Chapter 8

General discussion
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Synopsis

In the studies presented in this thesis we investigated the effects of UVA-1 therapy in patients with atopic dermatitis, dyshidrotic eczema, generalized lichen planus and systemic lupus erythematoses. In this final chapter, the results of these and other studies on UVA-1 therapy in these four conditions, as well as reports of UVA-1 therapy in other T cell mediated skin disorders are discussed, and possibilities for future research are described.

Atopic dermatitis

UVA-1 has proven effective in the treatment of various T cell mediated diseases, of which atopic dermatitis has been studied most extensively. Some authors reported on good results obtained by high-dose (130 J/cm$^2$, 3 weeks) UVA-1 in the treatment of atopic dermatitis,$^1$ whereas others showed that also medium doses (50 J/cm$^2$, 3 weeks) were successful.$^2$ The latter appears preferable to minimize the risk of potential long-term side effects. In order to better determine the value of UVA-1 in the treatment of atopic dermatitis, not only different doses of UVA-1, but also different treatment schedules must be evaluated. Tzaneva et al. observed that after the usual successful 3 weeks of medium dose UVA-1 therapy, atopic dermatitis deteriorated relatively soon.$^3$ For that reason we investigated whether prolongation of the prevailing treatment schedule from 3 to 4 weeks leads to a longer therapeutic result. Chapter 2 describes an open prospective study of 32 patients with atopic dermatitis who were treated with medium dose UVA-1 radiation (45 J/cm$^2$), 5 days a week, during 4 weeks. Their therapeutic effect was retrospectively compared with that of medium dose UVA-1 therapy in 29 patients who were treated during the usual 3 weeks. Both the SCORAD (scoring atopic dermatitis) and the DLQI (dermatology life quality index) improved significantly during both
treatment schedules, but at the end of treatment the 4 weeks’ regimen did not prove to be more effective than the 3 weeks’ regimen. However, 6 weeks after cessation of therapy the patients from the 4 weeks treatment regimen still showed a significant improvement of their SCORAD and their DLQI when compared with pre-treatment values, whereas those who were treated during 3 weeks did not. We conclude that medium dose UVA-1 therapy can be used successfully as a monotherapy in the treatment of atopic dermatitis, with positive effects on both disease activity and quality of life. For the prolongation of its remission time, a 4 weeks’ treatment regimen is preferable to a 3 weeks’ regimen.

To determine the position of UVA-1 therapy in the treatment of atopic dermatitis, the efficacy of UVA-1 therapy should also be compared with other types of phototherapy commonly used in atopic dermatitis, such as UVA-UVB combination therapy, PUVA and narrow band UVB.\textsuperscript{4-7} Recent studies showed improvements of disease activity scores of 50\% for UVA-UVB, of 80\% for oral PUVA, of approximately 65\% for bath-PUVA and narrow band UVB\textsuperscript{4,5,8} and clearance or near-clearance of disease, in 14 of 15 patients in one study and in 74\% of patients in another study, after oral PUVA.\textsuperscript{9,10} In several controlled trials, both high- and medium-dose UVA-1 proved to be more effective than UVA-UVB combination therapy.\textsuperscript{1,2,11,12} In our patients, the SCORAD improved 49\% in the 4 weeks’ treated patients and 27\% in those treated during 3 weeks. From the results from literature PUVA and narrow band UVB appear to be better than UVA-1. However, there have been no controlled studies comparing these phototherapeutic modalities so far.

All mentioned treatment modalities have advantages and disadvantages. Different UV therapies have different treatment schedules, which demand different efforts from patients. Approximately the same number of treatments is needed for best results of UVA-1, PUVA or narrow band UVB therapy. UVA-1 is more time-consuming than PUVA and narrow band UVB with irradiations 5 times a week, but it has a shorter treatment period of 4 weeks.
Although more time-consuming, our experience is that many patients find the UVA-1 therapy rather relaxing. They often bring their own music to listen to while lying on the bed in the UVA-1 cabin. A disadvantage of these UVA-1 beds is that during irradiations the shadow areas in the pubic area and on the sides are not sufficiently treated (unpublished observation). Consequently, this kind of UVA-1 cabin is less suitable for treatment of malignant skin disorders, like cutaneous T cell lymphomas, for which complete clearance on all sides of the body is essential. However, other UVA-1 cabins are comparable to the usual PUVA and UVB cabins, and require patients to stand up during therapy.

Another difference between the treatment options concerns the side effects. Photosensitivity, caused by psoralens in PUVA therapy, requires protection of both eyes and skin against sunlight during the rest of the day. Furthermore, up to 20% of patients suffer from gastrointestinal side effects of oral psoralens. In narrow band UVB therapy patients may burn more easily, compared with UVA-1 therapy. Apart from a slight erythematous reaction, no short-term side effects are usually observed during UVA-1 therapy. Other potential short-term side effects for all mentioned phototherapeutic options are induction of UV sensitive photodermatoses and herpetic infection. Possible long-term side effects are skin aging and development of cutaneous malignancies. Experimental studies (summarized in chapter 1) suggest that PUVA and UVB are more mutagenic than UVA-1. However, long-term follow-up studies to assess skin cancer risk in UVA-1 treated patients have not yet been performed.

Although to our opinion the arguments are in favor of UVA-1 in the treatment of atopic dermatitis, the pros and cons should be discussed with the patient, before deciding which therapy will be used.
General discussion

Dyshidrotic eczema

Phototherapy also belongs to the standard treatment options of dyshidrotic eczema. Both oral, cream-, and bath-PUVA have been reported to have some beneficial effects.\textsuperscript{14-16} The first report on the successful use of UVA-1 in the treatment of chronic dyshidrotic eczema of the hands concerned an uncontrolled study of 12 patients.\textsuperscript{17} They reported 81% improvement of the dyshidrosis area and severity index (DASI). However, since the severity of dyshidrotic eczema tends to fluctuate and spontaneous remissions may occur, the efficacy of UVA-1 needed to be established in a controlled manner. In a double blind, placebo controlled study (Chapter 3) we investigated 28 patients with dyshidrotic eczema of the hands. The results showed a 52% decrease of the DASI, after 3 weeks UVA-1 therapy, whereas after placebo treatment the DASI had slightly increased. Thus, UVA-1 treatment proved significantly better than placebo therapy.\textsuperscript{18} In a recent study UVA-1 and PUVA therapy were equally effective.\textsuperscript{19} These results further support the efficacy of UVA-1 in the treatment of dyshidrotic eczema. Since UVA-1 seems to be less carcinogenic than PUVA we prefer UVA-1 in the treatment of dyshidrotic eczema.

Lichen planus

Lichen planus (LP) is the third T cell mediated condition we investigated. Although it is generally self-limiting, LP may exist for many years, may be generalized and difficult to treat. Usually, it occurs on a limited number of localizations, in which case topical treatment usually suffices. In generalized LP, local therapy is too laborious and frequently unsuccessful. Since the 1970s, beneficial effects of oral photochemotherapy (PUVA) and bath PUVA for both localized and generalized LP have been described.\textsuperscript{20-23} In these publications, clearly
defined evaluation parameters were usually lacking, making comparison of results difficult. Results were formulated as excellent, good, complete clearance or at least 50% improvement in most patients. Furthermore, there was only one small controlled study among them, concerning hemi-corporeal oral PUVA therapy in 10 patients, and no randomized, controlled studies comparing different forms of light therapy have been published so far. 

In chapter 4 we described the favorable effect of UVA-1 therapy in 4 patients with therapy-resistant, generalized lichen ruber planus. A controlled study was not possible, as the generalized form of LP is relatively rare. Patients were treated with 45 J/cm² for 5 days per week during two 4-week treatment periods with a 3-week interval. After UVA-1 therapy nearly complete clearance was achieved in 3 patients, and considerable improvement in one. However, the tenacious thick plaques on the ankles showed only moderate improvement. Both the visual analogue scores for itch and the DLQI showed considerable improvement. In one patient, biopsies were taken before and after therapy. Histopathologic results showed that at the end of treatment the characteristic features of LP had normalized and only a sparse infiltrate remained. Our results, although concerning a limited number of patients, support the efficacy of UVA-1 therapy in generalized LP.

**SLE**

It has been known for a long time that a large proportion of patients with systemic lupus erythematosus (SLE) is sensitive to sunlight. Mainly UVB and, to a lesser extent UVA, are held responsible for this photosensitivity. Consequently, the first reports of beneficial effects of UVA-1 in patients with SLE were rather unexpected. McGrath was the first to show clinical improvement in an uncontrolled study of 10 SLE patients. This was later confirmed by a double blind, placebo controlled, crossover study in 26 patients. Unfortunately, both
studies were flawed due to use of an inappropriate disease activity scoring system, lack of wash out periods risking carry over effects, and failing in correct evaluation of placebo effects. Despite the imperfect design, the clinical results appeared interesting enough to warrant another double blind placebo controlled study.

Being aware of the risk of photosensitivity we originally exposed eleven patients with SLE to only 6 J/cm$^2$ of UVA-1 and to the same number of minutes of placebo light (see Chapter 5). In two consecutive 12-week periods patients were treated with UVA-1 and placebo therapy respectively, or vice versa, followed by a 9 weeks’ wash-out period. The primary variables, SLE disease activity index (SLEDAI) and SLE activity measure (SLAM) showed a significant decrease after three weeks of UVA-1, but not after three weeks of placebo treatment. Although the MOS SF36 subscore for vitality improved more during UVA-1 than during placebo therapy, the difference was not statistically significant.

Chapter 6 describes a second study in which we applied a higher dose of 12 J/cm$^2$ in the same study design. UVA-1 treatment resulted in a significant decrease of both SLAM and SLEDAI at the end of the third week of therapy, whereas neither score improved significantly during placebo treatment. Furthermore, when UVA-1 treatment was compared with placebo treatment, the decrease of SLAM was statistically significant. However, the decrease of SLEDAI was not.

Two patients in the second study with a history of photosensitivity, experienced transient skin reactions 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 this 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.

In all four patients with anti-SSA antibodies decrease of titres was recorded after UVA-1 therapy in the first study. In the second study the anti-SSA titre of one patient and the anti-
RNP titre of another showed a marked decrease, suggesting immunomodulating effects of UVA-1 therapy.

Although the pathogenesis of SLE remains unclear, B lymphocytes are thought to play a major role in the immune dysregulation that underlies the disease process.\textsuperscript{23,31} A significant proportion of therapeutic strategies in SLE are based on decreasing the production or the selective removal of circulating autoantibodies.\textsuperscript{23,32,33} Based on this information, the known deep penetration of UVA-1 radiation, and the observed decrease of auto antibody titres after UVA-1 therapy, we formulated the following hypothesis: UVA-1 induces suppression of immunoglobulin production by activated B cells in the dermal capillaries, which could be (partly) responsible for the observed improvement of disease activity in patients with SLE.

In chapter 7 is explained how this hypothesis was confirmed. In order to obtain an estimate of the proportion of UVA-1 radiation that can reach the superficial dermis where blood capillaries are present, we measured the penetration of UVA-1 through isolated epidermis using a UVA-1 measurement device. The average penetration was 39\%, which implies that a large part of a given UVA-1 dose is indeed able to reach the superficial dermis and affect the function of circulating lymphocytes, monocytes and other cells in the capillary network of the skin. The toxic effect of UVA-1 radiation was determined by evaluating the viability of irradiated peripheral blood mononuclear cells (PBMCs). A dose as low as 2 J/cm\textsuperscript{2} UVA-1 caused around 20\% death of PBMCs. This toxic effect further increased with rising UVA-1 doses. However, pre-incubation with catalase totally prevented this UVA-1-induced cell death, suggesting that generated hydrogen peroxide plays an important role in UVA-1 toxicity. Flow cytometric analysis showed that in comparison with CD20 positive cells (B cells) and CD3 positive cells (T cells), CD14 positive cells (monocytes) seem to be the cells most sensitive to UVA-1.
A dose-dependent decrease of IgM, IgG, IgA and IgE production was observed after UVA-1 radiation of PBMCs in a well-established CD40-CD40L B cell activation system with IL-10 or IL-4 stimulation. Twenty percent of cell death in the PBMC population was observed 24 hours after exposure to 2 J/cm² UVA-1. However, a 47%, 44%, 36% and 60% decrease of IgM, IgG, IgA and IgE production, respectively, was observed following daily irradiations of PBMC cultures with the same dose of UVA-1. It is very likely that UVA-1 irradiation causes not only B cell apoptosis, but also affects immunoglobulin production of the surviving B cells. In addition, the cumulative effect of daily irradiations may bring about more cell death and even more decreased immunoglobulin production.

Whereas pre-incubation with catalase totally prevented UVA-1-induced cell death, no convincing effect of catalase on immunoglobulin production could be discerned. This could possibly be explained by the fact that catalase removes hydrogen peroxide exclusively extracellularly. This enables it to prevent UVA-1 induced cell death by lipid peroxidation of the outer cell membrane, since hydrogen peroxide, in contrast with catalase, can penetrate the cell membrane. However, extracellular catalase apparently does not have any profound effect on the intracellular concentration of UVA-1 induced hydrogen peroxide.

The observed effect of UVA-1 on immunoglobulin production suggests that UVA-1 therapy could also be effective in the treatment of other auto-immune diseases, apart from SLE. A likely prerequisite for success in the disease in question is the presence of activated circulating B cells and plasma cells in dermal capillaries. However, not all auto-immune diseases have B cells or plasma cells that produce antibodies outside the spleen and lymph nodes. A relevant auto-immune disease could be Sjögren’s syndrome, in which the presence of antibody-producing cells in the peripheral blood has already been demonstrated. In the treatment of SLE it is important to realize that this disease can be activated by UV radiation. Furthermore, different UVA-1 lamps have different emission spectra. Treatment with lamps
emitting even very small amounts of UVB should be avoided, because this radiation could cause apoptosis of epidermal keratinocytes with consequent activation of the auto-immune process.

In conclusion, we have found evidence that long-wave UVA radiation is able to lower the production of antibodies by activated B cells and plasma cells. This observation can, at least partly, explain the clinical improvement observed in SLE patients after UVA-1 therapy.

**UVA-1 for other T cell mediated skin diseases**

Apart from the four (skin) diseases discussed before, there are several case reports and small uncontrolled studies reporting on the beneficial effects of UVA-1 therapy in various other T cell mediated skin disorders. The results of these studies are summarized in Table 1. The results of UVA-1 therapy in sclerotic skin diseases are of particular interest and are discussed in more detail below.

**Sclerotic skin diseases**

Since the mid-1990s several reports on the effect of UVA-1 on localized scleroderma (morphea) have been published. Induction of interstitial matrix metalloproteinases (MMP), especially collagenase (MMP-1) is held responsible for hydrolysis of collagen in the skin after UVA-1 therapy, leading to improvement of sclerotic skin diseases.\(^{35-37}\) Apart from collagenase induction and T cell apoptosis,\(^{38}\) increased vascular endothelial growth factor (VEGF) expression and reduced apoptotic endothelial cell turnover may also contribute to amelioration of disease activity by improving vascularization.\(^{39}\) In one study, after 30 exposures, high dose (130 J/cm\(^2\), \(n=10\)) was superior to low dose (20 J/cm\(^2\), \(n=7\)) UVA-1 therapy. High dose UVA-1 therapy resulted in obvious reduction and softening of sclerotic
plasques, decreased skin thickness measured by 20 MHz ultrasound, and decreased skin
elasticity determined by elastometry. Nevertheless, others reported complete clearance of
80% of the lesions in 10 patients after 24 irradiations with only 20 J/cm², 4 times a week for
6 weeks, and disappearance or marked improvement of 80% of sclerotic lesions in 18 out of
20 patients after 30 treatments with 20 J/cm².55,56

Also in patients with systemic sclerosis, softening of skin lesions on forearms and hands,
improved passive range of motion of hand and wrist joints, improved cutaneous elasticity, and
healing of ulcerations were observed.57-59 Some small studies and case reports were published
on the effect of UVA-1 on some other sclerotic skin diseases like extragenital lichen
sclerosus, sclerodermic graft-versus-host disease of the skin, scleredema, keloid, and
nephrogenic fibrosing dermopathy.60-66 Although we have only limited experience in UVA-1
treatment of patients with keloids and scleredema, we could not fully confirm the reported
positive effects in these patients. PUVA therapy has been found effective in the treatment of
both localized scleroderma and systemic sclerosis as well.67-69 To our knowledge, no studies
comparing the effect of UVA-1 with PUVA therapy have been published so far.
<table>
<thead>
<tr>
<th>Reference</th>
<th>N=</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granuloma annulare</td>
<td>4</td>
<td>130 J/cm², 5/7, 3 wks</td>
<td>1/4 cc, 3/4 pc</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
<td>130 J/cm², 4/7, 25 exposures</td>
<td>Considerable improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 J/cm², 4/7, 50 exposures</td>
<td>cc</td>
</tr>
<tr>
<td>REM</td>
<td>1</td>
<td>90 J/cm², 5/7, 18 exposures</td>
<td>cc</td>
</tr>
<tr>
<td>Grover’s disease</td>
<td>1</td>
<td>50 J/cm², 6/7, 3 wks, 2/7, 3 wks</td>
<td>Nearly cc</td>
</tr>
<tr>
<td>Pityriasis lichenoides</td>
<td>8</td>
<td>60 J/cm², 5/7, max. 30 exp.</td>
<td>6/8 cc, 2/8 &gt;75% improvement</td>
</tr>
<tr>
<td>Pityriasis rubra pilaris</td>
<td>1</td>
<td>100 J/cm², 5/7, 3 wks + 25 mg acitretin</td>
<td>Dramatic improvement</td>
</tr>
<tr>
<td>Cutaneous T cell lymphoma (CTCL)</td>
<td>3</td>
<td>130 (n=2), 60 (n=1) J/cm², 5/7, 16-20 exp.</td>
<td>cc, stage IA, IB CTCL</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>cc, mucinosis follicularis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Considerable improvement, large cell CTCL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11/13 cc, 2/13 pc, plaque (8), nodular (4), erythrodermic (1) MF</td>
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<tr>
<td>Cutaneous mastocytosis</td>
<td>22</td>
<td>130 J/cm², 5/7, 2 wks (n=10)</td>
<td>Considerable improvement of itch in most patients</td>
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<td></td>
<td></td>
<td>60 J/cm², 5/7, 3 wks (n=12)</td>
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</tr>
<tr>
<td></td>
<td>4</td>
<td>130 J/cm², 5/7, 3 wks</td>
<td>Relief from itching, diarrhea, migraine</td>
</tr>
<tr>
<td>HES</td>
<td>3</td>
<td>50 J/cm², 5/7, 3 wks</td>
<td>Improvement itch, skin lesions, neuropathy, and GI complaints</td>
</tr>
<tr>
<td>M. Wells (unpubl. observation)</td>
<td>2</td>
<td>45 J/cm², 5/7, 3 wks</td>
<td>Considerable improvement</td>
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</table>

cc= complete clearance, pc= partial clearance, REM= Reticular erythematous mucinosis, HES= Hypereosinophilic syndrome, GI=gastrointestinal, MF=mycosis fungoides
Conclusion

UVA-1 radiation is a useful therapeutic option for various T cell mediated and sclerotic skin diseases. We think that UVA-1 is the phototherapy of choice in atopic dermatitis and dyshidrotic eczema, and that this treatment could be a valuable therapeutic option in patients with generalized lichen planus and sclerotic skin diseases. To minimize potential carcinogenic risks, medium dose UVA-1 regimen are preferable to high dose regimen. Controlled studies are needed for further validation of the place of UVA-1 therapy in the dermatological practice. Interesting possibilities for future research comprise the effect of UVA-1 therapy in the treatment of auto-immune diseases, other than SLE.
Chapter 8

References


