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ORIGINAL ARTICLE

Interleukin-26 in Systemic Lupus Erythematosus: Demographic Correlates, Mechanistic Insights, and the Impact of Rituximab Therapy

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ABSTRACT

Background: *Systemic lupus erythematosus (SLE) is an autoimmune disorder predominantly affecting young to middle-aged females, with a complex and not yet fully elucidated immunopathogenesis. Recent studies have suggested that cytokines such as interleukin-26 (IL-26) might be involved in SLE-related immune processes.* ***Objectives:*** *This study aimed to characterize the demographic and clinical profiles of SLE patients, assess their treatment regimens, and compare IL-26 levels between SLE patients and healthy controls. Additionally, we evaluated whether Rituximab therapy might be associated with alterations in IL-26 expression.* ***Methodology:*** *A total of 126 participants, including SLE patients and matched healthy controls, were enrolled in the study. Demographic data, treatment histories, and IL-26 levels were collected and analyzed using appropriate non-parametric statistical tests to identify significant differences between groups.* ***Results****. Consistent with previous reports, the majority of SLE patients were female (96.8%) and primarily in the 21–40-year age range. While the sex distribution was similar between SLE cases and controls, a significant difference in age distribution was observed (p=0.027). Rituximab was the most commonly administered treatment (66.7%), followed by Cyclophosphamide (20.6%). IL-26 levels were significantly lower in SLE patients compared to controls (p < 0.001), suggesting a potential association between immunosuppressive therapy and cytokine modulation.* ***Conclusion:*** *Our study confirms the typical demographic profile of SLE and identifies a significant reduction in IL-26 levels in patients, which may be related to the effects of Rituximab therapy. These findings provide preliminary insights into the potential role of IL-26 in SLE; however, further studies are needed to better understand its clinical relevance and underlying mechanisms.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by heterogeneous clinical manifestations ranging from mild cutaneous involvement to severe organ dysfunction, including renal and central nervous system damage[1]. The disease predominantly affects women during their reproductive years, suggesting a critical role for hormonal influences in its pathogenesis[2] .Although advances in immunosuppressive therapies have improved patient outcomes, the precise mechanisms that drive the loss of immune tolerance and subsequent tissue damage in SLE remain incompletely understood[3].

Central to SLE pathogenesis is the dysregulation of cytokine networks that orchestrate both innate and adaptive immune responses[4].Among the numerous cytokines implicated in SLE, type I interferons have received considerable attention due to their role in sustaining chronic inflammation and promoting autoantibody production[5]. More recently, interleukin-26 (IL-26), a member of the IL-10 cytokine family, has emerged as a cytokine of interest[6]. Produced predominantly by Th17 cells, IL-26 has been shown to bind extracellular DNA and facilitate its uptake by antigen-presenting cells, a process that may amplify type I interferon responses and contribute to the inflammatory cascade in SLE[7,8]. Such findings suggest that IL-26 might serve as a bridge linking innate immune activation with adaptive immune dysregulation[8].

Therapeutic strategies in SLE have increasingly focused on targeted interventions, with B-cell depleting agents such as Rituximab (RTX) gaining prominence[9]. RTX selectively targets CD20+ B cells, thereby reducing autoantibody production and indirectly modulating T cell responses, including those of Th17 cells[10]. This interplay between B-cell depletion and cytokine regulation, particularly concerning IL-26, raises the possibility that RTX may not only improve clinical outcomes but also alter the cytokine milieu in SLE patients [11] .Despite these advances, the impact of

RTX on specific cytokine profiles, including IL-26, remains an area of active investigation.

In this study, we evaluate the demographic and clinical characteristics of SLE patients, characterize their treatment regimens, and compare serum IL-26 levels with those of healthy controls. By integrating these data, we aim to elucidate the mechanistic role of IL-26 in SLE pathogenesis and assess its potential as a biomarker for disease activity and a target for future therapeutic interventions.

METHODOLOGY

Study Design and Participants

This cross-sectional study enrolled a total of 63 blood specimens were collected from individuals diagnosed with systemic lupus erythematosus, along with an equal quantity from healthy controls. Both male and female participants, aged between 10 and 60 years, were enlisted from Al-Merjan Teaching Hospital and Al-Qassim General Hospital between August 1, 2024, and January 31, 2025. a total of 126 participants, comprising SLE patients and healthy controls matched by age and sex. SLE diagnosis was based on established classification criteria (e.g., ACR/SLICC). Informed consent was obtained from all participants, and the study protocol was approved by the institutional ethics committee. Ethical approval was granted by the Institutional Review Board (Ministry Of Health, Babylon Health Directorate, Approval Number: 1542), and all participants provided written informed consent before their inclusion in the study. The research protocol was designed and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki[12].

Data Collection:

Demographic data (age, sex) and clinical history were collected using standardized questionnaires and verified through medical records. The treatment regimens, including the use of Rituximab (RTX), Cyclophosphamide (CYC), combination therapy, or alternative immunosuppressive agents, were documented from patient files.

Estimation of Parameters:

Demographic Parameters:

Sex and age distributions were recorded directly from patient records. Data were categorized into age groups (11–20, 21–30, 31–40, and 41–50 years) to assess the distribution among SLE patients and controls.

Treatment Regimens:

The type of immunosuppressive therapy was extracted from clinical records. The frequency of each treatment (e.g., RTX, CYC) was calculated as a percentage of the total SLE patients.

IL-26 Measurement:

Blood samples were collected from all participants, and serum was separated by centrifugation. Serum IL-26 levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (BT Lab), following the manufacturers protocol. The assay's detection limit, intra-assay, and inter-assay variations were noted to ensure reliability. Absorbance was measured at the recommended wavelength using a microplate reader, and IL-26 concentrations were determined from a standard curve.

Statistical Analysis:

Statistical analyses were conducted using SPSS version 28 (IBM Corp., Armonk, NY, USA) or an equivalent statistical software package. Data for categorical variables (sex, age groups, treatment modalities) are presented as frequencies and percentages. Differences in categorical variables between SLE patients and controls were assessed using the Chi-square test. For continuous variables, including IL-26 levels, non-parametric tests (Mann–Whitney U test) were employed due to the non-normal distribution of the data. A p-value of <0.05 was considered statistically significant[13].

RESULTS

In this study of 126 Participatants **(Table 1),** 96.8% were female and 3.2% were male, reflecting the well-known female predominance of the disease. The largest proportion of patients fell into the 21–30 (38.9%) and 31–40 (38.1%) age groups, with fewer in the 11–20 (4.8%) and 41–50 (18.3%) categories.

Table 1: Demographic Characteristics and Age Distribution of Patients with SLE [a]

		Frequency	Percent
Sex	Female	122	96.8
	Male	4	3.2
	Total	126	100
Age group/ Years	11- 20	6	4.8
	21- 30	49	38.9
	31- 40	48	38.1
	41- 50	23	18.3
	Total	126	100

Data are shown as frequency (percentage); SLE = Systemic Lupus Erythematosus; Age groups are presented in years.

In **Table 2**, the sex distribution is identical between the case and control groups (both 96.8% female), showing no significant difference (p=1.000). However, the age distribution differs significantly (p=0.027), with a higher proportion of individuals in the 31–40 year range among controls.

Table 2: Comparison of Demographic Characteristics between SLE Cases and Controls[a]

Variable		Case (n=63)	Control(n=63)	Total	P-Value
Sex	Female	61(96.8%)	61(96.8%)	122(96.8%)	
	male	2(3.2%)	2(3.2%)	4(3.2%)	1.000
	Total	63(50%)	63(50%)	126(100%)	
Age groups/ years	11-20	3(4.8%)	3(4.8%)	6(4.8%)	0.027
	21-30	22(34.9%)	27(42.9%)	49(38.9%)	
	31-40	20(31.7%)	28(44.4%)	48(38.1%)	

[a] SLE, Systemic Lupus Erythematosus. Data are shown as n (%). p-values were obtained using the Chi-square test. Statistically significant differences were considered at $p < 0.05$.

In **Table 3**, table of 63 SLE patients, the majority (66.7%) were receiving Rituximab alone, followed by Cyclophosphamide (20.6%). A smaller percentage (4.8%) were on combination therapy with Rituximab and Cyclophosphamide, while the remaining therapies—Azathioprine, Mycophenolate Mofetil, Cortisone, Decadron, and others—each accounted for 1.6% of treatments.

Table 3: Distribution of Drug Therapies among SLE Patients [a]

Drug history	
Drug	**No of Patients**
Rituximab (RTX)	42(66.7%)
Azathioprine (Muran)	1(1.6%)
Cyclophosphamide (Endoxan)	13(20.6%)
Mycophenolate Mofetil (Cellcept)	1(1.6%)
Cortisone	1(1.6%)
Endoxan & RTX	3(4.8%)
Decadron	1(1.6%)
others	1(1.6%)
Total	63(100%)

[a] Data are presented as n (%); SLE, Systemic Lupus Erythematosus; RTX, Rituximab; Muran, Azathioprine; Endoxan, Cyclophosphamide; Cellcept, Mycophenolate Mofetil.

Table 4 Using the Mann–Whitney test to compare IL-26 levels between SLE cases and controls (each n=63), the control group showed a higher mean rank (75.22) than the case group (51.78). This difference was statistically significant ($p < 0.001$).

Table 4: Comparison of IL-26 Levels between SLE Cases and Controls [a]

Parameters	Case (n=63) Mean Rank	Control(n=63) Mean Rank	Mann-Whitney	Z	P-Value
IL-26	51.78	75.22	1246.000	-3.604-	0.000
*** level of significant variance (P < 0.05), P values were computed by the Mann-Whitney test**					

[a] Data are presented as mean rank. p-values were computed using the Mann–Whitney test. A p-value < 0.05 is considered statistically significant. Abbreviations: SLE, Systemic Lupus Erythematosus.

DISCUSSION

The examination of our demographic data (Tables 1 and 2) confirmed a marked female dominance among SLE patients, with 96.8% females versus 3.2% males—a finding that is consistent with well-established epidemiological trends[14-16] . This female predominance may be explained by hormonal factors, notably estrogen's role in enhancing immune activation and autoantibody production; genetic vulnerability, given the presence of numerous immune-related genes on the X chromosome; and environmental exposures, such as infections and UV radiation, which are more pronounced in females[16,17].

Age distribution analyses revealed that SLE predominantly affects individuals in early to mid-adulthood. The highest frequencies were observed in the 21–30 and 31–40-year age groups, whereas younger

(11–20 years) and older (41–50 years) patients were less represented. Moreover, a statistically significant difference in age distribution between SLE patients and healthy controls ($p = 0.027$) underscores the potential influence of age-related hormonal activity and environmental stressors in disease onset. In early adulthood, fully mature immune systems and lifestyle factors—ranging from work-related stress to hormonal fluctuations during pregnancy or due to contraceptive use—could contribute to triggering the disease[18].

Therapeutically (Table 3), our study found that Rituximab (RTX) was the predominant treatment, administered to 66.7% of SLE patients, followed by Cyclophosphamide (20.6%), with a small fraction receiving combination therapy or alternative immunosuppressants. The preferential use of RTX is justified by its targeted action against CD20+ B cells—a cell population pivotal in SLE pathogenesis[19]. By depleting B cells, RTX not only directly reduces autoantibody production but also indirectly modulates T cell responses, including those of Th17 cells, which are key producers of IL-26 [20]. In this context, our cytokine analysis (Table 4) revealed a significant reduction in IL-26 levels among SLE patients compared to healthy controls. IL-26, mainly produced by Th17 cells, plays an essential role in mediating autoimmune inflammation[7,8].

Mechanistically, IL-26 binds to extracellular DNA and facilitates its uptake by antigen-presenting cells, thereby enhancing type I interferon responses—a central pathway implicated in SLE pathogenesis[8]. The observed decrease in IL-26 in SLE patients likely reflects the immunosuppressive effects of RTX. By depleting B cells, RTX disrupts the critical crosstalk between B and T cells, subsequently attenuating Th17 cell activity and reducing IL-26 secretion. Furthermore, inter-individual variations in B-cell activating factor (BAFF) levels and patterns of B-cell regeneration may contribute to differential IL-26 modulation following RTX treatment[21,22].

Clinically, these findings suggest that reduced IL-26 levels might serve as a useful marker for monitoring disease activity and therapeutic response, especially in patients treated with RTX. However, given the modest sample size and the cross-sectional design of this study, further investigations are necessary to better understand the role of IL-26 in SLE pathogenesis.

Our study is strengthened by the well-characterized patient and control groups and the integrated analysis of demographic, therapeutic, and immunological data. However, limitations include a modest sample size and the inherent constraints of a cross-sectional design, which preclude definitive causal inferences. In addition, the lack of stratification by disease activity and potential variations in treatment response may limit the broader applicability of our results.

CONCLUSION

In conclusion, our results indicate that IL-26 levels are lower in SLE patients compared to healthy controls, potentially associated with RTX-mediated B-cell depletion. While these observations are consistent with current understandings of SLE immunopathogenesis, additional studies are needed to confirm these findings and to determine whether IL-26 can reliably serve as a biomarker or therapeutic target in SLE management.

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Declaration

Conflict of Interest: We declare that there are no conflicts of interest associated with this manuscript.

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Author's contribution:

D.S.S (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

E.H.S (Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing)

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