CED
Clinical and Experimental Dermatology

Broadband ultraviolet A* vs. psoralen ultraviolet A in the treatment of vitiligo: a randomized controlled trial

M. El Mofty, M. Bosseila, H. M. Mashaly, H. Gawdat and H. Makaly

Phototherapy Unit, Dermatology Department, Cairo University, Cairo, Egypt

doi:10.1111/ced.12099

Summary

Background. Psoralen ultraviolet A (PUVA) and narrowband (NB)-UVB have been shown to be efficacious in the treatment of vitiligo. With large and repeated doses, UVA may lead to immediate skin darkening and to delayed tanning. Our previous experience with broadband (BB)-UVA in vitiligo showed encouraging results.

Aim. To test the efficacy of BB-UVA in vitiligo and to evaluate if it could provide an alternative treatment for this condition.

Methods. This prospective, randomized, controlled, comparative clinical trial enrolled 45 patients with vitiligo, who were randomly divided into three groups, with group A receiving UVA 15 J/cm^2/session, group B receiving UVA 10 J/cm^2/session, and group C receiving PUVA. The patients received three sessions/week for 5 months, with 60 sessions in total.

Results. At the mid-point of treatment, clinical response was significantly higher in patients receiving PUVA than in the other two groups At the end of the study, clinical response was comparable for groups A and C (UVA 15 J/cm^2 and PUVA, respectively), and both were significantly higher than the group receiving UVA 10 J/cm^2. Patients in the PUVA group responded mainly with perifollicular pigmentation, whereas those receiving UVA responded mainly with lesional tanning.

Conclusions. BB-UVA at a dose of 15 J/cm^2/session gives results for vitiligo that are comparable to PUVA, suggesting it might be useful when oral psoralens are contraindicated.

Introduction

Vitiligo is a common acquired skin disorder characterized by one or more patches of skin depigmentation, caused by the destruction of cutaneous melanocytes.[1]

Various therapies exist to treat vitiligo, including ultraviolet (UV) irradiation.[2] UV light is considered the 'gold standard' of treatment for vitiligo. There are several types of UV treatment, including psoralen (P)UVA,[3] narrowband (NB)-UVB (311 nm),[4] UVA-1, and broadband (BB)-UVA (320–400 nm).[6] PUVA and NB-UVB are well known for their effectiveness in treating patients with vitiligo.[7] BB-UVA has the ability to produce mainly immediate pigment darkening (IPD) and to a lesser extent, delayed tanning (DT) of human skin, but at large (8–25 J/cm^2/session) continuous doses, BB-UVA may result in both IPD and DT.[6] BB-UVA is not as well studied as the other methods for vitiligo treatment. In a previous pilot study, BB-UVA15 J/cm^2 was shown to be as effective as or more effective than NB-UVB, and it was also superior to the smaller dose of BB-UVA 5 J/cm^2/session.[8]

We performed a prospective, randomized, controlled, comparative study to compare the effect of BB-UVA phototherapy with PUVA (which is

Correspondence: Dr Heba Makaly, Phototherapy Unit, Dermatology Department, Cairo University, No. 8 El Sheikh El Ghazaly Street, off Mossadak Street. Dokki. Cairo, Egypt
E-mail: hebamash2@gmail.com

Conflict of interest: none declared.

Accepted for publication 26 October 2012

Correction added on 19 August 2013, after first online publication: *Typo corrected in title: 'Broadband ultraviolet B' has been changed to 'Broadband ultraviolet A'.

considered an established line of treatment) for treatment of vitiligo, and thus evaluate the possibility of UVA phototherapy as an alternative treatment method for this condition.

Methods

Ethics approval

The study was approved by the Dermatology Research Ethics Committee (Derma REC), and written informed consent for participation in the study was obtained from all patients.

Patients

In total, 45 patients with vitiligo (32 women, 13 men; mean ± SD age 29.3 ± 10.5 years, range 13–60) were recruited from our dermatology outpatient clinic over a period of 18 months (May 2009–December 2010).

Inclusion criteria were presence of generalized vitiligo in patients of either gender; and age > 12 years; with normal results for liver function and eye fundus examination. Exclusion criteria were presence of focal, segmental and acrofacial vitiligo, and any contraindication to photo(chemo)therapy exposure, such as pregnancy or presence of malignant or premalignant skin lesions.

A complete history was taken from all patients, and full clinical examination carried out. Photographic documentation of lesions was performed before and at the end of the study.

Study design and follow-up

This was a randomized controlled clinical trial, with randomization using the envelope concealment method. A patient flow chart, prepared according to CONSORT guidelines for reporting randomized controlled trials, is presented in Fig. 1.[9] The author responsible for assessing treatment response was blinded to the treatment allocation; the other two authors were not blinded.

The patients were treated with phototherapy (BB-UVA) or photochemotherapy (PUVA), three times per week for 5 months with a total of 60 sessions. Clinical evaluation was performed before (session 0), at the midpoint (session 30) and at the end (session 60) of treatment. The patients were randomized into three groups of 15 patients each. Group A received BB-UVA at a fixed dose of 15 J/cm^2 each session; any patients who could not tolerate the full session duration had their session split into two 10-min sessions with a 10-min break between sessions. Group B received broadband UVA at a fixed dose of 10 J/cm^2 per session. Group C was the control group and received PUVA therapy; they took 8-methoxypsoralen 0.5–0.7 mg/kg (10 mg/tablet; Neo-Meladinine®; Memphis Pharmaceuticals, Cairo, Egypt) with a meal, 2 h before exposure to UVA. For this group, sessions were started at a dose of 1 J/cm^2, and the doses were increased by 20% increments according to the patients' response and tolerance.

The radiation source for all groups was a UVA 1000 phototherapy cabin (Waldmann Industries, Schweinningen, Germany) equipped with 26 UVA

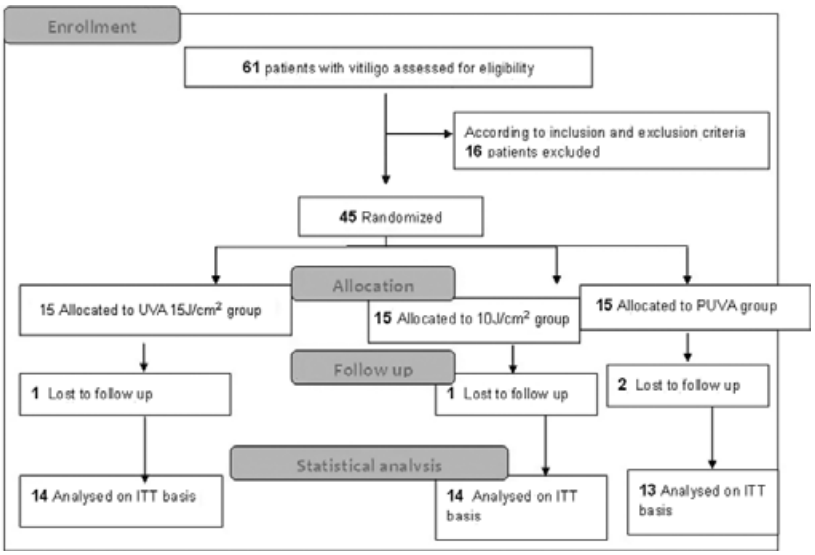

Figure 1 Patient flow chart, prepared according to CONSORT guidelines for reporting randomized controled trials (Schulz *et al.*[9]).

lamps, with a radiation spectrum of 315–400 nm, and a peak at 365 nm.

For follow-up, patients were clinically examined once a week during the study period, and findings were recorded and analysed at sessions 30 and 60. Extent of response was scored as 0–20% (1+; poor); 20–40% (2+; moderate); 40–60% (3+; good); 60–80% (4+; very good); > 80% (5+; almost complete response of the lesion (excellent).

Type of response (whether perifollicular pigmentation, marginal and/or tanning), clinical response (evidenced by gradual diffuse darkening of the whole vitiligo lesion, without perifollicular pigmentation), and side-effects such as phototoxic reactions (itching, burning sensation or erythema), thickening of the skin or koebnerization, were documented.

Statistical analysis

Numerical data were summarized using means ± SD, and categorical data were summarized as percentages. Comparisons between the three groups were performed for numerical variables using the Kruskal–Wallis test for numerical variables and for categorical variables using the χ^2 test or the Fisher exact test for small sample sizes.[10]

Results

The clinical data of patients are summarized in Table 1. At the start of the study, all groups were homogenous. Four patients (one woman in group A, one woman in group B and two men in group C) did not finish the study because of lack of compliance (three patients) and failure of response (one patient); these patients dropped out at sessions number 19, 20, 26 and 30. Thus, 41 patients finished the study.

The overall extent of response at the mid-treatment point and after treatment is presented in Table 2. The overall extent of response after treatment was as follows. For group A (UVA 15 J/cm^2/session), response was excellent in 7% of patients, good in 57%, and moderate in 36%; for group B, response was good in 29%, moderate in 64%, and poor in 7%; and for group C, response was very good in 23% and good in the remaining 77%.

Comparing the extent of response at mid-therapy (after 30 sessions), group C (PUVA) was significantly

Table 1 Summary of clinical data of patients in all groups at baseline.

	Group A (UVA 15 J/cm^2), *N* = 14	Group B (UVA 10 J/cm^2) *N* = 14	Group C (PUVA), *N* = 13
Age, years (mean ± SD)	24.4 ± 10.9	31.4 ± 14.0	30.3 ± 10.5
Disease duration, years (mean ± SD)	5.2 ± 3.3	8.3 ± 5.4	8.2 ± 7.6
Body involvement, % (mean ± SD)	0.30 ± 0.15	0.44 ± 0.23	0.34 ± 0.21
Male, *n* (%)	3 (21.4)	2 (14.3)	6 (46.1)
Female, *n* (%)	11 (78.6)	12 (85.7)	7 (53.9)
Disease activity*, *n* (%)	11 (78.6)	10 (71.4)	9 (69.2)

PUVA, psoralen ultraviolet A; UV, ultraviolet. *Defined as he appearance of new lesions or increase in diameter of the current lesions throughout the study.

Table 2 Extent of response at the mid-point and after therapy.

	Response			
Time	Group A (UVA 15 J/cm^2), *n* = 14	Group B (UVA 10 J/cm^2) *n* = 14	Group C (PUVA), *n* = 13	*P*
Mid-point	Moderate	Poor to moderate	Moderate to good	0.01*
After therapy	Moderate to excellent	Poor to good	Good to very good	< 0.001*

PUVA, psoralen ultraviolet A; UV, ultraviolet, *Significant.

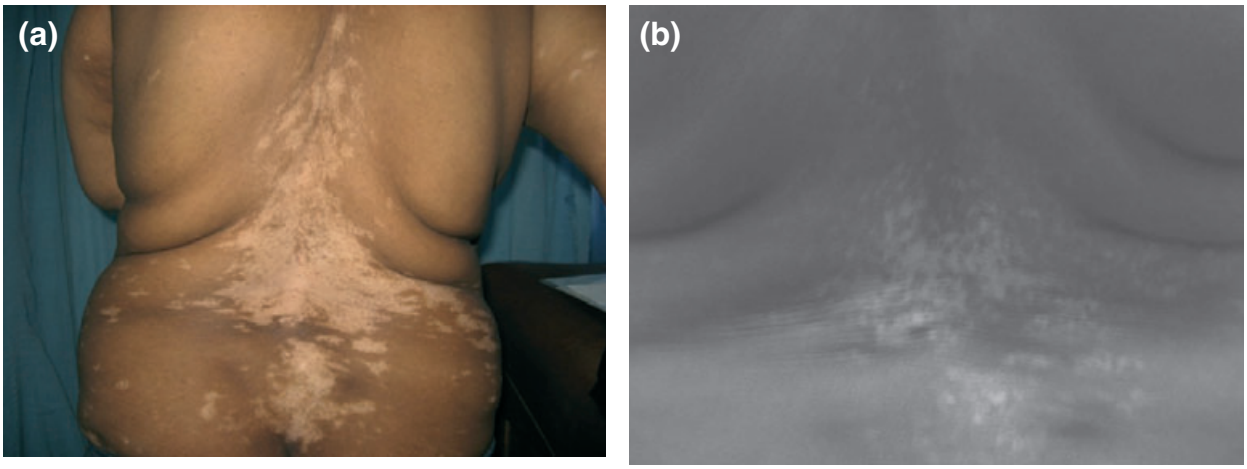

Figure 2 A pre-therapy and post-therapy comparison of the clinical response of a patient receiving UVA 15 J/cm^2 (Group A).

Table 3 Comparison between the type of response and side-effects between the two ultraviolet (UV)A groups.

After 60 sessions of therapy	Group A (UVA 15 J/cm^2), n = 14	Group B (UVA 10 J/cm^2) n = 14	P
Response after 60 sessions			
Perifollicular	8 (57.1)	7 (50.0)	1.00
Marginal macular	3 (21.4)	3 (21.4)	1.00
Tanning	13 (92.9)	11 (78.6)	0.60
Side-effects			
Phototoxic	3 (21.4)	5 (35.7)	0.68

better than both UVA groups (P = 0.01), whereas at study end, response was comparable for both groups A and C (UVA 15 J/cm^2 and PUVA respectively), and both were better than group B (P = 0.001; Table 2). Comparison of the clinical response of a patient receiving UVA 15 J/cm^2 is shown in Fig. 2.

Further assessment indicated that 100% of the patients achieved responses rated at least as 'good' in the PUVA group compared with 64% in the higher-dose UVA immunotherapy group (36% difference, 95% CI 11–61%; P < 0.02), indicating that PUVA was more effective, but nevertheless showing a greater improvement for the higher than for the lower dose of UVA, suggesting that the higher dose did have a effect.

There was no significant difference between groups A and B (UVA 15 and 10 J/cm^2, respectively) in type of clinical response or incidence of side-effects (Table 3). However, comparison between groups A and C and between groups B and C showed that patients responded to PUVA therapy mainly with perifollicular pigmentation (P < 0.01 for both), whereas patients responded to UVA therapy (both doses) mainly with DT of the vitiliginous patches (P < 0.001 for both; Table 4).

Phototoxic reactions were found to be higher in patients receiving PUVA (group C) than in patients receiving either dose of UVA (Table 4), but were significantly higher in patients receiving PUVA than in patients receiving the higher dose of UVA 15 J/cm^2 (group A; P < 0.02; Table 4).

Table 4 Comparison of types of response and side-effects between groups A and C, and between groups B and C, after 60 sessions.

	Group A (UVA 15 J/cm^2), N = 14	Group B (UVA 10 J/cm^2) N = 14	P	Group B (UVA 10 J/cm^2) N = 14	Group C (PUVA), N = 13	P
Type of response						
Perifollicular pigmentation	8 (57.1)	13 (100.0)	< 0.01	7 (50.0)	13 (100.0)	< 0.01
Marginal macular pigmentation	3 (21.4)	2 (15.4)	0.69	3 (21.4)	2 (15.4)	0.69
Tanning	13 (92.9)	1 (7.7)	< 0.001*	11 (78.6)	1 (7.7)	< 0.001*
Side effects						
Phototoxic	3 (21.4)	8 (61.5)	0.03	5 (35.7)	8 (61.5)	0.18
Thickening	0 (0.0)	3 (23.1)	0.06	1 (7.1)	3 (23.1)	0.24

PUVA, psoralen ultraviolet A; UV, ultraviolet. *Significant.

Discussion

In previous studies, both PUVA and NB-UVB have been shown to give very satisfactory response in treating vitiligo. However, the side-effects of psoralen intake in PUVA therapy, including nausea, continuous need for eye protection, and contraindications such as liver problems, young age and pregnancy limit its use. The fact that UVA, if given in large and repeated doses, may lead to IPD and DT, probably through an increase in the number and function of active melanocytes[11] was the rationale behind this study to use two different doses of UVA for vitiligo treatment.

In a previous pilot study,[6] BB-UVA 15 J/cm^2/session gave encouraging results, and was superior to the lower dose of 5 J/cm^2/session. The study suggested that BB-UVA may induce pigmentation by two different mechanisms: through DNA damage (UVA2) and/or through an oxygen-dependent mechanism (UVA1). The study also recommended trying other doses of UVA for vitiligo treatment, including the dose of 10 J/cm^2/session.

Based on the encouraging findings of the earlier pilot study,[6] and aiming to take a further step in evaluating the usefulness of BB-UVA as an alternative line of therapy, we undertook testing of different doses of UVA against PUVA. Although patients treated with BB-UVA at either dose achieved a significantly lower response than patients treated with PUVA at the midpoint (30 sessions), patients receiving the higher dose (15 J/cm^2/session) achieved a comparable response to those receiving PUVA therapy by the end of therapy (session 60).

Accordingly, UVA therapy without psoralen seems to produce a delayed response compared with PUVA therapy, and the response is dose-dependent. Thus, increasing the dose (e.g. up to 20 J/cm^2) or number of sessions might lead to a better response, as previously reported by El-Mofty *et al.*[6] It has also been suggested that BB-UVA sessions should be response-adjusted, rather than administered as a fixed dose, similar to the way in which treatments are adjusted for other types of phototherapy. Mahmoud *et al.*[12] came to a similar conclusion, noting that there was a dose–response correlation between the melanin content of patients and the UVA1 dose delivered at all time points of his study.

In the current study, there was variation in patient response at the end of therapy. BB-UVA phototherapy at 15 J/cm^2/session was comparable to PUVA, with the lowest response produced by BB-UVA 10 J/cm^2/session. Moreover, the subjects treated with BB-UVA responded mainly with DT (diffuse pigmentation) of their vitiliginous lesions, whereas those treated with PUVA responded mainly with perifollicular IPD. It has been shown previously that the IPD noticed with UVA irradiation can be explained by upward migration of melanin from the basal cells to the upper layers of the epidermis.[12]

Patients with pigmented skin of phototype III or higher were found to be able to tolerate maximum levels of light exposure (20–30 min of UVA light) without showing photoxicity.[13] This was similar for our patients, whose skin phototypes were all III or higher, with BB-UVA phototherapy at 10 and 15 J/cm^2/session producing a lower rate of phototoxic side-effects. Compared with PUVA, there was a significantly lower incidence of side-effects in the higher-dose UVA group, but not in the lower-dose UVA group. It would seem more logical for the lower dose to have fewer side-effects, and this difference may be related to the patients' skin type, as after randomization, it so happened that the lower-dose group comprised mainly skin types III and IV, while the higher-dose group comprised mainly skin types IV and V.

As mentioned above, UVA may induce pigmentation of vitiligenous skin through increased tyrosinase activity and formation of new melanin, leading to increases in the number of melanocytes and melanosomes, the degree of melanization, and the number of melanosomes transferred to keratinocytes.[11,14] The photoimmunological effects of UVA radiation in the form of production of various soluble mediators with anti-inflammatory and immuno-suppressive properties (e.g. interleukin-10, α-melanocyte-stimulating hormone and prostaglandin E2) may also be one of the possible mechanisms of UVA-induced skin regimentation in cases of vitiligo.[15] The fact that BB-UVA can induce skin pigmentation without clinical or histological signs of 'sunburn' damage, epidermal hyperplasia or thickening of the stratum corneum is an advantage of BB-UVA phototherapy.[16]

Conclusion

BB-UVA 15 J/cm^2 could offer a new alternative therapy for vitiligo when contraindications for psoralen exist, especially in patients with dark skin phototypes who can tolerate this dose of UVA without developing phototoxicty. However, further studies need to be performed on larger numbers of patients to further assess and confirm the efficacy and safety of BB-UVA for the therapy of vitiligo.

References

1 Kemp EH, Gavalas NG, Gawkrodger DJ, Weetman AP. Autoantibody responses to melanocytes in the depigmenting skin disease vitiligo. *Autoimmun Rev* 2007; **6**: 138–42.

2 McKay B, Chen F, Perumalswami CR *et al.* The tumor suppressor p53 can both stimulate and inhibit ultraviolet light-induced apoptosis. *Mol Biol Cell* 2000; **11**: 2543–51.

3 Parsad D, Kanwar AJ, Kumar B. Psoralen-ultraviolet A vs. narrow-band ultraviolet B phototherapy for the treatment of vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20**: 175–7.

4 Borderé AC, Lambert J, Van Geel N. Current and emerging therapy for the management of vitiligo. *Clin Cosmet Investg Dermatol* 2009; **12**: 15–25.

5 Bulat V, Situm M, Dediol I *et al.* The mechanisms of action of phototherapy in the treatment of the most common dermatoses. *Coll Antropol* 2011; **2**: 147–51.

6 El-Mofty M, Mostafa W, Youssef R *et al.* Ultraviolet A in vitiligo. *Photodermatol Photoimmunol Photomed* 2006; **22**: 214–16.

7 Wu CS, Lan CC, Wang LF *et al.* Effects of psoralen plus ultraviolet A irradiation on cultured epidermal cells *in vitro* and patients with vitiligo in vivo. *Br J Dermatol* 2007; **156**: 122–9.

8 El-Mofty M, Mostafa W, Youssef R *et al.* A comparative study between different ultraviolet modalities in the treatment of vitiligo. *Egypt J Dermatol Androl* 2011; **31**: 35.

9 Schulz KF, Altman DG, Moher D. CONSORT statement: updated guidelines for reporting parallel group randomised trials. *Br Med J* 2010; **340**: c332.

10 Dawson B, Trapp GT, eds. *Basic and Clinical Biostatistics*. Norwalk, CT: Appleton and Large, 2001.

11 Pathak MA. Effect of UV-A, UV-B and psoralen on *in vivo* human melanin pigmentation. *Pigment Cell* 1976; **3**: 291–8.

12 Mahmoud BH, Ruvolo E, Hexsel CL *et al.* Impact of long-wavelength UVA and visible light on melanocompetent skin. *J Invest Dermatol* 2010; **130**: 2092–7.

13 Hinds GA, Heald P. Cutaneous T-cell lymphoma in skin of color. *J Am Acad Dermatol* 2009; **60**: 359–75.

14 Luger TA, Schwarz T. Effects of UV light on cytokines and neuroendocrine hormones. In: *Photoimmunology*, (Krutmann J, Elmets C, eds). Oxford: Blackwell Science, 1995; 55–76.

15 Kullavanijaya P, Lim H. Photoprotection. *J Am Acad Dermatol* 2005; **52**: 937–58.

16 Mutzhas MF, Hölzle E, Hofmann C, Plewig G. A new apparatus with high radiation energy between 320 and 460 nm. physical description and dermatological applications. *J Invest Dermatol* 1981; **76**: 42–7.