Autoantibodies against Type I Interferon's Correlate with Low CD169/SIGLEC1 and Severe Non-Viral Infections in SLE Iraqi Patients

Dheyauldeen Aftan Alhayani[1], Anfal Fawzi Farhan[2], Ruqiya Ahmed jasim[2]

[1] Department of Biology, College of Science, University of Al Maarif, Al-Anbar 31001, Iraq. diaaal-din.aftan@uoa.edu.iq

[2] Department of Medical Laboratories Techniques, College of Health and Medical Technology, University of Al Maarif, Al-Anbar 31001, Iraq.

Abstract

Background: Immune deregulations and activation of the type I interferon (IFN-I) pathway are hallmarks of systemic lupus erythematous (SLE), a chronic autoimmune illness. Anti-IFN-I antibodies and CD169/SIGLEC1 expression are two biomarkers linked to IFN-I signaling that have lately drawn interest as indications of immunological dysfunction and disease activity in SLE patients.

Objective: In patients with systemic lupus erythematous, this study sought to assess the association between IFN-I-related immunological markers, such as anti-IFN-I antibodies and CD169/SIGLEC1 expression, and disease duration, infection history, and therapy intensity.

Methods: Patients with SLE diagnoses participated in a cross-sectional study. Clinical information was documented, such as age, length of illness, history of infection, and course of treatment. Using the proper immunological tests, serum anti-IFN-I levels and CD169/SIGLEC1 expression were measured. To find associations between clinical factors and immunological markers, statistical studies were carried out.

Results: The findings showed strong correlations between IFN-I-related biomarkers, treatment intensity, infection history, and disease duration. Anti-IFN-I levels and disease duration were shown to be positively correlated, while CD169/SIGLEC1 expression was negatively correlated with disease duration. Reduced CD169/SIGLEC1 expression and elevated anti-IFN-I levels were substantially correlated with infection history. Furthermore, there was a strong correlation between treatment intensity and both immunological markers, indicating a link between immune modulation and therapeutic intervention. The assessed immunological markers did not significantly correlate with age.

Conclusion: The results emphasize the significance of IFN-I-related biomarkers in reflecting treatment exposure, infection burden, and disease chronicity in SLE patients. The potential use of anti-IFN-I antibodies and CD169/SIGLEC1 expression in precision medicine techniques for the treatment of autoimmune illnesses is supported by their potential as useful instruments for disease monitoring and risk assessment in SLE.

Keywords: Systemic Lupus Erythematous (SLE); Type I Interferon's; Autoantibodies; CD169/SIGLEC1; Innate Immunity; Immune Deregulations; Non-viral Infections; Immunopathogenesis.

Introduction

Immune deregulations, autoantibody generation, and multi-organ involvement are the hallmarks of systemic lupus erythematous (SLE), a chronic systemic autoimmune illness. Persistent activation of type I interferon (IFN-I) signaling, which encourages dendritic cell activation, B-cell differentiation, and amplification of autoimmune responses, is a defining feature of SLE pathogenesis [1,2]. In SLE patients, increased IFN-I activity and interferon-stimulated gene (ISG) expression have been repeatedly linked to disease activity and severity [3]. The complicated systemic autoimmune illness known as systemic lupus erythematosus (SLE) is typified by dysregulated immune responses and persistent inflammation .The up-regulation of type I interferon (IFN-I) pathways and downstream interferon-stimulated genes, which contribute to autoantibody formation, immunological activation, and tissue damage across organ systems, is a key aspect of SLE pathogenesis. A percentage of individuals paradoxically have neutralizing autoantibodies against type I interferon's, which can effectively reduce IFN-I signaling and change immunological homeostasis. Historically, the majority of research has concentrated on the harmful significance of high IFN-I activity in SLE. [1,2].

Recent research has shown that a specific subset of SLE patients produce neutralizing autoantibodies against type I interferon, despite the harmful effect of IFN-I. ISG expression can be suppressed as a result of these autoantibodies' substantial reduction of IFN-I bioavailability and signaling [4,5]. Among IFN-I-induced markers, CD169 (SIGLEC1) expressed on monocytes has emerged as a reliable surrogate biomarker of IFN-I activity. While CD169 is typically upregulated in IFN-high SLE, patients with anti-IFN-I autoantibodies exhibit markedly reduced CD169/SIGLEC1 expression, reflecting functional interferon blockade [6,7].

Anti-IFN-I autoantibodies have significant clinical ramifications in addition to their immunological effects. When it comes to innate immune response against viral and non-viral infections, IFN-I signaling is essential. Patients with autoimmune illnesses like SLE have been linked to increased susceptibility to severe infections, particularly bacterial and opportunistic infections, due to impaired IFN-I activity caused by neutralizing autoantibodies [8–10]. These results demonstrate the dual function of IFN-I in autoimmune and host defense and emphasize the potential utility of measuring CD169/SIGLEC1 expression and anti-IFN-I autoantibodies for infection risk assessment and individualized treatment in SLE.

Materials and Methods

Study Design and Population

This case–control study was conducted on Iraqi participants between **1 February 2024 and 1 December 2025**. The study included a total of **60 individuals**, comprising **40 patients diagnosed with systemic lupus erythematous (SLE)** and **20 apparently healthy controls**.

SLE patients were recruited from rheumatology and internal medicine clinics and were diagnosed according to the **American College of Rheumatology (ACR) / EULAR classification criteria**. The control group consisted of age- and sex-matched healthy individuals with no history of autoimmune diseases, chronic infections, or immunodeficiency disorders.

Sample Collection

Venous blood samples were collected from all participants during the study period. Approximately **5–10 mL of peripheral blood** was obtained under aseptic conditions from each subject. **EDTA tubes** were used for whole blood analysis and cellular marker assessment. **Plain tubes** were used for serum separation. Blood samples were allowed to clot at room temperature and then centrifuged at **3000 rpm for 10 minutes** to separate serum. Serum samples were aliquoted and stored at **−20°C to −80°C** until further laboratory analysis.

Laboratory Investigations

Serum samples were analyzed for: **Autoantibodies against type I interferons (IFN-I)** using enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's instructions. **CD169 (SIGLEC1) expression**, assessed as a surrogate marker of type I interferon activity (measured either by flow cytometry).

Statistical Analysis

Data were analyzed using **Statistical Package for the Social Sciences (SPSS)** software. Quantitative variables were expressed as **mean ± standard deviation (SD)**, while qualitative variables were presented as frequencies and percentages.

Comparisons between SLE patients and healthy controls were performed using the **independent samples t-test** for normally distributed variables.

Correlations between anti-IFN-I autoantibody levels, CD169/SIGLEC1 expression, and clinical parameters were assessed using **Pearson or Spearman correlation coefficients**, as appropriate.

A **p-value < 0.05** was considered statistically significant

Results and Discussions

1- Demographic and Clinical Characteristics of Systemic Lupus Erythematous (SLE) Patients and Healthy Controls

The absence of a statistically significant age difference between SLE patients and healthy controls indicates appropriate age matching, minimizing age-related confounding effects on immunological parameters. The predominance of females in the SLE group is consistent with the known epidemiology of SLE, which disproportionately affects women. This gender distribution supports the representativeness of the study population. The reported mean disease duration reflects a cohort with established disease, allowing meaningful assessment of chronic immunological changes.

Table 1. Demographic Characteristics of Study Groups

Variable	SLE Patients (n = 40)	Healthy Controls (n = 20)	p-value
Age (years), mean ± SD	32.4 ± 8.6	30.8 ± 7.9	0.48
Female, n (%)	34 (85.0%)	14 (70.0%)	—
Male, n (%)	6 (15.0%)	6 (30.0%)	—
Disease duration (years), mean ± SD	6.9 ± 4.1	—	—

2. Distribution of Disease Duration Among Systemic Lupus Erythematous (SLE) Patients

Most SLE patients had been afflicted for five to ten years, indicating that the majority of participants were in a mid-to-late stage of the disease. This distribution makes it possible to assess immunological dysregulation and long-term disease activity. Although the lower percentage of patients with a disease duration longer than ten

years may be the result of better disease care or survival bias, it nevertheless sheds light on the long-term immunological changes linked to chronic SLE.

Table 2. Disease Duration Distribution in SLE Patients

Disease Duration	n	%
< 5 years	15	37.5
5–10 years	17	42.5
> 10 years	8	20.0

3. Comparison of Infection History Between SLE Patients and Healthy Controls

Both viral and non-viral infections were more common in SLE patients than in healthy controls, with non-viral infections being especially common. This result probably represents immune system deregulations brought on by SLE and exacerbated by immunosuppressive treatments. Infection is a major clinical burden in SLE patients, as evidenced by the large percentage of healthy controls without a history of infection.

Table 3. History of Infections Among Study Groups

Infection History	SLE Patients (n = 40)	Healthy Controls (n = 20)
Viral infections	9 (22.5%)	3 (15.0%)
Non-viral infections	18 (45.0%)	2 (10.0%)
No infections	13 (32.5%)	15 (75.0%)

4. Current Treatment Regimens Among Patients with Systemic Lupus Erythematous (SLE).

The majority of SLE patients needed multi-drug treatment to control disease activity, indicating moderate to severe disease, based on the prevalence of combination therapy. The requirement for strong immune regulation and active immune involvement are further demonstrated by the use of corticosteroids and immunosuppressive drugs. It is crucial to take therapeutic intensity into account when evaluating immunological results because these treatment patterns may have a direct impact on immune biomarkers and infection risk.

Table 4. Current Treatment Regimen in SLE Patients

Treatment Regimen	n	%
Corticosteroids	10	25.0
Hydroxychloroquine	8	20.0
Immunosuppressive agents	7	17.5
Combination therapy	15	37.5

5. Relationships Between Interferon Pathway Biomarkers and Disease-Related Factors in SLE

Anti-IFN-I levels and CD169/SIGLEC1 expression do not correlate with age, indicating that the observed immunological alterations are disease-related rather than age-dependent.

Anti-IFN-I levels and disease duration are positively correlated, suggesting that prolonged disease is linked to enhanced or persistent activation of the type I interferon pathway. On the other hand, in chronic SLE, the negative connection between CD169/SIGLEC1 expression and disease duration may indicate immunological exhaustion or changed monocyte activity with time.

The importance of infections as powerful inducers of interferon responses in SLE patients is supported by the high correlation between infection history and elevated anti-IFN-I levels. Concurrently, deregulated innate immune signaling during recurrent infection episodes is suggested by the inverse connection with CD169/SIGLEC1.

Finally, the correlations observed with treatment intensity indicate that patients receiving more aggressive immunosuppressive therapy exhibit heightened interferon activity and reduced CD169/SIGLEC1 expression. This may reflect more severe disease requiring intensive treatment or treatment-induced modulation of innate immune markers.

Table 5. Correlation Between Immunological and Clinical Parameters in SLE Patients

Variable	Anti-IFN-I (r)	CD169/SIGLEC1 (r)	p-value
Age	−0.18	−0.21	>0.05
Disease duration	0.41	−0.46	<0.01
Infection history	0.52	−0.58	<0.001
Treatment intensity	0.44	−0.49	<0.01

Discussion

The type I interferon (IFN-I) pathway is a key pathogenic factor in the severe immunological deregulations that characterizes systemic lupus erythematous (SLE). The current investigation supports the mounting body of

evidence suggesting IFN-I-mediated processes play a critical role in the course of SLE and clinical outcomes by demonstrating substantial relationships between disease duration, infection history, treatment intensity, and immunological markers.

Anti-IFN-I levels and CD169/SIGLEC1 expression do not significantly correlate with age, indicating that these immunological changes are mostly disease-driven rather than age-dependent. This result is in line with earlier research showing that intrinsic autoimmune mechanisms rather than demographic variables are responsible for IFN-I activation in SLE [8].

Infection history was strongly associated with increased anti-IFN-I levels and decreased CD169/SIGLEC1 expression. SLE patients are known to have increased susceptibility to infections due to both disease-related immune dysfunction and the use of immunosuppressive therapies (Danza & Ruiz-Irastorza, 2023). Viral and bacterial infections can act as potent triggers of IFN-I production, further amplifying autoimmune responses and perpetuating disease activity (Crow, 2022). Recurrent infections may therefore contribute to sustained interferon activation while simultaneously impairing effective innate immune signaling.

The association between treatment intensity and immunological markers observed in this study further highlights the complex interplay between disease severity, therapy, and immune function. Patients requiring combination therapy or intensive immunosuppression often have more severe or refractory disease, which is itself associated with heightened IFN-I activity (Morand et al., 2023). Additionally, corticosteroids and immunosuppressive agents can directly influence monocyte activation and SIGLEC1 expression, potentially contributing to the negative correlations observed (Rose et al., 2024).

Overall, the findings of this study reinforce the concept that IFN-I–related biomarkers, including anti-IFN-I antibodies and CD169/SIGLEC1, reflect disease chronicity, infection burden, and treatment exposure in SLE. These markers may have clinical utility in disease monitoring, risk stratification for infections, and evaluation of therapeutic responses, in line with recent advances in precision medicine for SLE (Morand et al., 2023; Rönnblom & Leonard, 2023).

Research Significance Statement

This study highlights a potential immunological mechanism linking **anti–Type I interferon autoantibodies** with impaired innate immune signaling (via CD169/SIGLEC1) and increased susceptibility to **severe non-viral infections** in SLE patients, particularly within the Iraqi population.

Contribution Statement

The findings contribute to a better understanding of **immune dysregulation in SLE**, emphasizing the clinical importance of interferon pathways as potential biomarkers for infection risk and disease severity.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding Statement

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Ethical Statement

The study was conducted in accordance with ethical standards and approved by the appropriate institutional review board. Informed consent was obtained from all participants.

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