Development of new treatment modalities for atopic dermatitis
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Medium dose long wave ultraviolet A (UVA1) provided by fluorescent tubes is effective and safe as treatment for severe atopic dermatitis

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submitted for publication
Summary

High dose UVA-1 is a new modality for the treatment of atopic dermatitis. It is effective, but the long-term side effects of these high doses are unknown. For high doses expensive high pressure mercury lamps are used with additional filters and air-conditioning. Medium dose UVA-1 therapy can be provided by the use of fluorescent tubes, it is less expensive, and may have a lower risk of long term side effects. For these reasons we evaluated the effectiveness and safety of medium dose UVA-1 therapy by fluorescent tubes for the treatment of severe atopic dermatitis.

Thirteen adults with moderate to severe atopic dermatitis were treated with fifteen successive daily doses, starting with 3, 6, 12, and 24 J/cm$^2$ to prevent erythema. From the fifth treatment the daily dose was 48 J/cm$^2$. The total cumulative dose was 573 J/cm$^2$. The SCORAD was assessed during all visits to the outpatient clinic.

After fifteen treatments the improvement of the SCORAD value was 50%. The improvement was more pronounced for pruritus (45.8%) and the extent of the dermatitis (73.9%) in comparison to the improvement of the intensity of the dermatitis (42.8%). Ultraviolet induced erythema (sunburn) was not reported.

Medium dose UVA-1 therapy provided by fluorescent tubes is an effective treatment for severe atopic dermatitis. No therapy related side effects were seen. Because of the lack of erythema (sunburn), there is no reason to start with low dose UVA-1. This study indicates the potential of UVA-1 in the treatment of atopic dermatitis.
INTRODUCTION

In the ultraviolet treatment of atopic dermatitis several wavelengths are used: UVA(1), PUVA(2), UVA+UVB(3), and UVB(4). We know that UVB radiation (295-315nm) is not suitable for acute exacerbations and is therefore restricted to chronic cases(4). Combinations of UVB with UVA (300-400nm) are more effective than UVB alone(6) and the result can be improved by increasing the UVA portion(3). Systemic photo chemotherapy, PUVA, is more effective than ultraviolet as mono therapy, but is associated with a number of side effects such as the rebound-effect and an increased risk of developing skin cancer(7).

Long wave UVA (UVA-1) is a new therapeutic option for atopic dermatitis and has a wavelength of 340-400nm (8-12). This wave length is interesting because of its side effects profile(13). A frequent reported side effect of ultraviolet irradiation is erythema, caused by irradiation with wave lengths below 330 nm. When the tubes used for this therapy give no radiation below 340 nm, no erythema is to be expected and relatively high doses can be used. The effect of UVA-1 is attributed to effects on IgE-bearing epidermal Langerhans' cells as well as modified secretory patterns of dermal mast cells and keratinocytes(14).

UVA-1 is used as low-dose (up to 20 J/cm² per treatment), medium-dose (20-50 J/cm² per treatment), and high-dose (50-130 J/cm² per treatment). Other indications for UVA-1 under investigation are urticaria pigmentosa(15), localized scleroderma (morphea)(16), and chronic vesicular dyshidrotic hand eczema(17).

Published studies about UVA-1 treatment for atopic dermatitis were studies with high-dose UVA-1 provided by high-pressure mercury lamps. These devices are expensive, especially because they need additional cooling (air-conditioning). Low dose and medium dose UVA-1 can be provided by fluorescent tubes. These tubes are les expensive as high pressure mercury lamps, and they don't produce so much heat as the mercury lamps. Additional heat-filters and air-conditioning are therefore not necessary for fluorescent tubes.

To study the effectiveness of this new therapeutic option, we needed an appropriate scoring system: widely used, accepted, and validated for ultraviolet therapy in adult patients with atopic dermatitis. A widely used scoring system in Europe is the SCORAD index. This index was developed in the early nineties, by the European Task Force on Atopic Dermatitis. In their consensus report two variants of an assessment system were compared(18). The most practical and simple system was preferred for easy routine use in outpatient
clinics. With a good within- and between-observer variability the RES-1 system was renamed into SCORAD (SCOring Atopic Dermatitis) for easier memorization. The SCORAD system was originally designed for the use in children, mainly for the evaluation of topical drugs. Ultraviolet therapy is not used for the treatment of children because of practical reasons and contraindications. Although the SCORAD is now also widely used in studies with adult patients, there is no experience in ultraviolet therapy.

We decided to perform a pilot study with the SCORAD to evaluate UVA-1 therapy. In this study we were looking for practical usefulness in an outpatient clinic setting. If the therapy improves the dermatitis, it is expected that this is reflected in all parts of the measuring system. Atopic dermatitis is a chronic skin disease, which improves gradually when treated appropriate. Other objectives of this study were to evaluate the treatment schedule of 15 treatments in three weeks. Side effects and concomitant medication were monitored. The efficacy of the treatment itself can also been used for power calculations for future clinical studies.

MATERIAL AND METHODS

Patients

The study was designed as a phase 2, open label, non-comparative study performed in one academic dermatology outpatient clinic. Thirteen adult patients with atopic dermatitis as defined according to the criteria of Hanifin & Rajka(19) as well as according to the Millennium Criteria(20) participated. At least 10% of their body surface area (BSA) was affected. The study started in mid-winter and ended in mid-spring.

Thirteen adult patients were included: 7 males and 6 females. The mean age was 27.9 year (SD 8.1). Baseline values were 5.9 (SD 2.6; range 0-10) for pruritus, 42.8% (SD 18.2) of the BSA for mean extent of the disease. The mean SCORAD index at baseline was 45.4 (SD 8.8).

The major exclusion criteria were: skin type I, active herpes infection, known to be HIV positive(21), a history of skin cancer, the use of phototherapy (UV) or intensive sunbathing or systemic therapy (steroids, cyclosporin) within 1 month prior to and during the study; the use of oral antibiotics within 2 weeks prior and during the study; the use of oral antihistamines within 1 week prior and during the study. In addition, the patients had to agree not to use phototoxic drugs or topical medications (corticosteroids, tar preparations, antibiotics, antihistamines) during the study.
Medium-dose UVA-1 in atopic dermatitis

All patients were informed of the study procedures and study therapy and gave their written consent.

Treatment
For the UVA-1 therapy we used an Waldmann 7001 cabin with Philips TL 100W/10R fluorescent lights. The subjects started the radiation on week-days (Monday, Tuesday, Wednesday, Thursday or Friday), continuing once a day on the next week-days. No interruption was allowed, only the obligatory weekend (Saturday and Sunday) breaks.

Starting with 3 J/cm² the first day, the dose was doubled in the next days: 6 J/cm² the second day, 12 J/cm² the third day and 24 J/cm² the fourth day. From the fifth day on the dose was 48 J/cm², for eleven times. The 48 J/cm² radiation lasts approximately 45 minutes. Total exposure per patient was 573 J/cm². This treatment scheme was successfully used in a previous study with medium dose UVA-1 therapy for atopic dermatitis(12,22).

Patients who missed more than three scheduled therapy sessions during the study, were considered as drop-out from the study; non-compliance.

Assessments
The evaluations for efficacy and safety were performed at the screening visit, on all 15 treatment days (just before the treatment) and at follow-up (7 days after the last treatment). Safety assessments were based on clinical adverse events reported by patients or observed by the physician. Adverse events and concomitant medication were monitored on a regular basis.

For efficacy evaluation the SCORAD index was used(18). This scoring system consists of three parts: part A is the extent of the involved area, part B is the sum of the six intensity items (erythema, edema/papulation, oozing/crust, excoriation, lichenification, dryness) and part C is the sum of the two subjective symptoms (pruritus and sleep loss). The extent of the dermatitis was scored using the rule of nine to assess the percentage of the total body area involved. The intensity items were all measured with a 4 point scale: 0 for absent, 1 for mild, 2 for moderate, and 3 for severe. The intensity items were scored at a mean lesional site, with exception of dryness. Dryness was scored at non-lesional sites. The subjective symptoms were both scored by the patients on a visual analog scale (range 0-10). The SCORAD was calculated from the A, B, and C parts with the formula: A/5 + 7B/2 + C. The extent determines 20% of the SCORAD, the intensity 60% and the subjective symptoms 20%. The minimum SCORAD index is 0, the maximum SCORAD index is 103. To minimize the inter-observer variation, one investigator performed 91% of the measurements (159 out of 175).
Each of the components of the SCORAD was tabulated separately. For each component of the SCORAD, the percentage change from baseline was calculated. P-values were calculated with the ‘Paired samples T test’ to test treatment effects.

RESULTS

Participants

Ten out of the thirteen severe (SCORAD >40) atopic dermatitis patients completed the study. One patient stopped after three treatments due to a lack of efficacy. He had the same experience with heat and with UVB treatment in the past. Unfortunately, this was not clear to the investigator at the screening visit. This withdrawal could have been expected, because of the warmth in the cabin during the long treatment sessions. The other two drop-outs were severe atopic dermatitis patients who had been treated with systemic immunosuppressive therapy (cyclosporin) before. They stopped the UVA-1 treatment due to a lack of immediate efficacy.

SCORAD analysis

After some practical instructions and training, the assessment for the SCORAD takes only about 5 minutes to perform. All together we needed only 10 minutes per visit for the study evaluations. The scoring of the pruritus and sleep loss on a visual analog scale (VAS) was done by the patients themselves. Scoring of the subjective items by the patients themselves, the daily attention of the investigator, and the daily improvement of the SCORAD index frequently shown to the patient in a graph were appreciated by the participating patients. For the evaluation of the coherence of the three constituents of the SCORAD (extent, intensity, and subjective symptoms) we calculated correlation coefficients. The A, B, and C parts of the SCORAD were correlated with coefficients between 0.62 and 0.75. The correlation between the subjective symptoms 'sleep loss' and 'pruritus' was 0.66. between pruritus and the extent of the dermatitis 0.58, and between pruritus and the intensity of the dermatitis 0.53. Sleep loss was correlated with the intensity of the dermatitis (0.81). The correlation with the extent of the dermatitis was 0.53. To the constituents parts of the intensity of the dermatitis, the sleep loss was correlated with the oedema/papulation (0.80) and dryness (0.79).

The correlation between successive measurements was computed to reflect the gradual improvement of the dermatitis, as seen by the patients and the investigators. The mean correlation between successive measurements of the SCORAD was 0.83 (range 0.58 - 0.97).

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Safety

For the evaluation of the treatment schedule the adverse events were monitored on a regular basis. Erythema is one of the most common side effects of ultraviolet therapy with a wavelength below 330 nm. Although we did not expect erythema from a treatment with a wavelength from 340 nm to 400 nm, we decided to start with a low dose and we gradually increased the dose. No erythema was seen in this study.

Adverse events reported by all patients (intention to treat population, n=13) were dizziness (3 patients) and eye infection/irritation (2 patients). There were no serious adverse events, and none of the patients withdrew because of adverse events.

Outcome

The symptoms worsened in the first days. The highest mean scores for pruritus (6.46), for the extent (44.0), and for the SCORAD-total (47.5) were reached at day 2. Levels returned to baseline after 3 (itch) or 4 (extent and SCORAD-total) treatments. After these first 3 to 4 treatments the symptoms improved gradually, reflected by a decrease of the SCORAD: see figure I. The improvement was more pronounced for pruritus (45.8%; p=0.03) and the extent of the dermatitis (73.9%; p=0.003) in comparison to the improvement of the intensity of the dermatitis (42.8%; p=0.001), see table II. One week after the last treatment a follow-up visit was planned. At this visit the improvement was still 46.9% (p<0.001).
<table>
<thead>
<tr>
<th>day</th>
<th>treatment number</th>
<th>treatment dose J/cm²</th>
<th>cumulative dose J/cm²</th>
<th>SCORAD total (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>3</td>
<td>3</td>
<td>45.4 (8.8)</td>
</tr>
<tr>
<td>2</td>
<td>II</td>
<td>6</td>
<td>9</td>
<td>47.5 (8.5)</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>12</td>
<td>21</td>
<td>46.2 (10.0)</td>
</tr>
<tr>
<td>4</td>
<td>IV</td>
<td>24</td>
<td>45</td>
<td>46.6 (12.3)</td>
</tr>
<tr>
<td>5</td>
<td>V</td>
<td>48</td>
<td>93</td>
<td>43.8 (9.7)</td>
</tr>
<tr>
<td>8</td>
<td>VI</td>
<td>48</td>
<td>141</td>
<td>40.4 (9.9)</td>
</tr>
<tr>
<td>9</td>
<td>VII</td>
<td>48</td>
<td>189</td>
<td>39.1 (9.9)</td>
</tr>
<tr>
<td>10</td>
<td>VIII</td>
<td>48</td>
<td>237</td>
<td>39.4 (10.8)</td>
</tr>
<tr>
<td>11</td>
<td>IX</td>
<td>48</td>
<td>285</td>
<td>32.3 (9.9)</td>
</tr>
<tr>
<td>12</td>
<td>X</td>
<td>48</td>
<td>333</td>
<td>32.0 (10.8)</td>
</tr>
<tr>
<td>15</td>
<td>XI</td>
<td>48</td>
<td>381</td>
<td>32.6 (15.5)</td>
</tr>
<tr>
<td>16</td>
<td>XII</td>
<td>48</td>
<td>429</td>
<td>26.8 (9.6)</td>
</tr>
<tr>
<td>17</td>
<td>XIII</td>
<td>48</td>
<td>477</td>
<td>25.3 (9.8)</td>
</tr>
<tr>
<td>18</td>
<td>XIV</td>
<td>48</td>
<td>525</td>
<td>24.4 (11.2)</td>
</tr>
<tr>
<td>19</td>
<td>XV</td>
<td>48</td>
<td>573</td>
<td>23.1 (9.8)</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td>24.1 (8.4)</td>
</tr>
</tbody>
</table>

**Table 1.** Change of the mean SCORAD index before, during, and after treatment
Medium-dose UVA-1 in atopic dermatitis

**Figure 1.** Mean SCORAD index before, during, and after treatment in 10 out of 13 patients (last measurement is at follow-up, 1 week after last treatment)
<table>
<thead>
<tr>
<th></th>
<th>before treatment</th>
<th>after treatment</th>
<th>change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORAD total</td>
<td>42.6</td>
<td>21.3</td>
<td>-49.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>erythema</td>
<td>2.00</td>
<td>1.22</td>
<td>-39.0%</td>
<td>0.001</td>
</tr>
<tr>
<td>edema/papulation</td>
<td>1.67</td>
<td>0.67</td>
<td>-60.0%</td>
<td>0.003</td>
</tr>
<tr>
<td>oozing/crust</td>
<td>0.22</td>
<td>0.00</td>
<td>-100%</td>
<td>0.169</td>
</tr>
<tr>
<td>excoriation</td>
<td>1.00</td>
<td>0.44</td>
<td>-55.6%</td>
<td>0.013</td>
</tr>
<tr>
<td>lichenification</td>
<td>1.33</td>
<td>1.22</td>
<td>-8.3%</td>
<td>0.594</td>
</tr>
<tr>
<td>dryness</td>
<td>1.56</td>
<td>1.00</td>
<td>-35.7%</td>
<td>0.013</td>
</tr>
<tr>
<td>intensity</td>
<td>7.78</td>
<td>4.45</td>
<td>-42.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>extent</td>
<td>37.5</td>
<td>9.78</td>
<td>-73.9%</td>
<td>0.003</td>
</tr>
<tr>
<td>pruritus</td>
<td>5.33</td>
<td>2.89</td>
<td>-45.8%</td>
<td>0.030</td>
</tr>
<tr>
<td>sleep loss</td>
<td>2.56</td>
<td>0.56</td>
<td>-78.3%</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Table 2. Changes in mean SCORAD total and mean SCORAD parameters in the patients who completed the treatment

DISCUSSION

A randomized, double-blind study is nearly impossible for the evaluation of this new therapeutic modality. The treatment is characterized by the heat and long duration, in comparison to other ultraviolet treatments (UVA and/or UVB). We decided to perform a non-controlled pilot study to evaluate the potential of this new therapeutic modality.

In this study plasma levels of soluble interleukin-2 receptors and soluble interleukin-4 receptors were not measured. From other studies it is known that these plasma levels decrease under UVA-1 therapy(23). Because these plasma
levels gave no additional information, we decided to use only a clinical evaluation system. In this way we get more specific information about the different characteristics of the disease.

The last years there has been some criticism about the SCORAD. Especially the combination of objective and subjective symptoms has been criticized. New scoring systems are in development, such as the Eczema Area and Severity Index (EASI)(24,25). In this scoring system the subjective symptom 'itch' is also measured on a visual analog scale, only the evaluation of the itch is separate from the evaluation of the objective items. Because pruritus is the most important sign for patients with atopic dermatitis, it is unthinkable to design a measuring instrument for atopic dermatitis without consideration of the pruritus.

For 10 out of 13 patients medium dose UVA-1 therapy was an effective therapy. Only for two very severe cases, who stopped their cyclosporin therapy for this study, UVA-1 therapy was not effective. The last patient who discontinued the therapy could have been foreseen: atopic dermatitis can exacerbate when sweating. The long and hot UVA-1 therapy was not suitable for this patient. The remaining 10 severe atopic dermatitis patients completed the treatment per protocol, and their dermatitis improved. The first four treatment days were difficult for most patients. The relatively low doses in the first days were not very effective, and the patients stopped other treatments (usually a topical corticosteroid). From day 5 the treatment was performed with the maximum dose, and the efficacy was higher. The most important symptom of atopic dermatitis, the itch, is responding very well to the treatment. There is a slow improvement of the intensity symptoms, resulting in a slower improvement of the SCORAD index. In particular the symptoms 'dry skin' and 'lichenification' will not disappear in three weeks. These intensity symptoms determine 60% of the total value of the SCORAD. The good improvement of subjective symptoms (like itch) and the extent are of relatively minor weight in this evaluating system.

We started the treatment with a low dose because of limited experience with this new modality in our center. Retrospectively, it seems to be superfluous to start with a low dose. Also considering the ineffectiveness of a low dose in the first days, we recommend to start with a higher dose. A better response to the treatment in the first days, as well as a better overall response can be expected. For practical reasons we interrupted the treatment during the weekends. Most patients showed a increase in the severity of the disease after the weekends. The efficacy of the treatment may be better without interruption. This may be an option for hospitalized patients. During the treatment, the patients were only allowed to use emollients. Because tachyphylaxis is a well known side effect of
topical steroids, it came as no surprise that most patients reported an improved efficacy of topical steroids at the follow-up visit. This was also reflected in a persistent low value of the SCORAD after the UVA-1 therapy was stopped.

The adverse event dizziness is frequently (3/13) reported. Standing in a very warm, noisy and small (80 x 80 cm) cabin for 45 minutes without an orientating view and with eye protection may cause this dizziness. The use of a cabin in combination with a long duration of the treatment sessions may be unsuitable for some patients. The development of filters and additional cooling promoted as "cold light" UVA-1 therapy may lack this side effect(23). Eye irritation is often seen in patients with atopic dermatitis. It is unlikely that this adverse event is caused by the treatment. Perhaps the use of protection glasses may have contributed to this adverse event.

Although this pilot study is not a randomized, double-blind, controlled study, the outcome confirmed the potential of UVA-1 treatment with fluorescent tubes in atopic dermatitis, also considering the more favorable side effect profile in comparison to other ultraviolet treatments.

In conclusion, medium-dose UVA-1 provides a useful addition in the gamma of modalities available for the induction of partial remission in atopic dermatitis. We also conclude that the starting and subsequent UV-doses can be equal, i.e. 48 J/cm². A contraindication is previous exacerbation of atopic dermatitis by heat / sweating. Future studies should establish maintenance medium-dose UVA-1 treatment regimens as well as sequential combination with other modalities known to be effective in Atopic Dermatitis.

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Chapter II


