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Narrowband Ultraviolet Light - B Phototherapy Manipulating Levels of Interleukin-38 in Vitiligo

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ABSTRACT

Background: Vitiligo is a chronic autoimmune disorder that significantly impacts psychological well-being and quality of life. Interleukin-38 (IL-38), a cytokine with immunomodulatory properties, may influence the disease's pathogenesis. Narrowband ultraviolet B (NB-UVB) phototherapy, a standard vitiligo treatment, is known to modulate immune responses, but its effect on IL-38 remains underexplored.

Objectives: To assess serum IL-38 levels in vitiligo patients, evaluate their correlation with disease severity, and investigate the impact of NB-UVB therapy on IL-38 and clinical outcomes.

Patients and Methods: This case-control study enrolled 30 patients diagnosed with non-segmental vitiligo, alongside 15 healthy controls matched for age and sex. Serum IL-38 levels were measured using ELISA before and after three months of NB-UVB phototherapy. Disease severity was assessed using Vitiligo Area Scoring Index (VASI), Vitiligo Disease Activity (VIDA), and Dermatology Life Quality Index (DLQI).

Results: Baseline IL-38 levels were significantly higher in vitiligo patients compared to controls (median = 30.27 vs 15.14 pg/ml; $P < 0.001$). Post-treatment, IL-38 levels decreased significantly (median = 23.2 pg/ml; $P = 0.003$). VASI scores improved from a median of 5 to 2 ($P < 0.001$). IL-38 levels positively correlated with VASI ($r = 0.511$; $P = 0.004$), VIDA ($r = 0.419$; $P = 0.021$), and DLQI ($r = 0.434$; $P = 0.017$). Logistic regression indicated that each unit increase in IL-38 increased vitiligo risk by 24% (OR = 1.243; $P = 0.002$).

Conclusion: IL-38 levels correlate with vitiligo severity and decrease with NB-UVB therapy, suggesting its potential role as a biomarker and therapeutic target.

Keywords: Vitiligo, Interleukin-38, Narrowband UVB, Disease Severity, Cytokines.

INTRODUCTION

Vitiligo is an autoimmune disorder that progressively diminishes melanocyte function, leading to depigmented skin areas. It affects approximately 0.1%–2% of the global population. This condition can profoundly affect patients' psychological health and overall quality of life, frequently contributing to social stigma and emotional distress. Although the exact cause of vitiligo remains unclear, emerging research highlights a multifaceted pathogenesis involving genetic predisposition, environmental triggers, oxidative stress, and immune dysregulation, as proposed by the convergence theory [1].

A key aspect of vitiligo's autoimmune pathogenesis is the interplay between innate and adaptive immunity, particularly the involvement of T helper (Th) 17 cells. Elevated levels of inflammatory cytokines, such as IL-1β, IL-6, IL-17, and IL-23, further implicate immune-mediated mechanisms. As part of the IL-1 cytokine family, Interleukin (IL)-38 has gained attention due to its immunomodulatory properties. It functions as an antagonist by binding to IL-36 receptors, thereby inhibiting the activation of Th1 and Th17 pathways. This inhibition results in reduced production of inflammatory cytokines like TNF-α, IL-1β, and IL-17, suggesting IL-38's potential therapeutic relevance in immune-mediated diseases, including vitiligo [2].

Narrowband ultraviolet B (NB-UVB) phototherapy is a cornerstone treatment for vitiligo, known for its dual mechanism of action: modulating immune responses and stimulating melanocyte activity [3]. It downregulates pro-inflammatory cytokines, induces T-cell apoptosis, and promotes melanocyte proliferation, effectively halting disease progression and supporting repigmentation. Given its targeted 311 nm wavelength, NB-UVB minimizes side effects while achieving therapeutic efficacy. Despite its widespread use, the interplay between NB-UVB and cytokines like IL-38 remains underexplored [4].

This study aimed to investigate the serum levels of IL-38 in vitiligo patients compared to controls, focusing on its correlation with disease severity using Vitiligo Area Scoring Index (VASI) and Vitiligo Disease Activity (VIDA) scores. Additionally, the effects of NB-UVB therapy on IL-38 levels and its association with clinical improvement were evaluated. The Dermatological Life Quality Index (DLQI) was utilized to assess the impact of vitiligo on patients' psychological well-being and daily activities.

PATIENTS AND METHODS

Study Design and Population

This case-control study included 45 participants (30 Patients with non-segmental vitiligo, and 15 age- and gender-matched healthy volunteers), recruited from the Dermatology, Venereology, and Andrology Outpatient Clinic at Benha University Hospitals during the period from November 2022 to April 2024.

Eligibility Criteria

Patients aged 18 to 65 years with clinically diagnosed non-segmental vitiligo and no prior exposure

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to NB-UVB therapy within the last six months were qualified for inclusion.

Exclusion criteria encompassed systemic or topical treatment within the last three months, other autoimmune or chronic inflammatory diseases, pregnancy or lactation, and contraindications to NB-UVB phototherapy. Healthy controls were individuals with no history of vitiligo or autoimmune diseases.

All study participants were subjected to the following:

All study participants underwent a detailed evaluation that included comprehensive history taking and thorough clinical examination. Personal information, was documented, along with disease-specific details regarding the duration, onset, and progression of vitiligo. A detailed family history was documented to assess potential genetic predispositions, while previous systemic and topical treatments were thoroughly reviewed. Clinical examinations included a general assessment of the skin, oral mucosa, and genital areas to rule out other dermatological or autoimmune conditions. A focused local examination was performed to assess the site, extent, and pattern of vitiligo lesions, ensuring accurate characterization and baseline documentation of the disease**.**

Laboratory Investigations

Measurements of serum IL-38 levels were performed both before treatment and after three months of NB-UVB phototherapy to evaluate changes in cytokine levels using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) technique.

Venous blood samples were obtained, processed, and preserved at -20°C until further analysis. Serum levels of human interleukin-38 (IL-38) were quantified using a commercially available ELISA kit (Catalogue No: 201-12-7669, Shanghai, China).

For the assay, IL-38 from the sample was introduced into enzyme wells pre-coated with a monoclonal IL-38 antibody and incubated. Subsequently, biotin-labeled IL-38 antibodies were added, forming a complex with streptavidin-HRP. After incubation, the wells underwent thorough washing to eliminate any unbound enzyme.

Next, chromogen solutions A and B were introduced, leading to a colorimetric reaction where the solution initially turned blue. Upon acidification, the color changed to yellow. The intensity of the final color exhibited a direct correlation with the IL-38 concentration in the sample, allowing for quantitative analysis.

Following the addition of the stop solution, the optical density (OD) was recorded at 450 nm, with the blank well serving as the zero reference. The measurement was completed within 15 minutes to maintain accuracy.

All vitiligo patients were subjected to the following:

Severity Assessment

Disease severity was systematically evaluated using three established tools. The VASI was used to quantify the extent of depigmentation and lesion coverage [5]. The VIDA score provided an assessment of disease activity and progression [6]. To gauge the impact of vitiligo on participants' lives, the DLQI was employed, capturing the psychological, social, and functional effects of the disease [7].

Photographic Documentation

Standardized photographs of the vitiligo lesions were taken at baseline and after three months of NB-UVB phototherapy. These images, captured using a 64 MP Samsung S52 mobile camera, served as visual documentation to monitor treatment progress and outcomes.

NB-UVB Phototherapy

NB-UVB phototherapy was tailored to each patient following phototesting to determine their minimal erythema dose (MED). Treatment began at 70% of the MED, with subsequent dose increments of 10% until visible repigmentation was observed. Sessions were administered twice weekly on non-consecutive days over three months using an NB-UVB device (EMERGO EUROPE, Daavlin Distributing Company, USA). This approach ensured optimal efficacy while minimizing potential side effects.

Outcome Measures

The primary outcome of the study was the change in serum IL-38 levels measured before and after three months of NB-UVB phototherapy. Secondary outcomes included the correlation between serum IL-38 levels and disease severity, as evaluated by VASI and VIDA scores. Furthermore, improvements in quality of life were assessed using the DLQI, capturing the broader impact of treatment on patients' well-being.

Follow-Up

Participants were followed up for three months, during which regular clinical assessments and laboratory investigations were conducted. Post-treatment evaluations included the VASI, VIDA, and DLQI scores to assess clinical improvement and quality-of-life changes. A standardized protocol was implemented throughout the study to ensure consistency, accuracy, and reproducibility of the findings.

Ethical considerations:

Ethical approval was obtained from the Research Ethics Committee, Faculty of Medicine, Benha University (Approval No: Ms 52-10-2022), and official permission to conduct the study was granted by Benha University Hospitals. All patients

provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical methods

SPSS version 28 (IBM, Armonk, NY, USA) was used for statistical computations and data management. The assessment of quantitative data normality was conducted using the Shapiro-Wilk test along with graphical methods. Based on distribution characteristics, quantitative data were summarized as mean ± standard deviation for normally distributed variables or as median and range for non-normally distributed variables. Qualitative data were summarized as frequency and percentage.

RESULTS

The demographic characteristics, including age and gender, were comparable between the studied groups, with no statistically significant differences observed. All patients experienced an acute onset of symptoms, with the disease course evenly split between stationary and progressive forms, each constituting 50% of the cases. The disease duration varied widely, from 0.08 to 18 years, with a median of 3.5 years. None of the participants had taken any medication in the two months preceding the study. A majority of participants (80%) reported no family history of the disease, while 20% had a positive family history. The median VASI was 5. The VIDA score had a median of 0.5. The mean DLQI score was 15, with a standard deviation of ±5. Acrofacial and generalized involvement were the most frequent, each seen in 36.7% of cases **(Table 1)**.

Table 1: History, disease trajectory and affected sites of the patients' group

History and disease trajectory	
Drug intake	0 (0)
Family history	
Negative	24 (80)
Positive	6 (20)
Disease onset	
Acute	30 (100)
Course	
Stationary	15 (50)
Progressive	15 (50)
Disease duration (years)	3.5 (0.08 - 18)
VASI	5 (1.5 – 40.0)
VIDA	0.5 (0 – 4.0)
DLQI	15 ±5
Site affected	
Acrofacial	11 (36.7)
Face and neck	4 (13.3)
Extremities	3 (10)
Trunk	3 (10)
Generalized affection	11 (36.7)

Data are presented as n (%), Mean±SD, Median (Range), DLQI: Dermatology Life Quality Index, VIDA: Vitiligo Disease Activity, VASI: Vitiligo Area Scoring Index.

The studied patients demonstrated significantly higher baseline of IL-38 levels (median = 30.27 pg/ml) compared to the control group (median = 15.14 pg/ml). In the patients' group, after treatment, the median level dropped to 23.2 pg/ml. The reduction in IL-38 levels following treatment was statistically significant (P = 0.003) **(Figure 1A, 1B)**.

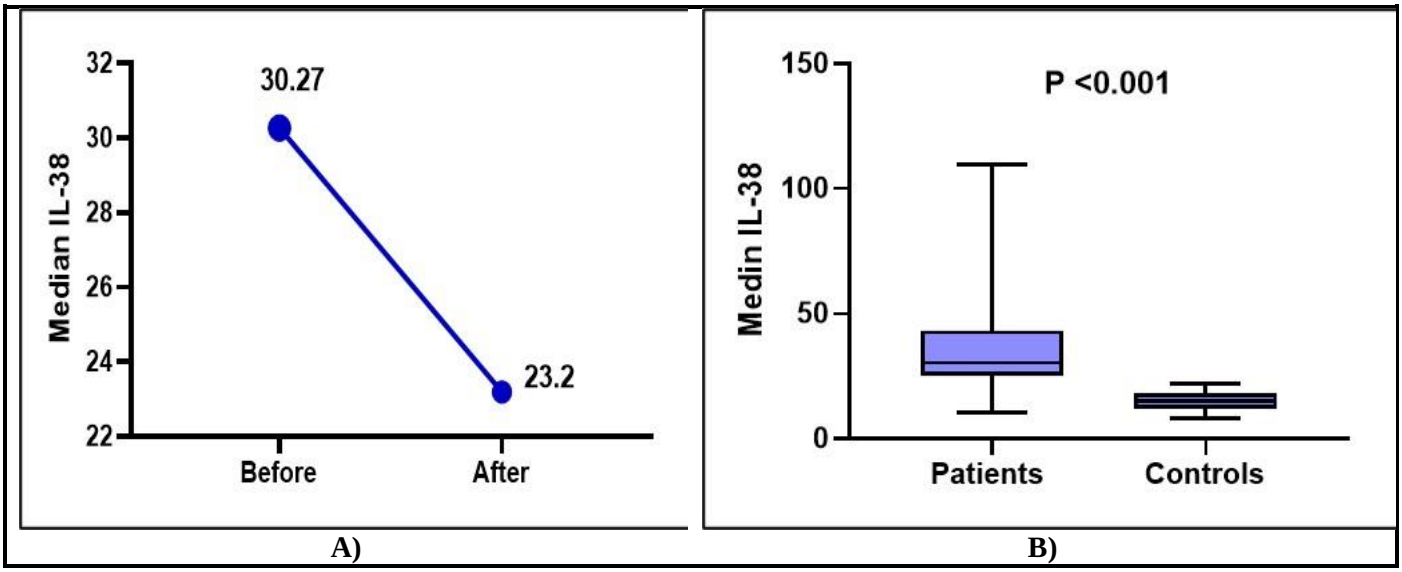

Figure 1: IL-38 level (A) in the studied groups, (B) before and after treatment in the patients' group.

The comparison of the VASI scores before and after treatment in patients demonstrates a significant improvement (P < 0.001). Initially, the median VASI score was 5, ranging from 1.5 to 40. After treatment, the median VASI score reduced to 2, with a much narrower range of 0.5 to 28 (P < 0.001).

ROC analysis of IL-38 to predict vitiligo **(Figure 2)**.

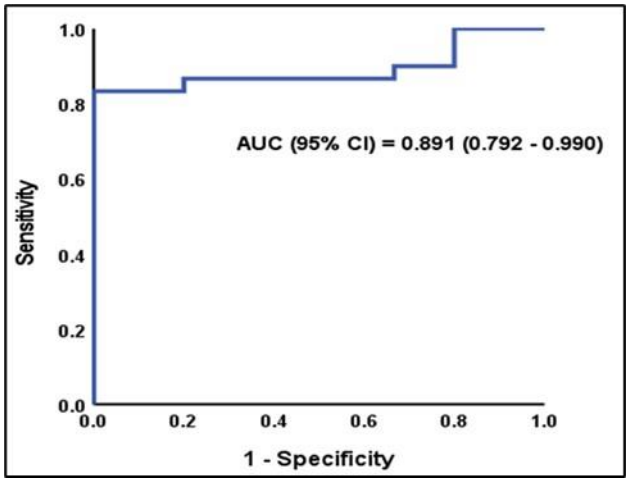

Figure 2: ROC analysis of IL-38 to predict vitiligo

The disease duration demonstrated a positive correlation with IL-38 levels (r = 0.447). Similarly, both VASI score and the VIDA score showed positive correlations with IL-38 levels, with correlation coefficients of 0.511 and 0.419, respectively. The DLQI also correlated positively with IL-38 levels (r = 0.434). **(Figure 3A, 3B, 3C, 3D)**. In contrast, age showed a non-significant correlation.

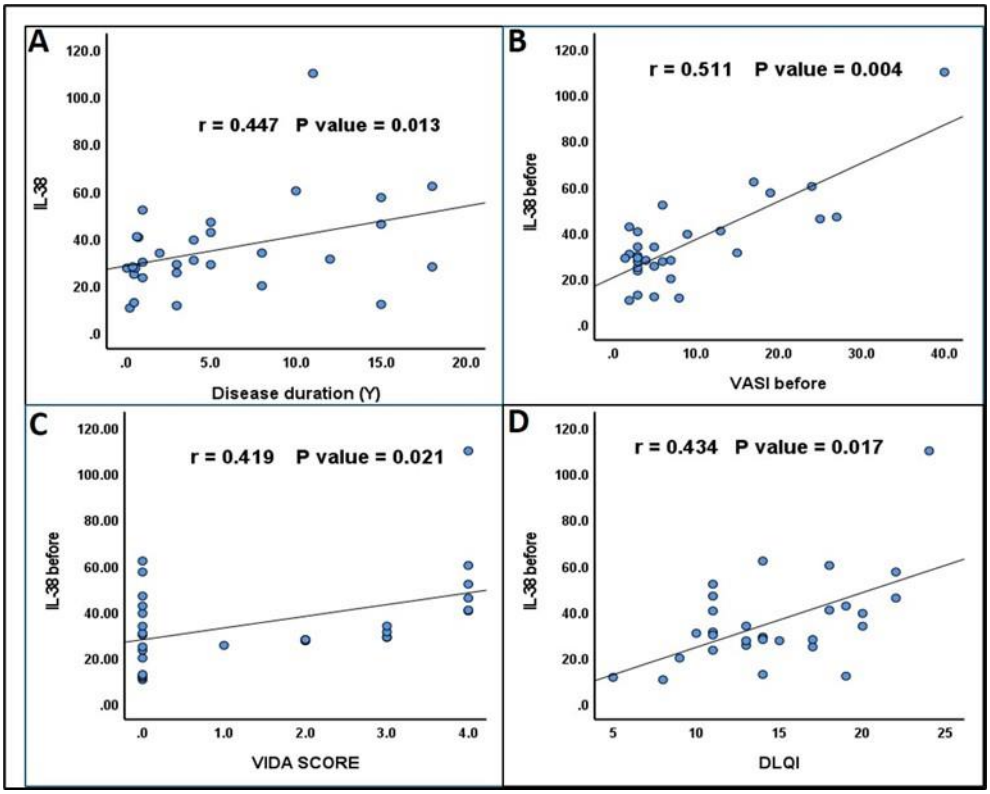

Figure 3: Correlation between IL-38 and (A) disease duration, (B) VASI, (C) VIDA, and (D) DLQI

Multivariate regression analyses demonstrated that IL-38 significantly predicted vitiligo and its severity. Logistic regression showed that each unit increase in IL-38 was linked to a 24% higher risk of vitiligo (OR = 1.243), controlling for age and gender. Linear regression revealed that IL-38 was associated with increases in both the VASI score by 0.384 (B = 0.384, 95% CI = 0.267–0.501, P < 0.001) and the Dermatology Life Quality Index (DLQI) score by 0.135 (B = 0.135, 95% CI = 0.059–0.212, P = 0.001), after adjusting for age and gender **(Table 2)**.

Table 2: Multivariate logistic regression analysis to predict vitiligo, VASI, DLQI according to IL-38

Vitiligo and its severity	B	S.E.	Wald	OR (95% CI)	P-value
Age (Years)	-0.038	0.036	1.103	0.963 (0.898 – 1.033)	0.294
Sex	0.106	0.924	0.013	1.112 (0.182 – 6.802)	0.909
IL-38 before	0.218	0.071	9.495	1.243 (1.082 – 1.428)	**0.002***
VASI				**B (95% CI)**	**P-value**
Age (years)				2.818 (-11.183 - 16.82)	0.682
Sex				-47.858 (-464.896 - 369.181)	0.815
IL-38				0.384 (0.267 – 0.501)	**<0.001***
DLQI				**B (95% CI)**	**P-value**
Age (years)				2.818 (-11.183 - 16.82)	**0.682**
Sex				-47.858 (-464.896 - 369.181)	**0.815**
IL-38				0.384 (0.267 – 0.501)	**<0.001***

*Significant P-value; B: Regression coefficient; S.E.: Standard Error; Wald: Wald Statistic; OR: Odds Ratio; CI: Confidence Interval; B: Regression coefficient, IL-38: Interleukin-38.

DISCUSSION

Vitiligo, characterized by melanocyte loss leading to depigmented patches, is primarily driven by autoimmune mechanisms involving CD8+ T cells and Th17 cells, with increased IL-17 and cytokine levels observed in patients. IL-38, part of the IL-1 cytokine family, suppresses Th1 and Th17 responses but remains understudied in vitiligo [8]. Narrowband UVB (NB-UVB) phototherapy, effective in reducing immune activity and promoting repigmentation, is a key treatment for generalized vitiligo. This study evaluated serum IL-38 levels in vitiligo patients, examining its correlation with disease severity and phototherapy outcomes.

The current study's findings regarding the mean age and female predominance in vitiligo patients align with several studies, including those by **Atwa *et al.*** [9], and **Eladl *et al.*** [10], though variations exist in other reports such as **Silpa-Archa *et al.*** [11] and **Ezzedine *et al.*** [12], reflecting the broad demographic diversity of vitiligo. The bimodal age of onset highlighted by **Jin *et al.*** [13] supports the influence of environmental factors. The observed higher prevalence among women may be linked to increased concern over skin changes affecting social life.

In the current study, 20% of patients reported a positive family history of vitiligo, aligning with findings from **Sarma *et al.*** [14] and **Abdallah *et al.*** [15], though **Abdullahi *et al.*** [16] reported a higher rate. This variability likely reflects the complex, polygenic nature of vitiligo inheritance, as suggested by **Mahajan *et al.*** [17]. In this study, the acrofacial and generalized regions were the most commonly affected areas, aligning with findings from **Ezzedine *et al.*** [12] and **Pradipta *et al.*** [18], which identified the face, acral regions, and trunk as common sites. Vitiligo typically affects sun-exposed and hyperpigmented areas, with extremities often impacted by the Köebnerization response [19].

This study's finding of significant improvement in VASI scores after 36 phototherapy sessions aligns with previous research by **Farag *et al.*** [20], and **Pradipta *et al.*** [18], which also reported a notable reduction in VASI scores following similar treatments.

The study observed higher baseline levels of IL-38 in vitiligo patients, with a significant reduction after treatment, consistent with **Mahmoud Marie *et al.*** [21], who also reported elevated IL-38 levels in vitiligo patients.

This study's results highlight a correlation between IL-38 serum levels and both the severity and activity of vitiligo, as reflected by clinical manifestations including Koebner's phenomenon, poorly defined borders, itching, and confetti-pattern depigmented lesions.

This aligns with **van Geel *et al.*** [22], who linked itching in vitiligo lesions to increased inflammatory cell infiltration, and **Le *et al.*** [23], who found that vitiligo activity correlated with overexpression of Th1 and Th17 cytokines. These findings suggest that the pro-inflammatory cytokine environment in active vitiligo may stimulate IL-38 expression from monocytes and keratinocytes to counterbalance excessive inflammation.

The current study found that IL-38 levels were positively correlated with disease duration, VASI, VIDA, and DLQI, indicating that higher IL-38 levels are associated with greater disease severity and a more significant impact on quality of life. IL-38 is a reliable biomarker for vitiligo, with high specificity and positive predictive value.

These findings align with **Mahmoud Marie *et al.*** [21], who also observed elevated IL-38 levels in patients with active disease and its correlation with disease severity. Elevated IL-38 may reflect an immune mechanism attempting to inhibit Th1 and Th17 activation. However, **Zarrabi *et al.*** [24] reported lower IL-38 levels in vitiligo patients, which may be attributed to variations in disease biology, sample size, and genetic factors.

IL-38 is elevated in conditions like rheumatoid arthritis and ST-elevated myocardial infarction (STEMI), where it may serve as a biomarker of disease severity or play a role in mitigating the impact of inflammation, as observed with other anti-inflammatory cytokines like IL-1Ra, IL-37, and IL-36Ra. Elevated IL-38 levels reflect the intensity of inflammation, suggesting its potential as a modulator in various inflammatory diseases[25,26].

In psoriasis, an immune-mediated inflammatory dermatosis, elevated serum levels of IL-38 have been reported, particularly in patients with pustular psoriasis, correlating with disease severity [27]. IL-38 mRNA expression was also increased in peripheral blood mononuclear cells, and stimulation with Th1 and Th17 cytokines, including IL-17A, TNF-α, and interferon-γ, further enhanced IL-38 expression, suggesting its role as a counter-regulatory mechanism to balance the heightened inflammatory responses in psoriasis [28].

IL-38 expression has been studied in various inflammatory and autoimmune diseases. **Khattab *et al.*** [29] found higher serum IL-38 levels in atopic dermatitis patients, correlating with disease severity and inflammatory markers. Elevated IL-38 levels were also observed in systemic lupus erythematosus [30] and systemic sclerosis [31], with a correlation to disease activity. Additionally, increased IL-38 levels in rheumatoid arthritis patients were linked to disease activity, and in primary Sjogren's syndrome, high IL-38 levels in labial salivary glands were hypothesized to counteract IL-36 and IL-17 overexpression [32].

These studies underscore the role of IL-38 in autoimmune and inflammatory conditions, including vitiligo, which shares genetic risk loci with atopic dermatitis, systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, and Sjogren's syndrome [29]. This highlights IL-38's potential as both a biomarker and a therapeutic target in vitiligo and related diseases.

Despite our great findings, this study has limitations, including a sample size that limits generalizability. Only IL-38 was explored, excluding other relevant anti-inflammatory cytokines, and the focus was on a single therapeutic modality, NB-UVB. Larger, multicenter studies with broader cytokine panels are needed to validate IL-38 as a biomarker in vitiligo across diverse populations.

CONCLUSION

IL-38 is significantly elevated in vitiligo patients and correlates with disease severity and activity. The improvement in VASI scores post-treatment suggests IL-38's potential as a disease progression and therapeutic response biomarker. Its association with clinical manifestations supports its role in vitiligo's pathophysiology, possibly acting as a counter-regulatory mechanism to mitigate.

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