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Targeted Medium Dose UVA-1 Phototherapy for the Treatment of Localized Scleroderma in the Skin of Color: Pros and Cons

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Abstract: Morphea is a connective tissue disorder characterized by skin homogenization. No protocol of therapy is agreed upon, due to the variation in disease presentations as well as follows up methods. UVA-1 is an effective therapy due to deep penetration of the skin. The aim of the study was to evaluate the efficacy, safety and side effects of medium dose (30 J/cm^2) UVA-1 phototherapy for the treatment of cases of morphea in darker skin types (Skin type III and IV). Twenty patients with plaque or linear morphea, received 30 sessions of medium dose UVA-1 phototherapy (30 J/cm^2), at a rate of 3 sessions per week for 10 weeks. Assessment was done by clinical score, collagen homogenization scores, MMP-1 immunohistochemistry and ultrasound (50 MHz) assessment of skin thickness before and 6 months after treatment. Results: Significant improvement on clinical assessment *(p=0.003)*, increase in collagen breakdown marked by significant increase of MMP-1 staining *(p=0.000)* and decrease skin thickness by ultrasound *(p=0.015)*. It can be concluded that medium dose UVA-1 phototherapy is effective and safe tool for the treatment of morphea in skin of color.

Key words: Morphea · UVA-1 phototherapy · Treatment · Skin type III-IV

INTRODUCTION

Morphea (localized scleroderma) is a rare connective tissue disease characterized by fibrosis of the skin +/- underlying tissues [1]. According to the extent of affection, morphea is classified into variable types: plaque, generalized, bullous, linear and deep morphea [2]. Clinically, morphea pass through three phases. First, the inflammatory phase with the lilac ring, second, the white ivory sclerotic plaque and finally, the atrophic depressed plaque [3]. Each of these clinical stages is a reflection of the underlying pathogenesis. Initiated by an external factor, the inflammation starts with vascular injury, which triggers an autoimmune response. The end result is disturbed collagen metabolism with excessive fibrosis and homogenization on one side and defective collagen breakdown on the other [3, 4]. Treatment options are variable, depending on the type of lesion, age of patient, degree of severity and feasibility of treatment. UVA-1 phototherapy is a promising treatment of cases of morphea owing to its long wavelength and deep penetration of the skin [5]. The aim of the study was to evaluate the efficacy, safety and side effects of medium dose (30 J/cm^2) targeted UVA-1 phototherapy for the treatment of cases of plaque or linear morphea in darker skin types (Skin type III and IV).

MATERIALS AND METHODS

The current prospective study included 20 patients. Patients were recruited from Dermatology Outpatient Clinic, Kasr Al Aini Hospital, Cairo, Egypt. The study protocol was approved by the Dermatology Research Ethical Committee (Derma REC) at Kasr Al-Aini Hospital. Informed consents were obtained from all patients.

Patients: The study included 20 patients with plaque or linear morphea.

Inclusion Criteria:

- Clinical and histopathological diagnosis of plaque or linear morphea.
- Study cases either newly diagnosed or stopped any treatments for the last three months.

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Table 1: Clinical evaluation of morphea lesions using Localized Scleroderma Cutaneous Assessment Tool (LoSCAT):

Parameter definition	0	1	2	3
Surface area score (SA): The extent of surface area involvement within each anatomic site	No involvement	= 1/3	>1/3-2/3	= > 2/3-3/3
Erythema (ER): The degree of erythema at the edge of a lesion	Normal or post inflammatory hyper or hypopigmentation	Slight erythema /pink	Red / clear erythema	Violaceous /marked erythema
Skin thickness score (ST): adopted from the modified Rodnan skin thickness system (compared to unaffected contralateral side)	Normal	Mild increase in thickness	Moderate increase in thickness, difficult to move skin	Severe thickness, unable to move skin
Lesion extension	--	--	--	Enlargement of an existing lesion

Exclusion Criteria:

- Atrophic cases of morphea.
- Patients with deep and systemic types of morphea.
- Contraindications to phototherapy (photosensitivity or skin cancers).

Plan of Therapy:

UVA-1 Treatment: UVA-1 phototherapy targeted lamp unit (Waldmann, UV 109 A, Germany) was used with a radiation spectrum in the range from 350 nm to 400 nm with a maximum peak at 370 nm. The dose per session was 30 joules/cm^2. A total of 30 sessions of UVA-1 phototherpay were delivered at a rate of 3 sessions per week over 10 weeks.

Assessment: To provide accepted comparability to previously conducted studies, several methods of assessment were used.

Clinical Assessment: Clinical scoring using the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) [6] (Table 1) was done at baseline evaluation, on monthly basis till 6 months after treatment for clinical scoring. Longitudinal evaluation was done 12 months after treatment for detection of recurrence.

Histopathological and Matrix Metalloproteinase-1 (MMP-1) Immunohistochemical Evaluation: 3 mm punch biopsies were obtained from treated lesions before and after treatment. The degree of collagen homogenization in papillary and reticular dermis was assessed by a dermatopathologist blinded to mode of treatment as follows: 0= no fibrosis, 1= mild fibrosis (homogenization with preserved spaces), 2= moderate fibrosis (homogenization with attenuated spaces) and 3= severe fibrosis (homogenization with no spaces). MMP-1 (Lab Vision, Co, Fremont, USA) (Cat. #RB-1536-P0) was used for staining 5 mm sections of treated lesions. Quantitative morphometric studies of MMP1 immunohistochemistry of all skin sections were performed using the image analyzer (Leica Qwin 500 LTD image analysis computer system, UK).

Ultrasound Biomicroscopy: The skin thickness was measured before and after treatment by high frequency ultrasound 50 MHz (paradigm ultrasound biomicroscopy plus Model P45) and the mean difference in skin thickness was recorded.

Statistical Analysis: Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Wilcoxon signed rank test for paired (matched) samples. Correlation between various variables was done using Spearman rank correlation equation. *P* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

RESULTS

The current study included 20 patients, 3 males (15%) and 17 females (85%), suffering from plaque or linear morphea. Ages ranged between 10-48 years with a mean of 27±12.8 years. Skin color ranged between Fitzpatrik skin type III in 9 patients (45%) and type IV in 11 patients (55%). Types of morphea included plaque morphea in 12 cases (60%) and linear morphea in 8 cases (40%). The duration of diseases ranged between 6 to 36 months, with a mean of 14±9 months. After 6 months of treatment, UVA-1 treated lesions showed a statistically significant decrease of clinical scores *(p=0.003)* (Fig. 1), as well as the collagen homogenization scores *(p=0.014)*. As regards the MMP-1 staining the increase in mean area

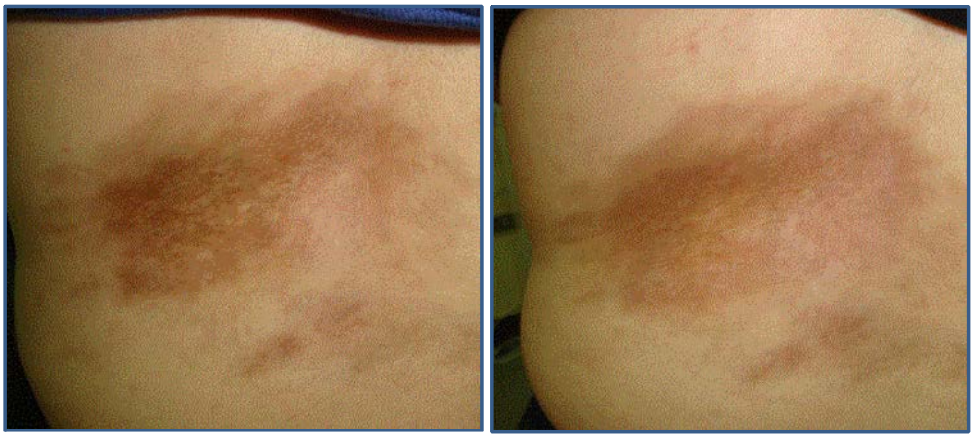

Fig. 1: Patient number 13, female patient aged 32 years with lesion of plaque morphea on the back, before (left) and after (right) UVA-1 treatment, with marked improvement of the sclerotic shiny appearance.

Table 2: Summary of results of patients' improvement after 6 months of treatment

Evaluation method	Treatment	UVA-1 phototherapy Mean± SD	*p* value
Clinical score (unit)	Before	6.24±1.32	0.003*
	After	4.53±1.21	
Collagen homogenization scores (unit)	Before	7.63±2.00	0.014*
	After	5.21±1.98	
MMP1 (Mean area%)	Before	15.389±4.031	0.000*
	After	41.632±6.53	
UBM dermal thickness (mm)	Before	1.23±0.18	0.015*
	After	1.03±0.15	

percent of staining before and after treatment was statistically highly significant *(p=0.000)*.Moreover, the mean decrease in skin thickness as assessed by 50 MHz ultrasound was statistically significant on the UVA-1 treated lesions *(p=0.015)*. Results are summarized in Table 2**.** Side effects included temporally pruritus related to the sessions in 3 patients (15%), hyperpigmentation of the treated lesions in 6 patients (30%). No cases of erythema or infection were reported. Follow up for 12 months showed disease recurrence in 5 (25%) of the study patients, 2 of which (40%) had activity at the same site of previously treated lesions while the remaining 3 (60%) had new lesions at new sites. The recurrence rate positively correlated with the disease duration (r= 0.673) (p=0.005), while patient's age and type of morphea did not show significant correlations.

DISCUSSION

Morphea is a fibrosing disorder of the skin [3] which has great impact on the patients' quality of life, either due to the related symptoms as pain or pruritus, cosmetic disfigurement or the disability associated with linear types overlying joints [7]. The management of scleroderma is challenging, with few published controlled trials in literature addressing the issue [1, 8]. All previous studies failed to provide a consensus for treatment, due to the variability of disease types and assessment parameters. However most of the previous work proved that UVA-1 phototherapy comes on the top of the treatment list [5]. UVA-1 (340-400 nm) gained its superiority through deep penetration of the skin causing apoptosis of the inflammatory T cells through the production of reactive oxygen species, thus achieving a state of immunosuppression [8]. Another target of UVA1 in morphea lesions is the increase level of MMP1 (matrix metalloproteinase 1) [9], which is a collagenase responsible for the breakdown of collagen. Anti MMP-1 antibodies were previously detected in patients with morphea [10], highlighting the importance of such pathway as a target of treatment. The current study emphasized the efficacy of UVA-1 through significant increase in the MMP-1 levels after treatment with UVA-1 phototherapy. Other suggested mechanisms in literature included downregulation of TGF-B (transforming growth factor beta), increase level of interferon-□ [8] and suppression of the proinflammatory cytokines TNF-α (transforming growth factor alpha) and interleukins 6 and 8 [9].

Most of the previously conducted studies on UVA-1 treatment of moprhea were localized to the United States and Europe, due to the availably of the high cost UVA-1 lamp units [8]. Accordingly, the evidence provided by those studies is restricted mainly to the category of fair skin individuals (Fitzpatrik skin types I&II). To the best of our knowledge, our group is one of the very few [11] to conduct studies on UVA1 use in dark skinned individuals. In accordance with previous studies [11-13], the current study proved the efficacy of UVA-1 in the treatment of cases of plaque/linear morphea. Our study is comparable to those studies as regards number of patients and treatment protocols. Moreover, we had multiple response assessment tools. However, the main issue of debate regarding UVA-1 treatment of morphea is the effective dose of therapy and factors influencing recurrence [1]. Starting the debate with the cut off points for definition of UVA-1 doses, where most European studies adopted the following dosage categories: low-dose UVA-1 (10-20 J/cm^2), medium dose UVA-1 (>20-70 J/cm^2) and high-dose UVA-1 (>70-130 J/cm^2) [8]. However, in The United States, doses are categorized as: low dose (20-40 J/cm^2), medium dose (>40-80 J/cm^2) and high dose (>80-120 J/cm^2) [14]. The current study proved the efficacy of medium dose UVA-1 phototherapy (30J/cm^2). Our results are in accordance with results provided by Su *et al.* [11], who also used 30 J/cm^2 of UVA-1 in the treatment of 35 patients with morphea of variable skin types (I, II, III and IV). In this study, patients showed significant clinical improvement as well as dermal thickness decrease via ultrasound (13 MHz). Another study yielded similar results when treated 17 morphea patients (skin type I & II) with medium dose UVA-1 [12]. Even lower doses of UVA-1 were proved effective by Prieira *et al.* [13], who treated 21 morphea patients (skin type I & II) with low dose 20 J/cm^2 and still achieved significant clinical improvement. On the other hand, some studies claimed that higher doses of UVA-1 are more superior in the treatment of fibrotic conditions [15]. However, a strong consideration is the hyperpigmentation induced by high doses of UVA-1 especially in skin of color, which might hinder further penetration of UVA-1. This theory suggests that lowerand less frequent doses of UVA-1 can provide longer term efficacy than high doses, especially in darker skin types [16]. Another major challenge in the management of morphea is the recurrence, where the recurrence ratesranged between 20 to 60% with different types of therapy [1]. Recurrence rate after UVA-1 treatment was around 46% as reported by Vasquez *et al.* [17]. Correlations showed that disease duration is the most important single predictive factor for recurrence. Other factors such as patient's age, type of morphea and disease activity did not show significant correlations with recurrence rates [17]. These data are in agreement with our results, where a follow up of 12 months detected a recurrence rate of 25%, positively correlating with disease duration.

In accordance with previous studies, Su *et al.* [11] andres *et al.* [12] and Prieira *et al.* [13] reported side effects of UVA-1 included pruritus and erythema, which were tolerable in all cases. Hyperpigmentation, on the other hand annoyed some patients due to unsatisfactory cosmetic outcome [8]. Among the important difficulties that were faced during case recruitment was the difficulty of compliance to the treatment protocol, which is a major drawback against UVA-1 phototherapy [8].

CONCLUSION

Medium dose UVA-1 phototherapy is an effective and safe tool for treatment of morphea in dark skinned individuals, limited by the availability of the UVA-1 units and long treatment protocols with an excepted incidence of recurrence.

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