Acta Dermatovenerol Croat 2007;15(1):10-14 ORIGINAL SCIENTIFIC ARTICLE

Treatment of Vitiligo with Narrow-Band UVB and Topical Gel Containing Catalase and Superoxide Dismutase

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SUMMARY Narrow-band UVB has been reported to be efficacious in patients with vitiligo. The epidermis of patients with vitiligo showed reduction in the levels of catalase, in association with high levels of hydrogen peroxidase (H_2O_2) that is toxic for melanocytes. Based on these findings, we studied the efficacy and safety of a topical gel containing catalase and superoxide dismutase (Vitix®) in combination with narrow-band UVB. The study included 22 patients of which 19 completed the 6-month study period. Patients applied the gel containing catalase and superoxide dismutase twice a day and received narrow-band UVB 3 times per week. Two different dermatologists evaluated the grade of repigmentation by photograph comparison. At the end of therapy, more than 50% of overall repigmentation was noticed in 11 of 19 (57.9%) patients. More than 75% repigmentation was recorded in three (15.79%), 26%-50% repigmentation in six (31.58%) patients and 1%-25% repigmentation in one (5.26%) patient, whereas one (5.26%) of 19 patients showed no repigmentation at all. The best response was achieved on the face and neck, with more than 50% repigmentation observed in 11 of 14 (78.6%) patients. Development of new lesions was not observed. Adverse events were mild and transient. The study showed that the combination therapy of narrow-band UVB and gel containing catalase and dismutase is a therapeutic option that could be considered in the management of vitiligo. Further evaluation of this combination in multicenter, double-blind, placebo-controlled studies should be undertaken.

KEY WORDS: vitiligo treatment, narrow-band UVB, catalase

INTRODUCTION

Vitiligo is an acquired idiopathic hypomelanotic disorder characterized by sharply demarcated depigmented macules of variable size and shape (1). The incidence is 1%-2% without sexual predilection (2,3). Functional melanocytes disappear from the lesional area of the epidermis although some authors have shown that melanocytes are still present even in the long-standing disease (4). The exact pathogenesis of vitiligo remains unknown. Several hypotheses on the pathogenesis exist, e.g., autoimmune, neural, self-destruction and biochemical, however, none is fully explana-

tory (3,5). The biochemical hypothesis on the melanocyte destruction in vitiligo in part refers to excessive production of oxidation products such as hydrogen peroxidase (H_2O_2) and low catalase activity in keratinocytes of the involved and uninvolved epidermis (3,6-8), which was demonstrated *in vivo* and *in vitro* (6,7). The overproduction of H_2O_2 is the result of high levels of monoamine oxidase A and of a defective recycling of tetrahydrobiopterin, which is an essential cofactor for the hydroxylation of phenylalanine to tyrosine *via* phenylalanine hydroxylase (9). The H_2O_2 overproduction could also account for the low catalase activity in keratinocytes (9).

According to this hypothesis, we conducted a study to investigate the efficacy and safety of a topical formulation containing catalase and superoxide dismutase (Vitix®) in combination with narrow-band UVB phototherapy in 22 patients.

PATIENTS AND METHODS

Study design

The study was open and uncontrolled. Patients were screened at a preliminary visit. Reviews were made monthly at each visit. The duration of the study was 6 months.

Patients

Nineteen patients with vitiligo (6 males and 13 females) from the outpatient clinic of the University Department of Dermatology and Venereology, Zagreb University Hospital Center, were included in the study. Three patients dropped out because of their non-compliance and not because of adverse effects. The mean age of study patients was 29.28, range 15-71 years. The clinical vulgaris subtype was present in 14, acrofacial type in 3 patients, and segmental and focal type in one patient each.

According to Fitzpatrick classification, nine patients had skin type IV, seven had skin type II and three had skin type III. The mean duration of the disease was 6.23 years, ranging from 3 months to 21 years. Family history was positive in three (15.7 %) cases. Twelve patients were previously treated: eight with topical corticosteroids, and four with PUVA therapy. Seven patients did not receive any therapy. Patients using medical treatment for vitiligo at the time of the study, patients with a history of skin cancer, dysplastic nevi, photosensitivity or using photosensitizing medicines, with psychiatric or epileptic disorders, renal failure, known substance allergies, and pregnant and breast-feeding patients were not included in the study. All patients were healthy and used no additional treatment.

Treatment protocol

Patients were assessed and instructed to apply the skincare gel product containing catalase and superoxide dismutase from the plant *Cucumis melo* (Vitix®, Life Science Inv. Ltd.) to the affected skin twice a day for the study period of six months. During the treatment period, patients were also exposed to the narrow-band UVB three times per week. The UVB source was a Waldmann-UV7001K. The first dose was 0.25 mJ/cm^2. Doses were gradually increased depending on the patient's response to the previous exposure. During the treatment, the eyes were protected by UV-blocking goggles. All patients kept their underwear on in order to shield the genitals from the narrow-band UVB exposure. Patients applied Vitix® gel much before taking phototherapy.

Evaluation of the treatment

Patients were seen monthly for clinical follow up, close-up photo-documentation and reassessment. Therapeutic response was expressed as 0% (no repigmentation), 1%-25% (poor), 26%-50% (moderate), 51%-75% (good) and 76%-100% (excellent) repigmentation. The repigmentation grade was estimated by two different dermatologists who compared the photographs.

The total number of treatments, cumulative narrow-band UVB dose, and adverse effects were recorded.

RESULTS

The χ^2-test and Mann-Whitney test were used on statistical evaluation. The level of significance was set at $p<0.05$. Twenty-two eligible patients were enrolled in the study. Three patients dropped out because of their non-compliance and not because of adverse effects, and 19 patients were evaluated for therapeutic efficacy. The mean number of narrow-band UVB exposures was 68.89 (range 63-74). The mean total UVB dose per patient was 41.67 J/cm^2 (range 30.10-67.65 J/cm^2). The first repigmentation occurred between the 6th and 26th exposure (mean 12.6 exposure).

At the end of the 6-month therapy, more than 50% of overall repigmentation was noticed in 11 of 19 (57.9%) patients. Of these, three (15.79%) patients showed more than 75% (excellent) repigmentation, six of 19 (31.58%) patients showed

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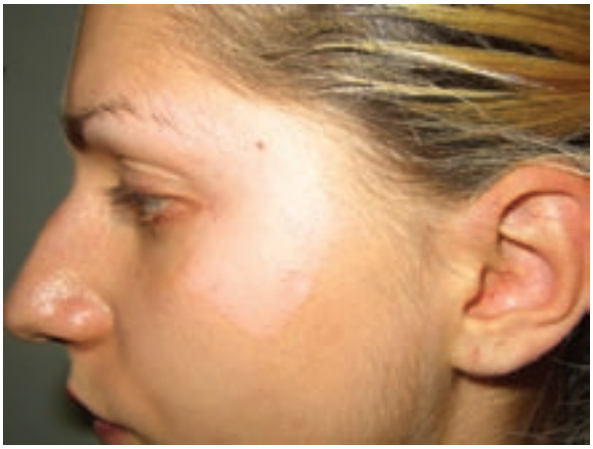

Figure 1.
A) Vitiligo on the face of an 18-year-old female patient

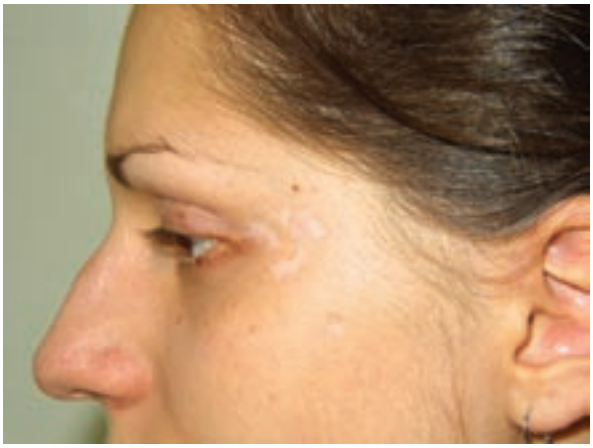

Figure 1.
B) Almost complete repigmentation after 6-month therapy

26%-50% (moderate) repigmentation, one (5.26%) patient showed 1%-25% (poor) repigmentation, and one (5.26%) patient showed no repigmentation at all.

Certain anatomic sites responded better than the others. The best response was achieved in the lesions located on the face and neck, followed by proximal extremities and trunk. Lesions on the hands and feet were most refractory to treatment. More than 50% repigmentation on the face and neck was recorded in 11 of 14 (78.6%) patients. Of these, five (35.7%) patients showed excellent repigmentation (Fig. 1). More than 50% repigmentation on proximal extremities and trunk was recorded in nine of 17 (52.9%) patients. Of these, five (29.4%) patients showed excellent repigmentation. More than 50% repigmentation on the hands and feet was observed in five of 13 (38.5%) patients. Excellent repigmentation on the hands and feet was seen in two (15.4%) patients (Fig. 2).

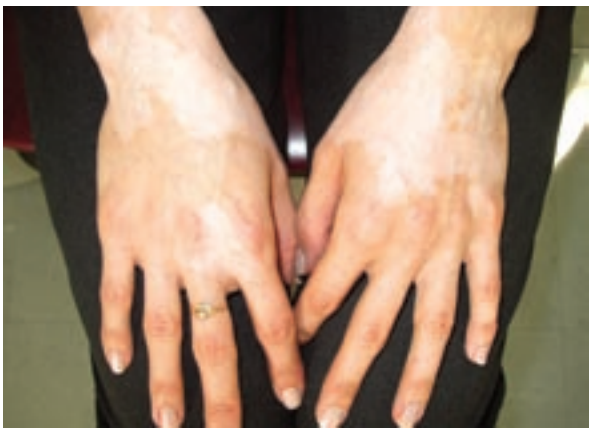

Figure 2.
A) Vitiligo on the dorsum of the hands of a 30-year-old female patient

There was no significant correlation between the disease duration and repigmentation grade (p=0.311), type of the skin and repigmentation grade (p=0.223), and previous therapy and repigmentation (p=0.477).

The development of new lesions was not recorded in our patients. Laboratory evaluation of serum and urine was unremarkable.

Thirteen of 19 (68.4%) patients reported mild erythema on depigmented areas, one (5.26%) patient reported mild erythema with stinging and itching at the site of Vitix® gel application, and five patients were free from side effects.

DISCUSSION

Although vitiligo is asymptomatic and does not affect mortality and physical morbidity, depigmentation on visible areas leads to severe cosmetic disfigurement and may cause considerable psy-

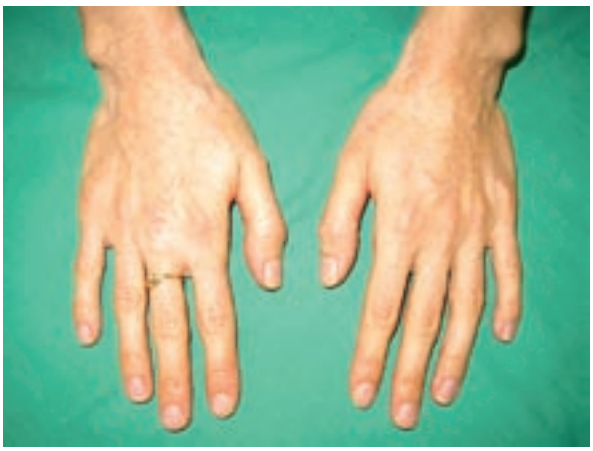

Figure 2.
B) Excellent repigmentation after 6-month therapy

chological distress. Patients with vitiligo have numerous treatment options available, but not all patients respond to the current treatment methods. Even among patients who respond to the treatment, there is a high potential for relapse.

Phototherapeutic options (narrow-band UVB and PUVA) are relatively efficacious in the treatment of generalized vitiligo. They are generally limited by the requirement of long-term treatment on a twice or three times a week basis for 12 months or even longer. Narrow-band UVB (311 nm) is considered as the first-choice therapy for adults and children with generalized vitiligo (5,10). Narrow-band UVB is equally or more efficacious than PUVA (11,12). Various studies report more than 75% repigmentation in 12.5%-75% of patients after one year of UVB narrow-band treatment (13-18).

The advantages of narrow-band UVB over oral PUVA therapy include the following: shorter treatment time; no systemic effects since oral drugs are not required; less burning incidents; less contrast formation between depigmented and normal pigmented skin: no need of post-treatment eye photoprotection; and allowed use in children and pregnant and lactating women (5,19). The mechanism of action of narrow-band UVB phototherapy in vitiligo is not completely understood. It induces local immunosuppression, stimulates the production of melanocyte-stimulating hormone, and increases melanocyte proliferation and melanogenesis (20).

Nowadays, there is accumulating evidence that the increased oxidative stress exists in the entire epidermis of these patients. Oxidation products such as hydrogen peroxide (H_2O_2) are toxic for melanocytes (7). The involved and uninvolved epidermis of patients with vitiligo showed a consistent reduction in the levels of catalase, a scavenger for highly reactive substances, in association with high levels of H_2O_2 (8). Based on these observations, a low-molecular weight complex called pseudocatalase has been synthesized. It has been hypothesized that epidermal H_2O_2 can be removed with topical application of a narrow-band UVB-activated pseudocatalase cream and such a combination has been tried in the treatment of vitiligo. In an uncontrolled study, 33 patients with vitiligo were treated with a twice-a-day application of pseudocatalase, calcium and narrow-band UVB twice a week. Complete repigmentation on the face and dorsum of the hands appeared in 90% of treated patients over a mean of 15 months (9). In another open, uncontrolled study, topical pseudocatalase in combination with narrow-band UVB showed no clear evidence of efficacy and there was even a slight tendency to worsening of the patients' vitiligo. The treatment period was 6 months (21). Thus, the use of pseudocatalase in the treatment of vitiligo remains a controversial issue.

In our study, at the end of 6-month therapy, 11 (57.9%) patients achieved more than 50% repigmentation. Only two (10.52%) patients showed poor or no repigmentation at all. The face and neck showed the best repigmentation response (78.6% of patients had more than 50% repigmentation). Lesions on the hands and feet were most refractory to treatment, yet our patients showed better results in these areas (38.5% of patients achieved 50% repigmentation) than patients in other studies where narrow-band UVB therapy was used (12,13,16,17). The duration of our study was not sufficient to achieve complete therapeutic response and this is probably the reason why only three (15.79%) patients achieved more than 75% overall repigmentation. For example, in the study by Westerhof *et al.*, only 8% of patients showed more than 75% repigmentation of the lesional skin at 3 months (18). However, at 12 months of treatment, 63% of patients showed more than 75% repigmentation on the lesional skin.

There is no consensus whether better response to the narrow-band UVB treatment correlates with a shorter duration of the disease or darker skin type. We found no correlation between the rate of response and disease duration or skin type.

In our study, no progression of the disease was observed during the treatment period. Vitix® gel was well tolerated and only one patient reported mild erythema with stinging and itching at the application site.

The manufacturer claims that this formulation, containing two free radical scavengers (catalase and superoxide dismutase) is an effective catalyst for the removal of H_2O_2 from the skin. However, another report indicates that Vitix® does not have a capacity to reduce H_2O_2 (22). Although our study was open and uncontrolled, most of the repigmentation observed could probably be attributed to the narrow-band UVB therapy, however, an additional effect of Vitix® gel is quite possible.

In conclusion, the present study showed that the combination therapy with narrow-band UVB and topical catalase and dismutase of a natural origin (Vitix®) is a therapeutic option that could be considered in the management of vitiligo. Further

evaluation of this combination in multicenter, double-blind, placebo-controlled studies should be undertaken.

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