UVA PHOTOTHERAPY OF ATOPIC DERMATITIS AN EXPERIENCE IN QATAR AND REVIEW OF LITERATURE

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ABSTRACT:

UVA alone was used on 54 patients with atopic dermatitis (AD) of different age groups, skin types and nationalities. Forty five (83%) had severe AD. After UVA treatment there was a marked reduction in primary and secondary lesions and the need for topical and systemic medications, including steroids, was reduced. The doses used were relatively high but accepted. AD, phototherapy and details of our treatment protocol and its results are discussed with a review of the literature.

INTRODUCTION:

Atopic dermatitis (AD) is a chronic relapsing eczema which has a characteristic pattern and a worldwide distribution. All age groups, but mainly infants and children, may suffer from the disease for a variable duration, extent and severity. AD is estimated to affect 10% of the Western population[1]. AD has nearly the same incidence in the Gulf region where it has been estimated to be 6.9% in Qatar[2], 6.8% in Dammam City, Kingdom of Saudi Arabia [3], 9.07% in the United Arab Emirates [2]. Despite the increased therapeutic armamentarium the disease still represents a challenge to the knowledge, experience and wisdom of the treating physician.

Recent developments in the management of atopic dermatitis include phototherapy, immunosuppressive therapy, cytokines, thymopentin, hyposensitization, Chinese herbal medicine, essential fatty acid supplementation, phosphodiesterase inhibitors, mast cell stabilizers and topical IgG [4].

Phototherapy includes UVB (290 - 3 20 nm), the narrow band UVB (311 nm), the short wave UVA (UVA2 320 - 340 nm), the long wave UVA (UVA1 340 - 400 nm), combination of UVA and UVB, photochemotherapy (PUVA) and extracorporeal photopheresis.

Since 1996 we have been using long wave UVA to treat severe cases of atopic dermatitis in children and adults. The aim of this study was to evaluate the efficacy and results of UVA in the treatment of atopic dermatitis (AD), the effect of UVA on other methods of treatment, to find the mean effective dose, remittance duration, effect on other manifestations of atopy and IgE serum level, and the relation between skin type and the response.

METHODS AND PATIENTS.

Fifty four patients with severe AD began the treatment but twenty were unable to continue and were excluded from the subsequent results. An evaluation sheet was completed for each patient giving personal details, medical history, description of lesions, treatment details, response and side effects as shown (Sheet 1) and the remaining thirty four patients (18 females and 16 males) underwent UVA therapy without psoralen or other photosensitizer using whole body machines from Daavlin Corporation or National Biologic Corporation. Each machine emitted UVA radiation ranging from almost 310 nm to 380 nm with a peak of 338 nm.

Twenty patients were below the age of 15 years, fourteen were older (the eldest being a 35 year old male Sudanese) giving a mean age of 19.1 years. The youngest patient (a six year old girl) was afraid of the treatment and continued intermittently for only nine sessions with 30% overall improvement.

The patients were of eight different nationalities (Table 1) with skin types varying from 1 to 6 on the Fitzpatrick scale (Table 2). Most patients had a history of childhood and/or adult eczema and nearly half of them had eczema of more than one type (Table 3). The duration of the disease varied from one year to 30 years, (mean duration 8.6 years) with 24 patients (70.58%) having AD since childhood between the ages of 1 to 12 years10 patients (29.41%) had a history of atopic manifestations, asthma, allergic rhinitis and urticaria (Table 4). 18 patients (52.9%) reported a family history of atopy. Lesions were present on various parts of the body but most commonly the flexurals which were affected in all the patients. (Table 5). The majority of the patients under treatment were suffering from severe AD. (Table 6). A small number of patients had concommitant disease with 2 patients (5.88%) being on ventolin, 2 patients (5.88%) receiving cough medication and 2 patients (5.88%) being treated for liver disease.

For most patients the UVA treatment commenced with a dose of 10 Joules although one patient started on 5 Joules and two were started on 7 Joules. This dose was increased by 2-5 Joules at each session with most patients receiving increments of 5 Joules regardless of skin type or the severity of the lesions. The intention was that each patient should undergo a schedule that involved a clearing phase with sessions three times a week until the AD was controlled at which time the frequency of the sessions would be reduced to a suitable maintenance level.

RESULTS

The mean duration of treatment with UVA was ten weeks (3-20 weeks) using a mean dose/session of 24.4 Joules(17.9-36 Joules/session) for a mean of 16 sessions (8-28 sessions). This resulted in a total cumulative dose (TCD) of 406 Joules (200-895 Joules). It was found possible to reduce to a weekly maintenance dose in 10 patients (29.41%) patients, to a maintenance dose every two weeks in 6 patients (17.47%) patients and to one session every third or fourth for 2 patients (5.88%) patients. It was necessary to keep 14 patients (41.17%) of the patients on the clearance phase with three sessions per week because less frequent sessions did not control the condition. The mean dose per maintenance session was 28.3 J(15-45 J/session). Generally the treatment was tolerated well with only a few patients complaining of a burning sensation or pruritis. Skin types 1-3 responded to doses relatively lower than those needed for skin types 4-6.

Doses necessary for an initial detectable improvement were recorded and it was found that the mean dose for initial response was 21.6 J (15-36J) which meant that some patients started to respond after the second session. The mean number of sessions for earliest response was 4.5 sessions (3-11 sessions). The mean dose for maximal improvement was 30.25 J(20-47J) and the mean number of sessions for maximal improvement was ten sessions (5-19 sessions).

All primary and secondary lesions improved with the UVA treatment and all signs of scaling, oozing, lichenification disappeared completely. (Table 7) Prior to the UVA treatment all the patients exhibited erythematous lesions and all complained of pruritis. After treatment only 4 patients (11.76%) showed erythematous lesions and only 6 patients (17.64%) complained of pruritis.

The need to use topical and systemic steroids, antihistamines and systemic antibiotics was reduced during treatment, and was markedly reduced after treatment (table 8). The most striking reductions being in the use of systemic steroids and antibiotics which were reduced from 82.35% to 5.88% and from 64.7% to 5.88% respectively. Patients were encouraged to use emollients freely and frequently and most continued to do so but even so their use was reduced with more than half using emollients only and a further one-third using the emollients with less potent steroids than those used before UVA treatment.

6 patients (17.64%) improved completely and a further 18 patients (52.94%) showed more than eighty per cent improvement. Those patients who showed less improvement included several who did not complete the course of treatment.

10 patients (29.41%) continued to be controlled for more than 19 months on emollients or mild topical steroids and 12 patients (35.29%) were controlled for more than 4 weeks. The 10 patients (29.41%) controlled for less than four weeks included patients who did not attend regularly for treatment. For various reasons it was possible to follow only 6 patients (17.64%) for an extended period of three years and in these the disease continued to be controlled with emollients and occasional mild topical steroids.

It seems that the UV treatment had no effect on IgE serum level, which was unchanged in 22 patients (64.70%), reduced in 8 patients (23.52%) and increased in 2 patients (5.88%).

Unfortunately the treatment was inconvenient both for the patients and for the clinicians. Although two UVA machines were used simultaneously, the long exposure times required caused queues of patients in the clinic and were especially annoying to patients needing only short exposures for other conditions. Because of other commitments (work, studies, etc) most patients found it difficult to attend for exposures of up to 50 minutes at a time, three times a week for several weeks, and for this reason several patients discontinued treatment or attended irregularly.

DISCUSSION

Atopic dermatitis (AD) is a pruritic, inflammatory cutaneous disorder [5] the prevalence of which has been on the rise for many years. It is found most frequently amongst patients with a personal or family history of atopic disease and is characterized by a typical morphology and distribution and a chroni-

cally relapsing course with frequent periods of exacerbation[6]. A primary defect is found in bone marrow cells with the most consistent abnormality relating to the overproduction of IgE. Pharmacophysiologic abnormalities include abnormal vascular responses, abnormal sweating responses, and a reduced threshold for itch [5].

A partial enzymatic defect in delta-6 desaturase has been reported. Such a metabolic anomaly could be responsible for the alterations in both the skin barrier function and in the Th2 inflammatory reactions which are in part mediated through IgE. Microorganisms colonizing the skin play an important causal role in the clinical exacerbations [7]. Many atopic dermatitis (AD) patients have exacerbations of their skin disease in winter. These exacerbations may be caused by non-immunological 'non-specific' factors, such as low sun exposure and low temperature [8].

The management of AD is directed primarily towards symptomatic relief, and treatment decisions depend upon cutaneous symptoms at any given time. During periods of acute exacerbation, therapy consists almost exclusively of topical or even systemic corticosteroid therapy. Since long-term corticosteroid therapy is known to have a variety of side effects, it is important to develop other methods of treatment of AD, such as phototherapy with ultraviolet radiation (PUVA, UV-B, UV-A-B) [6].

In Japan PUVA therapy may be a second choice or an adjunct to the primary treatment of atopic dermatitis if it has had a disabling effect or is resistant to conventional treatments [9]. In 1977 Lynch et al treated a small number of patients and concluded that the effect of PUVA on AD is only poor to fair.[10] but in 1996 several other studies showed a beneficial effect of ultraviolet radiation on eczema, especially atopic dermatitis [11] . Althogh topical corticosteroids are still the main methods of treatment, UV may reduce the potency and frequency needed[12] as seen in our studied group of patients.

It is well known that Staphylococcus aureus (S. aureus) proliferates on the moist skin lesion of atopic dermatitis. Reduction of bacterial colonization in skin lesions by using antibiotics has been reported to be effective for the treatment of atopic dermatitis. S. aureus produces superantigens which can activate T-cells and possibly enhance the inflammatory reaction. Photo(chemo)therapy has been successfully used for the treatment of severe cases of atopic dermatitis and has a bacteriostatic effect on S. aureus. The effect of UVB and psoralen plus UVA (PUVA) on superantigen production from S. aureus has been examined and the production of superantigens decreased in an ultraviolet dose-dependent manner. The suppressive effects of UV radiation on superantigen production may be involved in the therapeutic efficacy of photo(chemo)therapy for atopic dermatitis [13].

Yoshimura et al studied the anti-microbial effect of UV and found that PUVA and UVB treatment markedly inhibited proliferation in a dose-dependent manner and concluded that these results indicated that the antimicrobial effect of UV radiation possibly contributed to successful photochemotherapy of patients with atopic dermatitis [14]. Serum sICAM-1 and sELAM-1 are elevated in patients with severe atopic eczema but they seem not to be suitable markers of actual disease activity.[15]

Akiyama et al tried the effects of various salts and irradiation with UV light on the attachment of Staphylococcus aureus strains. His results suggest that the attachment of S. aureus cells isolated from atopic dermatitis lesions to the coverslip is suppressed in the presence of 10% salts and irradiation with UVA and UVB, and that plasma coagulation of S. aureus cells isolated from atopic dermatitis lesions is suppressed in the presence of 10% salts, irradiation with UVA, and heating[16].

Schempp et al also studied the effect of various salt solutions on ultraviolet B-induced erythema and pigmentation in psoriasis and atopic dermatitis and found that soaking the skin with salt solutions or tap water increased skin sensitivity to subsequent UVB irradiation. This may contribute to the effectiveness of salt water baths followed by UV irradiation and may account for an increased risk of sunburn after bathing [17]. UV doses should be adjusted accordingly if patients are preceeding exposure with bathing or salt water soaking at the seashore.

Salt water bathing prior to UVB irradiation leads to a decrease of the minimal erythema dose and an increased erythema index without affecting skin pigmentation. This sensitization to the effects of short-wave UVB radiation may increase the immunosuppressive effects of UVB radiation and lead to an increased efficacy of UVB phototherapy. Bearing in mind the increased risk of sunburn. [18]. Applications of pale sulfonated shale oil (ICHTHYOL pale) or hydrocortisone 0.5% gave a similar but greater efficacy of UV in the treatment of AD [19].

Hannuksela et al found that after UV treatment the need for treatment with topical corticosteroids had decreased in half of the patients and increased in only 2% of them. After two years the treatment was still effective in 94% of them and the need for topical corticosteroids had decreased in 85% of the cases and increased in none[20]. Topical psoralen photochemotherapy for atopic dermatitis is also effective [21].

Wulf suggested a UVB phototherapy protocol with very low dose increments as a treatment of atopic dermatitis. Fifteen patients with atopic dermatitis were treated with a new UVB treatment regimen guided by skin reflectance measurements. The treatment was characterized by very low dose increments from start to end of therapy with the median cumulative dose increment during therapy being only 20%. His study indicated that skin reflectance-guided UVB phototherapy might enable the dermatologist to lower the cumulative UVB exposure significantly without losing effect [22].

Grundmann et al evaluated the effect of UVB at 311 nm in the treatment of five patients with moderate to severe atopic dermatitis. In each patient a mean cumulative dose of 9.2 J/cm2 was applied over a mean of 19 irradiations. Narrow-band UVB notably reduced atopic dermatitis after three weeks in all patients [23].

UVA1 radiation exerts its effects in atopic eczema, at least in part, by inhibiting Langerhans cell migration out of the epidermis and, in particular, by reducing the number of IgE-bearing Langerhans cells and mast cells in the dermis. The density of Langerhans cells and mast cells is not decreased by UVA/UVB treatment [24].

Substance P seems to be involved in the pathogenesis of atopic dermatitis and substance P-containing nerve fibers are increased in the lesional skin of patients with atopic dermatitis. A reduced weal and flare reaction to the intradermal injection of substance P has been observed. UVA irradiations did not modify the epidermal distribution of substance P receptors but decreased their expression intensity on blood vessels. UVA irradiations seem to decrease skin inflammation through the modulation of NK-1 receptor expression on endothelial cells [25].

Histamine augments UVB-induced IL-6 production by keratinocytes predominantly via the H1 receptor at the level of transcription. This suggests a contributory role for histamine in the exacerbation of atopic dermatitis induced by sun exposure [26]. Because it is known that AD patients may have photoaggravation of their dermatitis or exacerbation secondary to a photodermatosis, such as polymorphic light eruption, actinic prurigo or drug-induced phototoxicity it is recommended that all AD patients who have a history of sunlight-induced exacerbation or marked intolerance of PUVA or ultraviolet B phototherapy should be phototested and patch tested.

Russell investigated in detail seven young patients with atopic dermatitis (AD) who presented with a marked photoexposed site dermatitis. The results of phototesting, patch testing and other investigations were compatible with the diagnosis of photosensitivity dermatitis/actinic reticuloid syndrome (PD/AR) or chronic actinic dermatitis [27].

In a paired-comparison study, 21 patients suffering from atopic dermatitis were treated with fluorescent tubes radiating mainly ultraviolet A (UVA) on one half of the body and with tubes radiating mainly UVB on the other. Equal results occurred with both UVA and UVB in nine of the patients but the total and overall evaluation scores were better with UVA therapy and most of the patients preferred UVA treatment [28].

In studies to evaluate the efficacy of different ultraviolet wavelengths in the treatment of atopic dermatitis, UVAB proved to be most efficacious and UVB the least efficacious. The efficacy of UVA was found to lie between UVAB and UVB [29].

High-dose UVA1 irradiation was found to induce asignificant clinical improvement of atopic dermatitis compared to UVA-UVB treatment. High-dose UVA1, but not UVA-UVB, significantly reduced the elevated serum level of eosinophil cationic protein in patients with atopic dermatitis [30]. None of five AD patients treated with UVB cleared completely but all were moderately improved, with reduction of the extent of eczema and decreased pruritus [31].

A multicenter trial confirmed the therapeutic effectiveness of high-dose UVA1 monotherapy for treatment of severe exacerbations of AD [32]. High doses of UVA1 reaching up to 50 J/cm2 five times a week for three weeks seem to be more effective than lower doses [33].

UVA-1 therapy seems to be a promising new alternative, especially for more severe cases. Although high-dose regimens work well, the hazards have not yet been fully elucidated and such regimens

should be reserved for very resistant cases where lower doses have been tried but found inadequate. PUVA is also very effective but, due to the long-term hazards, it should be reserved for the most severe cases of atopic dermatitis. UVAB seems to be superior to UVB and best suited for mild to moderate cases[34]. Non-responders to high doses of UVA1 with complicating infections might benefit from the combination of high-dose UVA1 therapy and antibiotic or antimycotic treatment [35].

Extracorporeal photochemotherapy (ECPC) was effective when tried on one AD patient but its effect was not mediated by a systemic immune response[36].

Although phototherapy is safe and effective in the management of AD, it is possible that the 'dirty neck' appearance is a form of post-inflammatory pigmentation due to previous eczema, ultraviolet exposure or even the application of photosensitizing products. This 'dirty neck' is a characteristic disorder of pigmentation which has been found previously to affect approximately 2% of adult atopics[37]. Phototherapy should be introduced carefully because some AD patients in Japan showed an abnormal papular response to single dose or 3-times consecutive UVB radiation doses above the MED (90 mJ/sq cm) [38].

In a ten year retrospective study to evaluate phototherapy in the treatment of 1692 patients with a variety of diseases (psoriasis, vitiligo, atopic dermatitis, mycosis fungoides, etc.) Park et al could not find any malignancy in the skin.

Since the maximum safe cumulative doses of UVA or UVB have not been established yet, it is difficult to decide when phototherapy should be discontinued [39].

In another study to record the potentially serious side effects of melanoma and non-melanoma skin cancers and ocular damage following long-term PUVA chemotherapy, Abdulla et al re-examined 198 of 242 patients (16 with atopic dermatitis) treated between 1977 and 1987 in their department. All patients had a yearly ophthalmological examination during the ten years. None developed cataracts, lens opacities or had impairment of their visual acuity[40].

CONCLUSION

UVA is an effective treatment for the control of atopic dermatitis. It markedly reduces the need for systemic treatments with steroids, antihistamines and antibiotics as well as reducing the frequency and potency of topical steroids needed.

The UVA doses needed to treat AD are relatively high but are accepted by patients because they are not given with photosensitizers and side effects are limited or minimal. The treatment does not affect IgE serum levels or other manifestations of atopy.

The need for long exposures and the consequent long waiting times are inconvenient for both patients and clinicians alike but might be solved by using machines with higher outputs.

Sheet: 1

I.D. Case No.:		Name :			File No. :
Age :		Sex: M / F		Nat. :	Skin Type :
Diagnosis (A.D)		Infantile		Childhood	Adulthood
HISTORY :	DURATION		Y		SINCE
ATOPIC MANIFESTATION :	ASTHMA		ALLERGIC R.		URTICARIA
FAMILY HISTORY OF ATOPY :					
Description : Extensiveness :	face	Flexural	LL	UL	Trunk Others
Severity & comp : erythema, scaling, oozing, infection, lichen, pruritus, others					
	Or mild	mod.	Severe		
Treatments: pre	: T.S.	S.S.	A.H.	Emollient	A.B. others.
During	: T.S.	S.S.	A.H.	Emollient	A.B. others.
after	: T.S.	S.S.	A.H.	Emollient	A.B. others.
Concomitant for other disease :					
UV	UVA		UVB		PUVA
Dose : T.C.D.	initial	increment	initial improve.		max. imp.
Mean Dose/session =		T.C.D/No. of session =			initial imp.
Session: Total No.	during	weeks / months			max. imp.
Frequency		C3	C2		
Maintenance : M1	M2	M3	M4	Dose.	
Response & results :					
Severity after R/: Erythema, scaling, oozing, infection, lichen, pruritus, Others :					
% of total improvement.					
Side effects: Burns		Burning sens.		Pruritus	others.
F.up. : for how long controlled:					
Earliest response : dose				session	
Max. response : dose				session	
Effect on other types of treatments :					
Effect on other manifestation of Atopy :					
Convenience : patient :				clinic:	
Photograph : before				after :	
Comments :					

AD = Atopic Dermatitis, LL = lower limbs, UL = upper limbs
T.S. = Topical steroids, S.S. = systemic steroids AH = Antihistamine
A.B = Antibiotic TCD = total cumulative dose
C3 = clearance phase,3 times weekly.
C2 = clearance phase,2 times weekly.
M1 = maintenance phase once weekly
M2 = maintenance phase every other week
M3 = maintenance phase every 3rd week
M4 = maintenance phase every 4th week

Table - 1
Showing the percentage - Nationalities of treated patients

% of patients	nationality
29.41%	Qatari
29.41%	Indian
11.76%	Egyptian
5.88%	Sudanese
5.88%	Palestinian
5.88%	Irani
5.88%	Australian
5.88%	British

Table 2
Showing the percentage of patients in relation to their skin type.

Percentage	Skin Type
29.41%	4
23.52%	5
23.52%	6
11.76%	1
11.76%	3

Table 3
Percentage of patient in relation to type of Eczema

Percentage	Type of Eczema
41.17%	Infantile
52.94%	Childhood
52.94%	Adulthood
47.05%	More than one type

Table 4
The percentage and type of atopic manifestations

Percentage	Type of atopic manifestation	
29.41%	atopic manifestation	
	Asthma	50%
	Allergic rhinitis	33%
	Urticaria	17%

Table 5
Distribution of lesions and the affected sites

Percentage	Affected sites
100%	flexurals
94.11%	extremities
64.70%	trunk
41.17%	face / or eyelids
35.29%	neck

Table 6
Showing severity percentage

Percentage	Type
82.35%	Severe AD
11.76%	Moderate AD
5.88%	Mild AD

Clinical evaluation and finding before and after treatment: (Table 7)

Table 7
Clinical finding before and after treatment

	before	after
Erythema	100 %	11.76 %
Pruritus	100 %	17.64 %
Scaling	94.11 %	0 %
Oozing	8.23 %	0 %
Lichenification	52.94 %	0 %
Secondary infection	41.17 %	0 %

Table 8:
Comparison of needed treatment before, during and after UVA therapy.

	T.S	S.S	A.H	Em	A.B	Others
Before	100%	82.35%	100%	100%	64.70%	5.88%
During	88.23%	29.41%	58.82%	100%	11.76%	0%
After	70.58%	5.88%	5.88%	94.11%	5.88%	0%

T.S. = Topical steroids. S.S.= systemic steroids. A.H. = Antihistomine. EM = Emollients. AB = Antibiotic.

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