Evaluation of Efficacy and Safety of Combination of Narrow Band Ultraviolet B and Topical Calcipotriol Versus Narrow Band UVB alone in the Treatment of Vitiligo

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Abstract

Background: Narrow band Ultraviolet B (NBUVB) has been used successfully for the treatment of vitiligo. Recently, topical calcipotriol has also been used as immunotherapy or as a part of combination therapies. The aim of this study was to compare the clinical efficacy and safety of NBUVB and NBUVB plus topical calcipotriol in the treatment of generalized vitiligo.

Methods: NBUVB phototherapy was given to 26 patients with generalized, symmetrical vitiligo three times weekly. Topical calcipotriol cream was only applied on the lesions located on one side of the body. Treatment was continued until cosmetically acceptable repigmentation occurred, but total cumulative dose of NBUVB did not increase from the mean of 113.4 ± 47.0 j/cm. The efficacy of treatment was evaluated by visually scoring the percentage of regimentation of the lesions at 12-session intervals by an investigator unaware of the side of calcipotriol application.

Results: The mean daily dose of NBUVB was 1.4 ± 0.6 j/cm. The median number of exposure for initial regimentation was 26.5 (range 14-38) on the side of combination therapy with calcipotriol and 25.3 (range 20-40) on the other side. After 24 sessions of treatment, 14 patients (53.9%) showed minimal to moderate improvement on the calcipotriol treated side as compared to 21 patients (80.8 %) on the other side. After 60 sessions of treatment, 16 patients (16.5 %) showed moderate to marked regimentation on the side of combination therapy with calcipotriol as compared to 19 patients (73 %) on the other side.

Conclusion: These findings indicate that concurrent use of topical calcipotriol does not enhance the efficacy of NBUVB in the treatment of vitiligo.

Keywords: narrow – band ultraviolet B, calcipotriol, vitiligo

Introduction

Vitiligo is a common, idiopathic, acquired depigmenting disorder of great cosmetic importance, affecting about 1 percent of the world population without sex or skin color predilection[1]. The etiology of this disorder is unknown; however, vitiligo is frequently associated with autoimmune diseases, and patients also have various autoantibodies in sera, including antibodies reacting to melanocytes in the skin[2].

Spontaneous repigmentation occurs in fewer than 50% of patients and it can be associated with great cosmetic and social problems[3]. A large variety of therapeutic agents have been tried for the treatment of vitiligo, but it is still one of the most difficult dermatological disorders to treat[1-4].

Potent topical corticosteroids and phototherapy are the mainstay of treatment, but it often requires long periods of time and carry potential risks of skin atrophy and carcinogenesis. The most common treatment for generalized vitiligo is phototherapy. Although psoralen plus ultraviolet A (PUVA) therapy has been recognized as the most prevalent and effective mode of phototherapy, it is also known to have many limitations. Narrow – band UVB (NBUVB) phototherapy, which is introduced rather

recently, has gradually replaced PUVA as the first – line treatment for generalized vitiligo[5].

There have been several reports of hyperpigmention after the combined use of topical calcipotriol and phototherapy (PUVA and NBUVB) in psoriasis. Hyperpigmentation develops only around calcipotriol – treated psoriatic plaques. It has also been reported that calcipotriol and NBUVB have a synergistic effect[6-8].

In addition, some studies have shown regimentation of vitiliginous lesions with both topical calcipotriol and with PUVA plus topical calcipotriol[7,9,10].

Calcipotriol is a synthetic, low calcemic analog of nuclear hormone 1,25 – dihydroxy vitamin D3 (calcitriol) synthesized in 1985. Binding of calcipotriol to its receptor, vitamin D receptor (VDR), induces several biological effects, including suppression of kerationocyte proliferation, immune modulation, and inhibition of cytotoxic and natural killer T-cell activity[11,12]. Recent in-vitro studies have shown that vitamin D3 increases melanin biosynthesis by stimulating defective calcium uptake, and thus enhances tyrosinase activity[13-15].

The combination of topical calcipotriol and PUVA therapy was more effective in patients who had previously received nothing but PUVA therapy for 3 months[16]. There is increasing evidence that both broad – band UVB and NBUVB are more effective than UVA phototherapy[17-19].

There have been several studies using the combination of calcipotriol and oral PUVA in the treatment of vitiligo. It was demonstrated that calcipotrial could also be effective as an immunotherapy[7,10,16,20,21]. However, it should be noted that in one study calcipotriol was not effective as monothorapy[9], and in another the addition of calcipotriol to PUVA did not lead to a significant increase in the response rate compared with PUVA alone[22]. More recently, studies on the efficacy of adding topical calcipotriol to NBUVB phototherapy have been reported[6, 23, 24].

In this study, we compared the efficacy of NBUVB as monotherapy with NBUVB in combination with calcipotriol in the treatment of generalized stable vitiligo.

Patients and methods

This study was conducted in Razi Hospital, Tehran, from April 2006 to May 2007. Informed consent was obtained from all of the patients. Twenty – six patients (9 males and 17 females) with generalized symmetric vitiligo were recruited into this prospective, single – blinded, right/left comparison clinical trial. Exclusion criteria were: less than 2% body surface area involvement (estimated using the 'hand – palm rule' in which the size of the patient's hand palm equals 0.5% of the total body surface), segmental – type and acrofacial –type vitiligo, any evidence of spontaneous repigmentation, known hypersensitivity to calcipotriol, abnormal reactions to UV radiation, any topical or systemic therapy for vitiligo in the previous 6 months, impaired renal or liver function, hypercalcemia or hypercalciuria, history of urolithiasis, thyroid or parathyroid disease, cataracts, photosensitivity, hypertension, cardiovascular disease, malignancy, arsenic exposure, pregnancy, lactation, concomitant use of vitamin D, calcium and any other drug that influence calcium homeostasis.

All patients underwent a thorough clinical and laboratory examination. The personal and family history, skin phototype, duration of disease, the localization and the extent of cutaneous involvement (as determined by the hand – palm rule), and previous therapies were recorded.

All patients were treated in a phototherapy unit (Waldmann NBUVB) containing a bank of 26 fluorescent tubes (TL – l00 w / 01, PREHEAT – BIPIN,Waldmann, Holland) with peak emission between 311 and 312 nm. The NBUVB treatment was applied to the whole body, except for the male genitalia, three times per week on nonconsecutive days. The initial dose of 200 mj / cm^2 was given in all cases. Treatment dose was increased by 15-20 % per treatment. If the patient reported moderate erythema and pruritus, irradiation was held constant or 10% reduced until symptoms were resolved.

Topical calcipotriol 0.05 mg/g cream was applied as a thin layer on the lesions of one side of the body selected by the patient twice daily. The other side was left untreated as an intra-individual control. Patients with extensive lesions were instructed to apply topical calcipotriol to the exposed skin surface only. The application was done at least 2 hours before / after NBUVB treatment session. Calcipotriol application was limited to approximately 30 g / week to avoid systemic side effects.

The patients were monitored and photographed at the end of every 12-session intervals. The clinical investigator was unaware of the side of calcipotriol application during the course of the study. The outcome was visually scored as the percentage of repigmentation of the depigmented lesions. Repigmentation was scored as no response (<1%),

minimal response (1-25%), moderate response (26-50%), marked response (51-75%), and excellent response (76-100%).

SPSS statistical software (version 13.0 for Microsoft windows) was used to conduct the statistical analysis. Repigmentation rate in the two sides of the body in every 12 sessions were compared by the Wilcoxon test. A statistical significance level of 0.05 was used in the analysis.

Results

Twenty six patients completed the study (table 1). The average age of the patients was 24.1 years (range 14-44) and the duration of disease was from 1 to 36 years (mean: 8.9 years). Two patients had skin phototype II, 18 patients had skin phonotype III, and 6 patients had skin phototype IV. None of the patients had a personal history of autoimmune diseases, but 4 patients had a family history of vitiligo. Prior therapy included topical potent corticosteroid (n=15), topical PUVA (n=10), and topical pimecrolimus (n=1) with minimal improvement. All patients had stopped therapy at least 6 months before entering the study.

The number of treatment sessions for acceptable repigmentation was 70 - 110 sessions. The mean total UVB dose delivered to the patients was113.4 ± 47.0 j/cm². The mean of maximum daily dose of UVB was 1.4 ± 0.6 j/cm². The median number of exposures for initial repigmentation was 26.5 (range 14-38 sessions) on the side of combination therapy with calcipotriol, and 25.3 (range 20-40sessions) on the side of NBUVB alone (table 2), which was not significantly different (p>0.05).

Overall repigmentation after 24 sessions of phototherapy was as follows: 14 patients (53.9%) showed minimal to moderate improvement on the calcipitriol – treated side as compared to 21 patients (80.8%) on the other side. After sixty sessions, 16 patients (61.5%) showed moderate to marked repigmentation on the side of combination therapy with calcipotriol as compared to 19 patients (73 %) on the other side. Final evaluation of regimentation revealed 16 patients (61.5 %) with marked to excellent response on the side of combination therapy with calcipotriol as compared to 18 patients (69.3%) on the other side (table 3).

Table 1. *Profile of patients*

Number of patients	26
Male:female	9:17
Mean age (range)	24.1 years (14-44 years)
Race	All Caucasians
Mean duration of disease (range)	8.85 years (1-36 years)
Mean body surface involved (range)	30.6 % (15-50%)
Mean onset age (range)	15.3 years (7-40 years)

Excellent repigmentation (76-100 %) was observed in 30.8 % (8/26) patients in sides not treated with calcipotriol compared with 7.7% (2/26) in sides treated with calcipotriol in the end of treatment ($p<0.05$). There was a statistically better response on the side that calcipotrial was not applied at the 24th session ($p<0.05$), but no statistically significant difference was found between the two sides at 60th session (table 4).

Table 2. *Number of phototherapy sessions at the time of initial repigmentation*

Side of treatment	Maximum sessions	Minimum sessions	Mean
NBUVB + calcipotriol	38	14	26.5
NBUVB	40	20	25.3

Table 3. *Moderate to excellent response rate according to sessions of treatment*

Session of treatment	NBUVB+calcipotriol	NBUVB
12	0%	0%
24	7.7%	30.8%
60	61.5%	73%
Final	100%	100%

NBUVB was generally well tolerated. Addition of topical calcipotriol to NBUVB did not increase adverse effects. Only two patients experienced erythema and pruritus on the calcipotriol-treated sides, which healed with a reduction in the dosage of NBUVB. The laboratory parameters in serum and urine were unremarkable.

Discussion

Currently there is no effective medical or surgical modality for the treatment of vitiligo. Narrow – band UVB is now the treatment of choice for patients with moderate to severe vitiligo[5,25-29]. The use of NBUVB for vitiligo was first reported by

Table 4. *Response rates according to sessions of treatment (Wilcoxon Test)*

Sessions of treatment	Excellent		Good		Moderate		Poor		No response		P value
	N	N+C	N	N+C	N	N+C	N	N+C	N	N+C	
12	۰	۰	۰	۰	۰	۰	۰	۰	100%	100%	1
24	۰	۰	۰	۰	30.8%	.7%۷	٥۰	46.2%	19.2%	46.2%	0.05
60	۰	۰	11.5%	7.7%	61.5%	53.8%	26.9%	38.5%	۰	۰	0.285
Final	30.8%	7.7%	38.5%	53.8%	30.8%	38.5%	۰	۰	۰	۰	0.03

N : Narrow band UVB; C : Calcipotriol

Westerhof and Nieuweboer-Krobotova in 1997. These investigators compared twice weekly topical PUVA with twice weekly NBUVB. After 4 months of treatment, 67 % of patients treated with NBUVB showed repigmentation compared with 46% of patients receiving topical PUVA[17].

The mechanism of action of NBUVB is not completely understood, but it probably leads to the release of cytokines and inflammatory mediators in the skin, which stimulates melanocyte migration and proliferation[18]. Few studies have evaluated the efficacy of NBUVB in the treatment of vitiligo. In a study by Njoo et al. 53 % of children experienced more than 75% regimentation following NBUVB therapy (6 % of this group showed complete repigmentation)[30]. Scherschun et al. reported a retrospective study of seven patients with vitiligo who were treated with NBUVB as monotherapy three times a week. Five of the seven patients achieved more than 75% repigmentation with a mean of 19 treatments[18].

In a recent study, Yashar et al. reported that 39% of 71 patients with vitiligo treated with NBUVB experienced significant improvement, 22% moderate improvement, 21% mild improvement, and 10% minimal or no improvement. The number of treatments ranged from 15 to 23 with total cumulative doses of 7-485 J/cm^2 [31]. Natta et al. in an open study demonstrated that NBUVB therapy was effective in 42% of Asian patients with recalcitrant vitiligo who achieved more than 50% repigmentation[32]. Ercan et al. indicated that NBUVB phototherapy was an effective therapeutic option in generalized vitiligo with good results in only two weeks of treatment[33].

Calcipotriol has been reported to induce repigmentation of vitiligo when used in combination with sun exposure or PUVA or NBUVB therapy[7,10,16,20,21]. It is likely that calcipotriol, a vitamin D analog, may play a role in the regulation of 1, 25 – dihydroxy vitamin D3 receptors on melanocytes and / or by the regulation of defective Ca^{2+} homoestasis[10]. Calcipotriol has also an immunomodulator effect on treated cells, especially antigen – presenting cells. This effect of calcipotriol on melanocytes may be direct or by means of its immunomodulatory action[34].

Topical calcipotriol as monotherapy has recently been shown to be ineffective in the treatment of vitiligo[22]. Parsad et al. conducted an open study on 18 children with limited vitiligo, in whom they applied topical calcipotriol once a day followed by sun light exposure; 78% (14 of 18) of the patients responded to the treatment[21]. However, Chiaverini et al. reported their experience on 24 cases of patients with vitiligo treatment by topical calcipotriol monotherapy. At the end of the treatment (mean duration of 3.9 months), 21 patients (87.5 %) had no repigmentation[22]. A recent study on 21 patients with vitiligo who were instructed to use topical corticosteroids in the morning and topical calcipotriol in the evening indicated that 38% of patients responded to the therapy with an average of 95% repigmentation, even in those who had not previously responded to topical corticosteroid alone[35].

There are studies suggesting that the efficacy of PUVA can be enhanced when it is used in combination with topical calcipotriol. Ameen et al. conducted an open study on 26 patients with vitiligo affecting 5 - 40% of their skin surface. Twenty – two patients were treated with twice daily topical calcipotriol and 4 patients were treated with a combination regimen of topical calcipotriol and PUVA. 77% of those treated with calcipotriol showed 30 - 100% improvement and 3of 4 patients on combination treatment showed good response[7]. Ermis et al. conducted a double-blinded, placebo controlled study using topical calcipotriol and twice-weekly PUVA and concluded that this combination therapy achieved a faster and more satisfactory repigmentation as compared to placebo or PUVA alone[10].

Yalcin et al. reported that the combination of PUVA and calcipotriol might be effective[16].

On the other hand, studies with contradictory results are available. Bayasal et al. compared the effectiveness of PUVA with combination of PUVA and topical calcipotriol in the treatment of vitiligo in 22 patients in an open, right / left comparative study. They concluded that addition of calcipotriol to PUVA treatment did not lead to a significant increase in the response rate of the patients[9].

There are few studies on the combination of NBUVB and calcipotriol. In the first report, combination of calcipotriol and NBUVB was used in only one patient. Calcipotriol and placebo creams were applied to the right and left lower limbs, respectively. Within 2 months of treatment, numerous perifollicular macules and marginal repigmentation were observed over vitiligo patches. After 6 months, repigmentation was almost complete on the right limb, whereas it was less than 50% on the left limb[6].

Recently Hartmann et al. compared the efficacy of NBUVB and broad – band UVB (BBUVB), calcipotriol and placebo in two patients. They applied NBUVB to the upper part, BBUVB to the

lower part, calcipotriol to the right side and placebo cream to the left side of the body. Although they found that NBUVB was more effective than BBUVB, they did not observe a significant difference between calcipotriol and the placebo[36].

However another prospective, single – blinded, right / left comparison clinical trial showed that NBUVB was effective by itself in vitiligo and addition of topical calcipotriol did not improve treatment outcome[24]. Goktas indicated that concurrent topical calcipotriol potentiated the efficacy of NBUVB in the treatment of vitiligo, and provided earlier pigmentation with lower total UVB dosage and less adverse effects, and also reduced the duration and cost of treatment[37].

In the present study, complete repigmentation and perifollicular repigmentation started after 14 - 36 sessions of phototherapy on the side treated with calcipotriol plus NBUVB and 20 - 40 sessions in the side treated with NBUVB alone. In conclusion, this study confirms that NBUVB is effective in the treatment of generalized vitiligo, but its combination with topical calcipotriol does not seem to improve the efficacy of NBUVB and does not reduce the dosage of UVB and duration of treatment. Further evaluation of this combination in randomized, double - blinded, placebo – controlled, clinical trials should be undertaken.

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