

LIGHT TREATMENT MODALITIES FOR ATOPIC DERMATITIS

Elma D. Baron, MD, and Seth R. Stevens, MD

Treatment of atopic dermatitis (AD) has been an ongoing challenge to clinicians. An increase in its worldwide prevalence has been observed over the last decade.^{60, 61, 65} The multifactorial nature of this disease is now well known, and studies have provided a better insight into the various pathogenic mechanisms behind this chronic dermatosis, particularly the immunologic events that account for the persistent inflammation that is characteristic of eczematous lesions.^{31, 55} Consequently, therapeutic options geared toward many of these contributory mechanisms have been investigated, yielding diverse clinical outcomes.^{31, 47} Standard therapy with anti-inflammatory agents such as topical corticosteroids, together with proper skin care and avoidance of aggravating factors, remains the most logical initial approach (see article by Boguniewicz and Nico elsewhere this issue). In a significant number of cases, however, the condition persists into adulthood and follows a chronic course with periods of exacerbations and remissions. Adjuvant therapy with another modality, such as phototherapy, may become necessary at some point in the disease process.

DEVELOPMENT OF ULTRAVIOLET LIGHT AS TREATMENT FOR ATOPIC DERMATITIS

The solar ultraviolet (UV) light spectrum is divided into three major portions (Fig. 1): UVC (200–290 nm), UVB (290–320 nm), and UVA

From the Skin Study Center, Department, of Dermatology University Hospitals Research Institute, Case Western Reserve University (EDB, SRS); and the Louis Stokes Veterans Administration Medical Center (SRS), Cleveland, Ohio

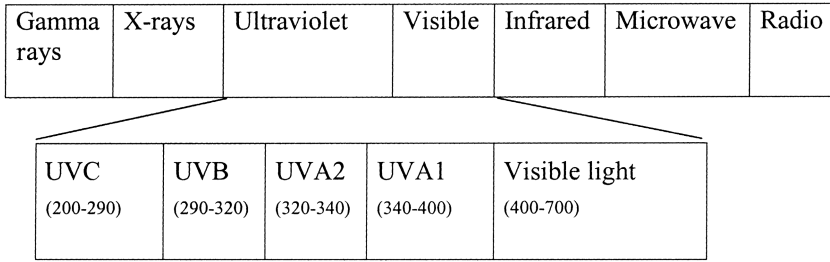


Figure 1. The UV light wavelengths within the electromagnetic spectrum.

(320–400 nm). Because UVC is filtered by the ozone layer, only solar UVB and UVA are capable of contributing to biologic effects in humans. In the practice of phototherapy, UVB and UVA have important functions. UVA has been divided further into UVA2 (320–400 nm) and UVA1 (340–400 nm).

Jekler provided a brief historical background on the use of UV light for treating AD.¹⁴ In the early 1900s, sunlight was believed to aggravate atopic dermatitis, and the potential aggravation of AD by natural sunlight exposure still is acknowledged. In 1929, however, the German dermatologist Buschke reported that the effect of sea climate on atopic dermatitis was “simply surprising.” By the 1940s, Lomholt and Norrlind observed general improvement in their patients in the summer months. In 1948, after interviewing patients with atopic dermatitis, Nexmand found that 54% of patients improved in the summer. He was the first to conduct an experiment, on 57 patients, using a carbon arc lamp, which resulted in 17.5% of patients with clearing and 40.4% with improvement. Studies using fluorescent UV lamps began in the 1970s, which led to greater appreciation of UV light as a useful treatment for AD. Psoralen plus ultraviolet A (PUVA) and broadband UVB, which were being used for psoriasis at the time, likewise were found effective for AD. Over the past decade, newer light sources with more selective wavelengths, namely narrowband UVB (311 nm) and UVA1 (340–400 nm), have been shown to be effective modalities.^{23, 28, 48} The effects of UVA1 in particular provide further understanding of the immunologic processes present in AD.²⁴ The possible role of extracorporeal photopheresis (ECP) also has been investigated.^{34, 42–44}

SPECIFIC PHOTOTHERAPEUTIC MODALITIES FOR ATOPIC DERMATITIS

UVA1

UVA1 (340–400 nm) has been effective in controlling acute severe exacerbations of AD (Table 1). In the initial pilot study by Krutmann et

Table 1. PHOTOTHERAPEUTIC MODALITIES FOR ATOPIC DERMATITIS

Indication	Modality	Comment	Sample Protocol
Acute/severe	High-dose UVA1	Only phototherapy proven effective as monotherapy	130 J/cm ² daily for 10–15 treatments
	PUVA	Long-terms risks may outweigh benefits	Oral 8-MOP at 0.5 mg/kg, UVA starting dose is Fitzpatrick skin type (FST) dependent or 70% minimum phototoxic dose (MPD); treat 3 times/wk, increase by 0.5–1.0 J/cm ² per treatment
	ECP	Promising results, but procedure is expensive and randomized trials are lacking	Oral 8-MOP at 0.5 mg/kg (or directly added liquid 8-MOP); UVA at 2 J/cm ² ; treat for 2 consecutive days every 2 weeks, then taper
Chronic/moderate	NB-UVB	Highly effective and has potential for long-term remission	Start at 70% MED, treat 3 times/wk, increase by 20%, 10%, 0% based on erythema response
	UVA and UVB	Photoaugmentative effect makes it more effective than broadband UVB alone	Start UVA at 5 J/cm ² , increase by 5 J/cm ² per treatment and hold at 20 J/cm ² ; give UVB as in NB-UVB protocol
	Broadband UVB	May be effective but has high incidence of acute side effects	Similar to NB-UVB protocol
	Low-dose UVA1	May be effective, but there is no prolonged remission	50 J/cm ² daily for 15 treatments
	Bath PUVA	Preliminary results show benefit, but procedure is inconvenient	Soak for 20 minutes in 0.0003% 8-MOP bath solution; immediately give UVA at 70% MPD, increase by 0.5–1.0 J/cm ² per treatment

al,²⁷ high-dose UVA1 phototherapy (130 J/cm²/d × 15 days) was compared with combination UVA and UVB therapy. Patients were assessed based on clinical scores of atopic dermatitis (SCORAD) and serum levels of eosinophil cationic protein, a marker that previously was shown to correlate with disease activity in AD.⁴ UVA1 treatment induced improvement more promptly than UVA and UVB therapy. A 50% reduction in severity was observed after six treatments with UVA1. Such a level of improvement was not observed in the UVA and UVB group, even after 15 treatments. Clinical response to UVA1 correlated with a reduction in the serum eosinophil cationic protein level. In a subsequent multicenter

trial, a total of 53 patients received either UVA1, UVA and UVB, or topical fluorocortolone for 10 days.²⁶ At day 10, UVA1 was superior to topical steroid in terms of clinical score, and UVA1 and topical steroid exceeded UVA and UVB in clinical efficacy.

The risk of carcinogenesis from long UVA wavelengths has been shown in a study in which pigmented, hairless mice developed squamous cell carcinomas after exposure to UVA1 in high doses.⁵⁸ In view of this risk and the fact that high-dose therapy is time consuming and often uncomfortable because of the large amount of heat generated by the light source, studies were done to determine the efficacy of low-to-medium doses. von Kobyletzki et al demonstrated that UVA1, delivered at a dose of 50 J/cm²/d for 15 days through a cold light source, was also more effective than UVA and UVB.⁵⁹ Significant clearance on day 15 was found in 41 (85.4%) out of 48 patients on UVA1 as opposed to 6 (37.5%) out of 16 patients in the UVA and UVB group. There was no significant recurrence during the 4-week follow-up period. Unfortunately, time-to-relapse information was not provided. Abeck et al¹ also investigated the efficacy of medium-dose UVA1 therapy. Their patient population experienced a significant reduction of symptoms, but none had complete clearing after 15 days of treatment. Although no relapse was noted within a month, a recurrence of symptoms to pretreatment levels was seen in all patients after 3 months. It was concluded that maintenance therapy with low-dose UVA1 or some other modality is essential. Whereas medium-dose UVA1 performed better than UVA and UVB, low-dose UVA1 (20 J/cm²) was found to be inferior to UVA and UVB therapy.²²

Risks and Side Effects

Few adverse effects have been reported from UVA1 phototherapy. Eczema herpeticum has been observed, prompting temporary discontinuation of treatment.²⁶ It is unclear if this is directly related to the phototherapy. Heat and sweating, which are known trigger factors in some patients with AD, are common complaints of patients on high-dose therapy. Hyperpigmentation of treated sites may be pronounced but is reversible over several weeks to months.

Photoaging,³⁰ carcinogenesis,⁵⁸ and melanoma induction⁴⁶ are risks associated with the long UVA spectrum. As mentioned previously, squamous cell carcinomas were noted on pigmented, hairless mice after exposure to high doses of UVA1.⁵⁸ Lavker noted that the spectrum for dermal damage in the UVA range is broad and extends up to 400 nm.³⁰ Setlow et al reported that this wavelength also can induce malignant melanomas.⁴⁶

Indications and Contraindications

Ultraviolet A1 therapy is beneficial for short periods to treat severe acute exacerbations of AD. High-dose treatment should be limited to a

maximum of 15 individual exposures per treatment course with no more than two courses in 1 year.²³ Its role in maintenance therapy is uncertain. Likewise, its usefulness and safety in children have not been explored, and it is not recommended for individuals less than 18 years of age. Medium-to-low doses may be used in mild-to-moderate AD. Adjuvant treatment with topical steroid is needed with low doses because UVA1 is not effective as a monotherapy at low levels.

UVA1 should not be used in patients with photosensitive AD or patients with primary idiopathic photodermatoses such as polymorphous light eruption. Caution must be taken when treating patients who receive systemic medications that are phototoxic or photosensitizing within the long UVA spectrum.

Systemic Psoralen plus Ultraviolet A

Oral psoralen-UVA photochemotherapy (PUVA) is effective in clearing acute exacerbations of AD. In 1978 Morison et al conducted a study of 15 adult patients with AD who were divided into the following three groups: (1) whole-body PUVA, (2) bilateral comparison of PUVA versus no treatment, and (3) bilateral comparison of PUVA versus UVB.³⁵ PUVA resulted in 99% clearance after 20 to 58 treatments in group 1, 95% clearance in 12 to 21 treatments in group 2, and 95% clearance in 7 to 12 treatments in group 3. The authors likewise observed a significantly greater decrease in pruritus and nail dystrophy among PUVA-treated sites. They noted, however, that regular therapy is required to maintain remission. Their findings also indicated that an average of 36 whole-body PUVA treatments was necessary to induce 99% clearance, which was almost twice the number of treatments required to treat psoriasis.⁴¹ A more aggressive maintenance protocol is essential for AD. Atherton et al found PUVA to be effective in inducing remission in 9 out of 15 adolescents with severe AD over 12 to 25 weeks.² Their study showed that high exposures were needed to clear and maintain these patients. The main benefit of PUVA in their population was restoration of normal growth patterns because of the consequent decrease in systemic steroid intake.

Risks and Side Effects

A number of side effects are associated with PUVA. Patients with AD who are treated with PUVA have experienced nausea, herpes infection, blepharitis, photo-onycholysis, and PUVA freckles.^{2, 35} Although neither life threatening nor debilitating, these side effects need to be addressed appropriately. The exception is eczema herpeticum, which would require systemic antiviral therapy.

Of utmost concern is the well-established risk of skin cancer among PUVA-treated individuals.⁵¹⁻⁵⁴ It has been documented that PUVA, especially at high cumulative doses, causes an increase in nonmelanoma skin

cancers,^{52, 53} genital tumors in males,⁵¹ and possibly melanoma.⁵⁴ The risk is greater for pediatric patients who need prolonged courses of therapy, which predisposes them to high cumulative doses over their lifetime. Risks related to the systemic administration of 8-methoxypsoralen (8-MOP), such as early cataract formation and prolonged ocular and cutaneous photosensitivity, are also present. Particular care must be taken with PUVA administration. PUVA-induced phototoxic reactions are more painful and last longer than burns caused by UVB. PUVA-induced phototoxic reactions become maximal at 72 hours; patients may receive subsequent treatment on top of an already excessive dose, further compounding the adverse effect.

Indications and Contraindications

Psoralen plus ultraviolet A is effective in clearing severe acute exacerbations of AD. Unfortunately, it can result in a rebound phenomenon once it is discontinued.³⁵ Its benefit as a long-term therapy must be weighed against its carcinogenic potential. Although its use as monotherapy can restore normal growth patterns in children and adolescents treated with systemic steroids, its safety in the long term is controversial. Although data regarding teratogenicity are lacking, PUVA is not recommended for pregnant women. It should be used with caution in individuals with photoaggravated conditions.

Topical Psoralen Plus Ultraviolet A

Data regarding the use of topical PUVA for AD are scarce. Because xerosis already is pronounced in AD, it is reasonable to suspect that the frequent soaking involved in bath PUVA might aggravate the condition. Three small studies, however, seem to indicate otherwise. Luftl et al demonstrated complete remission in three out of four patients with severe, recalcitrant AD after a mean of 18 treatments and a mean cumulative UVA dose of only 15 J/cm².³² Der-Petrossian et al found bath PUVA to be equally effective as narrow-band UVB (NB-UVB), resulting in a mean SCORAD score reduction of 65.7% in 10 patients in 6 weeks or less, without causing any serious adverse reactions.⁶ de Kort and van Weelden demonstrated an average improvement of 82.1% among 29 patients with AD after a maximum of 30 bath PUVA treatments.⁵ Topical PUVA with the use of 0.3% 8-MOP ointment also has been effective in AD. Ogawa and Yoshiike reported clearing in 50% of hospitalized patients treated daily and in 25% of outpatients treated weekly.³⁹

Risks and Side Effects

Topical PUVA has a better safety profile than its systemic counterpart. Nausea, which occurs in about 20% of patients who orally ingest psoralen, is avoided. The low-to-absent serum levels of psoralen through

topical delivery obviates the need for prolonged photoprotection of the eyes and skin. Based on studies involving patients psoriasis with who underwent bath PUVA therapy, the risk of carcinogenesis is not significantly different from the general population after a mean follow-up time of 14.7 years.¹² This observation, however, needs to be confirmed in future investigations because the number of patients with high UVA exposures was low compared with oral PUVA studies, in which an increased risk of skin cancer was seen after about 200 treatments.⁵³ In general, topical PUVA uses lower cumulative UVA doses than systemic PUVA.^{32, 39}

Similar to other forms of phototherapy, erythema and phototoxic side effects may occur with topical PUVA. Hyperpigmentation of lesions has been reported with the use of 8-MOP ointment, probably because of an increased absorption at these sites or uneven application of the medication. Bath PUVA affords a more uniform delivery of psoralen, but because photosensitization is accomplished by soaking for 15 to 20 minutes, lesions on the head and face cannot be treated using this modality. Because of the rapid decrease in skin psoralen levels after exiting the bath, bathing usually is performed in the phototherapy clinic, and many phototherapy centers consider this bathtub requirement impractical. This procedure also necessitates longer visits, which many patients find impractical.

Indications and Contraindications

The scarcity of data prevents the establishment of exact indications for this treatment. It remains an option for patients who cannot tolerate oral 8-MOP and patients without access to the newer modalities (e.g., UVA1 and NB-UVB). It is not recommended in children, and its safety in pregnancy is unknown.

Combination

Ultraviolet A and ultraviolet B therapy is beneficial in the treatment of mild-to-moderate AD in combination with topical steroids. In their comparison of UVA and UVB versus UVB alone, Midelfart et al demonstrated that although the number of treatments to induce clearing was approximately the same, UVA and UVB resulted in a significantly increased percentage of remissions.³³ In Falk's study, 94% of UVA and UVB patients achieved clearing in 18 treatments, whereas 84% of UVB patients cleared after 23 treatments.⁸ The difference was statistically significant. Although the reported improvement rates were high, the 3-month relapse rate was 52% for UVA and UVB and 68% for UVB alone, indicating that maintenance is required with either treatment. Both therapies diminished use of topical steroids. Episodes of erythema caused by overexposure were more common in UVB groups. Jekler and Larko, in a bilateral comparison of UVA and UVB and UVB alone in 30 patients,

demonstrated that although healing rates were the same between the two groups, the total clinical score, pruritus score, overall evaluation, and patient preference favored UVA and UVB therapy.¹⁷ Side effects such as xerosis and burns occurred with both treatment but were more pronounced with UVB therapy. Polymorphous light eruption and folliculitis were observed only in UVB-treated sides. Concomitant use of topical steroids was not prohibited in any of these trials.

Risks and Side Effects

Xerosis and minor burns have been reported.¹⁷ Theoretically, this combination treatment also predisposes the patients to risks inherent in each spectrum. There are no data regarding the actual carcinogenic potential of UVA and UVB treatment. It is considered safe than PUVA therapy.

Indications and Contraindications

Ultraviolet A and ultraviolet B therapy is effective when used in combination with topical steroids in patients of all ages with mild-to-moderate AD. Problems may arise among patients with photo-induced or photo-aggravated eruptions sensitive to UVA, UVB, or both.

Narrow-Band Ultraviolet B

Narrow-band UVB (311 nm), or UVB 311, originally was used for psoriasis and has shown efficacy in the treatment of AD. Like UVA and UVB, it is most beneficial when given in conjunction with other agents such as topical steroids. George et al delivered treatments with an air-conditioned NB-UVB unit, 3 times a week for 12 weeks in 21 patients with severe AD and found an average 68% decrease in severity score and 88% decrease in use of potent topical steroids.⁹ Follow-up evaluation at 6 months revealed a relapse in only six patients. Fifteen patients continued to demonstrate long-term benefits, and their steroid use was maintained 50% below prephototherapy needs. This study has the longest reported remission period as a result of phototherapy. The resolution of pruritus was dramatic and was evident within the first 2 weeks of therapy. Even with a non-air-conditioned unit, Hudson-Peacock et al treated 37 patients aged 5 to 71 years with severe AD and obtained good results with a twice-weekly schedule.¹³ They reported clearance in 43% of patients, improvement in 38%, no change in 14%, and deterioration in 5%. Significant improvement was noted after five exposures. Grundmann-Kollman et al reported a series of five patients with moderate-to-severe AD who showed a significant response in 3 weeks and complete clearing after 4-1/2 weeks of NB-UVB therapy.¹¹ No relapse was observed in the 8-week follow-up period. In a randomized investigator-blinded half-side comparison study of NB-UVB versus bath PUVA, both

treatments induced complete remission or marked improvement in 9 out of 10 subjects with severe chronic AD, with no serious adverse reactions to either regimen.⁶

Risks and Side Effects

Episodes of mild-to-moderate erythema, folliculitis, xerosis, herpes labialis, and eczema herpeticum have been reported among patients with AD on NB-UVB.^{3, 6, 9, 11, 13} The risk of developing skin cancer has not been established but is believed to be much lower than with PUVA. If carcinogenicity is related to erythemogenicity, NB-UVB should be safer than broadband UVB.⁵⁰ When given in equierythemogenic doses to experimental animals, however, induction of NB-UVB skin cancer was found to occur faster than with broadband UVB.⁶⁴

Indications and Contraindications

NB-UVB therapy is ideal for mild-to-moderate AD in conjunction with other therapies such as topical steroids. There is preliminary evidence that it might induce a prolonged remission period.¹¹ Although it is relatively new and data regarding long-term safety in humans are not available, it is considered appropriate for use in children and pregnant or lactating women.

Broadband Ultraviolet B

Conventional broadband UVB (320–400 nm) therapy is an effective adjuvant therapy for mild-to-moderate AD. Jekler and Larko, in a bilateral comparison of 17 patients who received treatment 3 times a week for 8 weeks, showed that UVB was more effective than visible light (placebo) in clearing the skin lesions of AD.¹⁹ Data regarding long-term efficacy were not provided. The same group of investigators compared the effect of 0.4 minimum erythema dose (MED) versus 0.8 MED and found no significant difference in the 25 treated patients.¹⁹ The calculated, erythemally effective dose of UVB required to clear AD was found to be less than the median dose necessary to clear psoriasis.¹⁶ A paired comparison study of UVA and UVB given thrice weekly for 8 weeks showed the former modality to be superior when the total clinical scores were analyzed.¹⁸ UVA was administered at an initial dose of 7, 9, or 11 J/cm² depending on skin type, and the dose was increased by 2 J/cm² every treatment and held at a maximum dose of 15 J/cm²; a standard MED-based protocol was used for UVB therapy. The two modalities were equal in overall healing rates and antipruritic effects. The major advantage of UVB over UVA therapy was the shorter duration of treatment sessions. A study conducted among children also suggests the efficacy and safety of broadband UVB in this population.⁵⁶ Tay et al's series of five pediatric patients with AD (mean age, 7 years) demon-

strated that an average of 41 treatments resulted in a significant reduction in pruritus and the amount of topical steroid use, although none of the patients achieved complete clearing.⁵⁶ A device that provides skin reflectance measurements to detect areas of active inflammation has been employed to guide UVB radiation dosimetry, resulting in decreased cumulative doses without compromising efficacy.⁶³ Side effects such as burns, xerosis, and inflammation of treated sites also were minimized.

Risks and Side Effects

Although UVB causes DNA photoadduction and thymine dimer formation, it generally is accepted that the risk of carcinogenesis from UVB is less than that from PUVA.⁴⁹ Larko et al showed no significant increase in the incidence of nonmelanoma skin cancers among patients who received 101 to 785 (mean, 249) UVB treatments for psoriasis, compared with a matched control group.²⁹ The follow-up interval ranged from 0 to 25 years. Because patients with psoriasis usually receive higher cumulative doses, a better safety profile might be necessary for patients with AD. Because broadband UVB contains the shorter and more erythemogenic wavelengths, there is a high incidence of erythema from overexposure and xerosis of the skin, which may result in further scratching and aggravation of the primary condition. Herpes infections and folliculitis also have been reported.¹⁹

Indications and Contraindications

Patients of all ages with mild-to-moderate AD may benefit from UVB therapy in conjunction with other treatments (e.g., topical steroids). Intake of systemic agents known to be photosensitizing or phototoxic within the UVB spectrum, such as sulfones and certain diuretics, warrants proper dose adjustments or temporary discontinuation of phototherapy. This therapy seems to be safe in children and pregnant or lactating women.

Extracorporeal Photopheresis

Extracorporeal photopheresis is an apheresis-based procedure that allows extracorporeal exposure of peripheral blood mononuclear leukocytes to UVA radiation in the presence of previously ingested or externally administered 8-MOP. Although developed for the treatment of cutaneous T-cell lymphoma, it has shown efficacy in treating a variety of immunologic disorders, including AD.⁴⁵ Prinz et al treated three erythrodermic patients with AD with ECP every 4 weeks for 6 to 12 months and observed improvement after the second treatment cycle.⁴³ Adjuvant therapy other than topical steroids was not allowed. ECP was continued at progressively longer intervals to maintain remission. Response to ECP was found to correlate with a decrease in previously

elevated levels of serum IgE. Richter et al administered ECP as monotherapy every 2 weeks for 20 weeks to three patients with AD refractory to glucocorticoids, cyclosporine, UVB, and PUVA.⁴⁴ All patients showed improvement based on clinical scores. In addition to a decrease in IgE level, a reduction in the serum eosinophil cationic protein level was noted after 10 ECP treatments. The largest published study on ECP for AD involved 14 patients with severe, recalcitrant disease, some of whom were erythrodermic.⁴² Extracorporeally administered liquid 8-MOP was used. This method offers the advantage of assuring adequate levels of the photosensitizer during irradiation and a reduced total dose given to patients. Complete remission was achieved in 29% of patients, and significant improvement, defined as 75% clearing, occurred in 36%. Another 7% of the study population had 50% improvement, and only four patients were found to be unresponsive to ECP. Full therapeutic response was observed after six treatment cycles. Improvement was relatively stable, allowing prolongation of ECP cycle intervals to 6 to 12 weeks. The four nonresponders demonstrated an increase in serum IgE levels after ECP. Their baseline CD4-CD8 ratios were normal and increased during the treatment period. The majority of responders exhibited a decrease in serum IgE level and a reduction or normalization of previously elevated CD4/CD8 ratios in peripheral blood. Although preliminary, these laboratory findings may serve as predictors of responses to ECP. The benefit of ECP on the objective skin severity and quality of life of a patient with severe AD who was recalcitrant to methotrexate, cyclosporine, azathioprine, IFN- γ , PUVA, and UVA and UVB phototherapy has been documented in a case report.³⁴

Risks and Side Effects

The studies mentioned previously did not report any adverse effects except for nausea secondary to orally administered 8-MOP. Theoretically, however, pulmonary edema and hypotension rarely may occur in patients who are unable to tolerate the requisite fluid shifts, particularly patients with previously existing congestive heart failure.³⁴ Overall, ECP is regarded as a safe and tolerable treatment. The risk of secondary infections and malignancies noted in conventional immunosuppressive therapies has not been observed in ECP.⁴⁵

Indications and Contraindications

Preliminary studies show that ECP is an effective and tolerable treatment for severe recalcitrant AD. Reduced serum IgE levels and peripheral blood CD4-CD8 ratios may serve as predictors of response. Because of the absence of randomized controlled trials and because this treatment is costly, further investigations are necessary to establish its exact indications.

MECHANISM OF ACTION

Cellular immune defects underlie the pathology of AD (see article by Leung elsewhere in this issue) (Fig. 2).^{31, 55, 62} Although not completely understood, these immunologic aberrations result in complex interactions that manifest clinically as a chronic, relapsing, and pruritic dermatitis. Characterization of the cellular components and cytokine patterns present in acute and chronic lesions provided a better understanding of the disease process and specific targets or pathways where UV light might exert its effects. At present, however, phototherapy is mainly a symptomatic treatment and has not been shown to prevent the initiation phase of AD.²³

In general, UVA and UVB exert their anti-inflammatory effects by modifying soluble mediators and cell-surface receptors and by inducing T-cell apoptosis.²⁵ Severity of AD is related to the level of IFN- γ ³¹; the observed increase in IL-10 as a consequence of phototherapy, which in turn causes a reduction in IFN- γ levels, may be important in the resolution of AD lesions.^{21, 38} Levels of the neuropeptide α MSH and prostaglandin E₂, which are both immune suppressive, are up-regulated by phototherapy.²⁵ The expression of the cell-surface receptor intercellular adhesion molecule (ICAM-1), a hallmark for inflammatory skin condi-

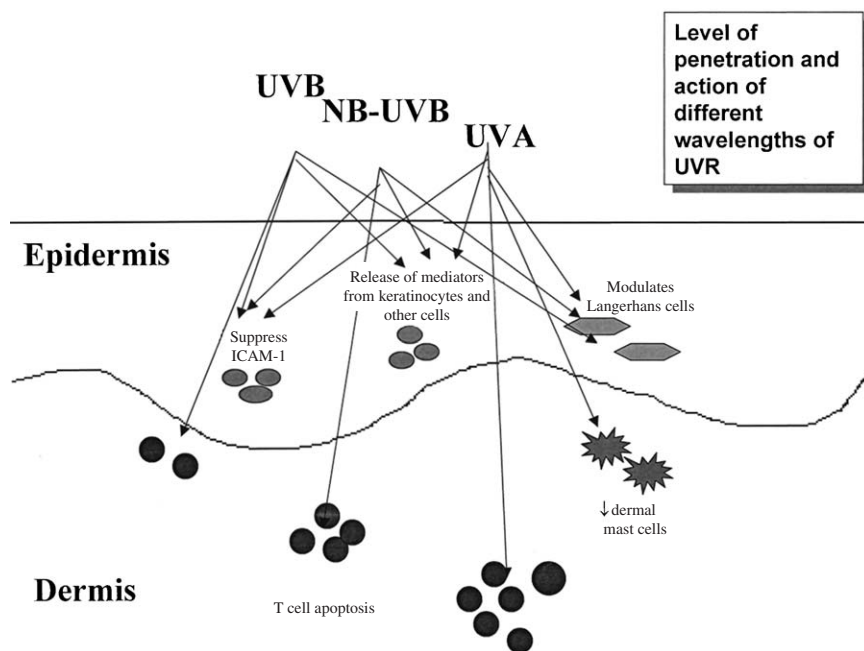


Figure 2. Penetration and action of the different UV wavelengths. Note that longer wavelengths penetrate more deeply into the dermis.

tions, is inhibited by UVA and UVB.²¹ Specifically for UVB, such inhibition coincides with thymine dimer formation.²⁵

It has been established that UV causes a depletion of activated T lymphocytes by way of apoptosis, which also results in reduction of IFN- γ and resolution of atopic skin lesions.^{36, 37, 40} UVA1 is a potent inducer of singlet oxygen species-mediated apoptosis.^{36, 37} Early and late forms of apoptosis are seen after UVA1 therapy.¹⁰ In contrast, PUVA and UVB are associated only with late apoptosis.²⁵

The superiority of NB-UVB over broadband UVB might be attributed largely to NB-UVB's deeper skin penetration which allows it to target a greater number of T lymphocytes.⁴⁰ It also has been shown that NB-UVB, to a greater extent than broadband UVB, causes a decrease in the levels of intralesional cytokine production and in the lymphoproliferative response to phytohemagglutinin (PHA).²⁰ Bath PUVA has demonstrated the capacity to suppress epidermal and dermal T lymphocytes.⁵⁷ Although most of the observations regarding NB-UVB and bath PUVA therapies were derived from patients with psoriasis, they also could be operative in AD.

T-cell apoptosis is also central to the mechanism behind ECP. In cutaneous T-cell lymphoma (CTCL) patients, it is postulated that ECP induces selective apoptosis of pathogenic T-cell clones, accompanied by activation of monocytes resulting in the increased ability to phagocytose apoptotic T cells.⁴⁵ These may serve as a "T-cell vaccine" to induce an immune response against pathogenic T cells. Further studies are needed to elucidate its action in AD.

Aside from its direct immunologic effects, phototherapy has been shown to exert antimicrobial properties that are beneficial in AD. It has been demonstrated in vitro and in vivo that UVB significantly reduces the *Staphylococcus aureus* colonization rate of clinically uninfected skin lesions.^{15, 66, 67} This effect may contribute to clinical improvement because toxins from *S. aureus* can act as superantigens that trigger a cascade of events that lead to sustained inflammation.³¹ Phototherapy, particularly with the more erythemogenic wavelengths, causes an increase in the thickness of the epidermis.^{7, 30} This theoretically results in a more effective physical barrier system against external antigens that may aggravate AD.³¹

SUMMARY

Developments in phototherapy have resulted in a wide range of treatment options for AD, all of which have been found effective as monotherapy or as an adjunct to other anti-inflammatory agents such as topical steroids. The newer modalities (i.e., UVA1, NB-UVB) have provided a better understanding of the mechanism by which phototherapy exerts its action at the cellular level. Factors to be considered in selecting a specific phototherapeutic modality include the severity of the disease,

patient characteristics, risks, side effects, and practical issues such as cost of the procedure and accessibility of the light source.

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Address reprint requests to

Seth R. Stevens, MD
 Department of Dermatology
 University Hospitals of Cleveland
 Case Western Reserve University
 11100 Euclid Avenue
 Cleveland, OH 44106

e-mail: srs@po.cwru.edu