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The Interplay Between IL-38 and TNF-α in Vitiligo: Investigating their roles as Opposing Immunoregulatory Cytokines in Autoimmune Skin Disease.

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Abstract

Pro-inflammatory and anti-inflammatory cytokines play an essential role in the development of an immune system imbalance seen in vitiligo. The pro-inflammatory cytokine, tumor necrosis factor-alpha (TNF-α), and the newly described anti-inflammatory cytokine, interleukin-38 (IL-38), appear to have opposing functions in the pathophysiology of vitiligo. **Objective:** The aim of this study is to assess the levels of serum IL-38 and TNF-α in vitiligo patients compared to healthy subjects and their correlations with clinical features, such as extent, duration, and activity. **Methods:** This cross-sectional study included 70 patients clinically diagnosed with vitiligo and 70 healthy control subjects. Serum cytokines were quantitatively detected using ELISA tests, and patients' disease activity was calculated using the Vitiligo Area Scoring Index (VASI). The statistical analysis included a t-test and Pearson correlation, with a significance value of $p < 0.05$. **Results:** In contrast to the control group, patients with vitiligo showed higher levels of both IL-38 (63.2 ± 12.2 pg/mL) ($p < 0.001$) and TNF-α (75.7 ± 16.8 pg/mL) ($p < 0.001$). The activity of lesions in vitiligo was related to high concentrations of serum cytokines. There were direct correlations between IL-38 and TNF-α ($r = 0.698$, $p < 0.001$), along with other vitiligo-related parameters, such as VASI score, extent of lesions, duration of the disease, erythrocyte sedimentation rate (ESR), and CRP. **Conclusion:** It seems that the upregulation of IL-38 and TNF-α plays a crucial role in regulating immune responses in vitiligo. The results of our study indicate that IL-38 can be considered a promising biomarker in vitiligo.

Keywords: Vitiligo; Interleukin-38; Tumor Necrosis Factor-alpha; Cytokines; Autoimmunity.

Introduction:

Vitiligo is an acquired, idiopathic, progressive depigmentation disorder of the skin, characterized by the selective destruction of melanocytes, leading to the development of well-circumscribed, white macules and patches on the skin and sometimes mucous membranes and hair [1]. Its estimated prevalence ranges from 0.1 to 2% all over the world. Even though it is not fatal, vitiligo markedly affects the quality of life for patients, especially when the face is affected [2]. Vitiligo is classified into two main forms: segmental vitiligo (SV) and nonsegmental vitiligo (NSV). The actual cause of vitiligo is not totally identified, although factors that include autoimmunity, generation of free radicals, and sympathetic neurogenic

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disturbance are believed to participate in its pathophysiology [3]. Damage of melanocytes is mediated by CD8 + cytotoxic T cells as demonstrated by increased T cell infiltrates in the affected area, displaying anti-melanocyte damaging activity [4].

Additionally, the affected areas are infiltrated by numerous innate immune cells such as macrophages and dendritic cells. In addition, in vitiligo cases, there is an increased serum level of innate immunity cytokines (such as TNF-α), T-helper1 (Th1), and Th17 cytokines [5]. IL38 is a member of the IL-1 family with anti-inflammatory features. Its sequence homology with IL-1 receptor antagonist and IL-36 receptor antagonist is 41 and 43%, respectively [6]. It was recorded that IL-38 is mainly expressed in epidermal keratinocytes [7]. In line with these findings about the biological functions of IL-38, several studies have focused on the specific role of this cytokine in some disorders, typically immune-mediated diseases. IL-38 gene polymorphisms have been studied in ankylosing spondylitis, rheumatoid arthritis (RA), psoriatic arthritis, and heart diseases [8]. Moreover, the levels of this cytokine have been raised in the sera of patients with systemic lupus erythematosus (SLE), RA, myocardial infarction, and childhood asthma [9].

Our study seeks to explore the immunoregulatory role of IL-38. Measuring its serum levels in patients with vitiligo may help us understand its role in disease pathogenesis and determine whether it can serve as a marker to monitor disease activity and severity.

Material and methods:

Study design & patients:

This case-control study was held in the outpatient clinic of Dermatology, Andrology, and STDs Department, Al-Sader Medical City, Al-Najaf, Iraq. Over 4months and included 70 patients aged 16-70 years with vitiligo. The control group included 70 apparently healthy age- and sex matched cases selected randomly from patient attendants. This study included both male and female vitiligo patients of any age with matched controls of age and sex. We excluded cases with vitiligo under treatment, patients with dermatological diseases with possible relation change in IL38 serum level other than vitiligo, such as psoriasis, atopic dermatitis, and systemic sclerosis, and patients with systemic or autoimmune disease, such as in many inflammatory disorders, comprising rheumatoid arthritis, Inflammatory Bowel Disease (IBD), and coronary heart disease.

Ethical consideration:

Approval was taken from the Al-Sader Medical City ethics committee to conduct the study. Informed and written consent was taken from each patient. All subjects were informed about the study and the procedure of the operation. All data was collected by the researcher himself.

Methods:

All cases in the study were subjected to complete history taking, including personal history (name, age, sex, occupation, residence), history of the current disease (onset, course, duration, triggering, and relieving factors), history of drugs (formula, route, dosage, duration, effects, and adverse events), family history of vitiligo or other dermatological diseases and history of any accompanying systemic, dermatological disease, or major surgeries. Complete clinical examination included measurement of BMI and a full dermatological examination to rule out any accompanying diseases. Examination of vitiligo included site, symmetry, extent, localization, clinical types, activity, and stability.

Biochemical and immunological analysis:

Venous blood samples were obtained from both cases and the control (5 ml) 2ml for ESR estimation. Coagulation of the rest of the sample at 22 C° 15 min was conducted, followed by centrifugation for 20 min (2000- 3000 rpm), then the supernatant was removed. The level of Serum IL-38 and TNF-α was evaluated using an enzyme-

linked immunosorbent assay (ELISA) approach (Elabscience, USA). The kit use sandwich method to estimate the level of IL38 and TNF-a in patients' samples.

Statistical analysis

The collected data were coded and analyzed using SPSS version 26 for Windows (IBM SPSS Inc, Chicago, Illinois, USA). Qualitative data were presented by frequency tables. The normality of data was first tested with the Shapiro-Wilk test, and the data were presented as Mean ± SD for normally distributed variables. The χ^2 test was utilized to assess the association between at least two qualitative variables. Student T Test was used to assess the significance of the difference between two independent study groups with parametric data. Person's correlation was utilized to test the correlation between two variables. The level of significance was set at a P value less than or equal to 0.05.

Results:

3.1 Demographic and Clinical Characteristics:

The mean age of vitiligo patients was 37.8 ± 6.7 years (range: 16–70), which did not differ significantly from controls (34.6 ± 3.4 years; $p = 0.608$). The cohort included 33 males (47.2%) and 37 females (52.8%), with no statistically significant sex difference relative to controls ($p > 0.05$). However, vitiligo patients exhibited a significantly higher mean BMI compared to healthy individuals (28.2 ± 2.3 vs. 23.5 ± 1.1 kg/m²; $p < 0.001$). The mean disease duration was 6.4 ± 1.3 years, and the mean VASI score was 5.2 ± 1.4. Non-segmental vitiligo was the predominant subtype, accounting for 67.2% of patients (n = 47), while segmental vitiligo was present in 32.8% (n = 23).

Active lesions were recorded in 57.2% of patients (n = 40), and 28.5% reported a positive family history of vitiligo, a proportion significantly greater than that observed among controls (7.2%; $p < 0.001$). Furthermore, comorbid autoimmune conditions were more prevalent among patients (25.8%) than controls (5.7%; $p < 0.001$).

3.2 Laboratory Findings:

Routine hematological parameters, including WBC count, hemoglobin levels, and platelet counts, did not differ significantly between the two groups ($p > 0.05$ for all). In contrast, inflammatory indices were markedly elevated in vitiligo patients: mean ESR was 36.2 ± 3.4 mm/hr compared to 12.5 ± 1.4 mm/hr in controls ($p < 0.001$), and mean CRP concentration was 18.7 ± 3.2 mg/L versus 5.6 ± 0.98 mg/L ($p < 0.001$). Anti-nuclear antibody (ANA) positivity was identified in 24.3% of vitiligo patients compared to only 4.2% of controls ($p < 0.001$), further underscoring the autoimmune dimension of the disease.

3.3 Serum Cytokine Levels: IL-38 and TNF-α:

Table 3 showed: Serum IL-38 concentrations were significantly higher in vitiligo patients overall (63.2 ± 12.2 pg/mL) relative to controls (29.5 ± 6.1 pg/mL; mean difference: 33.2 pg/mL, 95% CI: 31.2–36.8; $t = 16.54$, $p < 0.001$). Subgroup analyses revealed that IL-38 was substantially elevated in patients with active lesions (67.8 ± 14.1 pg/mL) compared to those with stable disease (51.2 ± 10.3 pg/mL), with both subgroups significantly exceeding control levels ($p < 0.001$ for each). Serum IL-38 did not differ significantly between segmental (65.3 ± 12.6 pg/mL) and non-segmental (62.5 ± 14.1 pg/mL) subtypes.

Similarly, serum TNF-α concentrations were markedly elevated in vitiligo patients (75.7 ± 16.8 pg/mL) compared to controls (25.3 ± 5.2 pg/mL; mean difference: 51.3 pg/mL, 95% CI: 46.6–55.8; $t = 22.21$, $p < 0.001$). Patients with active lesions demonstrated notably higher TNF-α levels (85.4 ± 18.7 pg/mL) than those with stable disease (57.6 ± 15.2 pg/mL), and both subgroups significantly surpassed control values ($p < 0.001$). TNF-α levels were slightly higher in non-segmental (76.4 ± 17.5 pg/mL) compared to segmental vitiligo (72.3 ± 18.6 pg/mL), though this difference was not formally compared for statistical significance.

3.4 Correlation Analysis:

Table 4: showed Pearson correlation analysis revealed a strong positive association between serum IL-38 and TNF-α in the patient cohort ($r = 0.698$, $p < 0.001$), indicating concurrent upregulation of both cytokines in vitiligo. No significant correlation was observed between these cytokines in the control group ($r = 0.189$, $p = 0.432$).

Among disease activity markers, IL-38 exhibited significant positive correlations with the VASI score ($r = 0.539$, $p < 0.001$), disease duration ($r = 0.514$, $p < 0.001$), lesion area ($r = 0.701$, $p < 0.001$), and number of lesions ($r = 0.654$, $p < 0.001$). TNF-α demonstrated comparably strong associations with these parameters: VASI score ($r = 0.605$, $p < 0.001$), disease duration ($r = 0.538$, $p < 0.001$), lesion area ($r = 0.559$, $p < 0.001$), and number of lesions ($r = 0.783$, $p < 0.001$).

Regarding inflammatory biomarkers, IL-38 positively correlated with ESR ($r = 0.567$, $p < 0.001$) and CRP ($r = 0.554$, $p < 0.001$). TNF-α similarly correlated with ESR ($r = 0.667$, $p < 0.001$) and CRP ($r = 0.654$, $p < 0.001$). Both cytokines also showed significant correlations with ANA titer (IL-38: $r = 0.444$, $p < 0.001$; TNF-α: $r = 0.454$, $p = 0.001$), the composite VASI × Duration variable (IL-38: $r = 0.675$, $p < 0.001$; TNF-α: $r = 0.786$, $p < 0.001$), and age at onset (IL-38: $r = 0.312$, $p = 0.05$; TNF-α: $r = 0.356$, $p = 0.03$). In the control group, neither cytokine demonstrated significant correlations with any clinical or laboratory parameter.

Table 1. Demographic and Clinical Characteristics of Vitiligo Patients and Healthy Controls

Characteristic	Vitiligo Patients (n=70)	Healthy Controls (n=70)	Statistical Test	p-value
Demographic Variables				
Age (years), Mean ± SD	37.8 ± 6.7	34.6 ± 3.4	1.65	0.608
Age range (years)	16 – 70	14 – 60	—	—
Male, n (%)	33 (47.2%)	40 (57.2%)	0.987	0.654
Female, n (%)	37 (52.8%)	30 (42.8%)	0.567	0.437
BMI (kg/m²), Mean ± SD	28.2 ± 2.3	23.5 ± 1.1	12.321	**<0.001**
Residence: Urban, n (%)	44 (62.8%)	50 (71.4%)	1.231	0.706
Clinical Characteristics				
Disease Duration (years), Mean ± SD	6.4 ± 1.3	—	—	—
VASI Score, Mean ± SD	5.2 ± 1.4	—	—	—
Lesion Type				
Segmental, n (%)	23 (32.8%)	—	—	—
Non-segmental, n (%)	47 (67.2%)	—	—	—
Disease activity				
Active Lesions, n (%)	40 (57.2%)	—	—	—
Stable Lesions, n (%)	30 (42.8%)	—	—	—
Family History, n (%)	20 (28.5%)	5 (7.2%)	4.245	**< 0.001**
Autoimmune Disease, n (%)	18 (25.8%)	4 (5.7%)	6.765	**< 0.001**

Table 2. laboratory findings among vitiligo patients Vs. control group.

Characteristic	Vitiligo Patients (n=70)	Healthy Controls (n=70)	Statistical Test	p-value
Laboratory Findings				
WBC (×10³/µL), Mean ± SD	8.4 ± 1.1	5.9 ± 0.89	0.989	0.234
Hemoglobin (g/dL), Mean ± SD	13.5 ± 2.1	14.6 ± 1.4	1.887	0.767
Platelets (×10³/µL), Mean ± SD	261 ± 33.2	254 ± 27.6	7.655	0.432
ESR (mm/hr), Mean ± SD	36.2 ± 3.4	12.5 ± 1.4	12.343	**< 0.001**
CRP (mg/L), Mean ± SD	18.7 ± 3.2	5.6 ± 0.98	6.787	**< 0.001**
ANA Positive, n (%)	17 (24.3%)	3 (4.2%)	3.212	**< 0.001**
WBC = White Blood Cell; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein; ANA = Anti-Nuclear Antibody.Significant p-values (< 0.05).				

Table 3. Level of cytokines in vitiligo Vs. control groups.

Parameter	Vitiligo (n=70) Mean ± SD	Controls (n=70) Mean ± SD	Mean Difference (95% CI)	t-statistic	p-value
IL-38 (pg/mL)					
Overall	63.2 ± 12.2	29.5 ± 6.1	33.2 (31.2–36.8)	16.54	**< 0.001**
Active Lesions	67.8 ± 14.1	29.5 ± 6.1	39.8 (33.4–44.9)	18.12	**< 0.001**
Stable Lesions	51.2 ± 10.3	29.5 ± 6.1	25.2 (18.8–27.7)	12.14	**< 0.001**
Segmental	65.3 ± 12.6	29.5 ± 6.1	34.9 (28.5–41.5)	13.11	**< 0.001**
Non-segmental	62.5 ± 14.1	29.5 ± 6.1	32.6 (28.9–36.8)	14.52	**< 0.001**
TNF-α (pg/mL)					
Overall	75.7 ± 16.8	25.3 ± 5.2	51.3 (46.6–55.8)	22.21	**< 0.001**
Active Lesions	85.4 ± 18.7	25.3 ± 5.2	62.6 (55.7–69.8)	19.55	**< 0.001**
Stable Lesions	57.6 ± 15.2	25.3 ± 5.2	33.8 (28.7–38.9)	12.33	**< 0.001**
Segmental	72.3 ± 18.6	25.3 ± 5.2	48.0 (40.8–55.7)	10.17	**< 0.001**
Non-segmental	76.4 ± 17.5	25.3 ± 5.2	52.6 (47.8–55.9)	20.19	**< 0.001**
SD: standard deviation; IL: interleukin; TNF-a: tumor necrosis factor alpha.					

Table 4. Pearson Correlation Analysis of IL-38 and TNF-α with Clinical and Laboratory Parameters.

Parameter	IL-38 (Patients)		TNF-α (Patients)		IL-38 vs Controls	
	r	p-value	r	p-value	r	p-value
Diseaseactivitymarkers						
VASI Score	0.539	**< 0.001**	0.605	**< 0.001**	0.087	0.331
Disease Duration (years)	0.514	**< 0.001**	0.538	**< 0.001**	0.065	0.463
Lesion Area (%)	0.701	**< 0.001**	0.559	**< 0.001**	0.077	0.309
Number of Lesions	0.654	**< 0.001**	0.783	**< 0.001**	0.089	0.542
Inflammatorymarkers						
ESR (mm/hr)	0.567	**< 0.001**	0.667	**< 0.001**	0.099	0.222
CRP (mg/L)	0.554	**< 0.001**	0.654	**< 0.001**	0.109	0.445
WBC (×10³/μL)	0.341	0.054	0.331	**0.05**	0.075	0.543
Inter-cytokinecorrelation						
IL-38 vs TNF-α (Patients)	0.698	**< 0.001**	0.698	**< 0.001**	—	—
IL-38 vs TNF-α (Controls)	—	—	—	—	0.189	0.432
Autoimmune&clinical						
ANA Titer	0.444	**<0.001**	0.454	**0.001**	0.098	0.434
VASI × Duration	0.675	**< 0.001**	0.786	**< 0.001**	0.077	0.512
Age at Onset	0.312	**0.05**	0.356	**0.03**	0.065	0.787

Discussion:

The current investigation examined the blood profiles of two immunologically disparate cytokines, TNF-α and IL-38, in a group of 70 vitiligo patients and matched healthy controls. The main conclusions challenge the simple opposing paradigm implied in the study's conceptual framework by showing that both cytokines are markedly raised in vitiligo, that their levels scale with disease activity and severity, and that they are substantially associated.

4.1 Serum level of TNF-α in vitiligo Vs. control groups:

This study's significantly higher TNF-α levels are in line with the cytokine's known function as a key mediator of autoimmune cutaneous inflammation. Activated macrophages, dendritic cells, and T lymphocytes are the main producers of TNF-α, which increases CD8 + T cell responses against melanocyte-specific antigens and induces melanocyte death by direct cytotoxic pathways [10,11]. TNF-α levels were significantly greater in

individuals with active lesions than in those with stable lesions (85.4 ± 18.7 vs. 57.6 ± 15.2 pg/mL), which is consistent with previous findings that TNF-α concentrations represent continuous melanocyte damage and progression of the condition. In similar lines, [5] found that vitiligo was associated with higher innate pro-inflammatory cytokines and identified TNF-α as a major driver of the inflammatory cascade. The usefulness of serum TNF-α as a proxy index of disease burden in clinical practice is further supported by the significant connection between TNF-α and lesion area (r = 0.559) and VASI score (r = 0.605).

The notable positive associations between TNF-α and the systemic inflammatory markers ESR (r = 0.667) and CRP (r = 0.654) highlight how the inflammatory process in vitiligo is systemic, going beyond its cutaneous symptoms. In line with the larger immunological framework outlined by [1], the increased ANA positive rate (24.3%) and concomitant autoimmune diseases (25.8%) further support the autoimmune etiology of the disorder.

4.2 The Elevation of serum IL-38 in Vitiligo:

The study's counterintuitive rise of the anti-inflammatory cytokine IL-38 in the context of active autoimmune illness may be its most conceptually significant discovery. The most recent member of the IL-1 superfamily, IL-38, was first identified as an immunosuppressive mediator due to its receptor binding profile, competitive inhibition of IL-36 receptor signaling, and suppression of innate and Th17 immune responses [12]. Its prominent expression in the skin's principal cellular component, epidermal keratinocytes, places it in an anatomically advantageous position to regulate local immune activity [13].

The high levels of IL-38 in vitiligo patients (63.2 ± 12.2 pg/mL compared to 29.5 ± 6.1 pg/mL in controls) might be a counter-regulatory or compensating reaction to the severe inflammatory environment caused by TNF-α and other pro-inflammatory mediators. This explanation is consistent with the theory of cytokine homeostatic feedback, which states that the immune system increases anti-inflammatory molecules proportionately to the level of pro-inflammatory activation. A similar contradiction has been seen in other chronic inflammatory disorders, which lends credence to this theory: Myocardial infarction, rheumatoid arthritis, and systemic lupus erythematosus disorders marked by persistent pro-inflammatory cytokine activity—have all been linked to increased IL-38 levels [14,15]. In these situations, the rise of IL-38 has been viewed as an inadequate or overpowered anti-inflammatory response rather than as proof of successful immunosuppression.

Additional confirmation that the IL-38 increase is reactive rather than protective is provided by the considerably greater levels in individuals with active lesions (67.8 ± 14.1 pg/mL) compared to those with stable disease (51.2 ± 10.3 pg/mL), increasing with inflammatory activity rather than decreasing it. The current pattern is in line with studies in psoriasis and other IL-1-family-driven dermatological disorders, as well as the findings of [16], who showed that immunological activation states influenced circulating IL-38 quantities.

4.3 The IL-38/TNF-α Intercorrelation:

A unique and clinically significant finding is the substantial positive connection ($r = 0.698$, $p < 0.001$) between IL-38 and TNF-α in vitiligo patients, which is not evident in healthy controls

(r = 0.189, p = 0.432). Both cytokines seem to increase in synchrony with the severity of the disease rather than showing a reciprocal or negative connection as would be expected if IL-38 successfully controlled TNF-α-driven inflammation. This co-upregulation points to one of two non-exclusive mechanisms: either the immunosuppressive ability of IL-38 is functionally insufficient to mitigate TNF-α-mediated inflammation in the case of vitiligo, or IL-38 elevation is a downstream outcome of triggering the same pro-inflammatory cascade that drives TNF-α expression.

The interaction between IL-1 receptor antagonist (IL-1Ra) and IL-1β in chronic autoimmune disorders, when the anti-inflammatory mediator is increased, but its molar excess over the agonist is inadequate to accomplish net inhibition, is comparable to this pattern [17]. Considering that IL-38 and IL-1Ra share 41% of their sequences, vitiligo may involve a similar competition receptor-binding dynamic. To ascertain if the amount of IL-38 generated in vitiligo is stoichiometrically insufficient to counteract TNF-α activity or whether downstream signaling pathways continue to be dysregulated even with sufficient IL-38 concentrations, more dose-response experiments and in vitro models are required [18].

4.4 Cytokine Correlations with Disease Severity Parameters:

As credible substitution markers of disease severity, IL-38 and TNF-α showed strong relationships with VASI score, lesion area, number of lesions, and illness duration. TNF-α is mechanistically linked to the spread of depigmentation, possibly through its effects on melanocyte survival and T cell trafficking to perilesional skin, according to the especially significant association between TNF-α and the number of lesions (r = 0.783). The significant connection between IL-38 and lesion area (r= 0.701) may indicate that the anti-inflammatory response is proportionate to the total surface area of continuing immune-mediated damage.

Considering that adipose tissue is an established source of TNF-α and triggers systemic low-grade inflammation, the statistically significant increase in BMI in vitiligo patients compared to controls (28.2 ± 2.3 vs. 23.5 ± 1.1 kg/m²; $p < 0.001$) presents a significant confounding factor [19]. To distinguish the distinct role of vitiligo-associated autoimmunity from metabolic inflammation, future research should either do sensitivity analysis in BMI-stratified subgroups or statistically account for BMI when assessing cytokine concentrations [20].

4.5 Clinical Implications and Limitations:

The results of this study have several ramifications from a translational standpoint. First, the association between the VASI score and both TNF-α and IL-38 indicates that assessing blood cytokine levels might be used in addition to clinical grading systems to track the course of the disease and the effectiveness of treatment. Second, the prospect that exogenously delivered recombinant IL-38 or IL-38-based therapies might boost the endogenous immunosuppressive response to a clinically effective threshold is raised by the rise of IL-38 during active vitiligo. Third, formal assessment in vitiligo clinical trials is necessary for current anti-TNF-α biological drugs that are often used in psoriasis and rheumatoid arthritis, especially for non-segmental active illness [21].

It is important to recognize that this study has a number of restrictions. Inference on the temporal dynamics of TNF-α and IL-38 during the natural history of vitiligo is not possible due to the cross-sectional design [22]. By eliminating therapeutic variables, the exclusion of patients undergoing treatment improves internal validity but restricts generalizability to treatment-naïve groups [23]. The sample's external generalizability to other ethnic and geographic populations may be limited because it was taken from a single tertiary center in Al-Najaf, Iraq. The limited availability of local tissue cytokine data (such as from skin biopsies) restricts mechanistic assessment, and cytokine-level measurements at a single time point do not capture changes linked to periodic disease progression.

Conclusion

According to this study, vitiligo patients' blood levels of TNF-α and IL-38 are simultaneously and considerably higher than those of healthy controls, and both cytokines have a positive correlation with the severity, activity, and inflammatory load of the illness. Instead of a straightforward antagonistic interaction, the high intercorrelation between these cytokines in patients but not controls points to a co-regulatory mechanism unique to the illness. These results corroborate IL-38's function as a reactive anti-inflammatory mediator in vitiligo, most likely as a compensatory immune response that is quantitatively inadequate to inhibit the inflammatory cascade caused by TNF-α. The IL-38 pathway deserves more research as a possible treatment target, and both cytokines show promise as serum-based indicators of vitiligo disease activity.

Conflict of interest: NIL

Funding: NIL

References

1. Boniface, K., Seneschal, J., Picardo, M., & Taïeb, A. (2018). Vitiligo: focus on clinical aspects, immunopathogenesis, and therapy. *Clinical reviews in allergy & immunology*, *54*(1), 52-67.
2. Leung, A. K., Lam, J. M., Leong, K. F., & Hon, K. L. (2021). Vitiligo: an updated narrative review. *Current pediatric reviews*, *17*(2), 76-91.
3. Marchioro, H. Z., Castro, C. C. S. D., Fava, V. M., Sakiyama, P. H., Dellatorre, G., &Miot, H. A. (2022). Update on the pathogenesis of vitiligo. *Anais brasileiros de dermatologia*, *97*(4), 478-490.
4. Bergqvist, C., &Ezzedine, K. (2020). Vitiligo: a review. *Dermatology*, *236*(6), 571-592.
5. Gholijani, N., Yazdani, M. R., &Dastgheib, L. (2020). Predominant role of innate pro-inflammatory cytokines in vitiligo disease. *Archives of dermatological research*, *312*(2), 123-131.
6. Teufel, L. U., de Graaf, D. M., Netea, M. G., Dinarello, C. A., Joosten, L. A., & Arts, R. J. (2022). Circulating interleukin-38 concentrations in healthy adults. *Frontiers in Immunology*, *13*, 964365.
7. Talabot-Ayer, D., Mermoud, L., Borowczyk, J., Drukala, J., Wolnicki, M., Modarressi, A., & Palmer, G. (2019). Interleukin-38 interacts with destrin/actin-depolymerizing factor in human keratinocytes. PLoS ONE, 14(11), e0225782.
8. Dinarello, C. A. (2018). Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological reviews*, *281*(1), 8-27.

9. Wang, M., Wang, B., Ma, Z., Sun, X., Tang, Y., Li, X., & Wu, X. (2016). Detection of the novel IL-1 family cytokines by QAH-IL1F-1 assay in rheumatoid arthritis. *Cellular and Molecular Biology*, *62*(4), 31-34.
10. Pérez-Bootello, J., Cova-Martin, R., Naharro-Rodríguez, J., & Segurado-Miravalles, G. (2023). Vitiligo: pathogenesis and new and emerging treatments. *International journal of molecular sciences*, *24*(24), 17306.
11. Alabd, S., Yameny, A. The association between Tumor Necrosis Factor-alpha level (TNF-α) and moderate COVID-19 patients in Egypt. *Journal of Bioscience and Applied Research*, 2021; 7(4): 223-228. doi: 10.21608/jbaar.2021.251241
12. Kim, M., Han, J. H., Ahn, J., Kim, E., Bang, C. H., Kim, C., ... & Choi, W. (2025). In vivo 3D photoacoustic and ultrasound analysis of hypopigmented skin lesions: A pilot study. *Photoacoustics*, *43*, 100705.
13. Sun, J. L., Cho, W., Oh, H., Abd El-Aty, A. M., Hong, S. A., Jeong, J. H., & Jung, T. W. (2024). Interleukin-38 alleviates hepatic steatosis through AMPK/autophagy-mediated suppression of endoplasmic reticulum stress in obesity models. *Journal of Cellular Physiology*, *239*(4), e31184.
14. de Graaf, D. M., Teufel, L. U., Joosten, L. A., &Dinarello, C. A. (2022). Interleukin-38 in health and disease. *Cytokine*, *152*, 155824.
15. Yameny, A. IL-6, TNF-α, IL-1β, and IFN-γ Cytokines as Core Inflammatory Biomarkers: Biological Roles, Diagnostic Utility, and Clinical Applications. *Journal of Bioscience and Applied Research*, 2025; 11(3): 1055-1061. doi: 10.21608/jbaar.2025.456942
16. Al Rasbi, Z., Orsud, H., Zoughbor, S. H., Hajar, M., Mahboob, A., &Sadek, B. (2025). The role of interleukin-37 and interleukin-38 in the development and remission of autism spectrum disorder: a comprehensive review of neuroinflammatory mechanisms and potential therapeutic implications. *Frontiers in Immunology*, *16*, 1716197.
17. Yi, M., Li, T., Niu, M., Zhang, H., Wu, Y., Wu, K., & Dai, Z. (2024). Targeting cytokine and chemokine signaling pathways for cancer therapy. *Signal transduction and targeted therapy*, *9*(1), 176.
18. Schonmann, Y., Cohen, N. T., &Czarnowicki, T. (2025). Evaluating cancer risk in a large cohort of 25,008 patients with vitiligo: insights from a comprehensive cohort population-based study. *Journal of the American Academy of Dermatology*, *92*(4), 741-752.
19. Diotallevi, F., Gioacchini, H., De Simoni, E., Marani, A., Candelora, M., Paolinelli, M., ... &Simonetti, O. (2023). Vitiligo, from pathogenesis to therapeutic advances: state of the art. *International Journal of Molecular Sciences*, *24*(5), 4910.
20. Mu, S., Wang, W., Liu, Q., Ke, N., Li, H., Sun, F., ... & Zhu, Z. (2024). Autoimmune disease: a view of epigenetics and therapeutic targeting. *Frontiers in Immunology*, *15*, 1482728.
21. Abu Ghalyun, S., Hamad, A. R., & Khalid, M. H. (2023). Serum interleukin-38 in patients with autoimmune skin disorders: A comparative cross-sectional analysis. Journal of Dermatological Science, 112(2), 45–52.

22. Chen, Y., Liu, H., Zhao, J., & Li, X. (2022). The IL-1 family cytokines in autoimmune skin diseases: Pathophysiological roles and therapeutic implications. Frontiers in Immunology, 13, 914258.
23. Eleftheriadou, V., Atkar, R., Batchelor, J., McDonald, B., Novak-Frazer, L., Bhatt, V., & Thomas, K. (2021). Standardisation in vitiligo outcome measures: A systematic review and recommendations from the Vitiligo Priority Setting Partnership. British Journal of Dermatology, 185(5), 1009–1017.