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ORIGINAL PAPER

Topical calcipotriol vs narrowband ultraviolet B in treatment of alopecia areata: a randomized-controlled trial

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Abstract

Alopecia areata is a chronic relapsing autoimmune inflammatory hair disorder with no novel therapy. The objectives of this study are to compare the efficacy of topical calcipotriol vs narrow band ultraviolet B phototherapy (NB-UVB) in the treatment of alopecia areata and its correlation with serum vitamin D_3 levels. A randomized-controlled trial has been conducted on 60 patients with scalp alopecia areata randomized into four groups; topical calcipotriol, NB-UVB, both and placebo. All patients were evaluated by assessment of severity of alopecia areata by severity of alopecia tool (SALT) score at baseline and 3 months after treatment and vitamin D_3 levels at baseline and after 3 months. SALT score and vitamin D_3 levels were significantly improved in all groups except placebo after treatment with ($P=0.026$, $P=0.005$, $P=0.004$, $P=0.140$) and ($P=0.028$, $P=0.011$, $P=0.003$, $P=0.725$), respectively. Combined therapy showed non-significant improvement in SALT score ($P=0.530$, $P=0.643$), respectively, and significant improvement in serum vitamin D_3 levels than each line alone with ($P=0.021$, $P=0.044$), respectively. Both topical calcipotriol and NB-UVB are effective therapies in the treatment of AA and associated with improvement of SALT score and vitamin D_3 levels.

Keywords Alopecia areata · Calcipotriol · NB-UVB · Vitamin D_3

Introduction

Alopecia areata (AA) is an organ-specific autoimmune disease characterized by non-scarring hair loss that targets anagen hair follicles [1, 2]. Aetiopathogenesis of AA is not fully understood. Many factors have been implicated, the most important of which are the genetic and immunological factors [1, 3]. Clinical patterns of AA range from limited patches (localized AA) to total scalp hair loss (alopecia totalis) or total body hair loss (alopecia universalis) and other different clinical patterns according to site and shape of hair loss [3].

Diagnosis and prognosis of AA depend mainly on clinical examination detecting the criteria and degree of hair loss and assessment of severity by severity of alopecia tool (SALT) score [4]. Dermoscopy is a highly valuable tool in diagnosis and follow-up of AA [5].

No novel treatment regimen is known for AA. Many treatment options are widely used with variable results. These include topical and intralesional therapies, systemic drugs, and phototherapy [5, 6].

Vitamin D_3 is synthesized in the epidermal keratinocytes by the UVB lights effects (290–315 nm) [7]. It has a vital role in the biology of the hair follicle. Vitamin D receptor (VDR) expression in epidermal keratinocytes was detected. It was established that decrease VDR expression is associated with impaired growth of hair follicle and reduction of epidermal differentiation [8]. It was found that patients with AA have a deficiency of serum vitamin D_3 levels and a decrease VDR expression in affected hair follicles [9–11].

Topical calcipotriol is a vitamin D analog that regulates keratinocytes proliferation and differentiation. It can induce hair regrowth in AA lesions by regulation of the differentiation of B cells, T cells, dendritic cells, and Toll-like receptor

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expression. There are few reports evaluating the effect of calcipotriol in AA [12–14].

Narrowband UVB phototherapy (NB-UVB) has high levels of efficacy and tolerability in many inflammatory and neoplastic skin disorders. There is little evidence of the efficacy of NB-UVB method for AA treatment [15].

Aim of the study is to compare the clinical efficacy of topical calcipotriol, NB-UVB, and NB-UVB plus topical calcipotriol in the treatment of AA, and correlate its outcome with serum VD_3 levels.

Patients

This randomized-controlled clinical trial (RCT) included 60 patients with scalp AA (32 females and 28 males) with their ages ranged from 14 to 40 years which have been recruited from the outpatient clinic of Dermatology, Venereology, and Andrology department, Aswan University Hospital, Aswan University in the period between October 2017 and December 2018.

Sample size calculation was performed using G*Power 3 software [16]. A calculated minimum sample of 60 patients divided into four groups (15 patients for each group) was needed to detect an effect size of 0.5 in the mean levels of vitamin D_3 and SALT score before treatment and after treatment, with an error probability of 0.05 and 80% power on a one-tailed test. Patients were randomized into four groups: group I received topical calcipotriol, group II received NB-UVB, group III received both topical calcipotriol and NB-UVB, and group IV received identical appearing placebo ointment.

Patients were distributed among the four groups based on randomized coded cards. Randomization was carried out using tables of random numbers that were arranged in a successive order. The allocation of patients and follow-up was performed by physician assistants (Fig. 1).

Patients with AA in other sites than scalp, patients with other causes of alopecia including scarring alopecia, androgenic alopecia, telogen effluvium and autoimmune diseases, and pregnant and lactating females were excluded from this study.

Methods

Each patient was assessed by complete history, general, and dermatological examination. SALT score and serum vitamin D_3 levels were measured at baseline and after 3 months of treatment. Treatment protocol was as follows: group I was prescribed calcipotriol ointment (0.005%) to affected areas twice a day for 3 months according to figure tip unit. Group II received NB-UVB (311 nm) two sessions weekly for 3 months by eight narrowband UVB lamp (TL01) of Waldman-type F 85/100W-01 (Waldman, Villingen-Schwenningen, Germany). The initial dose was 0.25 J/cm^2, and then, the dose was increased at each session by 10–20% with a maximum dose 740 mJ/cm^2 according to minimal erythema dose. Group III received both NB-UVB sessions (with the same schedule as group 2) and topical calcipotriol. Calcipotriol was applied 2 h after treatment on days of NB-UVB exposure to prevent UV inactivation. Group IV received equal amounts of identical appearing bland

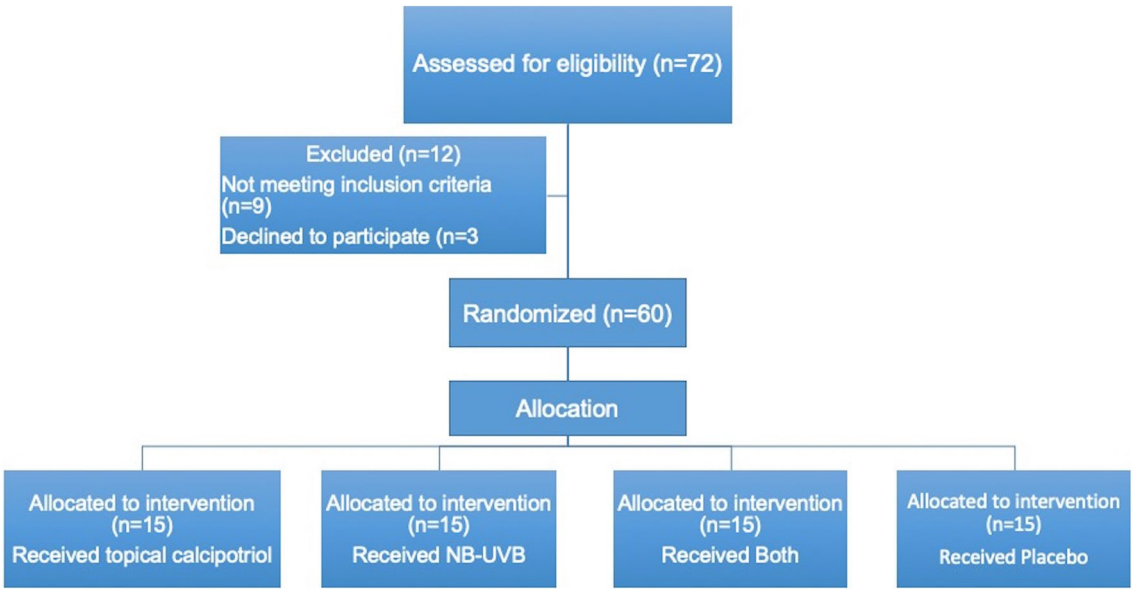

Fig. 1 Flow diagram of sample size calculation and patient allocation

ointment as a placebo. Photographs were taken at baseline and after 3 months of treatment using Nikon CoolpixS2500 camera12MP (Tokyo, Japan). Finally, blood sample was taken from each subject to detect serum vitamin D_3 levels by the ELISA technique using 25 (OH) vitamin D ELISA Kit (Calbiotech, California, USA) [17].

Statistical analysis

Data were verified, coded by the researcher, and analyzed using IBM-SPSS version 21. Descriptive statistics: means, standard deviations, and percentages were calculated. Test of significances: Chi-square test was used to compare the difference in the distribution of frequencies among different groups. ANOVA test was calculated to test the mean differences of the data between the treatment groups; post hoc test was calculated using Bonferroni corrections. Paired correlation analysis was used to test the association between variables (Pearson's correlation). A P value ≤ 0.05 was considered significant.

Ethical considerations

This study was approved from Ethics Committee of Faculty of Medicine Aswan University prior to study execution. The trial was registered on the clinical trial registration website https://clinicaltrials.gov/NCT03847441. In addition, all patients signed a written consent form. The informed consent was obvious and indicated the aim of the study, and their choice to participate or withdraw at any time without any obligation. Furthermore, participants' confidentiality and anonymity were assured by assigning each participant with a code number for the purpose of analysis only. The study was not based on any incentives or rewards for the participants.

Results

This trial was conducted on 60 patients with AA (32 females and 28 males) with their ages ranged from 14 to 40 years. There were no statistically significant differences regarding age and sex between the study groups with ($P=0.968$) and ($P=0.788$), respectively. The means of demographic variables are reported in (Table 1).

At the baseline of the study, mean SALT scores and serum levels of vitamin D_3 showed non-significant differences between the studied groups with ($P=0.976$) and ($P=0.894$), respectively (Tables 2, 3).

Serum vitamin D_3 levels were significantly increased in all groups except placebo group after the treatment period with ($P=0.028$, $P=0.011$, $P=0.003$, $P=0.725$) for groups I, II, III, and IV, respectively. A significant difference in vitamin D_3 was found between treated groups and placebo after treatment with ($P=0.012$, $P<0.01$, $P<0.001$) for groups I, II, III, vs IV, respectively (Table 2). Patients received both topical calcipotriol and NB-UVB which showed significantly higher serum vitamin D_3 levels after treatment than those treated with topical calcipotriol alone or NB-UVB alone with ($P=0.021$) and ($P=0.044$), respectively. There was no significant difference in vitamin D_3 levels after treatment between patients treated with calcipotriol and those treated with NB-UVB ($P=0.873$) (Table 2).

There was a significant decrease in SALT score after treatment in G I, II, and III, while G IV showed non-significant change with ($P=0.026$, $P=0.005$, $P=0.004$, $P=0.140$), respectively. There was a significant difference in SALT score between treated groups and placebo with ($P=0.041$, $P=0.037$, $P=0.025$) for group I, II, III vs IV, respectively. Patients treated with both calcipotriol and NB-UVB showed no significant difference in SALT score after treatment than those treated with calcipotriol or NB-UVB alone with ($P=0.530$, $P=0.643$), respectively. In addition, there was no significant difference in

Table 1 Socio-demographic differences between the studied groups

	Group I (No. = 15)	Group II (No. = 15)	Group III (No. = 15)	Group IV (No. = 15)	*P* value*
Age/year	22.93 ± 3.2	22.97 ± 2.7	21.00 ± 3.8	23.83 ± 2.6	0.968
P value**	*P*1 = 0.997	*P*3 = 0.714	*P*5 = 0.654	*P*6 = 0.879	
	*P*2 = 0.698	*P*4 = 0.881			
Sex					0.788
Female	8 (53.3%)	9 (60%)	7 (46.7%)	8 (53.3%)	
Male	7 (46.7%)	6 (40%)	8 (53.3%)	7 (46.7%)	

G I = topical calcipotriol, G II = NB-UVB, G III = both and G IV = placebo

*P*1 (G I vs G II), *P*2 (G I vs G III), *P*3 (G II vs G III), *P*4 (G II vs G VI), *P*5 (G III vs G VI), and *P*6 (G I vs G VI)

**Post hoc test with Bonferroni correction was used for pairwise comparison

Table 2 Effect of treatment on the level of vitamin D_3

	Group I (No. = 15)	Group II (No. = 15)	Group III (No. = 15)	Group IV (No. = 15)	*P* value*
Vitamin D level (ng/ml)					0.894
Before treatment					
	30.52 ± 3.2	33.37 ± 4.1	35.82 ± 5.2	30.70 ± 3.5	
P value**	*P*1 = 0.618	*P*3 = 0.416	*P*5 = 0.518	*P*6 = 0.980	
	*P*2 = 0.468	*P*4 = 0.718			
After treatment					0.025
	39.74 ± 3.1	40.77 ± 4.7	55.45 ± 2.8	32.65 ± 3.1	
P value**	*P*1 = 0.873	*P*3 = 0.044	*P*5 < 0.001	*P*6 = 0.012	
	*P*2 = 0.021	*P*4 < 0.01			
P value***	0.028	0.011	0.003	0.725	

G I = topical calcipotriol, G II = NB-UVB, G III = both and G IV = placebo

*P*1 (G I vs G II), *P*2 (G I vs G III), *P*3 (G II vs G III), *P*4 (G II vs G VI), *P*5 (G III vs G VI), and *P*6 (G I vs G VI)

*ANOVA test was used to compare the mean difference between groups

**Post hoc test with Bonferroni correction was used for pairwise comparison

***Paired sample *t* test was used to compare the mean difference before vs after treatment

Table 3 Effect of treatment on the SALT severity score

	Group I (No. = 15)	Group II (No. = 15)	Group III (No. = 15)	Group IV (No. = 15)	*P* value*
SALT score					0.976
Before treatment					
	4.01 ± 1.1	3.97 ± 0.7	4.27 ± 1.0	3.50 ± 0.9	
P value**	*P*1 = 0.977	*P*3 = 0.831	*P*5 = 0.651	*P*6 = 0.750	
	*P*2 = 0.854	*P*4 = 0.775			
After treatment					0.029
	2.84 ± 1.0	2.33 ± 0.7	1.73 ± 0.5	4.14 ± 1.0	
P value**	*P*1 = 0.891	*P*3 = 0.643	*P*5 = 0.025	*P*6 = 0.041	
	*P*2 = 0.530	*P*4 = 0.037			
P value***	0.026	0.005	0.004	0.140	

G I = topical calcipotriol, G II = NB-UVB, G III = both and G IV = placebo

*P*1 (G I vs G II), *P*2 (G I vs G III), *P*3 (G II vs G III), *P*4 (G II vs G VI), *P*5 (G III vs G VI), and *P*6 (G I vs G VI)

*ANOVA test was used to compare the mean difference between groups

**Post hoc test with Bonferroni correction was used for pairwise comparison

***Paired sample *t* test was used to compare the mean difference before vs after treatment

SALT score between patients treated with calcipotriol and those treated with NB-UVB with ($P = 0.891$) (Table 3; Figs. 2, 3, 4).

Regarding correlation between vitamin D_3 levels and SALT score before and after treatment, there was mild non-significant negative correlation between vitamin D_3 levels and SALT score in all groups with correlation coefficients and *P* values, as shown in Table 4.

Discussion

AA is a tissue-specific autoimmune disease occurring in genetically predisposed individuals exposed to certain triggers, and it is a multifactorial predominantly T-cell-driven disease [18]. Vitamin D deficiency is accused to have a role in many cutaneous and autoimmune diseases

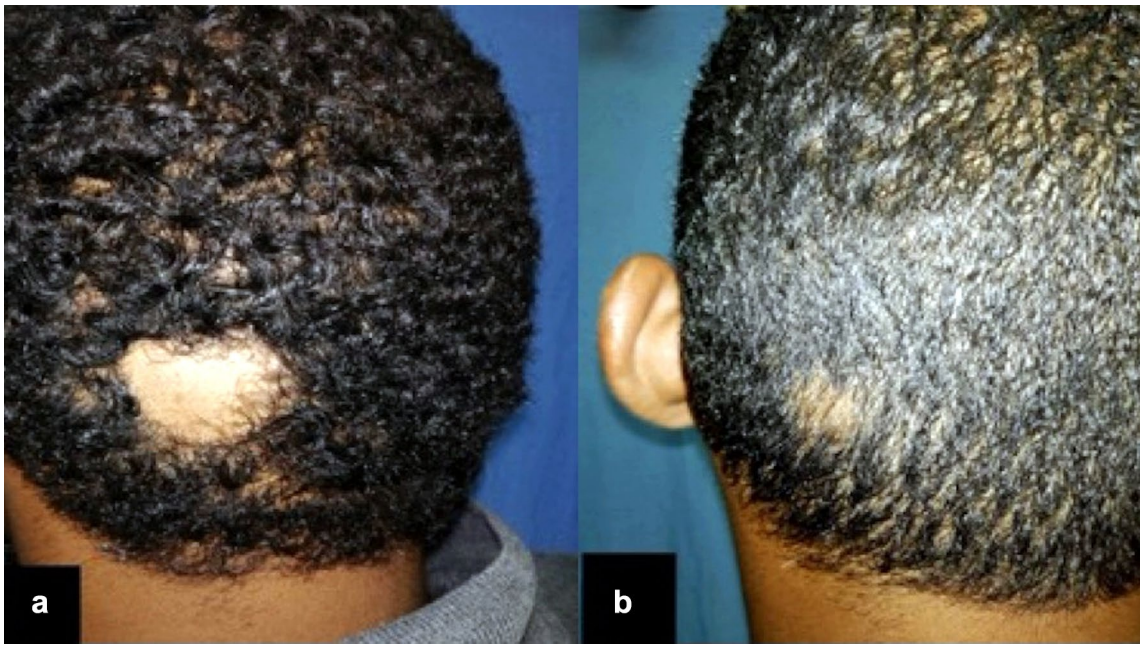

Fig. 2 A 18-year-old male patient with AA in the scalp: **a** before treatment and **b** 3 months after treatment with topical calcipotriol

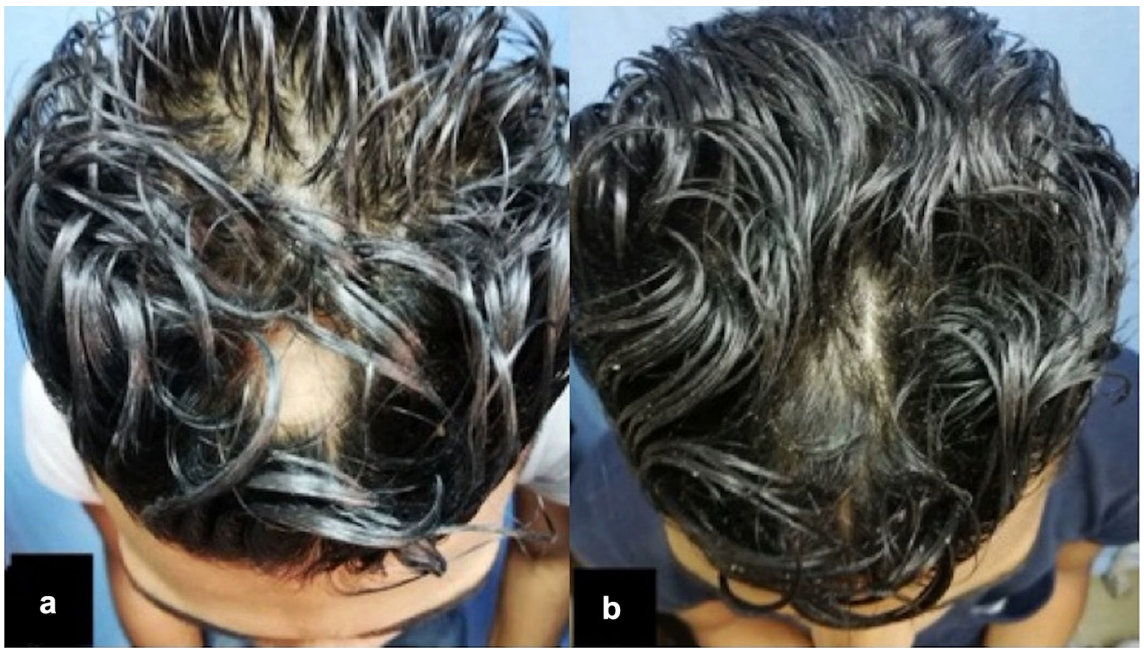

Fig. 3 A 30-year-old female patient with AA in the scalp: **a** before treatment and **b** 3 months after treatment with NB-UVB

such as AA due to the facts that it was synthesized mainly in skin and VDR which are widely expressed in keratinocytes and hair follicles [6, 19]. Moreover, it was supposed that treatment of vitamin D deficiency by vitamin D supplementation might have a preventive role in human autoimmune diseases such as AA [11, 20].

NB-UVB has been included as a treatment option in some AA treatment guidelines and it is known that NB-UVB has a positive effect on vitamin D synthesis by skin [10, 21]. The biological actions of vitamin D_3 derivatives include regulation of epidermal cell proliferation and differentiation and modulation of cytokine production [13, 22]. In addition,

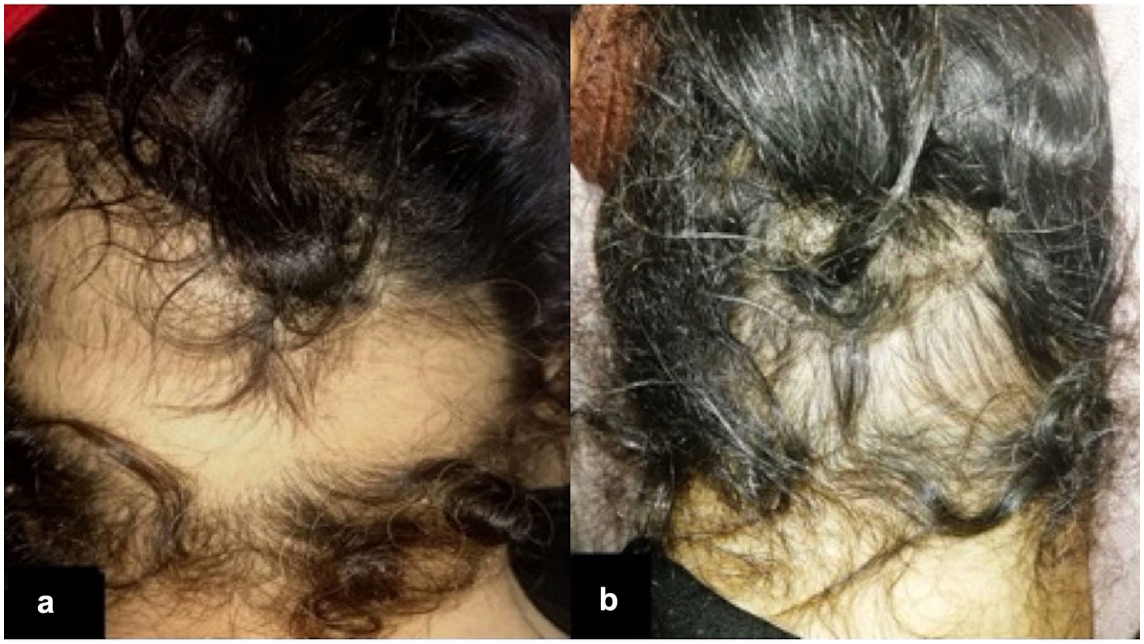

Fig. 4 A 23-year-old male patient with AA in the scalp: **a** before treatment and **b** 3 months after treatment with NB-UVB and topical calcipotriol

Table 4 Correlation between serum VD_3 Levels and SALT scores among the studied groups

	VD before R^a (P value*)	VD after	SALT after
G I			
VD_3 before	1	–	−0.382 (0.160)
VD_3 after	0.625 (0.013)	1	−0.254 (0.361)
SALT before	−0.174 (0.268)	−0.160 (0.248)	0.623 (0.012)
G II			
VD before	1	–	0.116 (0.720)
VD after	0.867 (0.001)	1	−0.232 (0.467)
SALT before	−0.041 (0.706)	−0.441 (0.139)	0.796 (0.002)
G III			
VD before	1	–	−0.076 (0.834)
VD after	0.583 (0.037)	1	−0.085 (0.584)
SALT before	0.235 (0.257)	0.024 (0.993)	0.815 (0.004)
G IV			
VD before	1	–	−0.369 (0.472)
VD after	0.246 (0.261)	1	−0.211 (0.491)
SALT before	−0.460 (0.358)	−0.360 (0.214)	0.813 (0.049)

*Based on normal approximation

[a]Pearson's correlation coefficient

activation of regulatory T cells can show the high efficacy of vitamin D analogs in the treatment of AA [23].

In this trial, we compared the efficacy of topical calcipotriol vs NB-UVB phototherapy in treatment of AA and correlated the results with serum vitamin D_3 levels. We found a significant improvement in SALT score after treatment of AA with topical calcipotriol for 3 months, and this finding concedes with those of Kim et al., who observed a complete regrowth of hair with topical calcipotriol in a refractory case of AA [13]. In addition, Narang et al. detected a high response rate of AA treated with calcipotriol reaching about 59.1% efficacy [24].

On the other hand, Cerman et al. found week efficacy of topical calcipotriol in AA in their work [14]. These findings may be explained partially by the biological actions of vitamin D derivatives which include regulation of epidermal cell proliferation, differentiation, and modulation of cytokine production [25]. Based on the fact that vitamin D derivatives mediate their biological effects by binding with specific VDR on the nuclei of target cells [26] and the finding that lack of VDR expression is associated with decreased hair growth and epidermal differentiation [27], this may also partially explain the effect of topical calcipotriol in AA.

The current study showed that NB-UVB phototherapy improved SALT score significantly after treatment period. In spite their wide range of indications in skin diseases, there are few studies evaluated the efficacy of NB-UVB in AA and little data are available about its effect [28]. In a previous report, NB-UVB was found to be less effective than intralesional steroid injection and their combination was not superior to intralesional injection a lone [29]. Dilek et al. reported that targeted NB-UVB not found to be highly effective in treatment of AA [30]. NB-UVB has an immunomodulatory effect by induction of T-cell apoptosis, induction of IL10, reduction of natural killer cell activity, and

lymphoproliferation, leading to down-regulation of immune attack against the hair follicle [31].

No previous studies were reported about our trial to combine topical calcipotriol and NB-UVB in treatment of AA. We found that combination of calcipotriol and NB-UVB is not superior to each line of treatment alone with no significant difference in SALT score between the study groups. In addition, no previous studies were reported about our trial to correlate topical calcipotriol and NB-UVB in treatment of AA. We found a significant increase in serum vitamin D_3 levels after using topical calcipotriol, NB-UVB, and combined treatment after the treatment period. Patients treated with combined topical calcipotriol and NB-UVB showed significant increase in serum vitamin D_3 levels than those treated with topical calcipotriol alone or NB-UVB alone. These findings support those of Bogh et al., who found in their study that serum vitamin D_3 levels have been elevated after treatment with NB-UVB [31].

In the present study, there was a negative non-significant correlation between serum vitamin D_3 levels and SALT score. This finding is in a congruence with D'Ovidio et al. who found non-significant difference in deficiency or insufficiency of vitamin D_3 between patients with AA and controls [23]. On the other hand, there are some reports detected lower levels of vitamin D_3 in patients with AA, and a negative correlation between serum vitamin D_3 levels and AA severity was found [8–10]. The non-significant correlation between serum vitamin D_3 levels and SALT score in the present study may be due to small sample size which can affect the level of significance. It was observed increase in serum vitamin D_3 levels in patients with clinical improvement after treatment is probably explained by vitamin D effective role in the proliferation and differentiation of keratinocytes [32].

Conclusion

We concluded that both topical calcipotriol and NB-UVB are effective therapies in treatment of AA and associated with improvement of SALT score and vitamin D_3 levels. Combined treatment are not superior to each line regarding clinical improvement, while it is associated with higher levels of vitamin D_3 levels in treated patients than each line of treatment alone.

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