A comparative study on efficacy of UVA1 vs. narrow-band UVB phototherapy in the treatment of vitiligo

Bakr Mohamed El-Zawahry[1], Dalia Ahmed Bassiouny[1], Rehab Mohamed Sobhi[1], Eman Abdel-Aziz[4], Naglaa Sameh Zaki[1], Dawoud Fakhry Habib[2] & Dalia Mamdouh Shahin[3]

[1]Department of Dermatology, Kasr El-Ainy University Hospital, Cairo University, Cairo, Egypt, [2]Department of Biochemistry, National Research Center, Cairo, Egypt, [3]Department of Dermatology, National Research Center, Cairo, Egypt and [4]Department of Dermatology, El-Talabah Hospital, Cairo, Egypt

Key words:
NB-UVB; serum IL2 R; UVA1; vitiligo

Correspondence:
Dr Dalia Ahmed Bassiouny, M.D., 51b Damascus Street, Mohandessien, Cairo, Egypt.
Tel: +202 7496759
Fax: +202 7496759
e-mail: daliabas73@yahoo.com

Accepted for publication:
30 November 2011

Conflicts of interest:
None declared.

Summary

Background/Purpose: Narrow-band ultraviolet B (NB-UVB) is considered the most effective and safe initial treatment for moderate-to-severe vitiligo but phototoxicity and possible carcinogenicity are the reported side effects. Ultraviolet A1 (UVA1) phototherapy has overlapping biological effects to NB-UVB and is relatively free of side effects associated with other phototherapy regimens.

Methods: Forty patients with vitiligo were included in this prospective, randomized controlled comparative clinical trial. Twenty patients received NB-UVB and 20 received UVA1 three times weekly for 12 weeks. The UVA1 group was divided into two subgroups. Ten patients received moderate and 10 received low dose of UVA1. Serum samples were collected before and after 36 sessions to assess soluble interleukin 2 receptor level. Patients were clinically evaluated before therapy then monthly according to Vitiligo Area Scoring Index (VASI) and Vitiligo European Task Force (VETF) scores. In addition, extent of response was determined by a blinded dermatologist comparing before and after therapy photographs. Pattern of response and side effects were recorded.

Results: NB-UVB was superior to UVA1 with a significant difference in blinded dermatological assessment ($P < 0.001$), percentage change in VASI score ($P < 0.001$) and percentage change in VETF area score ($P = 0.001$). No significant difference in side effects was observed between both groups. Comparing UVA1 subgroups, better response in moderate-dose group was found as regard to percentage change in VASI ($P < 0.001$) and percentage change in VETF area score ($P = 0.001$), while no significant difference was found in blinded dermatological assessment ($P = 0.121$).

Conclusion: NB-UVB phototherapy remains to be an effective and safe therapeutic option in vitiligo. Response to UVA1 in vitiligo seems to be dose dependent and seems to be of limited value in treatment of vitiligo as a monotherapy. Further studies combining it with other lines of therapy such as systemic steroids may prove beneficial.

Phototherapy is quite effective in treatment of vitiligo as 50–75% re-pigmentation can be routinely expected in vitiligo of recent onset (1). Phototherapy using oral psoralens and ultraviolet A (UVA) (320–400 nm) has been used for a very long time (2). Long-wave UVA1 (340–400 nm) therapy with low dose (10–30 J/cm^2), medium dose (40–70 J/cm^2) and high dose (up to 130 J/cm^2) has been available since 1981 (3). UVA1 penetrates deeper than UVA2 (320–340 nm) and thus is able to reach deep dermal components of the skin (4). UVA1 phototherapy has been successfully used in treatment of inflammatory skin diseases such as atopic dermatitis, localized scleroderma and granuloma annulare (5) with negligible side effects.

Serum levels of soluble interleukin 2 receptors (sIL2Rs) can be used to monitor *in vivo* immune activation and its elevation has been shown to be correlated with T cell-mediated immune diseases such as atopic dermatitis, psoriasis, lymphoma and systemic sclerosis (6). The pathogenesis of vitiligo was correlated with the activation of T lymphocytes. Serum levels of sIL2R were significantly higher in vitiligo patients than in healthy controls (7, 8). Several studies detected that serum level of sIL2R is significantly decreased in stable compared with active disease (9). The aim of this study was to determine the efficacy of UVA1 phototherapy in re-pigmentation of vitiligo lesions compared with the conventional narrow-band ultraviolet B (NB-UVB)

phototherapy. sIL2R level was measured as a monitor of disease activity during therapy.

Materials and methods

Forty patients with vitiligo were included in this prospective, randomized comparative clinical trial, in which the senior researcher who performed the final clinical assessment was blinded. The study was approved by the local ethical committee. Patients were recruited from the dermatology outpatient clinic in Kasr El-Ainy Teaching Hospital, Cairo University, and the study was performed over a period of 12 months (May 2010–May 2011). The patients included 15 males and 25 females; their ages ranged from 18 to 65 years. Inclusion criteria included the following: generalized vitiligo vulgaris involving more than 10% body surface area (none had segmental or localized acrofacial type; some patients had acral lesions as part of generalized vitiligo), age above 18 years and not receiving treatment for vitiligo within the past 4 weeks.

Patients were subjected to full history taking clinical evaluation using Vitiligo Area Scoring Index (VASI) score (10) and Vitiligo European Task Force (VETF) score (11) and photography using a Sony digital camera (8.2 megapixels, Minato, Tokyo, Japan) before, monthly and at the end of treatment. Informed consent was obtained from all cases. Blood samples (3 ml venous blood) were collected for assessment of serum level of sIL2R before and after 36 sessions of phototherapy (12 weeks).

Study design

Randomization was done using envelope concealed method. Patients were randomized into two equal study groups: group A which consisted of 20 patients received UVA1 phototherapy. Patients started at a dose of 5 J/cm^2/session and increased by 5 J/cm^2 every session. This group was subdivided into two subgroups. Group 1 included 10 patients who received a moderate dose of UVA1 (40–70 J/session). Patients, who could not tolerate the session duration, received it in two sessions with 10 min apart. Group 2 included 10 patients who received a low-dose UVA1 with maximum dose of 20 J/cm^2/session. The radiation source used was Waldmann lighting cabin (Waldmann GmbH, Villingen-Schwenningen, Germany) equipped with 40 UVA1 lamps, having a radiation spectrum of 340–400 nm. Phototherapy sessions continued three times weekly for 12 weeks. Group B consisted of 20 patients receiving NB-UVB phototherapy. A starting dose of 0.25 J/cm^2 was used and increased by 20% increments according to patient's response and tolerance until reaching minimal erythema dose then fixed. The radiation source was Waldmann lighting cabin (Waldmann GmbH, Villingen-Schwenningen, Germany) UV1000L. Two cabins were used (placed opposite each other to cover patient's whole body), with 26 lamps. Phototherapy sessions continued three times weekly for 12 weeks at Kasr EL-Ainy phototherapy unit. To record clinical response, the following was performed:

a. Percentage change in VASI score and percentage change in VETF area score were calculated before and at the end of 36 sessions.

b. Before and after therapy, photographs were evaluated by a blinded dermatologist, rating the response as poor, moderate, good, very good and excellent according to the extent of re-pigmentation (0–20%, 20–40%, 40–60%, 60–80% and > 80%, respectively).

c. Pattern of response was determined as perifollicular pigmentation, marginal macular pigmentation or diffuse tanning.

d. Side effects resulting from phototherapy were also recorded. They included phototoxic reactions (itching, burning sensation and erythema), thickening of the skin and koebnerization.

Measurement of sIL2R by enzyme-linked immunosorbent assay technique

Three millilitres of venous blood was aseptically collected from each patient. Serum sIL2R was determined by an enzyme amplified sensitivity immunoassay (enzyme-linked immunosorbent assay) according to Taniguchi and Minami (12) and the kit was purchased from BioVendor research and diagnostic products (BioVendor GmbH, Heidelberg, Germany).

Statistical analysis

Data were statistically described in terms of range, median, frequencies and percentages when appropriate. The data were non-normal and all the statistics were done using non-parametric methods. Comparison of numerical variables between the study groups was done using Mann–Whitney U-test for independent samples. Within group, comparison between pre- and post-values of IL-2 was done using Wilcoxon signed-rank test for paired (matched) samples. For comparing categorical data, chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than five. P value < 0.05 was considered statistically significant. All statistical calculations were done using Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and Statistical Package for the Social Science (SPSS) (SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

There was no significant difference between patients of both groups in the different parameters (Table 1). The number of patients with disease activity was the same in both groups (13 patients in each).

Response to therapy in group A vs. group B

Clinical assessment by blinded physician also showed significant difference ($P < 0.001$) with better response in NB-UVB patients. In group A, one patient (5%) had a good (Fig. 1), four (20%) had a moderate and 12 (60%) had a poor response, and three patients (15%) showed widening of vitiligo lesions. The pattern of response was in the form of perifollicular re-pigmentation in five patients (25%) and tanning in two patients (10%). In group B, however, one patient (5%) had excellent, five (25%) had very good (Fig. 2), seven (35%) had good, three (15%) had

Table 1. Comparison of different parameters between UVA1 and NB-UVB patients

	UVA1	NB-UVB	P value
Sex			
Males	9 (45%)	6 (30%)	0.327*
Females	11 (55%)	14 (70%)	
Disease activity	13 (65%)	13 (65%)	0.821*
Skin type			
III	9 (45%)	15 (75%)	0.53*
IV	11 (55%)	5 (25%)	
History of koebnerization			
−ve	10 (50%)	7 (35%)	0.337*
+ve	10 (50%)	13 (65%)	
+ve family history	16 (80%)	14 (70%)	0.465*
Median age (range)	24.5 (18–63)	22.5 (18–65)	0.573**
Median duration in years (range)	4 (0.5–20)	6 (1–20)	0.276**
Median VASI score (range)	8.9 (1.8–35.8)	13.8 (2.3–67.5)	0.159**
Median VETF			
Area score (range)	10.3 (2–36)	14.6 (3.5–74.5)	0.273**
Staging score (range)	8 (4–12)	8 (2–9)	0.379**

*P value calculated by chi square (<0.05 statistically significant).
**P value calculated by Mann–Whitney (<0.05 statistically significant).
NB-UVB, narrow-band ultraviolet B; UVA1, ultraviolet A1; VASI, Vitiligo Area Scoring Index; VETF, Vitiligo European Task Force.

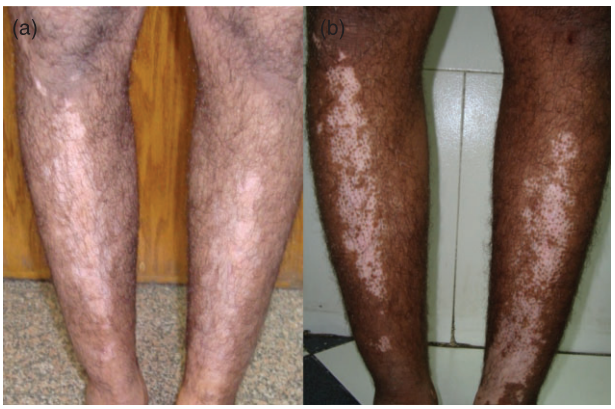

Fig. 1. A 60-year-old male patient (a) before therapy and (b) showing a good clinical response (40–60% re-pigmentation) after 36 sessions with ultraviolet A1.

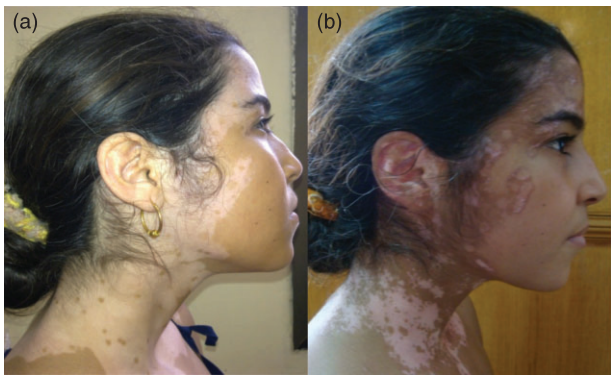

Fig. 2. A 20-year-old female patient (a) before therapy and (b) showing a very good clinical response (60–80% re-pigmentation) after 36 sessions with narrow-band ultraviolet B.

moderate and four (20%) had poor response. The pattern of response was in the form of perifollicular re-pigmentation in 14 patients (70%) and marginal re-pigmentation in three patients (15%).

Percentage change in VASI and VETF area scores: a highly significant difference was found between patients in UVA1 and NB-UVB groups as regard to percentage change in VASI ($P < 0.001$) and percentage change in VETF area score ($P = 0.001$) (Table 2).

Total cumulative dose in UVA1 group was 1055.33 ± 494.78 J/cm^2 [mean ± standard deviation (SD)], while in NB-UVB group, it was 46.12 ± 21.65 J/cm^2. *Side effects*: no side effects were reported in group A patients, while in group B, one patient (5%) had phototoxic reaction and one patient (5%) showed koebnerization with no statistically significant difference ($P = 0.349$).

Response to therapy in UVA1 subgroups (medium- and low-dose UVA1)

Clinical assessment by blinded physician showed no significant difference ($P = 0.121$). In the moderate-dose group, one patient (10%) had a good, three (30%) had a moderate and four (40%) had a poor response, and two patients (20%) showed widening of vitiligo lesions. The pattern of response was in the form of perifollicular re-pigmentation in three patients (30%) and tanning in one patient (10%). In the low-dose group, one patient (10%) had moderate response, eight (80%) had poor response and one patient showed widening of vitiligo lesions. The pattern of response was in the form of perifollicular re-pigmentation in two patients (20%) and tanning in one patient (10%).

Percentage change in VASI and VETF area scores: a highly significant difference was found between patients in both subgroups as

Table 2. Comparison of response to therapy in UVA1 and NB-UVB patients after 36 sessions

	UVA1 Median (range)	NB-UVB Median (range)	P value
% change in VASI score	0% (−13.3 to 37.9)	−6.7% (−50.9 to 26.4)	0.000**
VETF			
% change in area score	0% (−12.5 to 75)	−4.4% (−33.8 to 26.9)	0.001**
% change in staging score	0% (−25 to 0)	0% (−14 to 0)	0.971
% improvement by blinded physician			
Poor response	15 (75%)	4 (20%)	0.000*
Moderate-to-excellent response	5 (25%)	16 (80%)	

*P value < 0.05 statistically significant (calculated by Mann–Whitney).
**P value < 0.05 statistically significant (calculated by chi square).
NB-UVB, narrow-band ultraviolet B; UVA1, ultraviolet A1; VASI, Vitiligo Area Scoring Index; VETF, Vitiligo European Task Force.

Table 3. Comparison of response to therapy in low- and moderate-dose UVA1 subgroups after 36 sessions

	Low dose Median (range)	Moderate dose Median (range)	P value
% change in VASI	0% (−1.6 to 19.8)	0% (−13.3 to 37.9)	0.000*
VETF			
% change in area score	0% (−1.2 to 75)	0% (−12.5 to 14.9)	0.001*
% change in staging score	0% (−25 to 0)	0%	0.971
% improvement by blinded physician			
Poor response	9 (90%)	6 (60%)	0.121
Moderate-to-excellent response	1 (10%)	4 (40%)	

*P value < 0.05 statistically significant.
UVA1, ultraviolet A1; VASI, Vitiligo Area Scoring Index; VETF, Vitiligo European Task Force.

Table 4. Comparison of sIL2R levels in different patient groups before and after therapy

	sIL2R before therapy Median (range)	sIL2R after therapy Median (range)	P value
UVA1	1.1 (0–84.6)	0.4 (0–231)	0.167
NB-UVB	3.4 (0.02–21.5)	0.2 (0–36.1)	0.050
Low-dose UVA1	2.5 (0–84.6)	1.4 (0–231)	0.959
Moderate-dose UVA1	0.5 (0–64.4)	0.02 (0–0.8)	0.028*

*P value < 0.05 statistically significant.
NB-UVB, narrow-band ultraviolet B; sIL2R, soluble interleukin 2 receptor; UVA1, ultraviolet A1.

regard to percentage change in VASI ($P < 0.001$) and percentage change in VETF area score ($P = 0.001$) with better response in moderate-dose group (Table 3).

Total cumulative dose in moderate-dose group was 1494.5 ± 246.51 J/cm^2 (mean ± SD), while in low-dose group, it was 616.15 ± 165.622 J/cm^2 (mean ± SD). No Side effects were reported in both groups.

Serum levels of sIL2R

No significant difference was present in sIL2R level between both groups before therapy ($P = 0.715$). In group A, no significant difference between sIL2R levels before and after treatment ($P = 0.167$) was found, while a borderline significant decline was present in group B patients ($P = 0.050$). On analyzing sIL2R levels in UVA1 subgroups, however, a rise of sIL2R level was found in low-dose subgroup, while a significant decline in its level was present in moderate-dose patients ($P = 0.02$) (Table 4).

Discussion

Vitiligo vulgaris is an acquired chronic pigmentation disorder characterized by white patches, often symmetrical, which usually increase in size with time, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes (11).

The prevalence and mean age of onset of vitiligo vary considerably among different geographical regions and ethnic groups.

Approximately one-half of patients with vitiligo acquire the disease before the age of 20 years, and the incidence decreases with increasing age (13). The peak age of onset in all series was between 10 and 30 years (14), which was the case in our patients. Similar to our study, studies have shown a predominance of female patients, but this observation is not statistically significant and is most likely because of the greater likelihood of females to seek medical attention for cosmetic problems (13).

The aetiology of vitiligo is unknown and several hypotheses (including autoimmune, neural, radical, self-destruction and inherent defect theories) have been proposed to explain its pathogenesis (15). The autoimmune theory proposes that alterations in humoral or cellular immunity result in destruction of melanocytes (16). Destruction of melanocytes may be directly mediated by autoreactive CD8+ T cells which have been demonstrated in perilesional vitiligo skin. Melanocyte-specific T cells have also been detected in peripheral blood of vitiligo patients (17).

Ultraviolet radiation both in the range of UVB and UVA are first line treatment modalities for vitiligo affecting more than 10–20% of the skin surface (18). NB-UVB is considered to be the most effective and safe initial treatment of choice for the treatment of moderate-to-severe vitiligo (19). However, reported side effects with NB-UVB phototherapy include the following: erythema, pruritis and xerosis (20). NB-UVB radiation was also reported to be more carcinogenic than UVA radiation (21). The biological effects of NB-UVB include immunomodulatory and anti-inflammatory effects on human skin through the following: production of soluble mediators, modulation of expression of cell-surface markers, induction of apoptosis in pathogenetically relevant cells (22) and induced pigmentation in human epidermis (23).

UVA1 therapy is categorized as low dose (20–40 J/cm^2), medium dose (40–80 J/cm^2) and high dose (80–120 J/cm^2). It was found to be beneficial in several skin diseases including morphea, scleroderma and other sclerosing skin conditions, chronic graft versus host disease (GVHD), atopic dermatitis, cutaneous mastocytosis, pityriasis lichenoides chonica (PLC) and pityriasis lichenoides et varioliformis acuta (PLEVA), mycosis fungoides and systemic lupus erythematosus (24).

UVA1 phototherapy has similar biological effects to NB-UVB, which include induction of apoptosis in skin infiltrating leukocytes (25). Whereas UVA1 apparently does not increase IL-10 as UVB does, it suppresses proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and IL-12, which activate antibody-dependent cell-mediated cytotoxicity and inflammatory leukocytes such as eosinophils. UVA1 exposure, like UVB exposure, can also cause the photo-isomerization of trans-urocanic acid and increased levels of cis-urocanic acid, which is known to have immunoregulatory function and has been associated with TNF-α induction (26). UVA1 exposure can also lead to decreased levels of interferon gamma (IFN-γ) and intercellular adhesion molecule type 1 (ICAM-1), which are involved in lymphocyte activation and trafficking into tissues, respectively (27). Both types of UV radiation produce increased number and activity of melanocytes, increased melanin density, elongation and branching of dendrites, with increased transfer of more heavily melanized melanosomes to keratinocytes, which is seen by the naked eye as increased pigmentation or tanning (28). UVA1 therapy also is relatively free of side effects associated with other phototherapy regimens, including erythema and cellular transformation (24).

Broad-band (BB)-UVA alone, in appropriate dose, may be of important therapeutic value in vitiligo (4). However, no previous studies were done evaluating the possible therapeutic role of UVA1 in treatment of vitiligo. Given the beneficial immune modulatory and pigment inducing effects of UVA1 and the fact that it is relatively free of side effects associated with other phototherapy regimens, this comparative study exploring the possible therapeutic efficacy of two UVA1 dose regimens, medium and low dose, compared with NB-UVB in treatment of vitiligo was done.

Assessment of vitiligo was done in the present case series by the traditional method (a blinded dermatologist examining before and after photographs of the patients) as well as the more objective VASI and VETF scores recommended by the British association of dermatologists (29).

As regard to response to therapy in NB-UVB group, the results were similar to previous reports by Anbar *et al.* (30), where 75% of the patients showed marked improvement (48%) and moderate response (27%) while mild response was found in 25% of cases and by Chen *et al.* (31), who reported excellent-to-moderate improvement in 73% of his cases and <25% re-pigmentation in 27% of cases. In the present study, median VASI score was reduced by 6.7%. Moreover, median VETF area score was reduced by 4.4%, while the median staging score was not changed. Owing to the relatively recent recommendation of using VASI and VETF scores, no studies utilizing NB-UVB and these assessment methods were available for comparing with our results. Side effects in NB-UVB group of patients were minimal, which is similar to previous reports (20).

In patients of group A (UVA1), after 36 sessions of therapy, only 25% of cases showed improvement (5% very good and 20% moderate response) while 75% of cases showed poor response. Response pattern was mostly perifollicular pigmentation like group B patients. No phototoxic reactions occurred but 90% of cases complained of marked tanning of normal skin which exaggerated the appearance of vitiligo lesions. An additional drawback was the long duration of UVA1 sessions, which was more in patients receiving moderate dose. No previous studies were found using UVA1 in treatment of vitiligo.

BB-UVA was used in 20 selected patients with >60% re-pigmentation observed in 50% of cases suggesting UVA as an alternate therapy for vitiligo (4), which was not the case in the current series using UVA1. UVA therapy without psoralen shows a delayed onset of response than UVA therapy preceded by psoralen intake in that study, suggesting that maybe prolonging the duration of therapy with UVA1 more than 36 weeks might improve the response.

In the present study, the UVA1 group of patients was further subdivided into low- and moderate-dose subgroups. No significant difference was found when comparing assessment by

blinded physician in both subgroups. However, a significant difference was present in percentage of VASI score change in cases receiving low dose compared with those on moderate dose ($P < 0.001$). Similarly, a significant increase in VETF area score in cases receiving low dose compared with those on moderate dose was present ($P = 0.001$). These findings point to a slight improvement with higher dose of UVA1. The response of BB-UVA is dose dependent; increasing the dose/session leads to a better response if given more time (4), which might be the case in UVA1. However, the long duration of the sessions of the moderate group of patients was a source of discomfort to the patients, thus in the opinion of the authors using high-dose UVA1 would not be practical.

Although the number of patients with disease activity was the same in both groups and the patients were randomized, there was a difference in baseline sIL2R level which although high was statistically non-significant. It may however reflect a higher degree of disease activity which may have influenced the results. A borderline significant difference was present between sIL2R before and after treatment in group B patients, which points possibly to a reduction in T cell activity in the NB-UVB group, which was reflected in the form of clinical improvement. On the other hand, the insignificant decline of sIL2R level in low-dose UVA1 group opposed to the significant decline in moderate-dose group is a marker of reduced T cell activity and better disease control.

On comparing both lines of phototherapy, NB-UVB was clearly superior to UVA1 in all aspects of assessment. These findings denote that although both types of phototherapy have some overlapping biological activities, it seems that NB-UVB has an advantage over UVA1, which may be explained by the effect of UVB on melanocyte migration. Researches on mechanisms by which melanocytes migrate from the lower hair follicle to the epidermis have focused on cytokine release by keratinocytes. It has been postulated that basic fibroblast growth factor, which is released by cultured keratinocytes after UVB radiation, is the mitogen for melanocytes (32). Moreover, endothelin-1, a cytokine secreted by cultured keratinocytes constitutively and secondary to exposure to UVB light, causes proliferation and differentiation of melanocytes as well (33).

Conclusions

NB-UVB phototherapy remains to be an effective and safe therapeutic option in vitiligo. Although UVA1 has proved beneficial in several debilitating skin conditions, it seems to be of limited use in treatment of vitiligo as a monotherapy. Further studies, combining it with other lines of therapy such as systemic steroids, may prove beneficial.

References

1. Hercogova J, Buggiani G, Prignano F, Lotti T. A rational approach to the treatment of vitiligo and other hypomelanoses. *Dermatol Clin* 2007; **25**: 383–392.
2. Bhatnagar A, Kanwar AJ, Parsad D. Comparison of systemic PUVA and NB-UVB in the treatment of vitiligo: an open prospective study. *J Eur Acad Dermatol Venereol* 2007; **21**: 638–642.
3. Dawe RS. Ultra violet A1 phototherapy. *Br J Dermatol* 2003; **148**: 626–637.
4. El-Mofty M, Mostafa W, Youssef R *et al*. Ultraviolet A in vitiligo. *Photodermatol Photoimmunol Photomed* 2006; **22**: 214–216.
5. Rombold S, Lobisch K, Katzer K, Grazziotin TC, Ring J, Eberlein B. Efficacy of UVA1 in phototherapy in 230 patients with various skin diseases. *Photodermatol Photoimmunol Photomed* 2008; **24**: 19–23.
6. Yeo UC, Yang YS, Park KB *et al*. Serum concentration of the soluble interleukin-2 receptor in vitiligo patients. *J Dermatol Sci* 1999; **19**: 182–188.
7. Galadari I. Serum levels of soluble IL-2R in vitiligo patients in UAE. *Eur Ann Allergy Clin Immunol* 2005; **37**: 109–111.
8. Caixia T, Hongwen F, Xiran L. Levels of soluble interleukin-2 receptor in the sera and skin tissue fluids of patients with vitiligo. *J Dermatol Sci* 1999; **21**: 59–62.
9. Sun X, Xu A, Wei X. Genetic epidemiology of vitiligo: a study of 815 broadbands and their families from south China. *Int J Dermatol* 2006; **45**: 1176–1181.
10. Hamzavi I, Shapiro J, Jain H, McLean D, Zeng H, Lui H. Parametric modeling of narrowband UVB phototherapy for vitiligo using a novel quantitative tool. *Arch Dermatol* 2004; **140**: 667–683.
11. Taieb A, Picardo M. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. *Pigment Cell Res* 2006; **20**: 27–35.
12. Taniguchi T, Minami Y. The IL-2/IL-2 receptor system: a current overview. *Cell* 1993; **73**: 5–8.
13. Sitek JC. Vitiligo loss of cutaneous pigmentation. *Tidsskr Nor Laegeforen* 2006; **126**: 2370–2372.
14. Ortonne JP, Bahadoran P, Fitzpatrick TB, Mosher DB, Hori Y. Hypomelanosis and hypermelanosis. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, eds. *Fitzpatrick's dermatology in general medicine*, 6th edn. New York: McGraw-Hill, 2003, 839–847.
15. Namian AM, Shahbaz S, Samanpoor R, Namazi MR, Dehghani F, Sarvestani EK. Association of interferon-gamma and tumor necrosis factor-alpha polymorphism with susceptibility to vitiligo in Iranian patients. *Arch Dermatol Res* 2009; **301**: 21–25.
16. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their relatives. *Pigment Cell Res* 2003; **16**: 208–214.
17. Ongenae K, Van Geel N, Naeyaert JM. Evidence for an autoimmune pathogenesis of vitiligo. *Pigment Cell Res* 2003; **16**: 90–100.
18. Falabella R, Barona MI. Update on skin repigmentation therapies in vitiligo. *Pigment Cell Melanoma Res* 2008; **22**: 42–65.
19. Parsad D, Kanwar AJ, Kumar B. Psoralen-ultraviolet A vs narrowband ultraviolet B phototherapy for the treatment of vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20**: 175–177.
20. Martin JA, Laube S, Edwards C, Gambles B, Anstey AV. Rate of acute adverse events for narrow-band UVB and Psoralen-UVA phototherapy. *Photodermatol Photoimmunol Photomed* 2007; **23**: 68–72.
21. De Gruijl FR. p53 mutations as a marker of skin cancer risk: comparison of UVA and UVB effects. *Exp Dermatol* 2002; **1**: 37–39.
22. Krutmann J, Morita A. Mechanisms of ultraviolet UVB and UVA phototherapy. *J Invest Dermatol* 1999; **4**: 70–72.

23. Hachiya A, Kobayashi A, Yoshida Y, Kitahara T, Takema Y, Imokawa G. Biphasic expression of two paracrine melanogenic cytokines, stem cell factor and endothelin-1, in ultraviolet B-induced human melanogenesis. *Am J Pathol* 2004; **165**: 2099–2109.
24. York NR, Jacobe HT. UVA1 phototherapy: a review of mechanism and therapeutic application. *Int J Dermatol* 2010; **49**: 623–630.
25. Breuckmann F, von Kobyletzki G, Avermaete A, Kreuter A, Mannherz HG, Altmeyer P. Apoptosis of human dermal endothelial cells as a potential side effect following therapeutic administration of UVA1 irradiation: preliminary results. *Arch Dermatol Res* 2002; **294**: 303–309.
26. Skov I, Hansen H, Allen M *et al.* Contrasting effects of ultraviolet A1 and ultraviolet B exposure on the induction of tumour necrosis factor alpha in human skin. *Br J Dermatol* 1998; **138**: 216–220.
27. Szegedi A, Simics E, Aleksza M *et al.* Ultraviolet-A1 phototherapy modulates Th1/Th2 and Tc1/Tc2 balance in patients with systemic lupus erythematosus. *Rheumatology* 2005; **44**: 925–931.
28. McGregor J, Hawk J. Acute effects of ultraviolet radiation on the skin. In: Freedberg I, Eisen A, Wolf K *et al.*, eds. *Fitzpatrick's dermatology in general medicine*, 5th edn, Vol. 134. New York: McGraw-Hill, 1999, 1555.
29. Gawkrodger DJ, Ormerod AD, Shaw L *et al.* Guideline for the diagnosis and management of vitiligo. *Br J Dermatol* 2008; **159**: 1051–1076.
30. Anbar TS, Westerhof W, Abdel-Rahman AT, El-Khayyat MA. Evaluation of the effects of NB-UVB in both segmental and non segmental vitiligo affecting different body sites. *Photodermatol Photoimmunol Photomed* 2006; **22**: 157–163.
31. Chen GY, Hsu MM, Tai HK *et al.* Narrow-band UVB treatment of vitiligo in Chinese. *J Dermatol* 2005; **32**: 793–800.
32. Gordon PR, Mansur CP, Gilchrest BA. Regulation of human melanocyte growth, dendricity, and melanization by keratinocyte derived factors. *J Invest Dermatol* 1989; **92**: 565–572.
33. Norris DA, Horikawa T, Morelli JG. Melanocyte destruction and repopulation in vitiligo. *Pigment Cell Res* 1994; **7**: 193–203.