dose increments to a new regimen guided by skin reflectance. This open retrospective study was performed to compare the efficacy of the new skin reflectance-guided UVB treatment regimen with the traditional UVB treatment regimen. All patients with AD treated with UVB during 1988 to 1992 were included in the study. All data were extracted from the patients case records and the UVB treatment records.

Material and methods

Patients

All patients treated for AD with UVB during 1988 to 1992 were included in the study. The study com-

Table 1. Clinical characteristics of the patients treated with skin reflectance-guided UVB therapy and conventional UVB therapy with stepwise dose increments*

	Reflectance	Conventional
Number	15	17
Age, years	22 (20–25)	24 (21–28)
Sex, male/female	5/10	4/13
Severity of the disease [mean]	3 (2–3) [2.5]	2 (2–3) [2.1]
Daily use of topical steroids before UVB therapy		
III×2	8	10
III×1	2	2
II×2	2	3
II×1		1
Not using topical steroids	3	1

* Median values and (95% confidence interval)

III×2: Group 3, potent topical steroid twice daily; III×1: Group 3 steroid once daily; II×2: Group 2, moderately potent topical steroid twice daily; II×1: Group 2 steroid once daily.

Table 2. Number of patients receiving adjunctive therapies during the UVB treatment

	Reflectance	Conventional
Systemic antibiotics	4 (27%)	4 (24%)
Antihistamines	4 (27%)	9 (53%)
Oral antifungals	1 (7%)	2 (12%)
Topical antifungals	6 (40%)	6 (35%)

prised 32 patients (age range 11–53 years). All patients fulfilled the diagnostic criteria of Hanifin & Rajka (13). Most of the patients used topical steroids prior to their UVB treatment course (Table 1). During therapy the topical treatment with steroids was gradually reduced during the first week of UVB treatment and was withdrawn in the second week, if possible. Some of the patients received adjunctive therapy such as antimicrobials and antihistamines (Table 2). All patients were treated with emollients.

During 1988 to 1991, 17 patients were treated with a UVB treatment regimen with stepwise dose increments. The data from these patients were compared with the data obtained from 15 patients who were treated from 1991 to 1992 with a UVB treatment course guided by skin reflectance measurements of skin pigmentation. UVB was administered two to five times per week until complete clearance or considerable improvement had been achieved or the treatment was abandoned. The patient characteristics are summarized in Table 1.

Evaluated parameters

All data were extracted from the patient's files and UVB treatment records in which the extent of the disease, efficacy of the treatment, the number of side effects, the number of treatments, treatment duration in weeks, and initial, final and cumulated UV doses could be obtained for each patient. The extent of the disease was used to score severity. The grading of extent was performed as described in the SCORAD index (14). The patients were assigned a severity score from 1 to 3: 1, below 30% of skin involved; 2, between 30 and 70% of skin involved; and 3, more than 70% of skin involved. Other severity parameters such as erythema, edema, oozing, crust formation, excoriation, lichenification and dryness could not be quantified from the available information in the patient files. The efficacy of the treatment was evaluated with a score from 0 to 3: 0, worsened or unchanged; 1, somewhat improved; 2, considerably improved; and 3, cleared. The number of adverse effects was calculated as the occurrence of erythema reactions listed in the patients case records. Occasionally pa-

tients missed treatments for various reasons, unrelated to the treatment itself, during both the new and the conventional UVB treatment courses. Calculation of the duration of the UVB courses in weeks was adjusted according to that. The number of UVB exposures, the initial and final doses and the cumulative UVB dose were recorded for each patient.

Radiation source and UV dose

All patients were exposed to the same Philips TL12 UVB equipment. Irradiance was measured with a UV-meter (International Light 1700 research radiometer with an IL SED 400 detector with a W quartz diffuser and a WBS 320 filter) during 1988 to 1992. This ensured reliable and comparable dose delivery. The daily exposure doses varied from 1.2 to 29.8 standard erythema doses (SED). The exposure time varied from 20 s to 8 min.

All UV doses are shown as SED (15, 16). One SED is defined as 100 J/m² at 298 nm, CIE action spectrum. The 100 J/m² is the energy needed to elicit a just perceptible 24-h erythema on the buttock skin of the most sensitive persons among a group with Fitzpatrick skin type I (17). One SED is equivalent to 373 J/m² of the UVB lamp.

Skin reflectance measurement and UV exposure

In the skin reflectance group, the patient's skin pigmentation and erythema were measured with the UV-Optimize 555 instrument, Matic, Copenhagen, Denmark (UV-Optimize), which measures the reflection of red and green light by the skin. Equations for calculating the percentages of redness and pigmentation independently, and treatment time are built into the instrument (8). The newly improved instrument is reliable, with a high degree of reproducibility. The detector is designed so that it is insensitive to differences in pressure on the skin. The skin measurements were performed by nurses on non-lesional skin between the shoulder-blades and on the chest of the patient before every UVB treatment. These two areas were chosen since they are representative of the more UV-sensitive parts of the body. The lower of the two pigmentation readings was always used to determine the exposure dose. One measurement with the UV-Optimize took about 10 s to perform. The UV-Optimize was adjusted so that the initial UV exposure dose would be equivalent to the highest UV dose that was unable to elicit any visible sign of inflammation in the skin. This dose varied between 2.1 and 5.9 SED because of differences in skin pigmentation of the patients.

Thirteen of the 17 patients who were treated

with the UV protocol with stepwise dose increments started at a UV dose equivalent to 3.7 SED. The rest of the patients ($n=4$) were evaluated by the doctors to be UV-sensitive and started with a lower dose. The dose increments varied between 12.5 and 25%. The dose was increased every time when UV radiation was given three times a week or less. The dose was increased every second time when UV radiation was administered four or five times a week. UV dose was only increased until the patient reported a tightening reaction in the skin. Then the dose was kept at the same level for two treatments and then gradually increased again.

Statistics

The differences in the severity of the disease, the use of topical steroids, the efficacy of the treatment, the number of adverse effects, the number of treatments, the duration in weeks, the initial, final and cumulated UV doses, between the new and the conventional UVB treatment were compared using the Mann-Whitney U-test. The differences in sex ratio were compared using the chi-squared test. Differences were considered significant when $P<0.05$ (two-tailed).

Results

There were no significant differences in age, sex ratio, severity of the disease, or in daily use of topical steroids before UVB therapy between the patients treated with the reflectance-guided UVB treatment and the patients treated with stepwise dose increments (Table 1). There was no difference in the number of weekly treatments or in the number of patients receiving adjunctive therapy be-

Table 3. Evaluation of the two UVB therapies

	Reflectance ($n=15$)		Conventional ($n=17$)	
	<i>n</i>	%	<i>n</i>	%
Cleared	10	67	5	29
Considerably improved	2	13	5	29
Somewhat improved	3	20	3	18
Unchanged	0		3	18
Deteriorated	0		1	6
Daily use of topical steroids after UVB therapy				
III×2	1	7	3	18
III×1	0		0	
II×2	0		2	12
II×1	3	20	6	35
I	0		1	6
No steroids used	11	73	5	29

III×2: Group 3, potent topical steroid twice daily; III×1: Group 3 steroid once daily; II×2: Group 2, moderately potent topical steroid twice daily; II×1: Group 2 steroid once daily; I: Group 1, mildly potent topical steroid.

Table 4. Assessment of the severity of the disease before initiation of UVB therapy of patients that cleared or considerably improved

	Reflectance (<i>n</i> =12)		Conventional (<i>n</i> =10)	
	<i>n</i>	%	<i>n</i>	%
Severe	7	58	5	50
Moderate	5	42	4	40
Slight	0		1	10

tween the two groups (Table 2). The effect of the UVB treatment was significantly higher with the new reflectance-guided regimen compared with the old, $P<0.05$ (Table 3). This was also reflected in the use of topical steroids at the end of UVB therapy, $P<0.05$ (Table 3). The severity of the disease in patients who healed or improved considerably is listed in Table 4. There was no significant difference in the severity of the disease among the successfully treated patients in the two groups.

The number of UVB exposures, the duration of the treatment, the initial, final and cumulative UV doses of the skin reflectance-guided and the conventional stepwise UVB treatment courses, and the relevant statistical data are listed in Table 5. The cumulated UV dose was four-fold higher with the conventional UVB therapy compared with the skin reflectance-guided UVB treatment course, $P<0.005$. The skin reflectance-guided UVB therapy course was 22% shorter than conventional therapy and the number of irradiations to treatment success was lower; however, these differences were not significant. The initial UV dose was the same in the two groups, while final UV dose was significantly lower with skin reflectance-guided UVB therapy than conventional UVB therapy, $P<0.001$. In the skin reflectance group, the median increase in exposure dose during treatment was only 20%, and there was no significant difference between initial and final UVB dose, $P<0.1$ Wilcoxon matched-pairs test.

Erythema reactions around the armpits and under the mammae were described in four patient

case records among those treated with the new treatment modality, and in two patient case records with the conventional modality. There was not a significant difference in the occurrence of erythema between the two treatment regimens.

Discussion

The results of this study seem to indicate that UVB treatment for AD can be performed as an almost constant low dose therapy, and that it is possible to reduce the cumulative dose without losing effect. In a previous study Jekler & Larkö (18) treated 25 patients with increasing doses of UVB. The UVB dose was always equivalent to 0.8 MED on one half of the body and 0.4 MED on the other. MED was tested every second week. As the MED increased so did the exposure dose. The daily exposure dose more than doubled in both groups during a treatment period of 8 weeks. No statistically significant differences between these dosage regimens were found. This indicates that the UVB dose can be reduced without losing efficacy. In this study the median initial dose was 3.1 SED in the skin reflectance group, which was equivalent to 0.6 MED in the median patient. However, in contrast to the previous study (18), the exposure was almost constant throughout the treatment.

There may be several reasons for the effectiveness of the relatively low UV exposures. All forms of UV have potent inhibitory effects on antigen presentation by Langerhans cells, as well as inhibitory effects on T-lymphocyte activation in response to mitogenic signals, which may reduce both pruritus and inflammation (4). This photoimmunosuppression occurs already when the skin is exposed to low doses of UVB (5,19). Bacterial skin infections, primarily *Staphylococcus aureus*, may aggravate AD. Due to its anti-inflammatory property UVB radiation seems to reduce *Staphylococcus aureus* colonization (20). Finally, it has been reported at conferences that suberythematous doses of UVB induce an increase in the amount of stratum

Table 5. The number of UVB exposures, the duration of the treatment, the initial, final and cumulative UV doses of the conventional treatment modality with stepwise dose increments and the skin reflectance-guided treatment* (Only patients who cleared or considerably improved are included.)

	Reflectance (<i>n</i> =12)	Conventional (<i>n</i> =10)	Result of Mann-Whitney U-test
UVB exposures, numbers	10.5 (6–25)	15.5 (9–20)	NS [§]
Duration, weeks	3.5 (1.5–5.5)	4.5 (2–8.5)	NS
Initial UV dose, SED	3.1 (2.4–3.7)	3.6 (1.2–3.7)	NS
Final UV dose, SED	3.6 (2.4–4.7)	15.2 (7.4–29.8)	$P<0.001$
Cumulative UV dose, SED	34 (19–105)	161 (34–242)	$P<0.005$

* Median values and (95% confidence interval)

§ NS=not significant

corneum lipids that may improve the barrier function of the skin, which is defective in AD patients.

With conventional UVB therapy the increased exposure doses during the second week of treatment often induce xerosis and inflammation (3), which aggravate the disease and necessitate prolonged treatment. An aggressive UVB phototherapy, aimed at maintaining a trace of erythema is not successful. In a study, eczema increased in four of the five patients, while no change was observed in the last patient (21). The clinical impression with the new treatment is that the patients notice less itching during the second week of treatment. However, no objective evaluation or subjective registration of itch was performed.

This is the first study that demonstrates the use of skin reflectance technique in the clinic for treatment of AD. The technique has several advantages. First, it is possible to administer UVB individually without a MED test. Second, one avoids the clinical judgement and choice of a dose that is large enough to be effective, but on the other hand does not increase the risk of inducing an erythema in the patients. Third, the exposure dose is kept low during the therapy, because UV-Optimize calculates the UV dose from the skin pigmentation measurement alone and therefore can not correct for the UVB-induced increase in epidermal thickness. Last, the technique is fast.

A study with historical controls is more likely to produce biased results than a prospective double-blind controlled investigation. In the present historical study, we had no influence on the ordination of UVB therapy or on the decision as to when the therapy should cease. All data were extracted from old patient files and UVB treatment records. The study period was limited to get a sufficiently high number of treated patients within the shortest possible time. There was no significant differences in age, sex ratio, severity of the disease, or in daily use of topical steroids before UVB therapy between the two groups. This should reduce the risk of misinterpretating the data in this study due to differences in the patients, or in the behavior of the investigators. In this study the extent of disease was used to describe the severity of the disease. The parameter was easy to obtain from the description of the patient. This is not the only important parameter; however, often patients with extensive disease also have intense erythema, excoriations and lichenifications of the skin. In a prospective study it would have been obvious to include a clinical scoring system such as the SCORAD index and perhaps laboratory parameters such as the level of serum IgE or eosinophil cationic protein, which may reflect disease activity.

The UV-Optimize measures both skin pigmen-

tation and erythema. During the skin reflectance-guided UVB regimen, the redness of the patient's skin was measured. Therefore we know that a minor regional erythema occurred only four times, twice in one patient and once in two patients. During the conventional regimen the occurrence of erythema was described by the doctors at the department, and the description of this parameter may therefore be somewhat imprecise. First, not all minor erythematous reactions are noted in the patient files. Second, it may be difficult to distinguish between a UV-induced erythema and other erythematous reactions in patients with AD.

In conclusion, UVB therapy of AD guided by skin reflectance measurements may enable the dermatologist to lower the cumulative UVB exposure significantly without losing efficacy. However, this proposed beneficial effect will have to be verified in a prospective double-blind controlled study in the future. In our opinion skin reflectance measurements ensure a more biologically uniform and systematic UVB treatment of all AD patients, independent of different doctors' experience and preferences.

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