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Phototherapy in Atopic Dermatitis

*Aleksandra Lesiak, Magdalena Ciazynska
and Joanna Narbutt*

Abstract

Atopic dermatitis (AD) is an inflammatory, recurrent and chronic disease that occurs in 2–10% of the population. Therapy of AD could be divided into topical (corticosteroids, calcineurin inhibitors) and systemic (cyclosporine, methotrexate, azathioprine or biological treatment). Phototherapy is taken into consideration as a second-line treatment, when topical therapy is unsuccessful. We distinguish many types of phototherapy, e.g. narrowband UVB (311–313 nm), UVA-1 therapy (340–400 nm), UVA/B combination, UVA therapy plus 8-methoxypsoralens (PUVA), 308 nm excimer laser (EL) and blue light. Phototherapy is effective in many cases, whether in adults or in children. It should be remembered that during therapy possible side effects may occur. Among them the risk of carcinogenesis is the most severe.

Keywords: atopic dermatitis, phototherapy, eczema, NB-UVB therapy, UVA-1 therapy PUVA therapy, blue light

1. Introduction

Atopy refers to a personal tendency to heightened immune responses to small doses of allergens and as a result producing IgE antibodies. As a consequence a patient develops certain types of diseases, such as atopic dermatitis, allergic rhinitis and asthma.

Atopic dermatitis (AD) is a dermatosis that occurs in 2–5% of the population and is one of the most common dermatoses. Nowadays in developed countries over the past three decades the number of cases of AD has almost tripled. The main symptoms of the disease are pruritis, abnormally dry skin and erythema. Atopic dermatitis is characterized by chronic or relapsing course. The onset of AD in most cases is observed during early childhood. In infants, lesions appear mostly on cheeks and extremities, whereas in children and adults – in flexural areas. The lesions are combined with hyperkeratosis and lichenification. Triggering factors such as stress, wool intolerance or sweating may worsen the course of AD. During therapy avoiding those is highly desirable. *Staphylococcus aureus* is one of the microorganisms which can be found on the skin of AD patients. It is present not only on erythematous lesions, but also on a “healthy” skin.

The first line of AD therapy is a short-term regimen – when the patient uses medicines only when inflammatory lesions occur, but in recent years the therapy is more focused on proactive and long-term maintenance. Drugs should be applied continuously or one/two times a week. The basic rule in the therapy is to use emollients which restore epidermal barrier and create an occluding coating. Therefore,

they protect the skin from triggering factors. In mild course of AD using topical corticosteroids and topical calcineurin inhibitors is recommended. In moderate to severe cases of AD phototherapy, cyclosporine, methotrexate, azathioprine or systemic corticosteroids may be administered. Phototherapy (using ultraviolet light) is also useful in other inflammatory skin diseases, like psoriasis. We distinguish the following types of phototherapy:

- broadband UVB (290–320 nm),
- narrowband UVB (311–313 nm),
- UVA-1 therapy (340–400 nm),
- UVA therapy plus 8-methoxypsoralens (PUVA),
- 308 nm excimer laser (EL),
- blue light (BL).

2. Mechanism of action

Phototherapy (specifically broadband UVB) in atopic dermatitis has been used since 1970 and its effectiveness is clinically proven [1]. The mechanism of skin lesions development in atopic dermatitis is connected with activation of T-cell infiltration into the skin, which leads to increasing proliferation of keratinocytes and as a result thickening of the skin. Th2 cells accumulate and produce various cytokines, such as IL-4, IL-31, IL-13. Th1 cells, INF- γ , Th22 cells and IL-22 were also found in chronic atopic lesions [2]. Common type of drugs used in AD are immunosuppressants. We divide them into systemic (cyclosporine) and topical (tacrolimus, pimecrolimus) types. They act by inhibiting calcineurin which leads to a decrease in activation of T cells. It indicates that targeting T cells may be an effective approach in therapy of AD.

Artificial or natural ultraviolet radiation leads to deep immunosuppression which induces apoptotic death in activated T cells. Many factors, such as wavelength, dosage of radiation, amount of UV sessions have an impact on the intensity of immunosuppressive effect of UV radiation. In general UV radiation could be divided into UVB (with wavelength between 280 and 320 nm) and UVA (with wavelength between 320 and 400 nm). Overall UVB light has a higher immunosuppressive impact than UVA. Psoralens in PUVA therapy are molecules whose purpose is intercalation of DNA. After UVA radiation psoralens are binding to the DNA. This results in stopping cells proliferation [3]. Nowadays more and more diseases are treated with biological therapy. Owing to good safety profile, accessibility, only topical immunosuppression and cost-effectiveness of UV radiation, phototherapy is still a very popular AD therapy. Biological effects of UV radiation are complex and could be classified into instantaneous and delayed [4]. Damage of DNA and cytoplasmic membrane, induction of cytoplasmic transcriptional factors and chromophore's isomerization initiates immediate stunted growth and, as a consequence, apoptosis [5].

After UVB radiation, photon's absorption causes changes of DNA molecular structures. As a result, transcription of DNA is paused and cell cycle in fibroblasts and epidermal cells stops (phototype I reaction) [6]. In PUVA phototherapy after psoralen application with following UVA radiation, reactive oxygen species are

damaging DNA and cell membrane (phototype II reaction) [7]. After only one hour DNA starts to repair and the cells start to proliferate. As an effect in 48–72 hours after UV radiation short-term effects are reversing. Long term effects refer to inhibition of immune cells which causes immunosuppression. Induction of apoptosis in epidermal and dermal T cells is a crucial mechanism [8]. Apoptosis after UVB radiation concerns keratinocytes too, leading to lesions clearance. Moreover, UVB and PUVA activate T regulatory (Treg) cells and decrease the amount of presenting antigen in Langerhans cells [9].

After UV radiation cytokine secretion and number of macrophages are limited. Acting through reactive oxygen species, neutrophils and NK cells are suppressed [10]. As an effect cytokine balance is changed – decrease of inflammatory cytokines IL-2, IL-8, IL-9, IL-17, IL-22, IL-23, TNF- α and IFN- γ with simultaneous induction of immunosuppressive cytokine – IL-10 [11].

3. Types

3.1 NB-UVB

NB UV-B has been in use of AD treatment since 1990 [28]. It emits highly selective UV-B light wavelengths (from 311 to 313 nm, without shortwave length UVB) [12]. Sunburning potential of NB UV-B is evidently lower than broadband UV-B (BB UV-B) [13]. Due to the long list of advantages, like safety profile, effectiveness, accessibility NB UV-B could be pondered as a first-line treatment [14]. It has been established in many randomized trials that NB-UVB therapy improved the scores of AD and the necessity for applying potent topical corticosteroids was reduced [15]. These type of positive results remained up to six months after the scheme of NB-UVB was finished [16]. Contrary to UVA, NB UV-B does not penetrate the dermis, therefore it is limited to the epidermis [15]. Patient's tolerance to UV radiation and pigmentation of the skin determines the dosage of UV-B. When it comes to the methods of adjusting UV-B dose which should be administered, the most popular is defining "Minimal Erythema Dose" (MED). MED refers to the smallest UV-B dose which is capable of provoking minimal erythema on the patient's skin [17]. Skin phototype can play a role in determining UV-B dosage. Measuring skin reflectance is another way of UV-B dose calculation and it was derived from defining the skin pigmentation. It is called reflectance-guided UV-B and recently it has become highly popular [18]. Most physicians use NB UV-B treatment schedule which consists of three sessions of radiation every six weeks [19]. In early studies, researchers used nearly erythemogenic dose of NB UV-B, but recently it was proven, that reducing a dose by half can give similar outcome, higher tolerance and lower risk of carcinogenesis. Reports comparing UV-A1 and NB-UVB are ambivalent [15]. Some of them point to superiority of NB UV-B, other do not show statistically significant differences [20]. In some cases NB UV-B can be combined with UV-A1 in one therapy schedule with satisfying clinical effect [21].

In literature there is strong evidence proving efficacy of AD therapy using NB-UVB. In a study with a test group of 21 adults with severe course of the disease, administering air-conditioned NB-UVB thrice a week for twelve weeks caused reduction of severity (68%) and reduction of topical corticosteroid application (88%). 15 of 21 patients showed positive result 24 weeks after therapy ended [12]. Brazzelli et al. in their study reported efficacy of treating AD with NB UV-B, preceded by oral short-term cyclosporin A (four weeks) and four-six-week-long washout phase. Radiation was administered three times a week and lasted up to two months [22]. There were some studies concerning NB UV-B therapy of atopic

dermatitis in children. Jury et al. in their retrospective trial on 25 children with AD showed almost total reduction of lesions in 17 patients [23]. NB-UVB is a recommended therapeutic option in pregnancy [24].

Prospective clinical trial with 29 children (3–16 years old) pointed 61% reduction in SASSAD score (Six Area Six Sign Atopis Dermatitis) in a group exposed to NB UV-B radiation in comparison to untreated patients ($P < 0.05$). Moreover, children without therapy experienced a decrease in the quality of life with a rise of disease severity [25].

3.2 UVA1

Development of UVA1 (340–400 nm) lamps was a response to appearing side effects, such as long exposure time or risk of sunburn when using UVA-2 (320–340 nm) radiation. UVA-1 penetrates deeper into the dermis than UVA-2 and UVB [26]. We distinguish different types of doses:

- high dose (80–130 J/cm²),
- medium dose (40–80 J/cm²)
- low dose (<40 J/cm²) [27, 28].

It should be mentioned that a huge inconvenience of UV-A1 in high dose is overheating of the device, which can be unsafe. Studies showed that UV-A1 is more efficient in AD therapy and has higher efficacy than UV-AB. Krutmann et al proved that UV-A1 phototherapy effectiveness is approximately the same as therapy with fluocortolone [28]. Medium doses of UVA-A1 have the advantage over high doses of UVA-A1 when it comes to reducing adverse drug events and enhancing tolerance. The effectiveness and relapse time do not differ strongly between these two options of therapy. Therefore the UVA-A1 radiation should be the preferable one [1]. UVA-A1 in low doses is practically ineffective, thereby it is not considered to be a therapeutic agent [28]. Common treatment schedules of UVA-A1 at medium dose (maximum 80 J/cm²) in atopic dermatitis therapy are 3–5 sessions every 3–8 weeks. Patient should spend 10 minutes to 1 hour in every phototherapy session [15, 29]. Speaking of acute cases of AD, using UV-A1 radiation is more suitable, comparing to UV-B [15]. Majoie et al. examined 13 adults (20–56 years old) suffering from chronic atopic dermatitis in a randomized investigator-blinded trial and proved that NB-UVB and medium dose of UVA1 are comparably efficient in the reduction of AD symptoms [20]. The disadvantage of UV-A1 therapy is the cost and the size of UV-A1 lamps. Moreover, they demand a presence of ventilation machines, what could be financially unachievable for some centers [30]. To meet the expectations of the patients engineers created a filter to eliminate wavelengths above 530 nm and disperse the excessive heat. It is called Cold-light UV-A1 and it is consider a more effective option than UV-AB and classic UV-A1 in treatment of AD flares [31].

3.3 PUVA

PUVA (psoralen and ultraviolet A) is a combination of UVA light and psoralens – a substance causing photosensitizing effect. Nowadays in use there is an 8-methoxy-psoralen (8-MOP), which leads to permanent damage of DNA [13]. Psoralens are available in many various formulations, such as pills, cream or bath lotion [32]. In bath-PUVA, the patient is taking a bath in warm water with 8-MOP 20–30 minutes before UVA session. In case of choosing cream formulation, the regimen is conducted

30–60 minutes before radiation [32]. Using topical psoralens could be desired, for example in patients with strictly localized lesions. In literature it is proven that PUVA phototherapy could be a successful form of atopic dermatitis therapy [33]. Although, we should remember that in comparison with other inflammatory diseases treated by PUVA, in atopic dermatitis patients require more phototherapy sessions [15]. Der-Petrossian M. et al. in a randomized trial compared PUVA bath therapy with NB UV-B – there were no significant differences between these types of phototherapy [33]. In another study Tzaneva S. et al. showed that after PUVA therapy (using oral 5-methoxypsoralen, 5-MOP) patients had longer remission times and higher change in AD scoring compared to UV-A1 phototherapy [34]. Heinlin et al., in his randomized and placebo-controlled trial demonstrated superiority of balneophototherapy and NB-UVB combination over only NB-UVB. Patients' complex therapy had higher reduction of SCORAD score not only at the end of treatment, but also after 6 months. (P respectively <0,004 and < 0,04) [16]. Because of mutagenic properties of PUVA therapy, it should be reminded that it could not be a chronic form of therapy and using it should be limited [30].

3.4 UVA/B combination

UVA and UVA combination (280–400 nm) can be conducted by using special machines emitting these UV spectrums or as two separate sessions. In clinical trial Valkova and Velkova proved that combination UVA/B phototherapy with topical corticosteroids reduced the treatment duration significantly in comparison to only UVA/B (P = 0.02) [35]. Grandulad et al. investigated reduction of SCORAD, days in remission and the improvement in quality of life using ciclosporin and UVA/B. Ciclosporin had statistically significantly better scores compared to UVA/B phototherapy sessions [36]. Jekler [37] and Larko [38] showed that using the combination of UVA/B radiation is more effective than monotherapy of UVA or UVB.

3.5 Excimer laser

Monochromatic excimer laser (MEL) is a kind of single-wavelength light source of 308 nm. The advantage of this therapy is a frequency of sessions – every 7–15 days [39]. MEL could be used on the localized skin lesions. One study showed good ability of alleviation of prurigo in AD. However, further clinical trials are needed [40].

3.6 Blue light

Blue light (400–495 nm) is a novel therapeutic option. Becker et al. in his observational study showed that using blue light devices could be suitable in treatment severe atopic dermatitis. In addition, it provided long term improvement. Observed adverse effects were mild and transient – redness, warmth or itching the skin. [41] Kromer et al. is performing a multicenter, prospective randomized, placebo controlled, double blinded trial with 150 patients suffering from AD to investigate effectiveness of blue light devices. Currently there are no official results, but that investigation appears to be promising [42].

4. Side effects

Like every therapeutic agent, phototherapy may cause some side effects. Most of them are mild and short-term, for example skin burning (connected with wrong

dosage of UV or inadequate radiation schedule), pruritus, hyperpigmentation, dryness and tenderness. Induction of polymorphic light eruptions and viruses reinfection (such a herpes simplex) are also observed. When it comes to long-term adverse effects, photo-aging and induction of cutaneous malignancies can occur [14]. These cutaneous malignancies can be caused by combining UV radiation with other therapeutic factors. There is a reported case of a melanoma diagnosis in a patient with mastocytosis who was treated with UVA1 and PUVA bath therapy previously [42]. In literature we can find two cases of Merkel cell carcinoma after UVA1 therapy in patients who were treated with immunosuppressants for blood dyscrasias [43].

Lately new therapeutic options were presented. One of them is 308 nm monochromatic excimer light. It is dedicated for patients with localized and therapy-resistant lesions [44]. In comparison to other immunosuppressive agents, phototherapy has a better safety profile, adverse effects are milder and better-tolerated [23]. PUVA systemic therapy can cause hepatotoxicity, nausea, vomiting, cataract, long-term photosensitivity and probable skin cancer. Topical use of psoralens can limit or help avoid these inconveniences [45]. However, please note that atopic dermatitis is a chronic and recurrent disease which implicates many phototherapy sessions and increases the risk of carcinogenesis [16]. Many clinical trials showed that phototherapy in children with AD is effective and, in most cases, well tolerated. There is, nonetheless, high risk of photocarcinogenesis. In younger patients long-term maintenance therapy should be conducted in as short time as possible [23]. In conclusion, this way of AD treatment is one of the last therapeutic options. Claustrophobia and lack of cooperation is typical for small children and it has to be taken into consideration as a challenge in this kind of therapy [15]. Despite this, in children with refractory or severe atopic dermatitis we may consider using phototherapy. Generally, in such cases, NB UV-B is a therapy of choice and PUVA should be avoided [23]. It should be also remembered that there are no randomized trials of phototherapy of AD in pregnancy [30]. UV treatment require specific amount of time and availability, which can be problematic for patients who are attending school or have strict work hours. To meet these demands, there are some home phototherapy devices accessible.

5. Conclusions

Phototherapy is considered as a safe and successful therapy in management of atopic dermatitis. When topical corticosteroids and calcineurin inhibitors are ineffective, phototherapy could be considered as a second line treatment, whether in combination with systemic drugs or without them. The most effective types of phototherapy are UVA1 and NB-UVB; UVA1 should be pondered in acute flares whereas NB-UVB in recurrent atopic dermatitis. In children and pregnancy NB-UVB has a good safety profile. Using UVA1 medium dose of radiation has an advantage over others. Due to safety profile narrow-band UVB is favored over broad-band UVB. Potential adverse effects are usually mild and transient, although the risk of carcinogenesis should be always considered.

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Author details

Aleksandra Lesiak^{1*}, Magdalena Ciazynska² and Joanna Narbutt¹

1 Department of Dermatology, Pediatric Dermatology and Oncology, Medical University of Lodz, Lodz, Poland

2 Dermoklinika Centrum Medyczne, Lodz, Poland

*Address all correspondence to: lesiak_ola@interia.pl

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