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Phototherapy in sclerotic skin diseases

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Abstract**Introduction:**

UVA therapy is used in treatment of wide range of skin diseases, which proceed with hardening of the skin or inflammation. First use of ultraviolet radiation can be tracked down to 1896. Wavelength vary among diseases against which it is used. In literature as results of therapy are mentioned improvement of skin elasticity, reduction of inflammation, and protection from relapse. In terms of sclerotic skin diseases most promising effect is seen in reducing skin hardness in the mechanism of stimulating collagen breakdown. The therapy itself has a good safety profile, but is time-consuming due to the high frequency of irradiation. Effectiveness of treatment are determined by factors such as advancement of skin lesions, pigmentation and the intensity of the therapy itself.

Aim of study:

The aim of the study is to summarize the available knowledge about the UVA therapy in skin diseases. The way of work, effectiveness of treatment, side effects and potential new methods of use were summarized and described.

Materials and methods:

The literature available in PubMed database was reviewed using following keywords:

“UVA therapy”, “UVA”, “Scleroderma”, “Buschke’s Scleredema”, “Systemic sclerosis”, “Morphea”

Conclusion:

UVA1 therapy is one of the most effective therapeutic options in subtypes of morphea which affect only superficial tissues. Phototherapy accelerate healing of ulcerations on fingertips in

patients with Systemic sclerosis. Patient suffering from Buschke Scleroderma had good response to therapy. Observed side effects consist of hyperpigmentation, erythema, xerosis and pruritus in range from mild to severe. Carcinogenic effect has not yet been proven.

Key words: Scleroderma, Systemic; Scleroderma, Localized; Ultraviolet Therapy; PUVA Therapy

Introduction:

Ultraviolet radiation is commonly used in therapy of various skin diseases. As origin of modern phototherapy is considered year 1896 and achievements of Niels Ryberg Finsen, who fully healed his friend, who was suffering on lupus vulgaris with artificial made ultraviolet radiation. From this time on he treated over 800 people suffering on lupus vulgaris, by using focusable carbonarc torch [1]. For his discovery he was awarded in 1903 with Nobel Prize in medicine [2]. Great influence on development of phototherapy had introduction of lamps with fluorescent UVB tubes in early 1960s [3]. The beginnings of the use of UVB radiation in the treatment of psoriasis can be traced back to 1923, but the biggest advance was the popularization of photochemotherapy, which began in 1974. Orally administered psoralen in combination with UVB radiation (PUVA) was a milestone in the treatment of psoriasis [3]. Study performed by Plewig [4] and colleagues showed effectiveness of new super pressure mercury lamp. With use of filter platelet they created a device, which was emitting UV at wavelength of 340-400nm, so without UVB spectrum radiation. Ultraviolet radiation (UVR) covers the range of light radiation, which is from 10 nm to 400 nm in wavelength. As the wavelength increases, its energy decreases. In dermatology, the most common wavelengths used are UVB, which ranges from 290nm to 320nm, and UVA, which ranges from 320nm to 400nm and can be used topically or in combination with a photosensitizer. The most common wavelength range used in Europe is UVA1(340-400nm), and has a lower risk of side effects relative to UVB radiation (290-320nm). The effect that radiation has on human skin cells largely depends on the wavelength and exposure time. The use of photosensitizers (psoralens)

also has a not insignificant effect. Another important factor affecting the effectiveness of the therapy is the pigmentation of the patient's skin, as the melanin content of the epidermal cells increased, the effectiveness of specific doses of ultraviolet radiation decreased. The role of UVA1 in the therapeutic process is based mainly on inhibition of the immune response, stimulation of collagen metabolism and, consequently, reduction of skin thickness and inflammatory process. These properties have a huge role in the therapy of systemic scleroderma, limited scleroderma and lichen sclerosus [5]. UVA1 radiation activate apoptosis pathway[6], which is programmed cell death that allows phagocytic cells to absorb remains of destroyed cells. This process is caused by production of superoxide anions. The cellular mitochondria are being damaged and cytochrome c is being released to cytoplasm, resulting in activating the caspase-dependent apoptotic pathway [7].

Limited scleroderma (morphea):

Limited scleroderma (morphea) is considered as disease affecting epidermis and dermis. This process results in progressive diffuse thickening, sclerosis and atrophy of varying severity. It is a relatively rare disease, occurring in 2.7 per 100,000 people in the population (a study conducted in Olmsted County, Minnesota between 1960 and 1993) [8]. It occurs more often in women, at a ratio of 2.6:1, and is most often diagnosed between the ages of 20 and 50 [9]. Most popular classification of Morphea is based on 5 general types and was proposed by Peterson et al. [10]. Classification distinguished plaque morphea, generalized morphea, bullous morphea, linear morphea (with “en coup de sabre” subtype) and deep morphea. Eosinophilic fasciitis was classified as separate disease entity. Plaque morphea is defined as well-circumscribed round or oval shaped areas of shiny and hard skin [11]. Lesions are typically restricted to the dermis, without involvement of deeper skin tissue. In early stages of disease plaque is encircled by “lilac ring”, this is disease activity indicator. Generalized localized morphea is diagnosed when at least two anatomical regions are affected by four or more sclerotic foci with the 3 cm or more diameter. Most common it localizes symmetrically on the skin of the trunk and extremities. Face, foot and hands usually is not affected by disease [12]. The plaques exhibit mild inflammation, pigmentation, indistinct borders, increased thickness, and adherence to deeper layers [13]. In approximately 30% of cases may be concurrent lichen sclerosus in the genital area. Certain patients might experience subjective symptoms including muscle and joint pain, pruritus and fatigue[14]. Bullous morphea is identified by the development of subepidermal blisters alongside typical morphea or morphea

profunda. Lesions may manifest on extremities, trunk, face or neck and involve deep layers of skin. Formation of bullae has been linked to factors such as localized trauma or lymphatic obstruction induced by the sclerodermatous process [13,15]. Linear scleroderma is presented as one or more linear streaks of skin. It may involve dermis, subcutaneous tissue, muscle and underlying bone. Linear scleroderma affecting both sexes equally, most frequent is observed in childhood and adolescents [16,17]. Subtype “en coup de sabre” of linear scleroderma is limited to the hemiface, and has slowly progressive course. First time was describes by Addison in 1854 [18]. It influences mostly children, with the average onset is considered to be around 13 years of age and occur more often in females than males(3:1). There is link between time of onset of the disease and the time of menarche. It is presented as lesion with stiffness and contraction of affected area, where the groove begins to form. Groove may extend to scalp and provoke the occurrence of linear alopecia. There is also possibility of groove extension toward nasal region and upper lip [19]. Linear scleroderma is rarely linked with occurrence of ophthalmological and neurological symptoms, in pediatric populations extracutaneous changes presents with greater frequency than in the adult population [9]. Deep morphea occur as single lesion near shoulder area, near spine. It usually manifests itself as atrophic or hardened spot, in most cases it will be depressed. There are no particular symptoms reported by the patients [20]. Deep morphea typically does not present with preceding clinical signs of inflammation, skin discoloration or sclerosis. Additionally, instances of isolated deep morphea or comparable lesions linked to vaccine administration or intramuscular injection of vitamin K1 have been documented in the literature [21,22]. Nowadays, many authors point to the pro-inflammatory effect of CD4+ T-lymphocytes and excessive deposition of collagen deposits as the pathogenetic mechanism. The exact etiology and pathogenesis of the disease is unknown, however, we can find many research cases aimed at proving the validity of the hypotheses put forward by the authors. Some of them see the etiological factor in *Borrelia burgdorferi* infection, but currently we do not have reliable studies confirming the link between the infection and the development of the disease. The pathogenesis consists of three clinical events, each of which can be a therapy trigger point. Primary change in the microcirculation, characterized by elevated levels of SVCAM-1 and sE-selectin. These are indicators of endothelial activation and expression of adhesion proteins [23]. Fibroblast’s function is controlled via interleukin-4 and TGF-beta produced by perivascular CD4+ T lymphocytes. Results in differentiation toward Th2 lymphocytes, resulting in eosinophil activation and increased collagen production. Next step is production of collagen (I, II, III) and extracellular matrix proteins by fibroblasts[24]. Use of UVA1 in

morphea was first time described and published by Kerschmer and associates [25] in 1995. Since then, scientists from many countries have published follow up studies. According to current state of knowledge UVA1 therapy is considered to be one of the best therapeutic approaches in the above cases due to its effects on both collagen metabolism and inhibition of the inflammatory response. It is worth noting that light therapy with a wavelength range of 340-400 nm achieves similar efficacy to methotrexate treatment, while having a better safety profile [26]. According to current knowledge, medium and high doses of radiation (60J/cm², 3-5 times a week) up to 40 sessions are the most effective proven[26]. A study by Vasquez R. et al. that evaluated the efficacy of treatment in patients with generalized, limited and mixed scleroderma showed a 46% risk of relapse during the first 2 years of treatment. There was no association of relapse occurrence with scleroderma subtype, skin phenotype, total dose of irradiation or length of therapy [27]. For this reason, patients should be monitored during therapy to detect new sclerotic lesions. Crucial in treating patients with UVA1 phototherapy is proper patient selection. The standard is to avoid treating patients with soft tissue involvement(subcutaneous tissue, fascia, muscle), as UVA1 radiation does not reach such deep tissues. The treatment of choice in such patients remains systemic immunosuppressants. We have reason to expect a halt in lesion expansion and absorption of erythema within 2-3 months of therapy [27]. Another study was conducted among patients receiving low-, medium- and high-dose UVA1. The result of the collected research revealed that UVA1 therapy with high dose therapy was the most effective [28]. Subsequent comparative analysis, assessed efficacy of low dose and medium dose UVA1, and compared it with narrow band UVB(UVB-NB) therapy. The findings indicated that medium-dose UVA1 exhibited superior results to low-dose UVA1 and UVB-NB [29]. Tissue softening usually occurs over a period of several months to a year. Pigmented and atrophic lesions may not respond to UVA1 treatment, due to hyperpigmentation [30].

Systemic sclerosis (SSc):

Systemic sclerosis, despite a clinical presentation similar to limited scleroderma, is a separate disease entity. Main difference is presentation of sclerodactylia and occurrence of Raynaud syndrome on early stages of illness [31]. Susceptible pathogenesis of lesions is considered same as in morphea. Worth mentioning is fact, that in systemic sclerosis internal organs are affected by disease. Most common is changes in lungs, which are presented as image of frost glass and/or honeycomb image in computed tomography. With high frequency occur arrhythmia and conduction disorders in heart. In patients with swallowing disturbances we are

obligated to perform RTG with contrast of esophagus or scintigraphy of esophagus to determine, if esophagus is affected by SSc. Because of involvement of organ systems the most effective treatment is considered systemic immunosuppressive with methotrexate or mycophenolate mofetil. Nevertheless UVA1 therapy is considered as supportive therapy in reducing skin lesions. Von Kobyletzki G and partners [32] conducted study among small group of 8 patients, who were undergoing treatment composed of series of 50 exposures on medium dose UVA1, 4 times a week on lesions on fingertips. 7 out of 8 patients experienced improvement in range of motion and skin elasticity, as well as decreased number of digital ulcerations [32]. A follow-up study was performed by Kreuter A. and partners [33] among 18 patients treated with low-dose of UVA1 at varying frequencies. During the treatment patients observed reduction in skin thickness and hand edema. There is an histopathological evidence of effectiveness of phototherapy, biopsies revealed noticeable elevation of dermal collagenase on post-therapeutic MMP-1 Immunolabeling when compared to skin biopsies before phototherapy.

Buschke Scleroderma:

Buschke Scleroderma is one of the rarest diseases which presents as skin sclerosis, because of that information in popular research portals was heavily limited. It is recognized as diffuse cutaneous mucinosis group of disorders[34], and was first time described by A. Buschke [35] in 1902 in a 62-year-old man with personal history of longstanding dyslipidemia, hypertension and type II diabetes mellitus. Examination revealed diffuse skin sclerosis in the shoulders, back, buttocks and cervical region. Elevated levels of free lambda chains were identified in blood tests, and immunofixation revealed the presence of a monoclonal component. Pathological biopsy did not show any of epidermal lesions. Nevertheless increased mucopolysaccharides between collagen bundles and diffuse thickening in the middle and deep dermis was shown. Patient was subjected to treatment with prednisone, methotrexate, methylprednisolone, intravenous immunoglobulin and cyclophosphamide without major improvement in clinical state [36]. Treatment with UVA1, which were proven to be effective in other cases [37], was started at initial dose of 5J/cm², increasing up to maximum dose of 20J/cm². After 28 sessions was observed an improvement on mobility and reduction of skin stiffness on the neck. However condition of skin in buttocks area did not improved noticeable [35]. Worth noting is fact, this one case report cannot be used as certain source of evidence, there is need to conduct a follow-up on much larger group of patients.

Side effects of UVA1 therapy:

Most common side effects of UVA1 therapy is considered to be hyperpigmentation, erythema, xerosis and pruritus. Hyperpigmentation is linked to severity in affected skin. Other known side effects include activation of herpes simplex virus (HSV) and causation of polymorphic light eruption[38]. Some authors have theoretical concern of photocarcinogenesis in patients that received PUVA and UVA1 therapy. No research firmly establish link between UVA1 and melanoma. Nevertheless there is several studies which present some indications that DNA might be damaged during long standing UVA1 therapy, what may lead to tumor induction[39].

Conclusions:

High dose UVA1 therapy (60j/cm² 3-5 times per week) is one of the most effective therapeutic options in subtypes of morphea which affect only superficial tissues. Phototherapy accelerate healing of ulcerations on fingertips, and reduce the likelihood of relapse in patients with Systemic sclerosis. Patient suffering from Buschke Scleroderma had good response to therapy, nevertheless without follow-up studies effectiveness of UVA1 therapy in this condition is not proven. Side effects consist of hyperpigmentation, erythema, xerosis and pruritus in range from mild to severe. Some authors bring up the thesis according to which phototherapy, using UVA radiation, may lead to carcinogenesis in the future, but at the moment there is no direct evidence for this.

Supplementary materials

Not applicable.

Author's contribution:

Conceptualization, Bartłomiej Żmuda and Daniel Ślusarczyk; methodology, Bartłomiej Żmuda and Piotr Pisera; software, Filip Pactwa and Michał Żuberek; check, Daniel Ślusarczyk and Aleksandra Kiełkowicz; formal analysis, Bartłomiej Żmuda and Michał Żuberek; investigation, Bartłomiej Żmuda and Aleksandra Kiełkowicz; resources, Zuzanna Popińska and Filip Pactwa; data curation, Piotr Pisera and Michał Żuberek; writing - rough preparation, Bartłomiej Żmuda and Aleksandra Kiełkowicz; writing - review and editing, Bartłomiej Żmuda and Wiktoria Jakubowska; visualization, Bartłomiej Żmuda, Wiktoria Jakubowska and Zuzanna Popińska; supervision, Bartłomiej Żmuda and Daniel Ślusarczyk; project administration, Bartłomiej Żmuda; All authors have read and agreed with the published version of the manuscript.

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The authors of the paper report no conflicts of interest.

Data Availability Statement

The data presented in this study are available upon request from the correspondent author.

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