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REVIEW ARTICLE

# Management of atopic dermatitis using photo(chemo)therapy

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**Abstract** The conclusions that may be drawn by interpreting the current literature on the efficacy of photo(chemo)therapy in the treatment of atopic dermatitis (AD) are limited by several factors including publication bias, small sample sizes, high variability of parameters used in different studies, and in particular the lack of randomized controlled trials comparing different photo(chemo)therapeutic modalities. The newer ultraviolet (UV) modalities, such as medium-dose UVA1 and narrowband (NB) UVB, with a high output and a narrow emission spectrum may be considered the probably most efficacious regimens for treating acute and chronic AD, respectively, in particular when compared to conventional broadband UV regimens. There are no prospective trials on AD patients comparing NB UVB and UVA1 with more complex regimens such as heliotherapy, balneophototherapy, psoralen plus UVA (PUVA), and extracorporeal photophoresis. Support for the role of the aforementioned regimens in the treatment of AD is generally weaker than for the newer modalities including medium-dose UVA1 and NB UVB. When photo(chemo)therapy is considered for AD patients, its use is very much dedicated by the cost-effectiveness, availability, and the practicality of attending the clinic several times a week.

**Keywords** Atopic eczema · Phototherapy · Photochemotherapy · Ultraviolet A1 · Narrow-band UVB

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## Introduction

There are many skin disorders, including psoriasis, seborrhoeic and atopic dermatitis, and vitiligo, which significantly improve by exposure to natural or artificial ultraviolet (UV) radiation [11]. Along with topical and systemic therapy, photo(chemo)therapy is one of the three fundamental treatment options for managing atopic dermatitis (AD) which is a very common chronic inflammatory skin condition. A variety of studies have shown a beneficial effect of sunlight exposure (e.g., heliotherapy, climatotherapy) and photo(chemo)therapy in AD. Different broadband (BB) UV spectra (UVA, UVB, UVA/UVB) and combined treatment modalities, including salt water bath plus UVB (balneophototherapy) and psoralen plus UVA (PUVA) have been reported to be effective in moderate to severe AD, respectively. However, the past 15 years have seen the introduction of new photo(chemo)therapeutic modalities for AD [5, 11, 17, 28, 31, 40], including UVA1, narrowband (NB) UVB, and extracorporeal photopheresis (ECP). In the present non-systematic review, I briefly describe and discuss the results of previous studies using photo(chemo)therapeutic regimens in the treatment of AD.

## UVA/UVB phototherapy

The combination of UVA/UVB (wavelength region from 280–400 nm), was initially used to simulate the effect of natural sunlight. The management of AD with combined UVA/UVB phototherapy has been evaluated by a number of investigators [14, 19–21, 32, 46]. Hannuksela et al. [14] reported a study on 107 patients with AD who received either UVA/UVB or UVB only. Of the UVB treated patients, 93% had a good response with 50% of patients

reporting a reduction in steroid use after cessation of phototherapy, and of the UVA/UVB treated patients, 94% achieved a good response with 85% reporting reduction of steroid use after treatment. However, it has to be stressed that the data reported by Hannuksela et al. [14] is relatively weak since they used a retrospective study design. Midelfart et al. [32] published a randomised study on 56 AD patients comparing the efficacy of UVA/UVB and UVB. Of the patients treated with UVA/UVB, 96% had a good or even complete response with a mean of 18 treatments while those treated with UVB only, 85% showed a good or complete response with a mean of 20 treatments. Later, Jekler and co-workers [19–21] confirmed that UVA/UVB is superior to UVB as well as they reported a randomised, bilateral comparison study on UVA/UVB versus UVB. Patients were assessed according to improvements in clinical parameters such as lichenification, itch, scaling, xerosis, and overall healing of their dermatitis. Significant differences in favour of UVA/UVB were observed for all analysed variables, namely total score, pruritus score, and overall evaluation score. No statistically significant differences in healing rate were, however, seen. Twenty-five of 30 UVB treated, and 26 of 30 UVA/UVB treated, body halves healed or were considerably improved. Patients preference was overwhelmingly in favour of UVA/UVB. Twenty-three of 24 patients who completed an evaluation form preferred this treatment, whereas only 1 of 24 preferred UVB. The authors concluded that UVA/UVB is better than UVB in the treatment of AD due to the photoaugmentation and deeper penetration depth provided by UVA and the lower level of skin irritation from UVA/UVB phototherapy [20, 27]. Hence, it can be concluded that UVA/UVB is effective in AD. However, there is a lack of studies comparing UVA/UVB with UVA1 and NB UVB [16].

## NB UVB phototherapy

NB UVB is a term used for the UV radiation produced by a light source producing a narrow peak around 311 nm (TL01 bulbs, Philips, Eindhoven, Netherlands). Reynolds et al. [37] did a randomised controlled, double-blind trial to compare NB UVB, BB UVA, and visible light (placebo) phototherapy as second-line, adjunctive treatments in adult patients with moderate to severe AD. Phototherapy was administered twice a week for 24 exposures (starting doses: 0.4 J/cm$^2$ NB UVB, 5 J/cm$^2$ BB UVA). After 24 treatments, mean reductions in total disease activity in patients who received NB UVB (22 patients) and BB UVA (19 patients), respectively, were 9.4 points and 4.4 points more than the 19 patients who received placebo treatment. Mean reductions in extent of disease with NB UVB and BB UVA were 6.7 and −1% compared with placebo. Reassessment 3 months after the phototherapy phase showed that more patients in the NB UVB group than in the BB UVA and visible light groups exhibited lower disease activity. Hence, in this comparative trial NB UVB has been proven the most effective adjunctive treatment. Because the patients were permitted to use moderate-to-potent topical steroids in this study, it is, however, difficult to draw any conclusions on the efficacy of NB UVB alone. Moreover, differences in pigmentation following phototherapy may have broken the blinded status of investigators and patients [37]. Der-Petrossian et al. [7] conducted a randomised investigator-blinded half-side comparison study on 12 patients with severe chronic AD comparing NB UVB with bath PUVA. Half-side irradiation with threshold erythemogenic doses of NB UVB and bath PUVA was performed three times weekly during a period of 6 weeks. The mean baseline skin score decreased by 65.7% by bath PUVA and by 64.1% by NB UVB. The authors concluded that both phototherapeutic modalities appear to be equally effective and tolerated when administered in erythemogenic doses. Moreover, Legat et al. [29] performed a randomised half-side comparison study on nine patients with chronic AD treated with NB UVB and medium-dose UVA1, respectively. Clinical scoring and patients' self-evaluation demonstrated a greater therapeutic effect for NB UVB than for medium-dose UVA1: physician relative score reduction NB UVB 40% ($P = 0.004$) versus UVA1 33% ($P = 0.055$) and patient relative score reduction NB UVB 71% ($P = 0.004$) versus UVA1 40% ($P = 0.04$). Similarly, Hjierpe et al. [16] showed in a non-randomised half-side comparison study on ten patients with symmetric AD that NB UVB lowered the clinical score faster and more effectively than UVA/UVB treatment, but the difference was non-significant ($P = 0.069$). When pruritus was analysed separately, however, NB UVB produced a significant reduction after 6-week treatment compared with UVA/UVB ($P = 0.043$). Similar positive results have previously been supported in open prospective and retrospective trials on patients with moderate to severe adult or childhood AD using NB UVB as an adjunctive treatment combined with topical steroids [4, 13, 18]. In the above-mentioned studies, NB UVB did not only decrease the total clinical score, but also substantially reduced the use of potent steroids. We recently reported a randomized double-blind controlled crossover trial on AD patients who were treated with UVA1 as well NB UVB [12]. All in all, 28 patients completed both UVA1 and NB UVB phototherapy courses and were analyzed on an intention-to-treat basis according to the crossover design. Both interventions were associated with significant clinical improvement but there was no significant difference between both treatments in respect to the mean relative reduction of the clinical scores. There was no significant

difference in the mean relative reduction of the Skindex-29 after UVA1 and NB UVB phototherapy. Changes of the total IgE and ECP levels following UVA1 and NB UVB did not differ significantly. It is concluded that both phototherapeutic modalities may be considered comparably good with regard to efficacy and tolerability [12]. Moreover, Majoie et al. [30] recently performed a randomized investigator-blinded half-sided comparison study between NB UVB and medium-dose UVA1. In accordance with our results they found that NB UVB and medium-dose UVA1 seem equally effective in the management of AD [30]. Hence, on the basis of retrospective observations as well as randomized controlled trials, NB UVB may be considered effective in the management of AD. Furthermore, NB UVB appears to be as effective as UVA1 and bath PUVA and superior to BB UVA and UVA/UVB in the management of AD.

## UVA1 phototherapy

UVA1 phototherapy is a relatively new treatment modality using the longer wavelength region of the UVA spectrum (340–400 nm). Compared to UVA2, UVA1 is less erythemogenic and capable to penetrate deeper into the skin [24]. In pioneer investigations, UVA1 doses of 130 J/cm$^2$ (high-dose) were applied five times weekly over 2 or 3 weeks, resulting in a cumulative exposure dose of 1,300–1,950 J/cm$^2$ and a reduction of the baseline clinical score by 54 and 74%, respectively [25, 26]. In one of these studies [26], high-dose UVA1 was compared with UVA/UVB and topical steroids for the management of AD ($n = 53$). The greater efficacy of high-dose UVA1 monotherapy was demonstrated when compared to UVA/UVB and topical steroids. Another study examined the efficacy of high- and medium-dose UVA1 (60 J/cm$^2$) in patients with severe AD [44]. The patients served as their own experimental control; one half of the body was irradiated with high-dose UVA1 while the contralateral side received only medium doses. After 3 weeks of treatment, both high-dose and medium-dose regimens achieved similar results as indicated by reductions in clinical scores (34.7 and 28.2% reductions, respectively). No significant difference in efficacy was seen between the two dosage levels in regard to overall clinical response. Moreover, relapses appeared soon after therapy (median time of 4 weeks) regardless of the dosing regimen employed [44]. Kowalzick et al. [23] conducted a trial of 22 patients with acute AD, half of whom were selected to receive medium-dose UVA1 while the other half was treated with low-dose UVA1. Patients treated with medium-dose UVA1 had a 25.3% reduction in clinical scores after 3-week therapy, while low-dose regimen achieved only a 7.7% reduction. Von Kobyletzki et al. [47] investigated a novel UVA1 apparatus designed to minimize the enormous heat load generated by conventional UVA1 devices. The so-called UVA1 cold-light was compared with traditional UVA1 and with UVA/UVB in a study involving 120 patients with acute AD. The cold-light UVA1 regimen demonstrated superiority to both UVA1 and UVA/UVB for reducing disease severity as measured by the clinical score immediately after treatment for 3 weeks and at 1 month follow-up assessments. Furthermore, Abeck et al. [1] reported that medium-dose UVA1 is effective for alleviating acute exacerbated AD as shown by a significant reduction of clinical score ratings ($P < 0.001$) at the end of the active UV treatment period. A significant skin improvement was still present 1 month later ($P < 0.001$). However, at the end of the 3-month post-treatment observation period the skin condition had reached the pretreatment level. Hence, medium-dose UVA1 also works, is more effective than UVA/UVB for severe AD and more effective than low-dose treatment. Recently, Polderman et al. [34] compared the effect of 4 weeks therapy with the effect of the usual 3 weeks therapy in patients with AD ($n = 61$), using medium-dose UVA1 cold light (45 J/cm$^2$), 5 days weekly. Clinical score and quality of life improved significantly during both 3 and 4 weeks UVA1. The differences between the 3- and 4-week treatments did not reach statistical significance. However, 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 steroids in the follow-up period. Hence, the extension of UVA1 therapy from 3 to 4 weeks may result in a clinically relevant improvement of the outcome, and more prolonged therapeutic effects [34]. Thus, several controlled studies indicate that UVA1 is effective in AD and superior to broadband UV regimens, whereby medium-dose UVA1 may be the most cost-effective and safest regimen when compared to low-dose and high-dose modalities.

## Photochemotherapeutic modalities

The use of PUVA was reported in the management of AD earlier than other phototherapeutic modalities. However, it seems that the popularity of PUVA has been slowed by the greater complexities of its administration due to psoralen and to the recognized potential risk of skin cancers. Nonetheless, Yoshiike et al. [49] attempted to formulate a guideline for the selection of AD patients assigned to PUVA. According to this guideline, 114 patients were selected for PUVA treatment. Forty-five percent of the patients did not respond adequately to other conventional forms of treatment. Adverse effects from previous treatments, in particular steroids, occurred in almost 40% of the patients. After

PUVA, the skin lesions significantly decreased in 81% of the inpatients and 67% of the outpatients, while some lesions of the patients disappeared, despite that other forms of treatment had been unsuccessful in many cases. Atherton et al. [2] previously reported 15 adolescent children with severe, chronic AD who were treated with oral PUVA. Photochemotherapy resulted in initial clearance of AD in 14 of the 15 children, 9 of whom achieved a remission. Apart from its efficacy, notably, a major benefit of this therapeutic approach was that it was associated with resumption of normal growth in children who were previously growing poorly, either as a direct result of severe AD or its treatment. Atherton et al. [2] stressed in their conclusion that against the considerable advantages of PUVA for this group of patients have to be balanced the possible hazards, because relatively high exposures are required in some individuals, both initially to induce clearance and subsequently to maintain it. However, conclusions on the aforementioned studies can only very cautiously be drawn since these reports are based on retrospectively obtained data. Over a 6-year period, oral PUVA was used to treat 53 children with refractory severe AD [42]. Twice-weekly treatment resulted in clearance or near-clearance of disease in 39 (74%) after a mean of 9 weeks. Thirty-two (82%) of these 39 children were subsequently able to achieve remission of disease following gradual withdrawal of treatment; the mean duration of treatment to remission was 37 weeks; the mean cumulative UVA dose was 1,118 J/cm$^2$, and the mean number of treatments was 59. Recently, Uetsu and Horio [45] used oral PUVA for the treatment of 113 patients with severe AD. At 4 and 8 weeks after PUVA therapy, the severity score of AD had decreased by 51 and 80%, respectively. The amounts and strength of topical steroids were decreased during PUVA therapy. The quality of life of patients was greatly improved following treatment. The authors concluded that PUVA can be indicated in patients with refractory, severe, widespread AD. Use of psoralen in a dilute bath water solution (bath PUVA) is an effective alternative to systemic psoralen administration. It avoids many side effects, reduces cumulative UVA doses, and facilitates uniform psoralen application. For example, 35 adults with severe AD underwent bath PUVA up to a maximum of 30 sessions (maximum single dose: 12 J/cm$^2$). For those patients who did complete the study, a significant ($P < 0.001$) reduction in symptoms was noted at the end of treatment [6]. As mentioned previously, bath PUVA for AD patients was found to be equally effective as NB UVB [7]. Similar to psoriasis AD is responsive to PUVA. However, the data supporting the latter statement is much weaker when compared to data on PUVA treatment of psoriasis. In all, there is a lack of large controlled studies investigating PUVA in AD. Most studies in this field were performed on highly selected AD populations, had a retrospective design, had no comparator, or were simply too small to have sufficient statistical power.

ECP has been shown to be effective in a variety of diseases such as Sezary syndrome and graft versus host disease. The ECP procedure mainly includes the collection of peripheral mononuclear cells, the cell radiation by UVA in presence of 8-methoxypsoralen, and the reinfusion of the treated cells to the patient. Prinz et al. [35] aimed to determine the efficacy and safety of long-term ECP in the treatment of severe AD. Fourteen patients were treated with ECP in an open clinical trial at 2-week intervals. Disease activity was scored before each ECP cycle. A complete clinical remission was achieved in four patients (29%). Five patients (36%) experienced a substantial response with reduction of skin inflammation by at least 75%, whereas in one patient (7%) disease activity was reduced by more than 50%. However, four patients were withdrawn from the study because of inefficacy. Prinz et al. [35] concluded that ECP should be considered as a treatment modality for patients suffering from severe and otherwise refractory atopic skin disease. Encouraging results following ECP in patients with AD have also been observed in case series and small studies of other research groups [36, 38, 39]. Thus, ECP may be an effective photochemotherapeutic option for patients with AD. However, controlled trials are still outstanding comparing ECP with other photo(chemo)therapeutic regimens.

## Heliothalassotherapy and balneophototherapy

On the basis of retrospective studies, heliothalassotherapy (e.g., climatotherapy and spa treatment) have been advocated for the management of chronic skin diseases such as AD [15, 17]. In an uncontrolled prospective study by Autio et al. [3], a total of 216 AD patients participated on 6 different 2- or 3-week heliothalassotherapy trips (Canary Islands). The severity of AD was assessed prior to the start of heliotherapy, after 2 weeks and then 3 months after the end of heliothalassotherapy. A quality of life questionnaire was later mailed to all participants. The mean clinical score was reduced by 70% after 2 weeks of heliothalassotherapy and was still 45% lower 3 months after therapy ($P < 0.0001$). At 3 months, the use of topical steroids was still significantly reduced ($P < 0.0001$). The quality of life of patients was improved and their self-treatment and working capacity was increased. As the longer 3-week period provided no significant additional advantage over a 2-week period, 2 weeks of heliothalassotherapy can be considered superior [3]. In a large study on 1,718 patients with AD, Harari et al. [15] have shown that previous treatments at the Dead Sea and stays longer than 4 weeks caused a clearance greater than 95%, the length of sun exposure was no longer

than 5 h daily, and there was no impact of the percentage of skin involvement on the clearance of patients staying more than 4 weeks. However, the results of the aforementioned study are weak because of the retrospective study design [15].

As the aforementioned regimens are tied to special geographic settings, balneophototherapy was alternatively established in German rehabilitation centres, especially for the treatment of psoriasis. Balneophototherapy represents a combined phototherapeutic regimen with salt water baths and artificial UV radiation [9, 10]. In a controlled prospective study performed by Dittmar et al. [8] the efficacy of combined salt water bath and UVA/UVB phototherapy to a UVA/UVB monophototherapy was compared in patients with subacute AD. The patients in the balneophototherapy group ($n = 16$) were treated with baths containing 3–5% of a synthetic salt, followed immediately by UVA/UVB irradiation, while the other treatment arm ($n = 12$) received UVA/UVB phototherapy only. After 20 treatments the balneophototherapy group showed a statistically significant ($P < 0.0015$) reduction of the clinical score from 69.5 before to 36.8 after therapy. Surprisingly, no statistically significant reduction of the clinical score could be observed in the UVA/UVB phototherapy group (50.6 before to 44.3 after therapy) indicating that bathing in salt water was the crucial treatment component in this study setting. The results of the study of Dittmar et al. [8] are in sharp contrast to previous studies on UVA/UVB therapy for AD [14, 19–21, 32, 46]. In another open study, brine baths containing either 15% synthetic Dead Sea salt or 3% NaCl solution led to significantly better results in 80% of patients in the 15% salt water group [50]. It has to be stressed, however, that salt water baths in the range of 15% might not be tolerated by all patients with AD. Moreover, Schiffner et al. [41] conducted an uncontrolled multicentre trial on combined treatment with NB UVB and salt water baths in outpatients with AD. The use of concomitant topical treatment such as steroids was not reported, however. Relative improvement of the skin score (percent) was significant ($P < 0.05$) in 143 patients treated according to protocol (55%) and in 615 patients in an intent-to-treat group (41%). The authors concluded that this treatment modality is especially recommended for patients with chronic types of AD, high compliance, and time free for therapy. Unfortunately this large study did not include a NB UVB monotherapy arm. In all, the influence of bathing in salt water on the efficacy, tolerability, and practicability was not assessed independently in most studies on heliothalassotherapy and balneophototherapy of AD. Moreover, the heterogeneity of treatment modalities used in heliothalassotherapy and balneophototherapy does hardly allow a comparison of studies reported. Hence, unlike in psoriasis therapy it remains unclear whether bathing in salt water prior UV exposition is really superior to mono-photo(chemo)therapy of AD [9].

**Table 1** Recommendations for the use of photo(chemo)therapeutic options in the management of atopic dermatitis

| First line regimens | Second line regimens | Third line regimens |
|---|---|---|
| UVA1, NB UVB | UVA/UVB, BB UVA, BB UVB, Bath PUVA | Heliothalassotherapy, Balneophototherapy, Oral PUVA, ECP |

The above suggested recommendations are based on treatment efficacy, safety, availability, practicability, and cost-effectiveness

## Conclusions

The conclusions that may be drawn by interpreting the current literature on the efficacy of photo(chemo)therapy in the treatment of AD are limited by several factors including publication bias, small sample sizes, high variability of parameters used in different studies, and in particular the lack of randomised controlled trials comparing different photo(chemo)therapeutic modalities. Moreover, only few reports of previous controlled studies properly described statistical details including random allocation and power calculations. The quality of previous photo(chemo)therapeutic studies on patients with AD appears to be the best for regimens such as UVA1, NB UVB, and UVA/UVB. The recommendations for the use of photo(chemo)therapeutic options in the management of AD, which have been detailed in Table 1, represent a synthesis of previous data on treatment efficacy, safety, availability, practicability, and cost-effectiveness of photo(chemo)therapeutic modalities for AD. On the basis of the current data [31], newer UV sources, such as medium-dose UVA1 and NB UVB, with a high output and a narrow emission spectrum may be considered the likely most efficacious regimens for treating acute and chronic AD, respectively. There are no comparative studies on AD investigating the efficacy of UVA/UVB compared to NB UVB. However, it has been shown that conventional broader band UV regimens appear to be inferior to medium- and high-dose UVA1. Hence, UVA/UVB may be considered the second choice for the management of AD when compared to UVA1 and NB UVB.

There are no prospective trials on AD patients comparing NB UVB and UVA1 with more complex regimens such as heliothalassotherapy and balneophototherapy. Hence, the role of the latter treatment modalities in the management of AD remains unclear. Therefore, heliothalassotherapy and balneophototherapy have to be considered third line treatment regimens for AD, even though UV spectra used in these regimens are equal or at least similar to UVA/UVB and NB UVB. Support for the role of PUVA in AD is generally weaker as for comparators such as UVA1, NB UVB, and UVA/UVB, and PUVA carries potential risk of

squamous cell carcinoma and possibly melanoma, which may occur years after PUVA therapy has ceased [43]. Because of the relatively weak data on oral PUVA in AD and unfavourable risk-benefit ratio associated with this regimen, oral PUVA is considered a third line treatment options for AD (Table 1). By contrast, the evidence suggests that UVB and UVA phototherapy is a relatively safe treatment modality with regard to photocarcinogenicity [28, 48]. More common side effects associated with photo (chemo)therapy (e.g., UVB, UVA) include skin burning and premature skin aging, which again tend to be worse with PUVA. Bath PUVA, which is associated with less long-term hazards than oral PUVA, may be justified in patients with disabling AD who do not respond to first line photo(chemo) therapeutic regimens (Table 1). ECP is a very expensive treatment modality which is only available in specialized phototherapy units. The quality of previous studies exploring ECP in AD is relatively weak. Therefore, ECP is considered a third line photo(chemo)therapeutic option for AD.

Although photo(chemo)therapy is beneficial in most patients with AD, a small proportion of patients do not tolerate UV which not uncommonly lead to worsening of their condition (photoaggravated AD). Moreover, the heat from some types of lamps (e.g., UVA1) may also trigger the vicious itch-scratch cycle. When photo(chemo)therapy is employed, its use is very much dedicated by the cost-effectiveness, availability, and the practicality of attending the clinic several times a week. Careful planning and patient supervision are crucial to the successful delivery of photo(chemo)therapy.

Related articles recently published in Archives of Dermatological Research (selected by the journal's editorial staff) are [22] and [33].

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