

Review article

Phototherapy in the management of atopic dermatitis: a systematic review

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Background/purpose: Atopic dermatitis (AD) is a common and extremely burdensome skin disorder with limited therapeutic options. Ultraviolet (UV) phototherapy is a well tolerated, efficacious treatment for AD, but its use is limited by a lack of guidelines in the optimal choice of modality and dosing. Given this deficit, we aim to develop suggestions for the treatment of AD with phototherapy by systematically reviewing the current medical literature.

Methods:

Data sources: All data sources were identified through searches of MEDLINE via the Ovid interface, the Cochrane Central Register of Controlled Trials, and a complementary manual literature search.

Study selection: Studies selected for review met these inclusion criteria, as applied by multiple reviewers: controlled clinical trials of UV phototherapy in the management of AD in human subjects as reported in the English-language literature. Studies limited to hand dermatitis and studies in which subjects were allowed unmonitored use of topical corticosteroids or immunomodulators were excluded.

Data extraction: Included studies were assessed by multiple independent observers who extracted and

compiled the following data: number of patients, duration of treatment, cumulative doses of UV radiation, adverse effects, and study results. Data quality was assessed by comparing data sets and rechecking source materials if a discrepancy occurred.

Results: Nine trials that met the inclusion criteria were identified. Three studies demonstrated that UVA1 is both faster and more efficacious than combined UVAB for treating acute AD. Two trials disclosed the advantages of medium dose (50 J/cm²) UVA1 for treating acute AD. Two trials revealed the superiority of combined UVAB in the management of chronic AD. Two additional studies demonstrated that narrow-band UVB is more effective than either broad-band UVA or UVA1 for managing chronic AD.

Conclusion: On the basis of available evidence, the following suggestions can be made: phototherapy with medium-dose (50 J/cm²) UVA1, if available, should be used to control acute flares of AD while UVB modalities, specifically narrow-band UVB, should be used for the management of chronic AD.

Key words: atopic dermatitis; NBUVB; phototherapy; UVA1; UVAB.

Atopic dermatitis (AD) is a common chronic skin disease characterized by severe pruritus. It usually appears in infancy or childhood and may persist into adulthood. First introduced in the 1950s, topical corticosteroids have long been the standard of care for the treatment of AD (1). However, their long term use is limited by the prevalence of adverse effects, including epidermal atrophy, telangiectasias, striae, and systemic absorption leading to suppression of the hypothalamic–pituitary–adrenal axis. These limitations create the need for ‘steroid sparing’ alternative treatments. Non-steroidal therapies of AD include emollients, topical calcineurin inhibitors, antihistamines, and cyclosporine. These treatments again are

limited by lack of efficacy and side effects. Treatment with ultraviolet (UV) phototherapy has been successfully used in the management of this disease and may represent one of the most efficacious, well-tolerated treatments of AD.

In 1978, Morison et al. (2) published one of the earliest reports of UV phototherapy for AD. This study, prompted by the clinical observation that many atopic patients demonstrate appreciable improvement during the summer months, documented the benefits of psoralen photochemotherapy with UVA for patients with AD. This seminal study was followed by many reports on UV phototherapy for AD, but relatively few randomized controlled clinical trials

have been undertaken. Furthermore, there are no evidence-based, standardized therapeutic guidelines for UV phototherapy of AD, making decisions about the optimal therapy to choose, dosing, and the need for maintenance difficult for the clinician. This problem is compounded by the fact that trials actually providing this level of data are unlikely to be undertaken anytime soon.

In an attempt to address this deficiency, we aim to establish recommendations for UV phototherapy of AD by systematically reviewing the current medical literature on the subject.

Methods

Data sources

For this systematic review published guidelines were observed that recommend specific procedures for the conduct of the study. All data sources were identified through computer-assisted searches of electronic databases of medical references, accompanied by complementary manual searches of the literature. In collaboration with a research librarian, the MEDLINE database (via the Ovid Web Gateway interface) and the Cochrane Central Register of Controlled Trials were searched with the following key words: 'atopic dermatitis' and 'eczema' combined via the AND operator to the keyword 'ultraviolet therapy' after all search terms had been exploded by the Medical Subjects Heading (MeSH) thesaurus. Returned results were restricted to clinical trials. The two databases were searched for materials dating from their respective inception through May 2006. These search strategies yielded 35 published reports regarding phototherapy and AD. The references of relevant articles were reviewed as part of a complementary manual search.

Study selection

The titles and abstracts of all reports generated by the search were reviewed by multiple reviewers (N. Bhavani Meduri, Heather Rasmussen, and Heidi Jacobe). Only controlled clinical trials of UV phototherapy for the treatment of AD in human subjects in English were included. Studies limited to hand dermatitis and studies in which subjects were allowed unmonitored use of corticosteroids or immunomodulators were excluded from review. Of the initial 35 reports generated through the search, only nine studies fulfilled the inclusion/exclusion criteria. If a discrepancy arose regarding whether a particular study should be included for review, the full text article was reviewed.

Data extraction

Studies meeting criteria for inclusion were evaluated by three independent observers (B. M., H. R., H. J.) who extracted pertinent data and compiled this information into spreadsheet databases. The following parameters were cataloged for each study: number of patients, duration of treatment, cumulative doses of UV radiation, adverse effects, and study results. Discrepancies were resolved by review of the original manuscript.

Results

Data synthesis

On review of the nine eligible studies, two major investigational themes became evident. One group of studies (3–7) focused on treating severe, acute AD while a second group of studies (8–11) investigated treatments for chronic AD. Among those trials involving patients with severe, acute AD, three (3–7) set out to establish the optimal wavelength for treatment (Table 1 and Table 2) while two (6, 8) focused specifically on dosing regimens for treatment with UVA1 (Table 3). The four studies concerning patients with chronic AD were designed to determine the optimal wavelength for treatment.

UVA1 for the treatment of acute AD (please refer to Table 1)

Phototherapy with UVA1 (wavelength 340–400 nm) represents a relatively new treatment modality for AD. Krutmann et al. (3) demonstrated that high-dose UVA1 therapy (130 J/cm²), as compared with conventional therapy with combined UVA and UVB (UVAB), achieves a more substantial improvement in the severity of symptoms as measured with a scoring system devised by Costa et al. (12). A later study by Krutmann et al. (4) enrolled 53 hospitalized patients with severe, acute AD and randomized them into three treatment groups. One group was treated with high-dose UVA1 therapy, another group received only topical mid-potency corticosteroids, and a third group was treated with UVAB. Phototherapy with UVA1 was shown to be significantly superior to both alternatives after 10 treatments. Finally, von Kobyletzki et al. (5) investigated a novel UVA1 apparatus designed to minimize the enormous heat load generated by traditional UVA1 machines. The so-called UVA1 cold-light was compared with traditional UVA1 and with UVAB in a study involving 120 patients with severe, acute AD. The cold-light UVA1 modality demonstrated superiority to both UVA1 and UVAB for reducing disease severity as measured with

Table 1. UVA1 phototherapy for the treatment of acute atopic dermatitis

	Authors of report		Krutmann et al. (4)			von Kobyletski et al. (5)		
	Krutmann et al. (3)							
	High-dose UVA1 (<i>n</i> = 15)	UVAB (<i>n</i> = 10)	High-dose UVA1 (<i>n</i> = 20)	Topical steroids (<i>n</i> = 17)	UVAB (<i>n</i> = 16)	Medium-dose UVA1 (<i>n</i> = 50)	Medium-dose UVA1 cold light (<i>n</i> = 50)	UVAB (<i>n</i> = 20)
Number of patients	25		53			120		
Treatment regimen	5 times weekly for total of 15 exposures		Daily for total of 10 exposures			5 times weekly for total of 15 exposures		
Cumulative dose of UVA1 (J/cm ²)	1950		1300			750		
Cumulative dose of UVAB	NR (only final doses)		NR (only final doses)			NR (only final doses)		
Side effects	Xerosis and 'uncomfortable feeling' during last 15 min of UVA1 slight erythema after UVAB		'No serious side effects noted'			5 of 50 patients dropped out due to increased pruritus, discomfort, sweating, flares, and infection with conventional UVA1 (no dropouts in UVA1 cold light group) Marked tanning & freckling in both UVA1 groups		

NR, not reported; UV, ultraviolet.

Table 2. UVA1 phototherapy for the treatment of acute atopic dermatitis

	Authors of report		
	Krutmann et al. (3)	Krutmann et al. (4)	von Kobyletski et al. (5)
Results	Baseline Costa Score: ~ 52 Overall Costa Score after therapy: UVA1: 14 UVAB: ~ 37 Reductions were statistically significant 50% of effect noted by first 6 exposures	Baseline Costa Score: ~ 56–60 Overall Costa Score after therapy: UVA1: ~ 27 TS: 35 UVAB: 42 Reductions were statistically significant Most of effect seen in first week of treatment	Baseline SCORAD: ~ 70 SCORAD after therapy (SCORAD at one month follow-up): UVA1c: 23.3 (24.9) UVA1: 28.8 (30.8) UVAB: 41.4 (52.3) 30% of SCORAD reduction noted by end of first week

TS, topical steroids; UVA1c, UVA1 cold light.

Table 3. Dosing regimen of UVA1 for treatment of acute atopic dermatitis

	Authors of report	
	Tzaneva et al. (6)	Kowalick et al. (3, 4)
	High-dose UVA1 (130 J/cm ² or 1 MED)	Medium-dose UVA1 (half of high-dose)
		Medium-dose UVA1 (50 J/cm ²)
		Low-dose UVA1 (10 J/cm ²)
Number of patients	10 patients (half-body comparisons) Control: shielded buttocks	22 patients (11 patients in each group)
Treatment regimen		5 times weekly for 3 weeks
Cumulative dose of UVA1 (J/cm ²)	1710	750
Side effects	No serious side effects; painless erythema, moderate heat sensation	Not reported
Results	Baseline modified SCORAD: ~ 67 SCORAD after treatment: High-dose UVA1: 34.7% reduction Medium-dose UVA1: 28.2% reduction No report of complete clearance Rapid response in first week	Baseline modified SCORAD: ~ 64 SCORAD after treatment: Medium-dose UVA1: 47 Low-dose UVA: 60 No report of complete clearance Rapid response after 10 treatments in medium-dose group
Follow up	6 months Six of seven patients reported relapse by 12 weeks No half-side differences at follow-up	Not reported

UV, ultraviolet.

the SCORAD (13) system immediately after treatment for 3 weeks and at 1 month follow-up evaluations. In all three studies, most of the effect of UVA1 phototherapy was observed early in the course of treatment.

Comprehensive analysis of these three studies is limited by the fact that different doses, dosing regimens, and clinical scoring systems were used. Furthermore, no long-term follow-up or investigations into maintenance treatments were performed. Nonetheless, several important trends emerged. First, phototherapy with UVA1 achieves results faster than conventional UVAB when treating acute AD (UVA1 peak response after 10 treatments). UVA1 is also more efficacious than either UVAB or topical corticosteroids for managing acute AD. Because no long-term follow-up was reported, this conclusion can only be applied in the weeks to months following treatment. Finally, cold-light UVA1 is slightly superior to traditional UVA1 in reducing the severity of acute AD as measured immediately after treatment and 1 month later.

Dosing regimen of UVA1 for treatment of acute AD

Only two trials (6, 7) eligible for review specifically compared alternative phototherapy dosing regimens. Both of these trials set out to establish the optimal dosing schedule for UVA1 treatment of severe, acute AD. UVA1 phototherapy may be administered in high doses (130 J/cm²), medium doses (50 J/cm²), or low doses (10 J/cm²). Tzaneva et al. (6) enrolled 10 patients in a study to compare high-dose UVA1 to medium-dose UVA1. 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. To exclude the possibility of systemic effects of the phototherapy, the buttocks were shielded to prevent UV exposure. After 3 weeks of treatment (total 15 treatments), both

high-dose and medium-dose regimens achieved similar results as indicated by reductions in SCORAD scores (34.7% and 28.2% reductions, respectively). There was no statistically significant difference demonstrated between the two regimens. Moreover, relapses appeared soon after treatment (median time of 4 weeks) regardless of the dosing regimen employed. Kowalick et al. (7) 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 SCORAD scores after 3 weeks of treatment, while the low-dose regimen achieved only a 7.7% reduction. As with prior studies (3–5), most of the therapeutic results in both of these trials were achieved early in the course of treatment. The vast majority of results were observed after the first week of treatment (at five treatments per week) (6, 7).

UV phototherapy for chronic AD

Although UVA1 appears to be a better choice for acute AD based on the available evidence, no extrapolations can be made regarding its role in managing chronic AD. Several controlled clinical trials (8–11) have been conducted to determine the optimal wavelength of UV phototherapy for patients with chronic AD. In two separate paired-comparison studies (8, 9), Jekler and Larkö investigated the use of UV radiation for treating chronic AD (Table 4 and Table 5). Their first study (8) compared UVB to combined UVAB phototherapy. Thirty patients were treated with UVAB on one side of the body and with UVB on the contralateral side, with right-side and left-side assignments determined randomly. Statistically significant differences in favour of combined UVAB were demonstrated for three important parameters: pruritus score, overall evaluation score, and total score

Table 4. UV phototherapy for the treatment of chronic atopic dermatitis

	Authors of report			
	Jekler and Larkö (9)		Jekler & Larkö (8)	
	UVB vs. UVAB (paired comparison)	UVA vs. UVAB (paired comparison)	UVB	UVAB
Number of Patients	18	25	30 (paired comparison)	
Treatment regimen	3 times weekly for 8 weeks or until clearance	5 times weekly for 3 weeks or until clearance	3 times weekly for 8 weeks or until clearance	
Cumulative dose UVA (J/cm ²)	NA	361	NA	NA
Cumulative dose UVB (mJ/cm ²)	282	NA	NR	NA
Cumulative dose UVBA (mJ/cm ²)	558/130	466/109	NA	NR

NA, not applicable; NR, not reported; UV, ultraviolet.

Table 5. UVB phototherapy for the treatment of chronic atopic dermatitis

	Authors of report		
	Jekler & Larko (8)	Jekler and Larko (9)	
	UVB	UVAB	UVB vs. UVAB (paired comparison)
Results	Total score, pruritus score, and overall evaluation score with statistically significant improvement favoring UVAB over low-dose UVB No difference in reduction of extent of dermatitis 23 of 24 patients preferred UVAB and 14 of 25 patients thought it more effective		Total score, overall evaluation score, pruritus score, and healing score all with statistically significant improvement favoring UVAB over low-dose UVB 14 of 18 patients preferred UVAB and 16 of 18 patients thought it more effective
			UVA vs. UVAB (paired comparison)
			Total score, overall evaluation score, and healing score with statistically significant improvement favoring UVAB over low-dose UVB No difference in pruritus score 11 of 16 patients preferred UVAB and 18 of 25 patients thought it more effective

UV, ultraviolet.

Table 6. Narrow-band (NBUVB) phototherapy for the treatment of chronic atopic dermatitis

	Authors of report		
	Reynolds et al. (10)	Legat et al. (11)	
	NBUVB	BBUVA	NBUVB
			Medium-dose UVA1
Number of patients	69 (<i>n</i> = 22 in control group)	23	9 (paired comparison)
Treatment regimen	Twice weekly for 24 exposures visible light served as control	24	Three times weekly for 8 weeks UVA1 started at 10 J/cm ² and increased to 50 J/cm ² by 5th treatment
Cumulative NBUVB dose (J/cm ²)	24.8	NA	26.7 (median value)
Cumulative UVA dose (J/cm ²)	NA	315	NA
			1000

NA, not applicable; UV, ultraviolet.

(the sum of all measured variables) (8). No difference was seen with respect to the extent of dermatitis as calculated by body surface area. The second trial by Jekler and Larkö (9) enrolled a total of 43 patients into two treatment arms. One group of patients received low-dose UVB on one half of the body and combined UVAB on the contralateral side, while the second group was treated with UVA and combined UVAB in a similar fashion. Statistically significant results in favour of UVAB were again demonstrated in both study arms as measured by healing score, overall evaluation score, and sum total score. Of note, neither paired comparison trial by Jekler and Larkö used a control method (i.e. partial body shielding), so the possibility of a systemic rather than local effect of UV radiation cannot be excluded in either study (although other studies consistently fail to detect a systemic effect from these modalities).

Two later trials (10, 11) further investigated the optimal wavelength of UV radiation for treating chronic AD by comparing narrow-band UVB (NBUVB, wavelength 311 nm) to UVA modalities (Table 6 and Table 7). Reynolds et al. (10) enrolled a total of 69 patients, randomizing them into three separate treatment groups. One group received NBUVB, another group received broad-band UVA, and a third group was treated with visible fluorescent light to serve as a control. Although patients in this trial were allowed to use mid-potency topical corticosteroids, their use was quantified and considered as part of the evaluation of treatment efficacy. While trends supportive of the superiority of NBUVB were seen in most measured parameters, statistically significant differences in favor of NBUVB over UVA were only demonstrated for the mean reduction in extent of disease, patient-reported pruritus, and pa-

Table 7. NBUVB phototherapy for the treatment of chronic atopic dermatitis

	Authors of report	
	Reynolds et al. (10)	Legat et al. (11)
Results	Compared to visible light (control group) Mean Reduction in Total Disease Activity: 9.4 points with NBUVB 4.4 points with BBUVA Mean Reduction in Extent of Dermatitis 1.0% for BBUVA 6.7% for NBUVB Moderate improvement or greater after treatment: 38% of NBUVB 16% of BBUVA Patient-reported reduction in pruritus: 38% of NBUVB patients 11% of BBUVA patients Patient-reported improvement in sleep: 35% of NBUVB patients 16% of BBUVA patients	Reduction from baseline had to be >40% to be statistically significant. Reduction in COSTA Score: 40% reduction with NBUVB No statistically significant reduction with UVA1 Patient evaluation of reduction in disease severity: 71% reduction with NBUVB 40% reduction with UVA1 Pruritus score: No statistically significant changes in either group Patient Preferences: Patients did not indicate a preference for one form UV radiation over the other
3 month follow-up	36% more of the patients in the NBUVB group had lower total disease activity scores as compared to other groups. 32% more of the patients in the NBUVB group had moderate improvement or greater compared to visible light.	

NBUVB, narrow-band UVB; UV, ultraviolet.

tient-reported improvement in sleep. The advantage of NBUVB as determined by the mean reduction in total disease activity was statistically significant when compared with visible light but not to UVA. However, on follow-up evaluation 3 months after phototherapy, patients treated with NBUVB showed statistically significant improvement in disease activity as compared to those treated with either UVA or visible light. A more recent study conducted by Legat et al. (11) confirmed the advantages of NBUVB for treating chronic AD. This relatively small trial compared NBUVB to medium-dose UVA1 via half-side comparison in nine patients with chronic AD. Treatment with NBUVB reduced Costa scores by 40% while treatment with UVA1 did not achieve any statistically significant reductions. Furthermore, patients reported notably more improvement in disease severity with NBUVB. Taken together, these two trials imply NBUVB is a better option for the treatment of chronic AD.

Discussion

AD is a burdensome, chronic disorder with frequently inadequate therapeutic options. Phototherapy may represent a safe, efficacious option in the treatment of these patients, but there is no evidence-based, standardized protocol, impairing clinical decision making in the choice of optimum therapies for individual patients. In an attempt to address this deficit, we conducted a systematic review of the currently

published literature in order to create evidence-based treatment suggestions for UV phototherapy of AD.

The conclusions that may be drawn by systematically analyzing the current medical literature regarding phototherapy and AD are limited by several factors. First, as with any systematic review, publication bias must be considered. Trials yielding positive results are more likely to be published (14). Also, the small sample sizes of most of the trials make for poor statistical power and rarely disclose any uncommon adverse effects (14). The variability of the parameters used in different trials must be taken into consideration. Different methods for patient selection, administering and dosing UV radiation, and assessing the clinical response restrict our ability to draw detailed conclusions through a comprehensive review of available studies. Another limitation is the lack of trials meeting our inclusion criteria that examine combination therapy or maintenance therapy. Furthermore, these studies did not include children, hence we are unable to draw conclusions for paediatric AD patients. As a result, we are only able to make general recommendations about which phototherapy modality is appropriate for certain adult patients depending on clinical stage of disease and dosing recommendations for UVA1 therapy.

First, phototherapy with UVA1 is probably the most efficacious modality for treating acute AD, when it is available. Because medium-dose therapy (50 J/cm²) is as effective as high-dose therapy (130 J/

cm²) with less cumulative radiation exposure, medium-dose constitutes the optimal fluence for UVA1 phototherapy of acute AD. In addition, the maximal clinical response usually occurs within 2 weeks (or about 10 treatments) of beginning UVA1 phototherapy. Therapeutic response to UVA1 should not be expected to persist beyond 2 or 3 months. Therefore, UVA1 may be ideal for flaring AD patients in which rapid control is desired. The short-lived duration of response indicates that a plan for maintenance treatment with topical steroids, NBUVB, or with other modalities should be in place at the time UVA1 is discontinued. At this time, no recommendations can be made for the optimal maintenance regimen after UVA1 phototherapy for AD.

Phototherapy with UVB modalities, particularly NBUVB, should be used to manage chronic AD. In the absence of data specifying the most favourable dosing protocols, we anticipate that clinicians will extrapolate from guidelines for managing psoriasis when treating chronic AD with UVB phototherapy. In addition, these recommendations are limited by the fact that AD cannot usually be separated into acute and chronic phases, and no guidelines exist for this classification scheme. Furthermore, at this time the availability of UVA1 light sources is relatively limited. The most definitive conclusion is that phototherapy (any wavelength) is a valid therapeutic option for AD. This arrangement is suboptimal and highlights the need for further investigation.

To allow for cross-comparison and comprehensive review, standardized trial protocols should be instituted. If future studies employ standardized dosing regimens, cumulative exposures, UV wavelengths, and patient evaluation methods, we anticipate that comprehensive therapeutic guidelines could be established by systematically considering all study results.

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