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ORIGINAL CONTRIBUTION

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Correlation between serum IL-17A level and SALT score in patients with alopecia areata before and after NB-UVB therapy

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Summary

Background: There is strong evidence that alopecia areata is of immunological background; Interleukin-17 (IL-17) is a Th17 pro-inflammatory cytokine that has been allied to the pathogenesis of different autoimmune and inflammatory diseases.

Objective: This study aimed to measure serum IL-17A in patients with alopecia areata, and to study associations between IL-17A levels and disease severity before and after Narrowband-Ultraviolet B (NB-UVB), patient gender and age.

Methods: Twenty patients with AA of the scalp were treated with (NB-UVB), and 15 healthy subjects' age and sex matched were enrolled as controls. Patients were assessed clinically by SALT score. Assay of serum levels of IL-17A by ELISA was done in patients and controls.

Results: The mean level of IL-17A was (15.63 Â ± 10.89 Pg/mL) in AA patient group, and (16.50 Â ± 5.02 Pg/mL) in control group. No statistically significant correlation was detected between SALT score and IL-17A level before (NB-UVB) treatment while a significant negative correlation between SALT score and IL-17A level was observed after treatment ($r = -.448$, $P = .047$). Mean SALT score for patients was (14.03 Â ± 13.48), and correlated positively with age ($r = .446$, $P = .049$).

Conclusion: Although (NB-UVB) is an immune-modulatory type of treatment for alopecia areata of mild efficacy especially if it's used alone, it has shown significant decrease in serum IL-17A level among patients, and correlation to disease severity.

KEYWORDS
alopecia areata, IL-17A, narrowband-ultraviolet B

1 | INTRODUCTION

Alopecia areata (AA) is a T-cell–mediated disease with characteristic sudden patchy hair loss in any hair-bearing area especially the scalp, with exacerbations and remissions. Hair in the anagen phase is attacked by dermal perifollicular inflammatory infiltrates mainly $CD4^+$ and $CD8^+$ T lymphocytes, which leads to its destruction.[1]

Many theories participated in pathogenesis of alopecia areata where, viral, bacterial, or fungal pathogens have been implied as possible triggering factors. The pathogenesis of AA is multifactorial; however. it is also associated with other autoimmune disorders: vitiligo, atopic dermatitis, and autoimmune thyroid disease.[2]

Addressing the impressive immunological reaction in AA, both innate and adaptive cutaneous immune responses are sharing. It is characterized by upregulation of Th1 cytokines and downregulation of Th2 cytokines.[1] Psychological stress and chronic stress can shift activated lymphocytes toward a Th17 response.[3,4] The main source of IL-17 is Th-17 cells; also can be produced by $CD8^+$ T cells, neutrophils, eosinophils, macrophages, and natural killer T (NKT) cells in minor amounts.[5]

Infiltrating CD4 cells are Th1, Th2, Th17 and regulatory T cells, Th17 may be the main possible initiator of AA. Th17 cytokines are IL-17A, IL-17F, IL-21, IL-22, IL-6, and TNF-a, these cytokines are reported to be elevated in patients with AA suggesting a crucial role of these cytokines in the pathogenesis of AA.[6] Serum levels of IL-17A were high in patients with AA.[7,8] Also, dense infiltrations of IL-17-producing cells around the hair follicles and interstitial areas of the dermis have been proved together with high tissue level of IL-17.[9]

Narrowband-Ultraviolet B has shown an efficacy in the management of a number of immune-mediated skin disorders. NB-UVB works mainly in epidermis and superficial dermis, but the same efficacy has not been found in treatment of AA. It has an important role in immune suppression, as it may reduce the number of Langerhans cells, T lymphocytes, cytokine expression level, and cell cycle arrest which lead to disease activity suppression.[10]

We aimed to compare between levels of serum IL-17A in patients with AA and healthy control subjects, and to study the relation between serum IL-17A and severity of alopecia areata before and after narrowband ultraviolet B (NB-UVB) sessions. Our interest was to assess this interleukin level which indicates Th-17 cells activity, because they are more likely to be the home cells than other cell populations.

2 | PATIENTS AND METHODS

The study protocol was approved by Local Ethics Committee in accordance with Helsinki Declaration. Twenty patients with AA of the scalp, with or without the involvement of other body sites, were recruited from Narrow band Phototherapy Unit, Dermatology Department, Assuit University Hospitals, Egypt. Fifteen healthy age- and sex-matched subjects were included as controls. Patients were assessed clinically for extent of involvement by SALT score, together with general examination. Blood sample was taken at the start of treatment by phototherapy sessions, and after 24 sessions.

2.1 | Patient evaluation

Data were collected from patients including age, sex, duration of illness, and type of therapy. The lesion severity was calculated by SALT score, percentage of hair loss in each of 4 areas of the scalp (40% vertex, 18% right profile, 18% left profile, and 24% posterior part). They were divided into following grades according to their severity: (S0 no hair loss), (S1 <25% hair loss), (S2 25%-49% hair loss), (S3 50%-74% hair loss), (S4 75%-99% hair loss), and (S5 100% hair loss).[11]

2.2 | Exclusion criteria

Patients with a history of topical or systemic treatments (corticosteroids, intralesional steroid injection, immunosuppressive therapy, and immunomodulatory drugs within 4 weeks of the study) were excluded. Patients with a history of autoimmune, allergic, chronic liver, renal or renal diseases, atopic, parathyroid disorders were excluded from the study.

2.3 | Phototherapy sessions

The phototherapy was initiated at a dose of 0.2 J/cm2; dose was increased by 20% per session. (NB-UVB) treatments were given in (Waldman cabinet, Germany). Treatment sessions were achieved twice weekly on nonconsecutive days with shielding of eyes. During treatment, the patients were regularly assessed for erythema, response to treatment, and any side effects. In case of severe erythema with burning and pain, treatment was stopped until resolution of symptoms and restarted thereafter at the last tolerated dose.

2.4 | Measurement of serum IL-17A

Blood samples were collected from patients before start of phototherapy sessions and after 24 sessions; samples were left to clot for 30 minutes at room temperature, then centrifugation for 15 minutes. Serum was then separated using a pipette and stored at −20°C until the time of assay.

On the day of assay, Human IL-17A ELISA Kit (CAT no E-EL-M0047, Elabscience, China) was used on samples and reagents at room temperature, and concentrations of IL-17 were tested in patients and control according to the manufacturer's protocol. It is advised that all samples and standards should be assayed in duplicate. A standard curve was prepared from 7 human IL-17 standard dilutions, and serum IL-17 concentrations in samples.

2.5 | Statistical analysis

Data entry and analysis were conducted using SPSS software (v18; IBM, Armonk, NY, USA). The v2 test was used to compare qualitative variables (sex distribution), while Student's *t* test was used to compare quantitative variables (age and serum IL-17A). Pearson's correlation was used to explore the relationships between quantitative variables (serum IL-17A, SALT score). Differences were considered to be statistically significant at $P < .05$.

3 | RESULTS

The present study was carried out on 20 patients with alopecia areata of the scalp, and 15 healthy age-matched control individuals. The patients' age ranged from 9 to 46 years with a mean ± SD (28.20 ± 11.31 years). Five of the 20 patients (25%) had associated lesions on other body sites (Table 1).

3.1 | IL-17A levels in AA

Serum IL-17A in patients had a mean ± SD (15.63 ± 10.89 pg/mL), whereas in the control group was mean ± SD (16.50 ± 5.02 pg/mL) (Table 1).

TABLE 1 Mean values for age, sex, serum IL-17A level, and SALT score in studied patients and control groups

	Patients (n = 20)		Control (n = 15)		
	No.	%	No.	%	*P*-value
Sex					
Male	12	60.0	10	66.7	.686
Female	8	40.0	5	33.3	
Age (y)					
Mean ± SD	28.20 ± 11.31		21.53 ± 9.07		.083
Range	9.0-46.0		10.0-40.0		
SALT score					
Mean ± SD	14.03 ± 13.48		-		-
Median (Range)	10.5 (3.6-58.6)		-		
IL-17A before treatment					
Mean ± SD	15.63 ± 10.89		16.50 ± 5.02		.271
Median (Range)	14.0 (3.9-41.1)		15.0 (10.5-26.5)		
Body involvement					
Yes	5	25.0	-	-	-
No	15	75.0	-	-	
Type of AA					
Acute	10	50.0	-	-	-
Chronic	10	50.0	-	-	

3.2 | Serum Il-17A before and after treatment

Serum IL-17A was found to be significantly decreased in patients with AA after NB-UVB treatment ($P = .001$) (Table 2, Figure 1).

3.3 | IL-17A and gender

The study included 12 male and 8 female patients with AA. Serum IL-17A mean ± SD was (14.81 ± 10.06 pg/mL) in male patients and (16.86 ± 12.64 pg/mL) in female patients. Serum IL-17A levels showed no significant difference between male and female patients ($P = .817$), also no significant difference was observed between male and female patients in serum IL-17A levels after NB-UVB treatment.

3.4 | IL-17A and age

Age of the patients ranged from (9.0-46.0) years, control subjects with age range of (10.0-40.0) years. A significant negative correlation between serum IL-17A and age was detected in patients with AA before treatment ($r = -.583$, $P = .014$). (Figure 2) and also after treatment ($r = -.602$, $P = .005$).

TABLE 2 Serum IL-17A before and after NB-UVB in the studied patients

IL-17A	Before treatment (n = 20)	After treatment (n = 20)	*P*-value
Mean ± SD	15.63 ± 10.89	11.59 ± 8.12	.001*
Median (Range)	14.0 (3.9-41.1)	11.1 (3.5-33.4)	

Wilcoxon Signed Ranks Test.
*Statistical significant difference ($P < .05$).

FIGURE 1 Serum IL-17A level before and after NB-UVB in the studied patients

3.5 | SALT score

SALT score was measured for patients with a mean ± SD (14.03 ± 13.48) (Table 1).

3.6 | SALT score and age

A significant positive correlation between age and SALT score was detected in patients with AA ($r = .446$, $P = .049$) (Figure 2).

3.7 | SALT score and IL-17A

No statistically significant correlation was detected between SALT score and IL-17A level before NB-UVB treatment while a significant

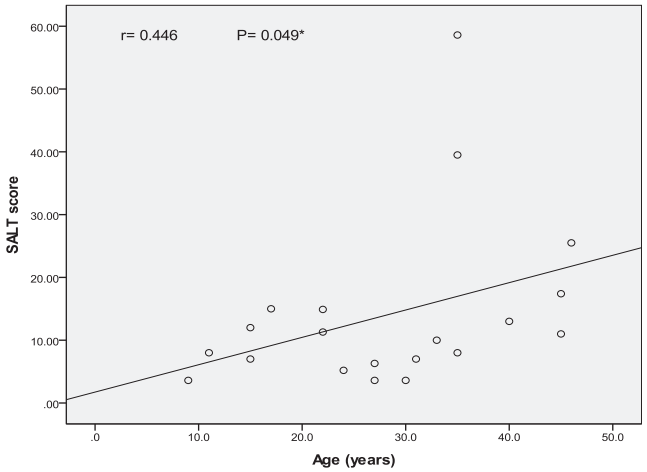

FIGURE 2 Correlation between age and serum SALT score

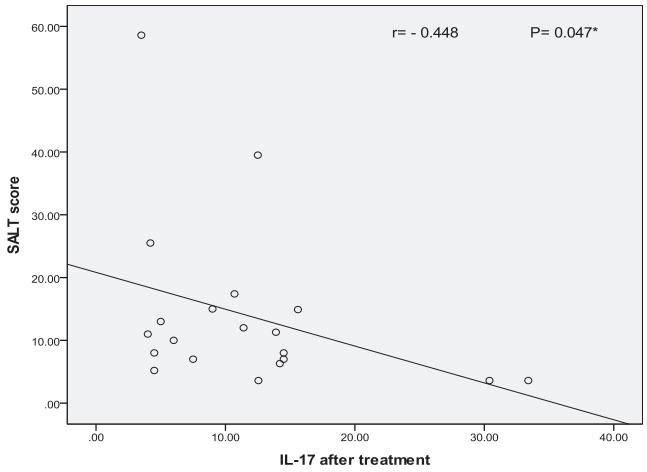

FIGURE 3 Correlation between SALT score and IL-17 after NB-UVB

negative correlation between SALT score and IL-17A level was observed after treatment ($r = -.448$, $P = .047$) (Figure 3).

4 | DISCUSSION

Many inflammatory and autoimmune disorders are associated with increased levels of serum IL-17. IL-17 inhibitors such as secukinumab have been investigated in clinical trials to modify T-cell activity and find new therapeutic approaches in these disorders. Alopecia areata is a recurrent T-cell–mediated disorder, with nonscarring destruction of hair follicles and UVB is a well-established treatment option in AA.

In the present study, patients with AA were found to have higher serum IL-17A levels than control subjects; this increase in serum IL-17A levels was not statistically significant, in accordance with Tembhre and Sharma whom reported increase in serum IL-17A levels.[8] Also, other studies have reported this increase in the cytokine level in patients with AA.[6,7]

In the current study, in accordance with Elmorsy et al,[7] serum IL-17A level was not influenced by gender. Although susceptibility to immune-mediated diseases is generally influenced by gender, no evidence of linking IL-17A with gender and disease susceptibility has been revealed.

Data from our results demonstrated significant negative correlation between serum IL-17A and age that was detected in patients with AA before and after phototherapy treatment, patient age, and serum IL-17A in agreement with Elmorsy et al[7] whom revealed same results, which indicated that under normal conditions, age does not seem to influence serum IL-17A levels.

We identified serum IL-17A to be significantly decreased in patients with AA after NB-UVB treatment ($P < .001$). This could be attributed to the immunomodulatory effect of (NB- UVB),[12] although it works in the upper dermis, and the inflammatory infiltrate is present in hypodermis, patients in our study have shown decrease in the cytokine level. The immunomodulatory effect of (NB-UVB) may affect T-cell aggregation, decrease the inflammatory infiltrate, and then may affect the serum level of this cytokine; this should be documented in further studies by biopsy from the lesion.

In the current study, we hypothesized that there would be an association between serum IL-17A levels and clinical severity score in AA (SALT score), and our study reported a significant negative correlation between SALT score and IL-17A level after (NB-UVB) treatment. A study performed by Bayramgurler et al (2011)[12] reported poor response at a rate 83% of the patients after (NB-UVB), and they explained this result due to UVB is absorbed in the upper dermis, whereas the early pathological changes in AA show lymphocytic infiltration around the hair follicle in hypodermis; as NB UVB cannot reach that depth.

In conclusion, although (NB-UVB) is a well-established treatment for alopecia areata (AA) of mild efficacy especially if it is used alone, serum IL-17A had shown significant decrease after (NB-UVB) sessions. IL-17A cytokine maybe of value in pathogenesis of AA, and its level maybe lagging behind disease severity and prognosis.

This study has some limitations; first, the study population was relatively small, and larger number of patients should be included in future studies. Second, we collected serum samples before and after 24 phototherapy sessions, a future study of assessment of serum IL-17A together with histopathological changes by taking a biopsy at start and end of treatment could provide more information about the relation of this cytokine and treatment efficacy.

CONFLICT OF INTEREST

No conflict of interest.

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