Chapter 6

Efficacy of UVA-1 cold light as an adjuvant therapy for systemic lupus erythematosus

M.C.A. Polderman, S. le Cessie, T.W.J. Huizinga, S. Pavel

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Abstract

Objective: The assessment of the efficacy of therapy of patients with moderately active systemic lupus erythematosus (SLE) with low doses of UVA-1 cold light.

Methods: A double blind, placebo-controlled, cross-over study design was used for the examination of the efficacy of low doses of UVA-1 radiation (12 J/cm²/day for 15 days) in 12 patients.

Results: UVA-1 treatment resulted in a significant decrease of well-validated disease activity indexes [the SLE activity measure (SLAM) (p<0.001) and the SLE disease activity index (SLEDAI) (p=0.007)], whereas neither score improved significantly during placebo treatment. Furthermore, UVA-1 therapy proved to be more effective (mean decrease 4.8 points) than placebo [mean decrease –1.7 points (i.e. an increase)] when measured by the SLAM (p=0.001, 95% CI -7.56 to -2.28), but not by the SLEDAI. Two patients had transient skin reactions at the beginning of treatment.

Conclusion: UVA-1 therapy appears to be a useful adjuvant treatment modality for patients suffering from moderately active SLE. Its effect could possibly be explained by reduction of B-cell function or apoptosis of plasma cells.
Introduction

Systemic lupus erythematosus is an autoimmune disease characterized by the production of a large variety of autoantibodies by B cells, leading to inflammation in various organs.¹ Current therapies, such as glucocorticoids, azathioprine and cyclophosphamide, are effective, but their side-effects may account for considerable organ damage in the course of the treatment.² One of the frequently occurring symptoms in SLE is photosensitivity. In addition, sunlight or exposure to artificial ultraviolet (UV) lamps is believed to be capable of activating the disease. Although the mechanisms of the photosensitive skin reaction and SLE activation may be different, both adverse effects of UV exposure are the reason why patients are recommended to avoid sun exposure.

For that reason, it was quite unexpected when McGrath Jr et al.³ described a favourable effect of UVA radiation on SLE activity in a mouse model of SLE. Later, McGrath Jr et al.⁴,⁵ reported encouraging results obtained in SLE patients treated with a long-wavelength fraction of the UVA spectrum (340-400 nm), called UVA-1. This part of UVA is known to have a positive immunomodulating effect in some inflammatory skin diseases.⁶,⁷

We have recently reported on our first experience with whole-skin UVA-1 cold light treatment of SLE patients.⁸ Being aware of the risk of photosensitivity we originally exposed our patients to only 6 J/cm² of UVA-1, five times a week. After 3 weeks of exposure the disease activity indexes SLE Activity Measure (SLAM)⁹ and SLE Disease Activity Index (SLEDAI)¹⁰ were lower than at the beginning of the phototherapy. However, some minor placebo response was observed as well, which possibly explains the lack of statistical significance when the effect of UVA-1 on SLAM and SLEDAI was compared with that of placebo treatment. No side-effects occurred during or after treatment.
These first results encouraged us to set up a new controlled clinical trial with the use of higher doses of UVA-1 cold light.

**Patients and methods**

After approval of the ethical committee we treated 12 patients with moderately active SLE, according to the revised criteria for SLE of the American College of Rheumatology. Patients with a minimal SLEDAI of 4, with no changes in therapy during the last 2 months and without discoid skin lesions were included after their written consent was obtained.

A BioSun Med CL 3000 cold-light unit (BioSun Sylt, Wennigstedt, Germany) was used for the irradiations. The apparatus emits photons with wavelengths of 340-500 nm. Owing to a filter system that eliminates all infrared irradiation and a ventilation system providing a cool breeze, this UVA-1 therapy is also called UVA-1 cold light therapy. Placebo treatment was carried out using a panel of thermoluminescent (TL) tubes covered with a blue plastic plate that could be inserted into the UVA-1 cabin, to mimic the blue UVA-1 light. Patients could recognize differences between the two treatments on account of the absence of the cool breeze and warmth during placebo therapy. However, they did not know which was the supposedly effective one. Patients were allocated by an independent investigator for total body irradiations with $12 \text{ J/cm}^2$ UVA-1 ($n=6$) or an equivalent time of total body exposure (6 minutes 40 s) to placebo light ($n=6$), five times a week for 3 weeks. After a 9-week wash-out period the patients received the alternative treatment.

The primary parameters followed during the treatment were the SLAM and the SLEDAI. Furthermore, the Medical Outcome Study Short-form 36 (MOS SF36) was used to evaluate quality of life and autoantibody titres [antinuclear factor (ANF), anti-double-stranded...
DNA (dsDNA), anti-SSA, anti-SSB, anti-ribonucleoprotein (anti-RNP), anti-Sm, anti-Scl70, anti-Jo-1] were measured. Apart from non-steroidal anti-inflammatory drugs (NSAIDs), patients were not allowed to change their medication during the whole trial period.

A paired $t$-test was used to assess changes in the SLAM, SLEDAI and the MOS SF36 and auto-antibody titers during both treatments. A non-paired $t$-test was used to evaluate differences between the effect of UVA-1 and placebo treatment. Analysis was performed according to the intention-to-treat principle. A power calculation showed that 11 patients were needed.$^8$ All variables were evaluated for carry-over and period effects.

**Results**

Twelve Caucasian patients (10 women, 2 men, age 23–58 yr), with moderately active SLE were included. Their mean SLAM and SLEDAI at time of inclusion were 13.42 (range 8-23) and 13.33 (range 6-23) respectively. At enrolment, their therapy consisted of low-dose prednisone (5/12), azathioprine (6/12), antimalarial drugs (7/12) and NSAIDs (8/12) (Table 6.1.).

As shown in Fig. 6.1., UVA-1 treatment resulted in a statistically significant decrease of both SLAM and the SLEDAI at the end of the third week of therapy, whereas during placebo treatment neither score improved significantly. Furthermore, UVA-1 therapy (mean decrease 4.8 points) proved to be more effective than placebo (mean decrease –1.7 points, *i.e.* an increase) when measured by the SLAM ($p=0.001$, 95% CI -7.56 to -2.28) (Table 6.2.). Frequently improving components were arthritis (6/9), myalgia/myositis (5/7), dyspnoea (4/4), fatigue (4/11), headache (4/4), leukocyturia/ erythrocyturia (4/7) and blood pressure (4/4).
Table 6.1. Patients’ characteristics

<table>
<thead>
<tr>
<th>F/M</th>
<th>Age</th>
<th>Duration SLE (yr)</th>
<th>Medication (mg)</th>
<th>Therapy 1 SLAM before 1</th>
<th>SLAM after 1</th>
<th>SLEDAI before 1</th>
<th>SLEDAI after 1</th>
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PR= prednisone, AZ= azathioprine, HY= hydroxychloroquine

Table 6.2. Decrease of parameters, during 3 weeks’ UVA-1 and placebo treatment: values are given as mean (SD; 95% confidence interval; p-value)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>UVA-1, n=12</th>
<th>Placebo, n=12</th>
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<td>SLAM</td>
<td>4.75 (–3.12; 2.76 to 6.72; 0.000)*</td>
<td>-1.67 (3.13; –2.15 to 1.82, 0.857)</td>
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<td>SLEDAI</td>
<td>3.67 (3.82; 1.24 to 6.09; 0.007)</td>
<td>1.83 (5.93; –1.59 to 5.26; 0.264)</td>
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<tr>
<td>MOS SF36**</td>
<td>-19.04 (80.61; –70.26 to 32.18; 0.431)</td>
<td>-53.56 (133.98; –138.70 to 31.55 ; 0.193)</td>
</tr>
</tbody>
</table>

*p= 0.001, when UVA-1 is compared to placebo treatment.

**A higher MOS SF36 means improvement of quality of life.
Figure 6.1. The effect of 3 weeks’ total body irradiation with UVA-1 cold light and placebo on SLE activity expressed in SLAM and SLEDAI scores. The results are expressed as means with standard deviations. NS= not significant.

SLAM and SLEDAI scores at the beginning of the first treatment period did not differ from the scores at the beginning of the second treatment period (p=0.096), nor were these scores before UVA-1 different from before placebo treatment (p=0.479).

There were no significant changes of the MOS SF36, the ESR, leukocyte and differential counts, and C3- and C4-levels during UVA-1 treatment. The anti-RNP titre in one patient decreased by 25 units (31%), the anti-SSA titer in another by 16 units (22%).

Photosensitivity may occur in patients with SLE when irradiated with UVA doses higher than 20 J/cm$^2$.\textsuperscript{13} Two out of seven of our patients, known to be photosensitive, experienced some slight problems at the beginning of UVA-1 therapy, which consisted of a transient facial erythema in one and a minimal activation of subacute cutaneous lupus erythematosus (SCLE) in the other. In the latter patient the dose was subsequently reduced to 6 J/cm$^2$ at the beginning of the second week and the skin changes slowly disappeared.
Chapter 6

Discussion

Whereas the dose of 6 or 12 J/cm$^2$ of short-wavelength UV (UVB) would cause serious burns with many apoptotic cells in the superficial skin, the same dose of UVA-1 does not generate any visible macroscopic or microscopic changes in the epidermis or dermis. Since it is known that UVA-1 photons penetrate easily to the superficial dermis, one must consider the possibility that UVA-1 radiation, by generating oxidative stress, may affect the metabolism of B cells and/or T cells in the capillary network of the skin.

SLE is one of the autoimmune diseases where expanded numbers of plasma cells are present in the blood. Recent investigations have shown that the number and frequency of circulating CD27$^{\text{high}}$ plasma cells is significantly correlated with SLE disease activity.$^{14}$ We suggest that these cells may be (one of) the targets of UVA-1 and that the irradiation might be able to suppress B cell activity or induce apoptosis of circulating activated B lymphocytes in the dermal and subcutaneous capillaries, resulting in lowered autoantibody production and subsequently in reduced disease activity. Alternatively, the B cell/T cell interaction could be affected.

SLAM appeared to be more suitable than SLEDAI for evaluation of therapeutic results over a course of time.$^9$ This could explain why UVA-1 therapy proved to be more effective than placebo when measured by SLAM, but not when evaluated by SLEDAI.

Our results show that UVA-1 irradiation is a safe, effective adjuvant treatment for patients with moderately active SLE.
Acknowledgements

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Chapter 6

References


