Chapter 2

UVA-1 cold light therapy in the treatment of atopic dermatitis: 61 patients treated in the Leiden University Medical Center

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Abstract

Background: UVA-1 has been shown to be effective in the treatment of patients with atopic dermatitis. However, its optimal therapeutic conditions are not yet fully established.

Methods: In an open prospective study we retrospectively compared the effect of 4 weeks therapy (32 patients) with the effect of the usual 3 weeks therapy (29 patients) in patients with atopic dermatitis, using a medium dose UVA-1 cold light (45 J/cm²), 5 days a week.

Results: Scoring atopic dermatitis index (SCORAD) and dermatology life quality index (DLQI) quality of life indexes improved significantly during both 3 and 4 weeks UVA-1. Patients who were treated for 4 weeks showed a superior improvement of the SCORAD index (23.12 points, 95% confidence interval (CI) 16.09-30.16, vs. 13.32 points, 95% CI 5.61-21.04, \( p = 0.059 \)), and the DLQI (5.41 points, 95% CI 2.38-7.88, vs. 3.86 points, 95% CI 1.88-5.84, \( p = 0.360 \)), compared with patients who were treated for 3 weeks. However, the differences did not reach statistical significance. Only patients who were treated for 4 weeks were able to maintain their improvement 6 weeks after therapy. In both groups 50% of patients had intermittently used mild topical corticosteroids in the follow-up period.

Conclusion: Extension of UVA-1 therapy from 3 to 4 weeks results in a clinically relevant improvement of the outcome, and more prolonged therapeutic effects, measured by the SCORAD index.
Introduction

Since the 1970s psoralens and ultraviolet A radiation (PUVA) therapy has been successfully used for the treatment of atopic dermatitis. Alternative forms of phototherapy for the same disease have been UVB, narrow-band UVB and UVA-UVB combination therapy. In the 1980s UVA-1 treatment was introduced. This long-wave (340-400 nm) UVA treatment appeared to be a promising phototherapeutic modality. Some authors have reported on good results of high-dose (130 J/cm², 3 weeks) UVA-1 in the treatment of atopic dermatitis, whereas others have shown that also medium doses of UVA-1 (50 J/cm², 3 weeks) could be successfully applied. In several controlled trials, both high- and medium-dose UVA-1 proved to be more effective than UVA-UVB combination therapy.

We observed (Fig. 2.1.), together with some other authors that after a successful 3 weeks of medium dose UVA-1 therapy, eczema deteriorated relatively soon. To investigate if the prolongation of treatment leads to a longer therapeutic response we treated 61 patients with atopic dermatitis with medium-dose UVA-1 during either 3 or 4 weeks, and we evaluated disease activity, quality of life and duration of improvement after a follow-up period of 6 weeks.

Patients and methods

In an open prospective study 32 patients with atopic dermatitis were treated with UVA-1 during 4 weeks. Their therapeutic effect was retrospectively compared with the effect of UVA-1 in 29 patients who were treated during the usual 3 weeks. The mean age of patients was 33.4 years (range 17-73), 19 were male, 42 were female. The majority of the patients had skin type II (24/61), or III (29/61). The remaining eight patients had skin type I (4/61) or V
Patients with moderate to severe atopic dermatitis [Scoring atopic dermatitis index (SCORAD) range 14.8-76.2] with insufficient effect of local corticosteroids, and no use of systemic corticosteroids or cyclosporine therapy in the previous 2 months, were included. A Photomed 250 000 unit (BioSun Sylt Service GmbH, www.biosunsylt.com), emitting photons with wavelength of 340-500 nm, with an irradiance of 31 mW/cm\(^2\), was used. Owing to a filter system that eliminates all infrared (i.e. heat producing) radiation and a ventilation system providing a cool breeze, this UVA-1 therapy is also called UVA-1 cold-light therapy.

Patients were treated with 45 J/cm\(^2\), 5 days a week, during 3 (29 patients) or 4 (32 patients) weeks. In the first week, the UVA-1 dose was increased from 3 J/cm\(^2\) on Monday to 15 J/cm\(^2\) on Tuesday, and further increased by 10 J/cm\(^2\) every day to a maximum of 45 J/cm\(^2\) on Friday. The cumulative UVA-1 doses were 573 and 798 J/cm\(^2\) for the 3 and 4 weeks treatment schedule, respectively. During therapy patients wore goggles. Before the treatment, weekly during treatment, and 3 weeks and 6 weeks after treatment, two scoring systems were applied: the SCORAD (maximum possible score 103)\(^6\) and the Dermatology Life Quality Index (DLQI, maximum possible score 30 = maximal discomfort).\(^6,7\) The examination of both scoring systems was performed by the same investigator who evaluated these parameters also in the 3 weeks’ treated patients.

Except for the first week during which the daily dose was gradually increased to 45 J/cm\(^2\), patients used no topical steroids or antihistamines until the follow-up. Emollients could be used infinitely until 3 h before irradiation to prevent glimmering of the skin and consequent radiation reflection. Temperature on the skin surface was measured after 10 min to compare with heat producing qualities of PUVA units reported in literature.\(^8\)

A paired \(t\)-test was used to assess changes in the SCORAD index, and the DLQI during and after treatment. A non-paired \(t\)-test was used to compare mean changes between the 3 and 4
weeks treatment regimen. Analyses were performed according to the intention to treat principle. Statistical significance was defined as $p \leq 0.05$.

**Results**

UVA-1 treatment resulted in a statistically significant decrease of the SCORAD index at the end of therapy [18.5 points, $p = 0.0001$, 95% confidence interval (CI) 13.26-23.67]. Baseline SCORAD ($p = 0.75$) and DLQI ($p = 0.59$) indexes of the 3 weeks’ treated patients did not differ from those of 4 weeks’ treated patients. The patients who had been treated for 4 weeks achieved better results (mean decrease of 23.12, SD = 19.52, $p < 0.001$, 95% CI 16.09-30.16) than those treated for 3 weeks (mean decrease of 13.32 points, SD = 20.28, $p = 0.001$, 95% CI 5.61-21.04) (Fig. 2.1.). However, this difference was just not statistically significant ($p = 0.059$, 95% CI –20.00-0.40). Furthermore, when both groups had been treated for 3 weeks, the difference in improvement of the SCORAD index was not statistically significant ($p = 0.256$). After a 6 weeks’ follow-up period 50% of patients were lost to follow-up in both groups. These patients had not responded better or worse to UVA-1 therapy than the patients who were not lost to follow-up. At that moment in time the SCORAD index of patients in both groups had increased by five points, which corresponded to a 21.6% loss of post-treatment effect for the 4 weeks’ treated group and a 37.5% loss of post-treatment effect for the patients who were treated for 3 weeks. The patients from the 4 weeks treatment regimen still showed a significant improvement of their SCORAD index compared with pretreatment values, whereas those who were treated during 3 weeks did not (Fig. 2.1.). In both groups approximately 50% of patients had intermittently used mild topical corticosteroids during the follow-up period. The patients who did not need topical corticosteroids during follow-up had not responded better or worse to UVA-1 therapy than
the patients who did use local corticosteroids during follow-up. The DLQI showed a significant decrease after both 3 (3.86 points, SD = 5.20, p<0.000, 95% CI 1.88-5.84) and 4 weeks (5.41 points, SD = 7.53, p = 0.001, 95% CI 2.38-7.88) of UVA-1 therapy. The effect of two treatment regimens did not differ significantly (p = 0.360, 95% CI –1.81-4.90). Similar to the SCORAD index, only patients who had been treated for 4 weeks were still significantly improved at 6 weeks after therapy (Fig. 2.2.).

UVA-1 cold light therapy was generally well tolerated by patients. During treatment the maximum temperature at body distance was 34°C (range 24-34°C). In PUVA-cabins temperatures up to 41°C were reported. Some side-effects occurred. Fifteen (24.6%) patients experienced slight erythema in the first week that did not require any treatment and resolved spontaneously in a few days. This could be explained by the relatively light skin type of these patients (2/15 skin type I, 11/15 skin type II, 2/15 skin type III). Eight patients (13.1%) dropped-out: Two of them developed a photosensitive reaction (one had solar urticaria, the other probably had a light phototoxic reaction because of cosmetics), six others exacerbated after 1 (n= 2) and 2 weeks (n= 4). Their inferior therapeutic results might explain the large standard deviations of both SCORAD and DLQI improvements.
Discussion

With the use of medium doses of UVA-1 a mean improvement of SCORAD indices of 38% after 3 weeks was comparable with the results reported in literature.\textsuperscript{9-11} A four weeks’ treatment regimen appeared to result in a better outcome immediately after therapy than the 3 weeks’ regimen. Although not statistically significant, the authors find the difference clinically relevant. Furthermore, compared with the 3 weeks’ regimen, the maintenance of achieved clinical results during follow-up was improved. The 1-week extension of therapy might thus partly overcome the problem of deterioration of eczema after three weeks of medium dose UVA-1 as also reported by others.\textsuperscript{5} However, as both groups deteriorated five points during the 6 weeks’ follow-up period, the authors realize that the improved maintenance of therapeutic results in the 4 weeks’ treated group is partly explained by the superior improvement of the SCORAD and DLQI indexes immediately after therapy in the 4 weeks’ treated group. The question remains whether the demanding treatment schedule, i.e. 5 days a week, is necessary and whether less frequent irradiations (2-3 /week) would have similar therapeutic effects.

PUVA therapy is a frequently used form of phototherapy in the treatment of atopic dermatitis. So far, there have been no studies published comparing the efficacy of UVA-1 with PUVA in the treatment of atopic eczema. Photosensitivity caused by psoralens requires protection of the eyes and the skin against sunlight during the rest of the day. Furthermore, up to 20% of patients suffer from side-effects of oral psoralens.\textsuperscript{12} In our study, apart from some slight erythema in the first week and a photosensitive reaction in two patients, no short-term side-effects were seen.
Figure 2.1. Mean Scoring atopic dermatitis index (SCORAD) ± standard deviation during 3 and 4 weeks UVA-1 and follow-up. 3 after/6 after: 3 and 6 weeks after UVA-1 therapy, *p = 0.001, **p ≤ 0.001.

Figure 2.2. Mean dermatology life quality index (DLQI) ± standard deviation during 3 and 4 weeks UVA-1 and follow-up. 3 after/6 after: 3 and 6 weeks after UVA-1 therapy, *p = 0.001, **p ≤ 0.001, #p = 0.015, ##p = 0.026.
PUVA and UVA-1 have different cellular targets. In PUVA therapy, psoralens bind to DNA molecules, followed by a UVA-induced photochemical reaction that is taking place in close vicinity of DNA molecules. Consequently, it is not surprising that long-term repetitive PUVA results in an increased risk of skin cancer.$^{13,14}$ UVA-1 photons are not absorbed by nucleic acids. The most important targets of UVA-1 radiation are located in the mitochondria that contain relatively large concentrations of UVA-1 absorbing co-enzymes of the redox chain. DNA damage is mediated indirectly by the production of radical oxygen species. Although animal studies suggest that UVA-1 is less carcinogenic than UVA-2 and UVB,$^{15}$ the long-term carcinogenic hazards of UVA-1 remain to be clarified and should not be underestimated. Some authors also showed that UVA-1 is capable of inducing squamous cell carcinoma in mice.$^{16,17}$ This radiation can induce expression of p53 and pyrimidine dimers in human skin and in murine skin, however much less effectively than UVB and solar simulated radiation.$^{18-20}$ It is not yet clear whether UVA-1 plays a role in the etiology of melanoma. A recent experimental work has brought some evidence that UVB, but not UVA irradiation initiated melanoma in transgenic mice.$^{21}$

UVA-1 radiation has been shown to generate singlet oxygen and superoxide anions.$^{22,23}$ Extensive production of such reactive oxygen species can, apart from contributing to carcinogenity, in certain cell types, lead to apoptotic death.$^{24}$ Lymphoid cells have frequently been used for the investigation of UVA-mediated apoptotic responses because of their lower threshold for switching to the UV-induced apoptotic program.$^{22,25}$ At least part of the therapeutic response to UVA-1 radiation could thus be ascribed to an apoptosis-inducing effect on the inflammatory infiltrate and especially on T-helper cells.$^{23,26}$

Our work supports the earlier studies of others showing that UVA-1 therapy can be successfully used as a monotherapy in the treatment of atopic dermatitis. For the prolongation of its therapeutic effects, a 4 weeks’ treatment regimen is preferable to a 3 weeks’ regimen.
Still, the place of UVA-1 in the treatment of atopic dermatitis needs to be better defined, e.g. by a multicenter comparative trial with other photo(chemo)therapeutic modalities.

Acknowledgements

We thank the nursing personnel for carrying out the greatest part of the daily irradiations.
References


