

Is Phototherapy Useful in the Treatment of Atopic Dermatitis in Asian Children? A 5-Year Report from Singapore

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Abstract: The goal of the current study was to review a cohort of Asian children with atopic dermatitis (AD) treated using phototherapy at a tertiary dermatologic center in Singapore. We performed a retrospective review of patients younger than 16 years old with a clinical diagnosis of AD treated with phototherapy at the National Skin Center, Singapore, over a 5-year period from 2004 to 2008. Twenty-five patients were identified who were ages 7 to 15 years at the time they underwent phototherapy, with equal sex distribution. The duration of disease ranged from 2 to 14 years. Most patients had extensive disease involving more than 70% of their body surface area. Fifteen patients were treated with narrowband ultraviolet B (NBUVB) phototherapy, with 10 (66%) showing improvement of symptoms. The duration of therapy was 3 to 30 months (mean 11 mos), with a mean of 60 treatment sessions (range 12–104). Nine patients were treated with combined ultraviolet A (UVA) and NBUVB phototherapy. Five patients (55%) improved, with four having good response and one having mild improvement. The duration of therapy was 1–6 months (mean 3.6 mos), with an average of 22 treatment sessions (range 10–44). Two patients underwent combined UVA/broad-band UVB (BBUVB) phototherapy. Both had worsening of disease requiring cessation of treatment. Phototherapy is a useful adjunct in the treatment of moderate to severe AD in children. More than half of the patients treated with NBUVB or combined UVA and NBUVB improved with phototherapy, but the usefulness of combined UVA and BBUVB requires further evaluation.

Atopic dermatitis (AD) is a common inflammatory skin disorder characterized by its chronic relapsing nature. Commonly affecting the flexures, it can

present with more extensive involvement in severe cases. The prevalence of AD has been reported to be 20.8% (1) in school-age children in Singapore, with a

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large majority of cases presenting before 10 years of age (2). The quality of life of patients with AD corresponds to the severity and extent of involvement (3).

In view of its high prevalence and psychosocial and financial burden, treatment modalities rendering good control of AD are vital. Mainstay treatments for AD include topical emollients, corticosteroids, calcineurin inhibitors, and immunomodulators. With topical treatments, patients might report suboptimal control despite strict adherence. Prolonged use of large amounts of topical corticosteroids can lead to local and systemic side effects. Similarly, systemic immunomodulators have been associated with serious short- and long-term side effects. Phototherapy has emerged as an effective yet safe alternative form of treatment for AD (4). Different phototherapy modalities have been studied, including broadband ultraviolet B (BBUVB; 280–320 nm), narrowband ultraviolet B (NBUVB; 311 ± 2 nm), ultraviolet A (UVA; 320–400 nm), ultraviolet A1 (UVA1; 340–400 nm), photochemotherapy (psoralen + UVA [PUVA], including bath PUVA), and combinations of UVA and UVB (5). The mechanism of action of phototherapy in AD is postulated to be effectuated through its immunomodulatory effects on T-lymphocytes, antigen-presenting Langerhans cells, and proinflammatory cytokines (6).

Few studies have sought to establish the efficacy of phototherapy in children, particularly in Asia. Our study aimed to evaluate the efficacy of different modalities of phototherapy in Asian children with AD seen at a tertiary dermatology referral center in Singapore: the National Skin Center. We performed a retrospective study of children with AD who had undergone phototherapy at our center over 5 years between 2004 and 2008, reporting on the clinical findings, treatment protocols, and treatment outcomes.

METHODS

Patients with AD younger than 16 years old undergoing phototherapy within a 5-year period (January 2004–December 2008) were identified from the National Skin Center computer database. A retrospective review of their electronic medical records was conducted. A thorough clinical history was taken during their clinic visits, with all patients fulfilling Hanifin and Rajka criteria of AD. Exclusionary tests such as patch testing were not routinely performed unless clinically suggested from history and examination.

Parameters included in the study were epidemiologic data (age, sex, race), disease-related factors (duration of disease, body surface area [BSA] involvement), and previous treatments. Data on specific phototherapy modalities, maximum dosage administered, duration and number of sessions of phototherapy, response to treatment, and any resultant complications were examined.

Treatment with NBUVB (311 ± 2 nm) was administered in a phototherapy cabinet (Daavlin, Bryan, OH) equipped with NBUVB radiators (Philips TL100W/01-FS72; Philips B.V., Eindhoven, the Netherlands). The initial treatment dose, based on Fitzpatrick skin phototypes IV to VI, ranged from 250 to 400 mJ/cm². The dose was increased by 10% to 20% of the previous dose if previous treatment caused no or slight erythema.

Treatment with combined UVA and NBUVB was administered in a unit (Spectra 3S UV2001-311/350-24/24; Daavlin) equipped with NBUVB radiators (TL100W/01-FS72; Philips B.V.) and UVA radiators (F72T12/BL/HO; Daavlin). The initial treatment dose was 1 J/cm² for UVA and 100 mJ/cm² for NBUVB, regardless of Fitzpatrick skin phototype. The dose was increased by 0.5 to 1 J/cm² for UVA and 50 to 100 mJ/cm² for NBUVB if previous treatment caused no or slight erythema.

Treatment with combined UVA and BBUVB was administered in a unit (Spectra 3S UV2001-305/350-24/24; Daavlin) equipped with BBUVB radiators (TL100W/12; Philips B.V.) and UVA radiators (F72T12/BL/HO; Daavlin). The initial treatment dose was 1 J/cm² for UVA and 10 mJ/cm² for BBUVB, regardless of Fitzpatrick skin phototype. The dose was increased by 0.5 to 1 J/cm² for UVA and 5 to 10 mJ/cm² for BBUVB if previous treatment caused no or slight erythema.

For all modalities of phototherapy, the treatment frequency was two to three times per week during the initial treatment phase, reduced to one to two times per week when AD had improved with phototherapy. Ethics approval for the study was obtained from the local domain-specific review board.

RESULTS

Patient Characteristics

Twenty-five patients were identified, with equal sex distribution (13 boys, 12 girls). Patients were ages 7 to 15 years at initiation of phototherapy. There were 22 Chinese, 2 Indian, and 1 Malay patient, with all patients having Fitzpatrick skin phototypes IV to VI.

The duration of disease ranged from 2 to 14 years (mean 9.7 yrs). Most patients had extensive disease of more than 70% BSA involvement. All patients were receiving topical therapy before initiation of phototherapy, as well as intermittent short courses of oral corticosteroids, antibiotics, or both. A single patient had previously been treated with oral cyclosporin.

Fifteen patients underwent NBUVB therapy, nine had combined UVA and NBUVB, and two had combined UVA and BBUVB.

The respective phototherapy modalities were allocated in a nonrandomized manner based on patients' individual skin photosensitivity and the degree of skin inflammation. The decision as to which phototherapy was used was left to the discretion of the primary physician.

Specialist dermatologists assessed clinical response and improvement during the course of treatment. Clinical parameters assessed included itch and BSA involved. Response was classified into three tiers: good ($\geq 70\%$ improvement), moderate ($40\% - 70\%$ improvement), and poor ($< 40\%$ improvement). Owing to the young age of some study subjects, objective scoring questionnaires were not used.

Phototherapy Treatment

NBUVB Phototherapy Fifteen patients were treated using NBUVB, with 10 patients (66%) showing good improvement of eczema. All patients had phototherapy administered two to three times per week at the initiation of treatment. The duration of phototherapy in these 10 patients ranged from 3 to 30 months (mean 11 mos), with a mean of 60 treatment sessions (range 12–104). Maximal doses reached ranged from 332 to 2,299 mJ/cm² (mean 1175 mJ/cm²). Topical treatments were continued in all patients, including moisturizers and topical corticosteroids. The 10 patients who responded to treatment reported using decreasing amounts of topical corticosteroids as their eczema improved. Of the 10 patients who had good response, 9 did not require a second course of phototherapy after 1 year of follow-up. One patient required two further courses of NBUVB when worsening of eczema occurred 2 months and again 2 years after stopping phototherapy. Side effects of NBUVB included increased itch (7/10 patients), skin peeling (3/10), and erythema (1/10). These side effects were mild and self-limiting and did not require cessation of treatment. Three patients reported poor response to NBUVB after 2 months and 10 to 16 sessions of treatment. One patient developed eczema herpeticum that required cessation of treatment, one had wors-

ening of eczema after 16 treatment sessions, and one developed severe sunburn reaction after the first treatment at 250 mJ/cm², requiring discontinuation of treatment.

Combined UVA and NBUVB Phototherapy Nine patients were treated with combined UVA and NBUVB phototherapy. Treatment was initiated at two to three sessions per week. Five patients (55%) had improvement of their eczema, with four reporting good response and one reporting mild improvement. The duration of therapy ranged from 1 to 6 months (mean 3.6 mos), with an average of 22 treatment sessions (range 10–44). Maximal doses reached ranged from 1 to 2.5 J/cm² (mean 1.3 J/cm²) for UVA and was 150 mJ/cm² for NBUVB. Three patients had poor response after 2 to 5 months of therapy and one had worsening of symptoms. Side effects reported included transient itch and erythema. One patient developed eczema herpeticum while undergoing phototherapy, requiring treatment with oral acyclovir.

Combined UVA and BBUVB Phototherapy Two patients underwent combined UVA and BBUVB phototherapy. Maximal doses of UVA reached ranged from 1 to 2 J/cm² (mean 1.5 J/cm²) and those of BBUVB ranged from 10 to 15 mJ/cm² (mean 12.5 mJ/cm²). Both patients had worsening of symptoms requiring cessation of treatment after 2 to 4 months of treatment. One of these patients subsequently underwent treatment with combined UVA and NBUVB phototherapy with good response.

DISCUSSION

AD is a common, chronic skin condition that can lead to severe physical and psychosocial impairment in children and adolescents (7). Special consideration should be given when treating children with AD. Common inherent side effects of treatment that adults tolerate may be less tolerated by children. It is imperative to keep toxicities and side effects to a minimum and to prescribe therapies that are easy to adhere to with minimal interruptions to their lifestyle.

Topical therapies, particularly emollients, topical corticosteroids, and topical calcineurin inhibitors are still the mainstay of therapy. More recently, bleach baths, wet wrap therapy, and proactive treatment have been introduced into the topical armamentarium for the treatment of AD (8–10).

Of paramount importance is treatment acceptability. Newer modalities (e.g., wet wraps) are

inconvenient and cause discomfort that might not be amenable to the lifestyle of active children with AD.

Even with good adherence, many patients with moderate to severe disease may not achieve optimal control, leading to repeated flares of disease. When traditional therapies fail, the use of second-line treatment modalities needs to be considered. The use of systemic immunosuppressives, such as cyclosporin, azathioprine, and methotrexate (MTX) is associated with short- and medium-term side effects, such as hypertension and renal toxicity (cyclosporin) and bone marrow suppression and liver toxicity (azathioprine and MTX). Long-term side effects, although uncommon in children, include immunosuppression and secondary malignancies.

In our study, subjects were select patients seen in a tertiary institution for difficult-to-treat eczema. These patients had all undergone trials of conventional treatment modalities (e.g., topical steroids), with their condition proving to be refractory. Specialist dermatologist reviews were then sought, explaining the slightly older age of our study population. Parents were also more acquainted with conventional treatment modalities, opting for other modalities only when AD remained persistent, with resultant psychosocial implications.

Our retrospective study has shown the relative efficacy of phototherapy, in particular NBUVB and combined UVA and NBUVB phototherapy, with more than half of patients reporting good response to treatment using these phototherapy modalities. A large proportion of patients also reported lasting control of disease after cessation of phototherapy.

A handful of previous studies have similarly demonstrated the effectiveness of phototherapy in the treatment of AD in children. A retrospective review by Clayton et al (11) of 50 children with AD treated using NBUVB demonstrated complete clearance or minimal residual activity in 40% of patients, good improvement in 23%, and moderate improvement in 26%. In a systematic review of phototherapy in the treatment of AD, Meduri et al (12) reported three studies that found the response to UVA1 to be faster and more efficacious than combined UVA and UVB phototherapy, whereas two trials reported the superiority of UVA and UVB. The review found two additional studies that demonstrated that NBUVB was more effective than BBUVA or UVA for chronic AD. In a further study by Pavlovsky et al (13), who reviewed 72 children with AD who had undergone NBUVB, 25% achieved clearance and another 44% had partial response.

The mechanism of UV light in the treatment of AD has not been fully elucidated, with many postulations extrapolated from studies performed on patients with psoriasis and other dermatoses. In a recent review the effects of NBUVB on epidermal cells included induction of apoptosis of Langerhans cells and T-cells, reducing the number of keratinocytes and promoting the acceleration of cell migration, wound healing, and barrier repair (14). UVB has also been shown to suppress proinflammatory cytokines, such as interleukin 12 (IL-2), IL-2, interferon alpha, and tumor necrosis factor alpha, and increase keratinocyte IL-10 production, a potent suppressor of inflammatory cytokines. NBUVB has also been shown to increase the expression of antimicrobial peptides such as beta-defensins and cathelicidins and to augment levels of calcitriol, which have immunomodulatory effects on keratinocytes and T-lymphocytes (15,16).

Patients were initially started on phototherapy three times per week before tapering to weekly or fortnightly during a prescribed maintenance phase. The short-term side-effect profiles of NBUVB and combined UVA and NBUVB used in our study appear to be mild and self-limiting. Complications that patients reported were mostly confined to erythema and itching. Only one patient treated with NBUVB developed a sunburn reaction that necessitated discontinuation of treatment. Because of the design of our study, we were unable to comment on the long-term side-effect profile of our patients. There are still concerns regarding the theoretical risks of photocarcinogenesis and photoaging, especially in children. Although the role of UVB in photocarcinogenesis can be inferred from the characteristic mutations in p53 found in human nonmelanoma skin cancers, the long-term skin cancer risk of NBUVB has been thought to be much less than that of PUVA (17). In addition, the use of combined phototherapy modalities, such as UVA and NBUVB, decreases the total dose of the individual modality used, theoretically leading to a decrease in short- and long-term complications (18,19).

Limitations

Our study was a retrospective review of a small study cohort of patients, without a control group. The maximum length of follow-up was 5 years because of its retrospective nature. Outcome measures were not standardized because different dermatologists reviewed the patients. Future studies, in particular prospective randomized control trials, should be performed.

CONCLUSION

While this study was limited to Asian children, our findings, together with previously published reports, lead us to recommend the use of NBUVB or combined UVA and NBUVB as adjunctive treatment in children with moderate to severe AD who are not optimally controlled on topical treatments. It is generally well tolerated, with mild, transient side effects, although the possibility of long-term side effects, in particular photocarcinogenesis, requires further evaluation.

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