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Immunohistochemical Outcomes of NB-UVB in Non-Segmental Vitiligo: A Case-Control Study

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Abstract

Background: Melanocytorrhagy is considered as one of the theories for the pathogenesis of vitiligo. NB-UVB being the 1st line phototherapeutic modality, could mediate its efficacy through immunohistochemical changes in the expression of adhesion molecules.

Aim of Study: To study the outcome of Narrow Band UVB on Melan A, as a melanosomal protein, E-cadherin as a representative of adhesion molecules, as well as integrin αvβ in non-segmental vitiligo.

Patients and Methods: Twelve vitiligo patients and 12 controls were included in this study. The vitiligo patients were subjected to NB-UVB exposure and skin biopsy taking (lesional, perilesional and non-lesional) was performed at base line and after 36 NB-UVB sessions. VASI and VIDA scores were conducted before and after treatment, for clinical scoring. All biopsies from patients and controls were stained immunohistochemically by anti-E-cadherin antibody, anti-. integrin αvβ and Melan-A.

Results: Melan-A expression was significantly lower in all sections in cases compared to controls. Melan-A expression increased significantly in lesional sections after NB-UVB exposure. Perilesional expression of E-cadherin increased after treatment but without significance.

Conclusion: Melan-A expression can be considered a strong indicator for NB-UVB-induced repigmentation. The increase of perilesional E-cadherin expression may account for stabilization of repigmentation, significantly detected by Melan-A expression.

Key Words: Vitiligo – Melan-A – NB-UVB – E-cadherin.

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Introduction

A PRIMARY melanocytorrhagic disorder has been proposed as one of the factors incriminated in the pathogenesis of non-segmental vitiligo (NSV). Friction and other stressful stimuli, induce loss of adhesion and subsequent transepidermal detachment of melanocytes, which may become reflected as depigmentation, the clinical hallmark of vitiligo **[1,2].**

Cadherins mediate melanocyte-keratinocyte interactions **[3].** E-cadherin is the main cadherin in the human skin **[4].** Baseline expression of E-cadherin was reported to be deficient in NSV compared to controls **[5].** Integrins are a group of proteins that account for the anchoring of cells to the extracellular matrix. Melanocytes (MC) express αvβ, heterodimers, along with other integrin subunits. Throughout the process, of repigmentation, it is anticipated that alterations in the expression of E-cadherin and integrin subunits in melanocytes may be detected, thus reducing cell adhesion and facilitating cell dissociation and hence movement **[6].**

Melan-A, a specific and sensitive melanocyte marker **[7],** was used to stain melanocytes before and after repigmentation, aiming to settle the localization of adhesion molecules in relation to melanocytes and to find any possible correlations between the melanocyte staining and changes in the expression of the adhesion molecules.

Published reports whether in vivo or in vitro presented inconsistent results regarding the alterations in expression of adhesion molecules following NB-UVB exposure **[5,8],** a chief treatment modality for NSV **[9].** Through conducting this study we aimed to highlight and clarify such changes, and their possible clinical implications.

Patients and Methods

This pilot study initially included 12 patients with non-segmental vitiligo, who were randomly recruited from the Outpatient Clinic of the Dermatology Department and the Histology Department of Kasr El-Ainy Hospital Cairo University, during the period from January 2022 to May 2023.

Ethical approval was given by the Research Ethical Committee, Cairo University. An informed written consent was taken from all patients. Nature of the therapy and possible side effects were explained to the patients before starting the treatment. No additional treatment was applied during the study.

Twelve healthy individuals age and sex matched with no family history of vitiligo were enrolled in this study and assigned as controls.

All patients included within this study, had non segmental vitiligo with different patterns of distribution, of both sexes, above 18 years of age and did not receive any treatment for vitiligo during the past 3 months. Patients with active vitiligo (VIDA+1 or above) were included in this study. Exclusion criteria included pregnancy, lactation, contraindications for phototherapy as in associated photosensitive disorders, previous NB-UVB sessions (>200-300 sessions) and/or high cumulative UVB dosage. Patients with current or past history of any dermatological diseases and/or systemic conditions affecting the immune system as autoimmune disorders and malignancy were also excluded from the study.

All patients were subjected to the following:

- Full history taking.
- Full dermatological examination.
- Investigations in the form of complete blood picture, liver and kidney functions, lipid profile, fasting and 2-hours postprandial blood sugar.

Treatment regimen:

Each patient received NB-UVB phototherapy for 36 sessions, three times weekly on non-consecutive days for 12 weeks. The sessions took place in a Waldmann W UV 100L cabinet with 40 narrowband UVB (310-315nm emission spectrum) fluorescent linear bulbs (Philips TL 100 W/01, Philips Company, Eindhoven, The Netherlands).

The dosing protocol included an initial dose of 0.3 J/cm^2, with increasing increments by 0.3 J/cm^2 every other session. Endpoint was faint erythema **[10]**. Eyes and genitalia were covered during treatment. The patients were followed-up every 2 weeks.

Minimal erythema dose ranged from 0.8-1.4 J/cm^2. It was calculated by the visual method, whereby the lowest UVR inducing positive erythema reaction (erythema affecting 50-100% of UV-irradiated skin area), was recorded **[11].**

Evaluation of treatment (outcome measures) were done at baseline and at the end of 36th session at the end of 12 weeks.

Clinical:

- Vitiligo Area and Severity Index (VASI) **[12].**
- Vitiligo Index for Disease activity **[13].**

Immunohistochemistry:

All biopsies from patients and controls were stained immunohistochemically by anti-E cadherin, anti-integrin αvβand Melan-A antibodies.

Sampling: Three mm skin biopsies were retrieved from all vitiligo patients at the following sites: Lesional (at the center of the vitiliginous skin), perilesional (at the pigmented border just adjacent to the vitiliginous skin) and non-lesional. The post-treatment biopsies were taken from sites adjacent to the pretreatment biopsies in either perilesional margins or non-lesional skin, while a non-lesional biopsy was taken from regimented skin. One biopsy was taken from normal non-exposed skin of healthy volunteers.

Staining: Paraffin sections were cut into 5μm sections and stained manually by mouse anti-human E-cadherin, Integrin alpha V beta 1 and Melan-A antibody monoclonal antibody (Thermo Scientific, Clone SPM471, CA, USA). The formalin-fixed sections were deparaffinized and rehydrated. The sections were incubated with hydrogen peroxide for 10-15 minutes to reduce non-specific background, then washed twice with buffer. Then sections were incubated with biotinylated Goat antipolyvalent antibody for 10 minutes at room temperature. The sections were again washed 4 times in buffer. Sections were incubated with streptavidin peroxidase for 10 minutes at room temperature, then washed 4 times in buffer. Then sections were incubated with peroxidase compatible chromogen according to the manufacturer's instructions. Then slides were covered and examined.

Image analysis: Data was obtained using leicaQwin 500 Software with Olympus BX4D microscope and Panasonic camera. Measurements were taken in 5 serial non overlapping high power fields. Mean + or – standard deviation was taken for every section (mean for lesional, perilesional, non-lesional separately). Parameters were measured as area in (mm^2) and area % within the standard measur-

ing frame. Brown color range, which is considered as positive, was selected using image detect menu, then masked by blue binary colors and measured. The image analysis assessor was blinded to the sections.

Photography was done using Olympus BX51 microscope with Olympus DP27 camera processed and taken on computer software call (cell sense). Photography was done using high power lens (upplane FI X 40, scale bar) was attatched with the photomicrographs.

Statistical methods:

Data were coded and entered using the statistical package for theSocial Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparison of serial measurements within each patient the non-parametric Wilcoxon signed rank test was used 14. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 15. Correlations between quantitative variables were done using Spearman correlation coefficient 16. *p*-values less than 0.05 were considered as statistically significant.

Results

Statistical analysis was performed on 12 patients with non-segmental vitiligo, who completed the study, and 12 healthy age and sex-matched individuals, who served as controls.

Demographic data:

No significant difference was found between cases and controls as regards to sex and age, (Table 1).

Table (1): Demographic data.

	Cases	Controls	*p*-value
Sex Count (%):			
Male	5 (41.7%)	4 (33.3%)	1
Female	7 (58.3%)	8 (66.7%)	
Age:			
Mean ± SD	32.08±14.30	34.50±14.57	0.799
(Range)	(15.00-57.00)	(16.00-56.00)	
Median	33.50	32.50	

- *p*-values less than 0.05 were considered as statistically significant.
SD: Standard deviation.

Clinical data:

Mean disease duration among studied patients was 7.00±8.03 years ranging between 1 and 30 years with a median of 4.50 years. VIDA score among vitiligo case group was below 6 weeks (4+) in 7 (58.3%) patients, from 6 weeks to 3 months (3+) in 4 (33.3%) patients and from 3 and 6 months (2+) in 1 (8.3%) patient. Six (50.0%) patients had positive family history of vitiligo. Regarding the associated diseases, 1 (8.3%) patient had thyroid and cardiac disease, and 1 (8.3%) patient had hypotension and irritable bowel syndrome, otherwise the rest of the patients did not present with any associated diseases.

Mean VASI decreased significantly (p=0.019) after treatment, when compared to baseline values with a 46.1% drop.

Laboratory data:

Comparisons at baseline:

Cases versus controls:

Expression of Melan-A before treatment was significantly lower among cases when compared with controls in each of lesional (p<0.001), perilesional (p=0.002), and non-lesional sections (p= 0.028). E-cadherin expression in lesional, perilesional and non-lesional sections were lower among cases, compared to controls, but without significance.

Figs. (1-2) illustrate control sections of E-cadherin and Melan-A expression.

Unfortunately, integrin αvβ, was not stained at all in any of the sections.

Comparisons between different sections within cases:

Expression of Melan-A before treatment in lesional sections was significantly lower when compared with perilesional (p=0.003), and non-lesional sections (p=0.02). Also, expression of Melan-A, before treatment, in perilesional areas was significantly lower when compared with non-lesional (p= 0.019).

As regards E-cadherin expression in non-lesional sections was the highest, followed by lesional then perilesional sections, but without significance.

Comparisons after treatment:

Comparison of E-cadherin and Melan-A expression between before and after treatment:

Table (2) demonstrates the change in expression of E-cadherin and Melan-A in lesional, perilesional and non-lesional sections.

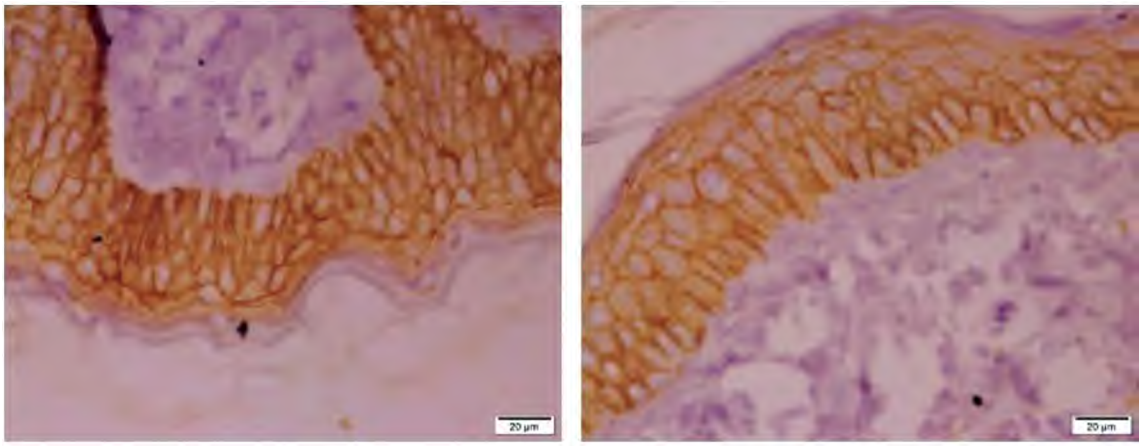

Fig. (1): E-cadherin expression in control sections (IHC, x200).

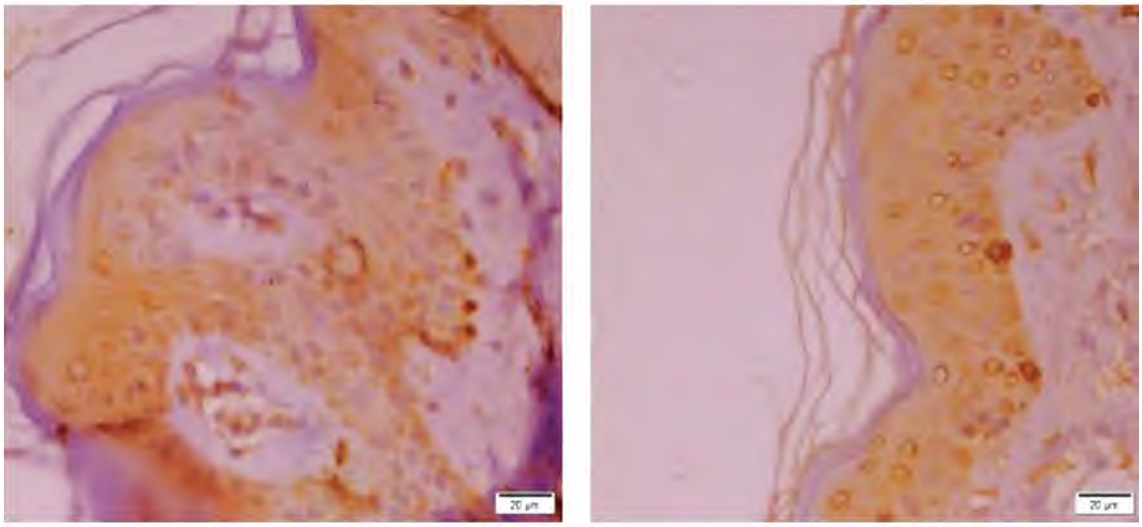

Fig. (2): Melan-A expression in control sections (IHC, x200).

Table (2): Comparison between different sections, before and after treatment.

Cases	Pre- ttt		Post- ttt		*p*-value
	Mean ± SD (Range)	Median	Mean ± SD (Range)	Median	
E-Cadherin:					
Lesional areas	20.89±5.73 (13.58-32.15)	20.36	20.14±4.69 (14.85-29.48)	19.41	0.530
Perilesional areas	19.52±4.67 (12.44-30.34)	19.06	20.80±3.61 (15.77-26.82)	20.29	0.480
Non lesional areas	21.23±5.68 (12.25-28.85)	20.82	19.11±5.23 (13.12-32.93)	18.70	0.308
Melan A:					
Lesional areas	2.35±3.73 (0.19-13.97)	1.28	4.05±4.26 (0.70-16.56)	3.09	0.006*
Perilesional areas	4.26±5.26 (0.71-20.12)	2.78	4.39±4.89 (1.14-19.09)	2.80	0.117
Non lesional areas	5.56±4.94 (1.88-18.43)	3.50	6.09±5.04 (2.06-19.38)	4.77	0.084

Non-parametric Mann-Whitney test was used for continuous variables.
p-values less than 0.05 were considered as statistically significant.
SD: Standard deviation. ttt=Treatment.

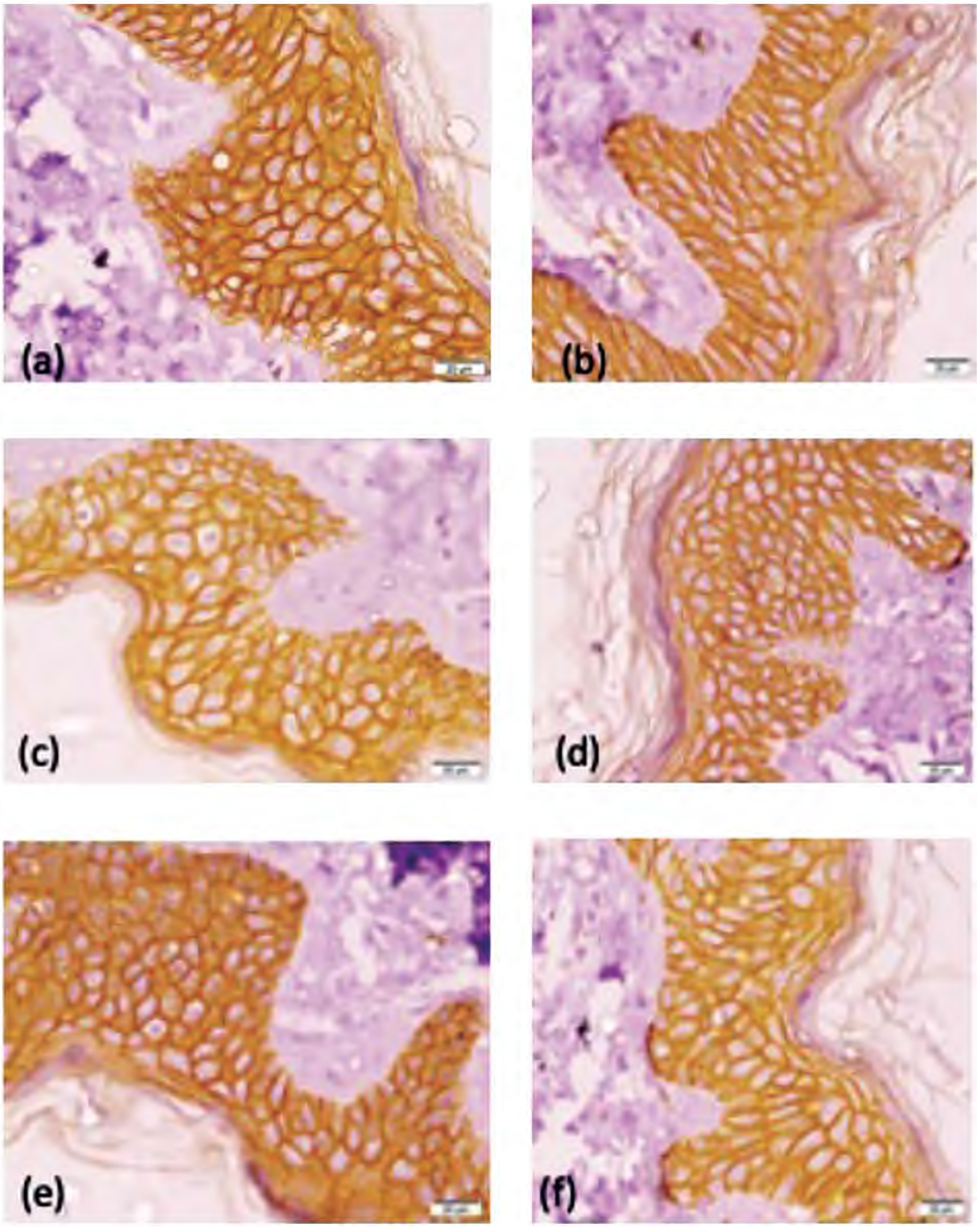

Fig. (3): Image analysis of E-cadherin expression lesional section before treatment (A) and after treatment (B), perilesional section before treatment (C) and after treatment (D) and non-lesional before treatment (E) and after treatment (F) (IHC, x200).

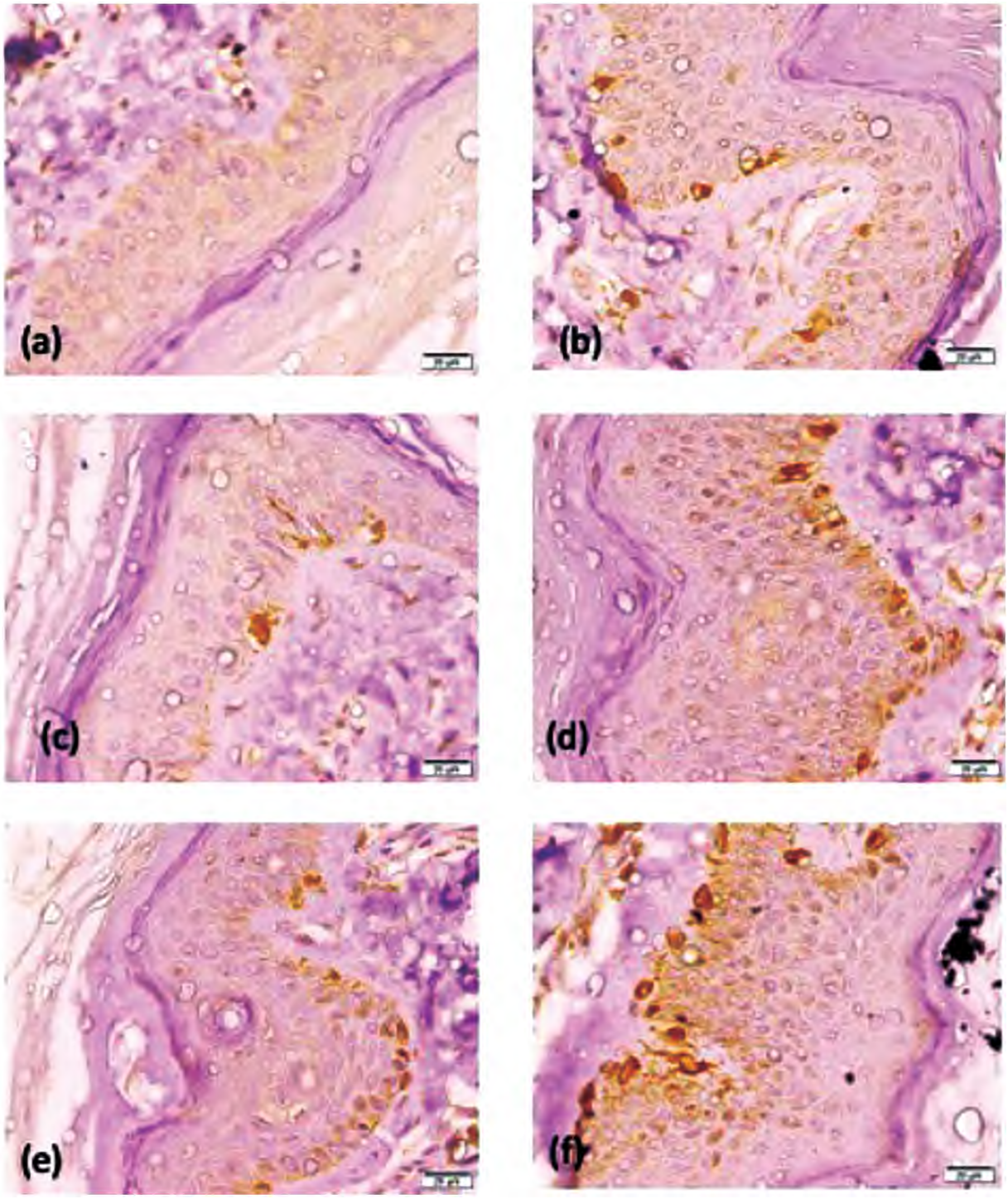

Fig. (3): Image analysis of Melan-A expression lesional section before treatment (A) and after treatment (B), perilesional section before treatment (C) and after treatment (D) and non-lesional before treatment (E) and after treatment (F) (IHC, x200).

Expression of Melan-A in the lesional sections significantly increased after treatment when compared with baseline values, (p=0.006). E-cadherin expression decreased in lesional and non-lesional sections, whereas it increased in perilesional sections, yet without significance.

Cases versus controls:

Expression of Melan-A after treatment was significantly lower among cases when compared with controls in each of lesional (p=0.002), perilesional (p=0.002), and non-lesional sections (p=0.039). While no significant difference was reported be-

tween cases and controls regarding expression of E-cadherin after treatment, which remained lower in cases than controls, in all sections.

Comparison between different sections within cases:

No significant difference was reported between lesional and perilesional sections regarding expression of Melan-A. However, significant Melan-A expression was found between non-lesional and both lesional (p=0.002) and perilesional sections (p=0.01). Non-significant expression of E-Cadherin was detected after treatment, with perilesional expression being the highest followed by lesional then non-lesional expression.

Comparison between E-cadherin and Melan-A area % change:

Mean % change of Melan-A in lesional sections was significantly higher than % change of E-cadherin (p=0.008). While no significant difference was reported between % change of Melan-A and % change of E-cadherin in perilesional or non-lesional sections.

Correlations:

VASI score after treatment positively correlated with expression of E-cadherin before treatment in perilesional areas (r=0.587; p=0.045). VASI % change positively correlated with expression of Melan-A before treatment in perilesional areas (r=0.601; p=0.039), as well as non-lesional areas (r=0.615; p=0.014).

VASI % change positively correlated with expression of Melan-A after treatment in lesional areas (r=0.683; p=0.014), as well as non lesional areas (r=0.769; p=0.003).

Discussion

This clinical trial is further reinforcing the role of NB-UVB in the repigmentation process of vitiliginous lesion, as evidenced by the significant decrease of VASI and the significant increase in Melan-A expression after treatment, on clinical and immunohistochemical grounds respectively.

Melan-A expression in lesional, peri-lesional and non-lesional were significantly lower than control sections. As regards vitiliginous sections, Melan A was significantly lower in lesional areas followed by perilesional areas while its highest levels were reported in non lesional areas.

Melan-A, a melanosomal protein, is mainly on expressed on melanocytes of the skin and retina. Analyzing changes of its expression in a disorder of melanocyte malfunction as in vitiligo, is of great importance since Melan-A acts as an immunogenic marker of melanocytes targeted by autoreactive circulating CD8+ T-cells **[17]**. Previous studies reported down-regulation of Melan-A expression in vitiliginous skin of NSV patients, as well as clinically intact skin **[7]**. This was also encountered in the current study, by the significantly lower expression of Melan-A in non-lesional skin compared to control skin.

Furthermore, Melan A significantly increased after treatment with NB-UVB. The superiority of Narrow-band ultraviolet B (NB-UVB) is attributed to its safety, efficacy and non-invasive nature, promoting stabilization of the disease activity and activation of hair bulge melanocytes **[9]**. NB-UVB is the cornerstone for the stimulation of melanocytes **[18]**.

Melan-A is considered as a differentiation antigen **[19]**, and was also found to be more specific and sensitive than other markers **[20,21]**. Within the context of this study, the significant increase of Melan-A, that denoted the strong repigmentation, can allow for categorization of Melan-A as a repigmentation marker for other therapeutic modalities aiming for repigmentation of vitiligo. Thus, it can be deduced that a modality inducing strong repigmentation detected by Melan-A expression, is a modality allowing for maturation and differentiation of melanocytes.

Perifollicular repigmentation following NB-UVB monotherapy is mediated primarily through upregulation of stem cell genes in follicular melanocytes **[22]** along with NB-UVB induced activation of the Wn't signaling, triggering differentiation of melanocyte stem cells in the hair bulge and migration of melanocyte precursors to the epidermis **[23,24,25]**. As melanocyte precursors reside in the upper infundibulum of the hair follicle, the pivotal zone for melanoblast differentiation into mature melanocytes, subsequently stained by Melan-A **[26]**.

As for the extrafollicular repigmentation, which involves glabrous skin, could be considered a consequence of functional melanocyte stem cells residing in the dermoepidermal junction, as evidenced by previous reports **[27,28]**. It is hypothesized that such melanocyte stem cells are derived from the neural crest, persist after birth in the superficial nerve sheath of peripheral nerves and provide a depot of melanocyte precursors **[29,30]**. Also, one should give ownership to a possible ectopic melanogenesis in the adipose tissue **[31,32,33]**.

Previous reports utilized Melan-A for descriptive and quantitative analyses of melanocytes in different vitiligo locations [7], or in relation to immune mediators [34], or compared to keratinocytes in vitiligo [35]. Melan-A has also been used for defining cut-off values for vitiligo diagnosis [36]. Other clinical trials compared efficacy of therapies by the immunohistochemical staining of Melan-A and counting by a blinded pathologist per field. To date, this is the first clinical trial to study the effect of Nb-UVB on Melan A expression, by the use of image analysis software, an objective relatively more accurate method of quantification.

The disappearance and/or defect of melanocytes, an initial step for pigment loss in vitiligo appears to involve cell adhesion defects [37]. Epithelial cadherin (E-cadherin) is an adhesive transmembrane protein mediating tight and strong cell–cell adhesion through homophilic interactions [38]. Unfortunately, no significant change was noted in the E-cadherin expression, as regards to baseline expression in cases compared to controls, and to the expression after NB-UVB exposure compared to baseline values. This can be explained by the small sample size, especially that E-cadherin expression is constantly interchangeable [1,39,40]. Also, the fact that the sections were taken at the end of the treatment and after repigmentation became established may explain why E-cadherin changes might possible have already occurred at an earlier state. However, the perilesional expression of E-cadherin did increase after treatment, yet without significance, which may be considered stabilization of repigmentation, evidenced by the significant rise of Melan-A expression.

The altered adhesion, incriminated as a pathogenetic factor for melanocyte loss in vitiligo, may either result from weak expression of adhesion molecules, namely E-cadherin, but may also arise from injured melanocytes, with secondary defected adhesion with surrounding keratinocytes (KC) [41].

The role played by E-cadherin in the pathogenesis of vitiligo, has been documented before in the literature [3,37,42,43]. E-cadherin is primarily responsible for adhesion of human MCs to KCs [43] and this interaction is of importance for melanocyte growth, function and stabilization within the epidermis [44], therefore the disturbance in this interaction could contribute to melanocyte loss in vitiligo. Furthermore, melanocyte proliferation, differentiation, melanogenesis and dentritogenesis are regulated by keratinocytes, which in turn are regulated directly by cell-cell adhesion and indirectly by growth factors [45]. The lack of E-cadherin expression on epidermal melanocytes renders them more susceptible to damage because of chemical and mechanical stresses [37]. In addition, the polymorphism of the gene CDH1 that encodes E-cadherin, was found in vitiligo as well as other autoimmune comorbidities [46].

In another context, E-cadherin also helps anchor Langerhans cells to KCs and hence is important for its tolerogenic differentiation, thus any disturbance in this mechanism may cause autoimmune /inflammatory diseases [47].

Researchers also believe that exposure to oxidative stresses may destabilize E-cadherin and β-catenin complexes resulting in low E-cadherin levels in melanocytes [37], suggesting that the disturbance in E-cadherin in vitiligo may be a secondary defect as well as a primary one.

Another report presented significant downregulation of E-cadherin in vitiliginous lesional and perilesional skin, as compared to control skin [5]. Repigmentation following NB-UVB exposure may be attributed to the dynamic nature of E-cadherin expression, in the sense that down-regulation primarily allows for dissociation and migration of melanocytes from perilesional skin, followed by upregulation that sets the stage for repositioning of melanocytes within depigmented skin [5]. Thus, it can be postulated that the repigmentation process following NB-UVB includes an array of factors that need further research.

This study was aiming at possibly linking changes in E-cadherin in respect to melanocytes through the Melan-A expression. Unfortunately, no significant correlation was found between Melan-A and E- cadherin expression.

Limitations of this study include the small sample size, and the lack of double staining of Melan-A and E-cadherin. Staged evaluation of E-cadherin at different checkpoints, for example every 12 sessions could have been useful to detect possible E-cadherin expression alterations during UVB therapy, though sequential biopsing from patient would have not been feasible.

It can be concluded that NB-UVB continues to stand as a reliable treatment strategy for vitiligo, providing good repigmentation, as evidenced by a significant rise in the Melan-A expression. NB-UVB is an established treatment for vitiligo and Melan-A estimation through the use image analysis provides accurate assessment of repigmentation. The rise in the E-cadherin expression, may still reflect the robust repigmentation, mediated by better

stabilization and anchoring of melanocytes, and detected by the strong Melan-A expression.

Study registered in Protocol Registration and Results System (clincaltrials.gov).NCT05287776.

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Conflicts of interest: None.

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The patients in this manuscript have given written informed consent to publication of their case details.

Consent for the publication of recognizable patient photographs or other identifiable material was obtained by the authors and included at the time of article submission to the journal stating that all patients gave consent with the understanding that this information may be publicly available.

Data availability: The data supporting findings of this study are available within the article. Raw data from which the findings of this study were obtained, are available from the corresponding author, upon request.

Author contribution: AS: Conceptualization, MF: Methodology, Writing - Review & Editing, Validation, RH: Conceptualization, RL: Data curation, SS: Investigation, Software, RF.H: Writing - Original Draft, Data Curation, Formal analysis.

All authors approved the final version and submission to the journal.

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النتائج المناعية الكيميائية للأشعة فوق البنفسجية ضيقة النطاق ب فى البهاق غير القطعى: دراسة حالة وشاهد

الخلفيـة: يُعتبر نزيف الخلايا–الميلانينية أحد النظريات المُسببة للبهاق. ويُمكن للأشعة فوق البنفسجية ضيقة النطاق ب، كونها الخط الأول للعلاج الضوئى، أن تُعزز فعاليتها من خلال التغيرات المناعية النسيجية فى التعبير عن جزيئات الالتصاق.

الهـدف: دراسة نتائج الأشعة فوق البنفسجية ضيقة النطاق (ب) على الميلانين أ، كبروتين ميلانوسى، واى الكادهيرين–كممثل لجزيئات الالتصاق، بالإضافة إلى الإنتغرين ألفا–بيتا فى البهاق غير القطعى.

المرضـى والطـرق: شملت هذه الدراسة اثنى عشر مريضًا بالبهاق واثنا عشر شخصًا من مجموعة الضبط. خضع مرضى البهاق لأشعة فوق البنفسجية ضيقة النطاق ب، وأُخذت خزعة جلدية (آفات، وحول الآفة، وغير آفات) فى بداية العلاج وبعد ٣٦ جلسة من الأشعة فوق البنفسجية ضيقة النطاق (ب). أُجريت درجات قبل العلاج وبعده، للتقييم السريرى. تم صبغ جميع الخزعات المأخوذة من المرضى وضوابطهم مناعيًا نسيجيًا باستخدام الأجسام المضادة لـ الميلانين أ، واى الكادهيرين والإنتغرين ألفا–بيتا.

النتائـج: كان التعبير عن الميلانين أ أقل بشكل ملحوظ فى جميع المقاطع فى الحالات مقارنةً بضوابطها. ازداد التعبير عن – عن الميلانين أ بشكل ملحوظ فى المقاطع الآفية بعد التعرض للأشعة فوق البنفسجية. ازداد التعبير عن ايالكادهيرين حول الآفة بعد العلاج، ولكن دون دلالة إحصائية.

الخلاصـة: يمكن اعتبار التعبير عنعلى الميلانين أ مؤشرًا قويًا على إعادة التصبغ الناجم عن الأشعة فوق البنفسجية. قد تُفسر زيادة التعبير عن اى الكادهيرين حول الآفة استقرار إعادة التصبغ، وهو ما يُكتشف بشكل ملحوظ من خلال التعبير عن الميلانين أ.