

UVA1 phototherapy in dermatological treatment

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Abstract

Literature data indicate the beneficial therapeutic effect of UVA1 irradiation, whose biological properties are significantly different from those of other UV light waves, which is connected with their deeper penetration into the skin. Taking into account immunomodulatory mechanisms of UVA1 action, which mostly influences the apoptosis of fibroblasts, mast cells, Langerhans cells, and T lymphocytes, UVA1 radiation is indicated in the treatment of four major groups of skin diseases: T-cell and mast-cell mediated skin diseases, connective tissue diseases, and dermatoses in HIV positive patients sensitive to phototherapy. This publication presents a review of the literature concerning indications for UVA irradiation, recommended doses, as well as the most often observed adverse events.

Key words: phototherapy, UVA1, skin diseases.

Introduction

The beneficial effect of light on the human organism has been known for centuries. The term phototherapy or light therapy applies to a treatment modality consisting of exposure to specific wavelengths of light. There are three ranges of radiation, infrared (800-3000 nm), visible (400-800 nm), and ultraviolet (100-400 nm), which are applied in phototherapy. Infrared radiation is mainly used in physiotherapy as it provides energy to heat up different parts of the body. Visible radiation is used in the treatment of mental disorders resulting from light deficiency, e.g. winter depression. Usually, a light beam above 2500 lux is used, i.e. the radiation is 10 times stronger than the light emitted by a normal electrical bulb.

Treatment of skin disorders most often involves the application of ultraviolet radiation (UVR) encompassing wavelengths of UVB (280-320 nm) and UVA (320-400 nm). The latest mode of phototherapy is associated with the use of a narrow band of UVA (340-400 nm), i.e. UVA1. In 1981, Mutzhas constructed the first devices emitting UVA1 radiation [1]. However, the first reports presenting a beneficial effect of this UV subtype on cutaneous lesions were published as late as in 1992 [2]. In the following years, attempts were made to use UVA1 in various skin diseases, with the suggestion of therapeutic protocols and evaluation of adverse reactions caused by UVA1 radiation.

Three UVA1 types of doses, low (10-20 J/cm²), medium (50-60 J/cm²), or high (130-150 J/cm²), are common-

ly used in phototherapy. UVA1 irradiation is performed 5 times a week, usually for 3-4 weeks. However, there are no strict indications for its use, and therefore the dose and number of irradiations can be adjusted to each patient individually, taking into account their different skin phototype and dermatosis.

According to Krutmann, patients with a positive history of skin carcinoma and the use of photosensitive and phototoxic medicaments should be excluded from light therapy. Moreover, the patient's individual sensitivity to light has to be established through determining the minimal tanning dose (MTD). MTD is a dose that induces a minimal perceptible pigmentation. Although this dose is not taken into consideration in therapeutic procedures, it can be determined to assess the degree of skin sensitivity to UVA1 [3] by irradiating six square areas of 2 × 2 cm on the patient's back, with gradually increasing doses of UVA1, while the remaining parts of the skin are completely covered. The dose as well as the exposure time of relevant areas depends on the skin phototype. An example of UVA1 radiation doses used in MTD determination is presented in Table 1.

Test results are read after 24 hours and then classified according to the recommendations of Mang and Krutmann [3]. The dose of UVA1 radiation inducing minimal perceptible tanning with well-defined outlines corresponds to 1 MTD. Table 2 shows tanning testing.

The fundamental mechanism of the action of UVA1 radiation is based on the induction of apoptosis mediat-

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Tab. 1. UVA1 doses used in minimal tanning dose determination

Skin phototype	UVA1 dose [J/cm ²]
I-II	10, 20, 40, 60, 100, 130
III-V	20, 40, 60, 80, 100, 130

Tab. 2. Tanning testing

Scale	Tanning testing
-	Lack of tanning
+/-	1MTD – minimal perceptible tanning with well-defined outlines
+	Mild tanning
++	Marked tanning
+++	Intensive tanning
x	Presence of oedema, erythema, papules, vesicles

ed by active oxygen molecules, such as singlet oxygen, hydrogen peroxide, or superoxide radicals. The UVA1 wavelength (340-400 nm) activates programmed and non-programmed cell death, which increases phototherapy effectiveness as compared to photochemotherapy with psoralens and a wide spectrum of UVA radiation (PUVA), leading only to programmed apoptosis [4-7]. Contrary to a more superficial action of UVB radiation which mostly affects keratinocytes and Langerhans cells, UVA1 penetrates deeper into the reticular layer of the dermis, influencing fibroblasts, dendritic and infiltrating inflammatory cells, particularly T CD4 lymphocytes, as well as mastocytes and granulocytes. UVA1 radiation induces the production of inflammatory process mediators and modulates the expression of superficial zone proteins [7]. It reaches the inside of the skin blood vessels, affecting the endothelium and some morphotic blood elements. Inducing T lymphocyte apoptosis, similarly to photopheresis procedures, may have a beneficial effect on the course of cutaneous T cell lymphoma (CTCL) [3, 4, 7]. Moreover, UVA1 exerts an impact on the extracellular matrix by activating fibroblasts to increase production of metalloproteinases. This mechanism is used in the treatment of sclerosing skin conditions [8].

Nowadays UVA1 radiation is indicated in the treatment of four major groups of diseases, i.e. those associated with the presence of T-lymphocyte or mastocyte infiltrates, connective tissue diseases, and dermatoses in patients with HIV infection.

Atopic dermatitis

The first clinical observations on effectiveness of UVA1 radiation concerned patients suffering from atopic dermatitis (AD). This disease is a chronic inflammatory der-

matosis characterised by genetic predisposition towards excessive synthesis of IgE antibodies in response to a commonly present environmental allergen. Immunochemical studies of atopic skin biopsies demonstrate the presence of infiltrates mostly composed of T CD4 lymphocytes. Furthermore, increased mRNA expression for IL-4, IL-5, IL-10, and IL-13 cytokines plays a key role in the pathomechanism of this disease [9, 10].

In 1992, Krutmann *et al.* [2] for the first time reported on beneficial results of high dose UVA1 (130 J/cm²) therapy in patients with atopic dermatitis exacerbation. Irradiation was applied 5 times a week for 3 weeks. The observations revealed immunomodulatory action of this radiation range through increased expression of interleukin 10, a cytokine that inhibits IFN- γ production via Th1 helper lymphocytes [3, 7, 11]. Subsequent research on the treatment of the acute phase of atopic dermatitis showed a greater effectiveness of high-dose UVA1 phototherapy in comparison to topically used corticosteroids or UVB/UVA irradiation [12].

Polish authors [13] have also observed an advantageous therapeutic effect while evaluating 13 patients with atopic dermatitis who demonstrated a considerable or moderate improvement after application of high doses of UVA1.

There have been some studies available in the literature indicating the possibility of achieving clinical remission of mild and moderate changes in the course of AD after using low doses of UVA1 radiation [11]. However, the number of researchers and clinicians supporting this type of therapy is low.

Successive studies have also demonstrated a beneficial effect of medium-dose UVA1. Gambichler *et al.* found that UVA1 radiation leads to changes in gene expression of cytokines involved in the pathomechanism of AD. After irradiation with the dose of 50 J/cm² for 6 weeks (cumulative dose 900 J/cm²), a considerable decrease in IL-5, IL-13, IL-31 mRNA expression was observed which correlated with the clinical improvement in skin condition and reduction in itching [9].

The study by Marloes *et al.* confirmed the effectiveness of medium-dose UVA1 in the course of atopic dermatitis. The objective of their work was to directly compare the effectiveness of treatment with medium doses of UVA1 radiation (45 J/cm², 5 times a week) depending on the length of therapy (3 or 4 weeks). Patients both with moderate cutaneous lesions and exacerbations were evaluated. Four-week therapy resulted in a quicker regression of symptoms. Similarly, a longer duration of remission was reached in this group of patients [5].

It is worth emphasising that contrary to other ranges of radiation, UVA1 is nowadays recommended even at the time of clinical exacerbations [14].

Summing up the clinical observations of numerous authors, the application of UVA1 radiation may be considered the method of choice even in severe clinical states

of AD, as well as in monotherapy. Results of phototherapy can be compared to topically applied strong glucocorticosteroids. However, it should be noted that the clinical effect closely correlates with the level of a single dose. Low doses of UVA1 radiation are not nowadays recommended because their therapeutic effect is comparable to other conventional methods of phototherapy with wide-band UVA, UVB or UVB-NB (311 nm) [15].

Scleroderma

The pathogenic process in scleroderma involves vascular disorders and increased immune-mediated fibrosis resulting from elevated type I and III collagen synthesis with reduced collagenase I expression. These phenomena are induced by the impairment of skin fibroblast functioning. The key role of immune reactions in the development of scleroderma was the indication for applying UVA1 [16, 17]. The basic mechanism of UVA1 action used in scleroderma is its impact on an increase in mRNA expression of matrix metalloproteinases (MMPs) and reduction in inflammatory infiltrate by inducing CD4 T lymphocyte apoptosis. The latest reports also show a decrease in mRNA expression of proinflammatory cytokines such as IL-1, IL-2, IL-6, and IL-8 [8].

Experimental *in vitro* studies on fibroblast culture indicated that only high-dose UVA1 radiation induced elevated production of collagenase I [18]. Initially, these observations made the investigators use this range of radiation in the treatment of clinically more severe forms of morphea.

High-dose UVA1 radiation therapy for morphea was used for the first time by Stege *et al.* in 1997 [11]. Subsequent studies compared high and low doses of radiation. Patients with morphea were irradiated with the dose of 130 J/cm² UVA1 versus 20 J/cm², 4 times a week for 5 weeks, and then twice a week for the next 5 weeks (cumulative dose 3900 J/cm² vs. 600 J/cm²). The application of high-dose UVA1 led to a definitely greater reduction in tension and sclerosing skin lesions as well as an increase in skin elasticity [11].

In 2001, Kreuter *et al.* provided evidence for the effectiveness of low-dose UVA1 (40 irradiations) in the treatment combined with topically applied calcipotriol (twice daily). A significant clinical improvement was observed after 10 procedures, and a complete regression of cutaneous lesions occurred at the end of therapy [11, 17]. In 2006, the same authors confirmed the effect of UVA1 radiation on the mRNA expression of human β -defensins (hBDs 1, 2, 3) and proinflammatory cytokines, i.e. IL-6 and IL-8, in the skin of patients suffering from limited systemic scleroderma (lSSc). Human β -defensins are peptides naturally occurring in the organism that have bactericidal properties. They are involved in inducing healing of the damaged tissues and also affect formation of scars. They are likely to play a role in the pathological process of fibro-

sis in patients with scleroderma, as greater mRNA expression of hBDs 1, 2, and 3 was found in their skin as compared to healthy subjects. Patients were irradiated with a dose of 20 J/cm² 5 times a week (all together 40 irradiations, cumulative dose 800 J/cm²). A clinical improvement was observed in all patients in the form of less pronounced skin hardening. The study proved that UVA1 phototherapy caused lower mRNA expression of hBDs 1, 2, and 3, as well as cytokines IL-6 and IL-8, in the skin of patients with lSSc, although it did not influence the skin lesions [8].

Successive reports have also revealed a beneficial therapeutic effect of medium doses (60 J/cm²) used even in 29 procedures. Breuckman *et al.* observed an improvement in skin elasticity and an increase in the range of joint movements. Clinical effectiveness of long wave UVA1 irradiation was also confirmed by microscopic studies [17].

Sakakibara *et al.* analysed ultrastructural changes in collagen fibres after UVA1 irradiation of arms and hands in patients with systemic scleroderma, both diffuse systemic scleroderma (dSSc) and lSSc. The initial dose was 10 J/cm² then it gradually increased up to 60 J/cm² (cumulative dose 1140 J/cm²). The microscopic analysis showed beneficial changes, mostly at the level of the upper part of skin reticular layer in the form of reduced diameter of collagen bundles [18].

In conclusion, it seems that due to limited possibilities of scleroderma treatment, especially of the systemic type, UVA1 phototherapy appears to be a promising option. A shorter time to achieve clinical improvement is also a positive aspect of such management as the effect of 30 irradiations performed for 6 weeks is comparable to 50 PUVA procedures requiring 5-6 months [15].

Cutaneous T-cell lymphoma

A favourable mechanism of UVA1 radiation inducing T lymphocyte apoptosis of skin infiltrating T lymphocytes, which is applied in the treatment of AD, has encouraged the investigators to utilize this phenomenon in the treatment of cutaneous T-cell lymphoma (CTCL) [19, 20]. Cutaneous T cell lymphoma is a neoplasm characterised by proliferation of type Th2 helper T cells. Pathological lesions mainly occur on the skin in the form of erythema, infiltrates, and tumours. UVA1 phototherapy is considered an alternative method of CTCL treatment, among others due to the ability to induce apoptosis. Plettenberg *et al.* used high- and medium-dose UVA1 in phototherapy of *mycosis fungoides* (stage IA and IB). Two patients were irradiated with 130 J/cm² (20 procedures, cumulative dose 2600 J/cm²), while one patient received a dose of 60 J/cm² (16 cycles, cumulative dose 960 J/cm²). All patients showed a local skin improvement as early as after 5 exposures to UVA1. Full recovery was achieved after 16-20 irradiations, irrespective of the dose used. Moreover, the therapeutic effect was also confirmed histologically. After the completion of

phototherapy, a complete remission of T lymphocyte infiltrates in the skin and the epidermis was revealed. The aforementioned study confirmed a positive effect of UVA1 phototherapy, both in lower and higher doses [4].

Zane *et al.* made similar observations with the use of high dose UVA1 (100 J/cm²), reaching a complete remission in 11 of 13 patients suffering from erythrodermic *mycosis fungoides* [21].

A subsequent case confirming the effective action of UVA1 radiation in CTCL treatment concerns a 68-year-old man with erythrodermic T-cell lymphoma. Due to the lack of clinical effect of the PUVA method and extracorporeal photophoresis, medium-dose UVA1 was used for 5 days a week (all together 15 irradiations) achieving remission of skin lesions and lymphadenopathy, as well as normalization of the T lymphocyte number, which shows the grade of malignancy [11].

Graft versus host disease

Graft versus host disease (GVHD) is one of the most frequently occurring complications in patients after allogeneic grafts of bone marrow or other organs, as well as after transfusion of blood and its products containing immunocompetent lymphocytes. It is provoked by T lymphocytes in the transplanted tissues which proliferate and contribute to the destruction of the host's organs and tissues, most frequently the skin. Scleroderma-like lesions are the most characteristic of GVHD; therefore UVA1 phototherapy may appear to be a promising method of treatment.

Grundmann-Kollmann *et al.* used low-dose (20 J/cm²) UVA1 therapy 4 times a week, 24 irradiations (cumulative dose 480 J/cm²) in a patient suffering from scleroderma-like GVHD, resistant to conventional treatment with chemotherapeutics. This therapy appeared to be effective in combination with mycophenolate mofetil (2 g daily) [11, 17]. Taking into account the advantages of UVA1 in phototherapy of scleroderma, Staender *et al.* [17] carried out a similar study that compared low and medium radiation doses in GVHD. Five patients with skin GVHD received a dose of 50 J/cm² UVA1 (5 times a week, 40 treatments, cumulative dose of 2000 J/cm²), while 1 patient received a dose of 20 J/cm² combined with the immunosuppressive treatment and extracorporeal phototherapy. In all cases the treatment resulted in an improvement manifesting with skin softening, increased range of motion in the affected joints, and epithelisation of erosive lesions. A positive effect of UVA1 phototherapy was documented by Calzovara-Pinton *et al.*, who treated 5 patients with skin GVHD using phototherapy with a medium dose of 50 J/cm² 3 times a week (cumulative dose 750-1650 J/cm²). As a result of the therapy, 3 patients achieved complete remission, and in the remaining subjects partial remission of lesions was observed [17].

Lupus erythematosus

One of the diagnostic criteria for lupus erythematosus (LE) is hypersensitivity to ultraviolet radiation occurring in the majority of patients. Thus, an attempt to apply UVA1 in the treatment of this disease has seemed controversial for years. Although solar radiation induces and exacerbates LE symptoms, there are some indications for immunosuppressive treatment due to the immune background of the disease. Deep penetration of A1 radiation into the inside of tissues and blood vessels elucidates both the topical and systemic effect of the therapy. This range of radiation causes the lowering of T and B lymphocyte activity and induces the process of apoptosis. The total biological effect depends on the dose [22, 23].

Mikita *et al.* demonstrated a positive impact of UVA1 radiation by conducting experiments on genetically modified MRL/lpr mice. The animals were divided into 3 groups and irradiated with UVA1 doses of 5 J/cm² versus 10 J/cm², 5 times a week for 4 months. The control group comprised animals without irradiation. A protective effect of UVA1 against the development of skin lesions characteristic of systemic lupus erythematosus (SLE) was observed. Mice that did not undergo phototherapy developed macro- and microscopic lesions typical of SLE [22]. The induction of inflammatory infiltration cell apoptosis, mostly skin mastocytes playing an essential role in this disease, has been postulated to be the main mechanism of UVA1 action responsible for prevention of SLE development. The first cases of clinical improvement following irradiation (9-week therapy, cumulative dose 186 J/cm²) were published in 1993. In later years, further studies were performed confirming the beneficial influence of UVA1. A report from 1994 indicated an improvement in the clinical state and lowering of the autoantibody level in SLE patients after low dose UVA1 of 6 J/cm², 5 times a week (total number of treatments – 15) [17]. In 2005, Mitra *et al.* presented a case of effective UVA1 therapy in discoid lupus erythematosus (DLE). A 35-year-old woman with DLE and lesions on the face, arms, and chest, without a positive effect after conventional treatment (anti-malarial and immunosuppressive medications and corticosteroids) was exposed to UVA1 radiation at the initial dose of 2.9 J/cm², which was gradually increased by 40% up to the maximum of 5.7 J/cm². After 15 irradiations, an improvement in the state of the skin was observed, and after 28 procedures (cumulative dose 155.1 J/cm²) the treatment was discontinued. Clinical remission was maintained for 6 weeks, and later new DLE lesions appeared on small areas of the skin [24].

The beneficial effect associated with the decrease in disease activity, the possibilities of reducing drug doses and lowering anti-dsDNA antibody titres after 3-week low-dose UVA1 therapy can be explained by its modulatory impact on cell immune mechanisms and apoptotic processes [25].

Despite several documented cases in which UVA1 phototherapy contributed to reaching remission, the risk cannot be excluded as it has been evidenced that systemic changes developed in a patient with subacute cutaneous lupus erythematosus (SCLE) after using high-dose UVA1 [26].

Although the application of phototherapy in patients with different types of lupus erythematosus evokes much controversy, numerous experimental studies on laboratory animals as well as clinical observations indicate the necessity of performing further studies to widen the offer of therapeutic options.

Lichen sclerosis

Lichen sclerosis (LS) is a dermatosis characterised by pathological fibrosis of the connective tissue within the skin. A great number of studies show a pathogenic effect of infiltrates composed of T lymphocytes producing IL-4, IL-6, and TGF- β 1, i.e. cytokines increasing fibrosis. Higher collagen IV and VII expression, changes in the structure of type I and II collagen, and a reduction in the number of elastic fibres can be found in the damaged tissues [20]. Kreuter *et al.* proved for the first time UVA1 effectiveness in the treatment of LS [17]. The authors observed an improvement in the clinical state of the patients after using low-dose UVA1 therapy (20 J/cm²) 4 times a week, 40 irradiations (cumulative dose 800 J/cm²) [17]. Beattie *et al.* [27] made an attempt to prove the effectiveness of UVA1 radiation in the treatment of atrophic lichen on the mucosa of sexual organs. Seven women with severe LS were subjected to different doses of UVA1 radiation (30-130 J/cm², 3-5 times a week). A minimum or moderate improvement was reached in all but two patients in whom no improvement was observed [27].

Dave *et al.* have focused attention on the possibility of different reactions to UVA1 depending on the site of pathological lesions. The application of low-dose UVA1 for 10 days resulted in repigmentation and a considerable softening confirmed by ultrasonographic examinations of the skin in the majority of patients with disseminated lesions. However, a markedly lower effectiveness of the therapy was noted in the case of eruptions in the region of the sexual organs [11].

On the basis of literature reports, one can assume that the treatment of lichen sclerosis with UVA1 radiation may be in some cases beneficial, but due to discrepancies in the results further analysis is required.

Cutaneous mastocytosis

The essential mechanism of UVA1 action in the treatment of cutaneous mastocytosis is the induction of mastocyte apoptosis. There are numerous literature reports confirming the effectiveness of high and low doses of UVA1 used in monotherapy [15, 28], which was manifest-

ed by regression of skin lesions, disappearance of diarrhoea and migraine headache, normalisation of histamine in 24-hour urine collection and serotonin in serum, as well as long-term clinical remission. The authors emphasise a spectacular influence of UVA1 on skin itching which decreased after as early as 3 irradiations [11]. Casuistic reports also concern a decrease in the number of bone marrow mastocytes [11]. Based on the clinical observations, no statistically significant differences between the action of medium and high doses of UVA1 were found.

UVA1 in patients with HIV infection

Safety of phototherapy and photochemotherapy in HIV carriers seems to be controversial. Although clinical studies have not shown their significant impact on the patients' immune system and a rise in serum viraemia, investigations carried out on cultured and transgenic cells of laboratory animals indicate increased activation of the virus after UVA or UVB irradiation. However, a complete regression of desquamating papules and plaques refractory to conventional methods of treatment was observed in the HIV carrier after 20-30 irradiations with high-dose UVA1 [15, 29]. As UVA1 therapy has been shown not to activate the virus in the skin, it is nowadays considered to be the treatment of choice in the group of patients with HIV infection.

Other therapeutic indications

A beneficial therapeutic effect of high-dose UVA1 (130 J/cm², cumulative dose 2860 J/cm²) has been observed in the case of hypertrophic scars and keloids [15, 30]. There are also a few reports revealing a favourable therapeutic effect of UVA1 on regression of lesions in dyshidrotic eczema and in *prurigo nodularis* [3, 31].

Side effects

To date, observations have shown high safety of the discussed method of treatment. The most common side effects include erythema, hyperpigmentation and itching caused by skin dryness. Symptoms typical of polymorphic light exanthema or herpetic eczema develop rarely [12, 21]. The scientific centre in Poznan with the greatest experience in using UVA1 therapy in Poland has not reported any serious complications in 33 patients after UVA1 treatment either. The most common complaints, especially during the initial period of treatment, concerned heat sensation and skin burning at the time of irradiation, as well as intensification of erythema and itching. In single cases activation of herpes simplex virus or a feeling of weakness and extravasations were reported, which the authors associated with the effect of high temperature [13]. There has been no evidence so far corroborating the effect of UVA1 radiation on carcinogenic skin. However, hairless

mice exposed to high doses of this radiation developed spinocellular carcinoma. Thus, it seems necessary to create a central registry of patients who undergo UVA1 therapy, monitoring their treatment and reporting any side effects.

Undoubtedly, implementation of UVA1 irradiation in medical practice signifies a great advancement in the therapy of patients with severe clinical states, in whom conventional treatment was not effective. In spite of very promising observations on this subject, the outcomes of the research should be viewed with some caution because of the small sample size and lack of randomised studies without considering the diversity of clinical forms of diseases and their intensity. All these pose some difficulties in the objective evaluation and comparison of different therapeutic methods and effectiveness of this type of phototherapy.

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