

Report

UVA-1 phototherapy for the management of atopic dermatitis: a large retrospective study conducted in a low-middle income countryMaría F. Ordóñez Rubiano¹, MD , Claudia M. Arenas¹, MD, and Juan G. Chalela², MD

¹Department of Dermatology, Hospital Militar Central, Universidad Militar Nueva Granada, Bogotá, Colombia, and ²Hospital Universitario Fundación Santa Fe, Bogotá, Colombia

Correspondence

María F. Ordóñez Rubiano, MD
Department of Dermatology
Hospital Militar Central
Universidad Militar Nueva Granada
Transversal 3 # 49 – 02
Bogotá, Colombia
E-mail: Mfordonezr@gmail.com

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Abstract

Background Medium-dose ultraviolet light A – 1 (UVA-1) phototherapy, given in short courses, has shown efficacy in atopic dermatitis flares; little is known about its use, efficacy, and side effects in prolonged exposure used in the chronic disease despite its extensive use.

Methods A descriptive retrospective study was conducted; convenience sampling of patients with atopic dermatitis treated with UVA-1 phototherapy was made; evaluation of clinical response by SCORAD, adverse effects, and protocols used in each patient were evaluated.

Results Patients exposed to UVA-1 phototherapy showed a decrease in the SCORAD (30.1 points) – total cumulative dose-dependent ($P < 0.0001$) – regardless of multiple variables studied. There were low rates of relapse and adverse effects. The most frequent doses were 30 and 60 J/cm², three times per week; patients had similar clinical responses and adverse effects in these groups independent of the other variables studied ($P = 0.057$).

Conclusion UVA-1 phototherapy can be an alternative for patients with severe atopic dermatitis even at lower doses than those described in other series (30 J/cm²) and not only for acute flares. Cumulative total dose is a variable that affects the clinical response directly. Large prospective studies are needed.

Introduction

Atopic dermatitis (AD) affects almost 25% of children and 2–3% of adults in the world.¹ Multiple therapies have been used in the disease including topical (emollients, steroids, calcineurin inhibitors) and systemic (cyclosporine A, methotrexate, mycophenolate mofetil, azathioprine, and phototherapy).^{1,2}

Phototherapy with ultraviolet light B or A (UVB or UVA) has been used in the disease.³ UVA-1 phototherapy (UVA-1) consists of light in the spectrum of 240–400 nm, and its mechanism of action is thought to be related with T and B lymphocyte apoptosis, less production of interleukins (IL): IL-5, IL-13, and IL-31, inhibition of calcineurin phosphatase, and decrease on antigen presentation by Langerhans cells.^{4–6} It has been used since 1992 when it was first described for acute exacerbations of AD.^{4,7} UVA-1 has been studied mainly in acute flares, and little is known about its role in chronic and prolonged therapy.^{3,7}

Studies of phototherapy for AD have been summarized in three systematic reviews. Briefly, UVA-1 has been studied in moderate and severe disease. Scarce data are known about its use in infancy and pregnancy; the response is faster with UVA-1 than with UVA-UVB in flares; UVA-1 is more effective for flares compared with broad band-UVB, UVA-UVB, and topical steroids;

UVA-1 and narrow band-UVB are equally effective for flares; and finally, high (130 J/cm²), medium (50 J/cm²), and low (10 J/cm²) doses have been studied, the former equally effective as medium and the last less than the medium-dose regimen.^{3,8,9}

Methods

A retrospective observational study was conducted including patients treated between January 2005 and December 2015 at a tertiary care hospital and a phototherapy center in Bogotá, Colombia. Three authors, throughout 2016, carried out data collection. The ethics committee of the hospital approved this study.

All medical records (MR) of patients diagnosed with atopic dermatitis (Eichenfield *et al.*, 2003 criteria were used¹) that received treatment with UVA-1 were susceptible for eligibility; incomplete MR were excluded.

Variables studied included gender, age, previous treatment (topical and systemic), initial condition (SCORAD), concomitant treatment (topical and systemic), per day dose (J/cm²), frequency (days in the week), treatment time (weeks), cumulative dose (J/cm²), initial and final clinical condition (SCORAD), response to treatment (difference between initial and final SCORAD), adverse effects (AE), and relapse (3 months). With

the intention to minimize bias, all data were collected and revisited first by two authors and then by a third; if not congruent, the patient was excluded.

Statistical methods

After analyzing the distribution of the variables, frequency tables, measures of central tendency, and variability were calculated. Subsequently, statistical hypothesis testing (Chi-squared test for proportions) was made, and confidence intervals were estimated. Akaike information criterion was used for choosing the best statistical model, and based on the distribution (biased to the right and strictly positive), a Student's log T semiparametric regression with 3 degrees of freedom was made.

Results

Four hundred and forty-five MR were examined for eligibility; after exclusion, 317 were included in the study. Gender distribution and its median age were similar, and additional demographic data are available in Table 1.

Treatments

Most of the patients were previously treated with two or three therapies; the most frequently used were emollients 303 (95.6%), topical steroids 233 (73.5%), azathioprine 96 (30.3%), and others – systemic steroids, antihistamines, cyclosporine, montelukast- 94 (29.7%). A total of 213 were on topical therapy

exclusively, and 113 were treated with azathioprine or methotrexate. During UVA-1 therapy, they were also treated with two therapies, emollients 306 (96.5%), and topical steroids 213 (67.2%). A total of 161 patients were exclusively on topical therapy, and 101 received azathioprine or metotrexate. No significant changes, in number and type, were identified between previous and concomitant therapies.

UVA-1 protocol

Two hundred and sixty patients had therapy three times a week, with a daily dose between 10 and 130 J/cm²; the most frequently used doses were 30 J/cm² (102 patients) and 60 J/cm² (150 patients). Median time treatment and cumulative dose were 12.6 weeks and 2280 J/cm², respectively. (Table 1)

Clinical response

Before treatment, 316 patients were classified as having a Severe SCORAD and one Moderate. Two-hundred seventy-three patients had a favorable response, and it was statistically significant ($P < 0.0001$); in this group, the median decrease in points in SCORAD was 30.1, and the percentage of decrease was 54.2%. The outcome was not dependent on being treated previously or concomitantly with systemic therapy. The difference on the percentage of patients having favorable response between medium and high dose, 88.5% and 78.3%, respectively, was significant $P = 0.038$ (IC 95% -0.009 to 0.213). The final SCORAD was Moderate in 210 patients. (Table 2)

The initial response started at a median of 6 weeks (P25 = 4 – P75 = 8), 19 sessions (P25 = 13 – P75 = 30), and a cumulative dose of 1.080 J/cm² (P25 = 600 – P75 = 1.600). The final

Table 1 Demographics and treatment protocol

Parameters, <i>n</i> (%) unless otherwise stated	Patients with AD treated with UVA-1 (<i>n</i> = 317)
Demographics	
Sex, female	160 (50.5)
Age, median $\pm$ SD	21 $\pm$ 14.7
<18 years	143 (45.1)
18–65 years	168 (53)
>65 years	6 (1.9)
Treatment protocol	
Daily dose	
Low dose	5 (1.6)
Medium dose	252 (79.5)
High dose	60 (18.9)
Frequency	
3 days	260 (82)
2 days	30 (5.9)
5 days	16 (5)
Number of sessions, median (P25–P75)	40 (20–72.6)
Treatment time in weeks, median (P25–P75)	12.6 (6.6–23)
Cumulative total dose J/cm ² , median (P25–P75)	2280 (1050–4420)

AD, Atopic Dermatitis; P25, Percentile 25; P75, Percentile 75; SD, Standard Deviation.

Table 2 Initial and final clinical condition

Parameters, <i>n</i> (%) unless otherwise stated	Patients with AD treated with UVA-1 (<i>n</i> = 317)
Clinical condition (SCORAD)	
Initial, median (P25–P75)	57.2 (52.2–62.2)
Severe	316 (99.7)
Moderate	1 (0.3)
Mild	0 (0)
Final, median (P25–P75)	27.6 (22.3–35.1)
Severe	57 (18)
Moderate	210 (66.3)
Mild	50 (15.7)
Clinical response	
Favorable	273 (86.1)
Number of decreased points SCORAD	30.1
Percentage of change in SCORAD	54.2
Unfavorable	43 (13.6)
Number of increased points SCORAD	7
Percentage of change in SCORAD	12.7
No change	1 (0.3)

AD, Atopic Dermatitis; P25, Percentile 25; P75, Percentile 75.

Table 3 Efficacy and adverse effects

Parameters, <i>n</i> (%) unless otherwise stated	30 J/cm ² (<i>n</i> = 102)	60 J/cm ² (<i>n</i> = 150)	<i>P</i>
Patients with AD treated with UVA-1 30 or 60 J/cm ² (<i>n</i> = 252)			
Clinical response			
Favorable	95 (93.1)	128 (85.3)	0.057
Unfavorable	7 (6.8)	21 (14)	
No change	0 (0)	1 (0.7)	
Final SCORAD			
Severe	14 (13.7)	27 (18)	0.367
Moderate	68 (66.7)	111 (74)	0.208
Mild	20 (19.6)	12 (8)	0.007
Number of decreased points SCORAD, median (P25–P75)	25.9 (18.2–32.5)	27.9 (20.4–33.5)	
Percentage of change in SCORAD, median (P25–P75)	50.1 (38.9–61.7)	53.5 (44.4–59)	
Adverse effects	22 (21.6)	38 (25.3)	0.491
Relapse (3 months)	17 (16.1)	20 (13.2)	0.584

AD, Atopic Dermatitis; P25, Percentile 25; P75, Percentile 75.

response was achieved at a median of 12.6 weeks (P25 = 6.6 – P75 = 23), 41 sessions (P25 = 20 – P75 = 74.6), and a total cumulative dose of 2.280 J/cm² (P25 = 1.080 – P75 = 4550).

The statistical model identified that the total cumulative dose is the only variable intervening on the response to treatment ($P = 5.371\text{e}^{-09}$), with a coefficient of 0.1189465.

Adverse effects

Eighty patients had AE (25.24%); the most frequent were pruritus (9.78%), exacerbation (9.46%), and erythema (7.26%). The others were present in less than 3% of the patients and included: desquamation, infection, tan, photosensitivity, edema, burn, headache, and skin pain. Patients having an unfavorable outcome had proportionally more AE than the favorable group, 72.73% (32 patients) and 17.59% (48 patients), respectively.

Relapse

From those patients having a favorable outcome (273), 86.1% were followed up for at least 3 months, from which 14.5% (34 patients) relapsed. Relapse rate was 0.029 on the first month, 0.089 at 2 months, and 0.144 at 3 months.

30 and 60 J/cm²

A ROC curve identified 30 and 60 J/cm² as the doses where the favorable response was more significant (value under the curve 0.6009), both with percentages of decrease in SCORAD greater than 50%. In both groups, the decrease in points and the percentage of decrease in the SCORAD were similar. Nevertheless, more patients achieved Mild SCORAD in the group of

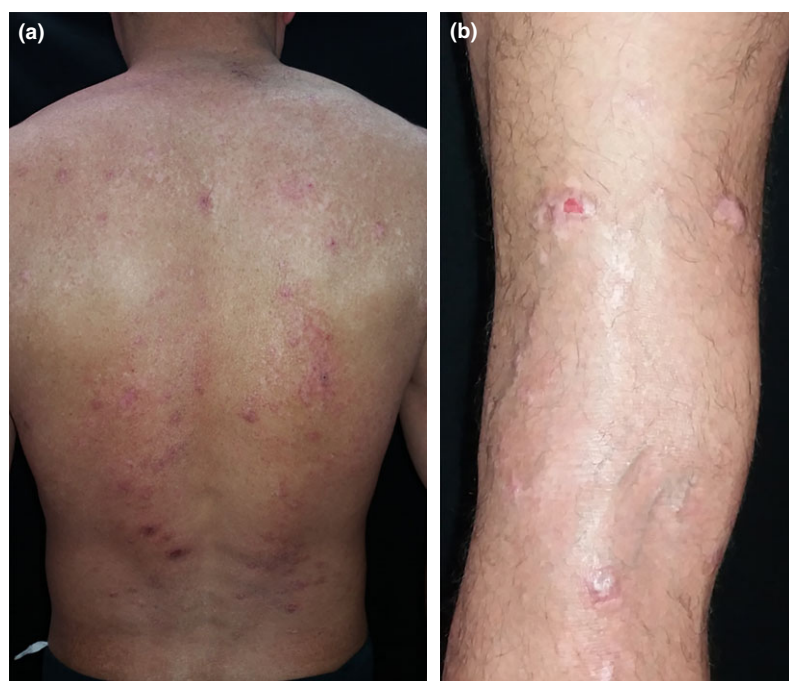


Figure 1 Adult male with chronic severe AD, intolerant to treatment with methotrexate and cyclosporine A and without response to azathioprine, before UVA-1. (a) Back. (b) Left lower limb.



Figure 2 After 30 sessions of UVA-1 and topical treatment with emollients and steroids. (a) Back. (b) Left lower limb.

30 J/cm². No differences in the percentage of adverse effects and in the relapse rate were identified (Table 3).

Discussion

UVA-1 has been utilized as a treatment for AD since 1992.⁷ The use of medium-dose UVA-1, in acute exacerbations of moderate to severe disease, and the use of narrowband-UVB for chronic scenarios is recommended by three systematic reviews of the literature.^{3,8,9} Although, treatment protocols are not standardized, medium-dose regimens (60 J/cm², between 30 and 70 J/cm²), administered in 10–24 sessions, 3–5 times per week for 3–8 weeks with a cumulative total dose of 276–1950 J/cm², are recommended in the literature.^{8,10} No studies have been made on the role of UVA-1 in chronic disease.

In this study, patients with severe disease – regardless of the type of AD – were treated with UVA-1; their clinical condition improved significantly (measured by SCORAD), independent of the number and type of topical or systemic treatment previously or concomitantly administered (Figures 1 and 2). The only variable that affected the positive outcome was the total cumulative dose; as it increases 1 J/cm², the final SCORAD decreases 0.1189465. The percentage of reduction in the SCORAD has been reported to be 7.7–34.7%; in our study, it was near 50% in all groups.^{3,8,9}

The most frequently used protocols for severe AD were medium dose, three times per week. For the initial response of our

cohort, the number of weeks,⁶ sessions (19), and cumulative dose (1080) were in the same range as those described in the literature, where it is only recommended for flares of the disease. However, for the final clinical response – statistically significant – more sessions (41), given in more weeks (12.6), and with a higher total cumulative dose (2280) were needed, giving a possible role as a chronically used therapy not previously reported.

In the systematic reviews, the presence of acute AE varies between 30.4% and 60%, and the risk of long-term side effects is not well established; in our study, AE were present in 25.24% of the patients; the rate of relapse is not clear, and in our study, it was low (0.144 at 3 months).^{3,8,9}

In the medium-dose group, two regimens were administered: 30 and 60 J/cm². In our study, both were equally effective, with a reduction in more than 50% of the SCORAD; also, there was no difference in AE and relapse. Nonetheless, more patients achieved mild SCORAD in the 30 J/cm² group. Therefore, UVA-1 either at 30 or 60 J/cm² is a good option; long-term effects and tolerability may favor the former.

Limitations

Limitations of this study include retrospective MR review, study design, the absence of control arm, and the difficulties of measuring the SCORAD based on MR.

Conclusions

For patients with severe atopic dermatitis, UVA-1 phototherapy is an effective alternative. Medium-dose 30 J/cm² administered three times per week is as safe and secure as medium-dose 60 J/cm² (recommended dose). This is the only study known by the authors that addresses therapy for a longer time and a higher cumulative dose in AD, with promising results owing to total cumulative dose as the variable that directly affects the positive outcome. Prospective studies are needed to confirm our findings.

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