Letters

RESEARCH LETTER

SIGLEC-1 Expression in a Cohort of Patients With Lupus Erythematosus Treated With Anifrolumab

Lupus erythematosus (LE) is an autoimmune disease with systemic and cutaneous manifestations that affect quality of life. Type I interferon (IFN-I) contributes to LE pathogenesis by promoting autoantibody production. Anifrolumab, a human monoclonal antibody blocking IFN-I receptor, was approved for moderate to severe systemic LE (SLE) in 2021.[1] While striking improvement in LE with anifrolumab has been reported,[2] phase 3 trials demonstrated less than 50% improvement in composite SLE outcomes, underscoring the need for accessible biomarkers to monitor response.[1]

Supplemental content

SIGLEC-1, an IFN-I–inducible lectin expressed on CD14-positive monocytes, is elevated in LE and can be readily measured by flow cytometry to provide a fast, cost-effective measurement of IFN-I activity.[3] However, its utility for tracking response to anifrolumab remains underexplored.[4] This study examined whether SIGLEC-1 expression is associated with disease activity in patients with LE before and during IFN-I blockade.

Methods | We conducted a prospective pilot study of adults with SLE (based on 2019 EULAR/ACR criteria) or biopsy-proven cutaneous LE (CLE) initiating anifrolumab at Brigham and Women's Hospital (BWH) between September 2022 and March 2024. The BWH institutional review board approved this study. All participants provided written informed consent. Blood samples were collected from December 2022.

Clinical SLE Disease Activity Index 2000 (cSLEDAI) and CLE Disease Area and Severity (CLASI)–Activity and CLASI-Damage indices were assessed. SIGLEC-1 was measured by flow cytometry using fresh whole blood. IFN-I 21-gene score[1] was assessed in 7 patients using previously published single-cell RNA sequencing data.[5] Spearman correlations and mixed-effects models tested cross-sectional and longitudinal associations (RStudio, version 3.4.1 [R Project for Statistical Computing]). Two-sided $P < .05$ were statistically significant. Data were analyzed in December 2024.

Results | Thirty-two patients were included (25 SLE/CLE, 4 CLE, and 3 noncutaneous SLE; 28 [88%] female; median [IQR] age, 41 [31-54] years). Twenty-nine patients were treated for refractory mucocutaneous disease, with 25 having severe discoid LE. Other cutaneous manifestations included 4 patients with subacute cutaneous LE, 3 with acute cutaneous LE, 2 with lupus panniculitis, and 1 with bullous lupus. Median (IQR) baseline cSLEDAI, CLASI-Activity, and CLASI-Damage were 4 (2-6), 17 (10-23), and 11 (7-18), respectively (**Table**).

Systemic and cutaneous activity improved significantly, while CLASI-Damage remained stable (**Figure**, A). Among 18

Table. Baseline Demographic and Clinical Characteristics of Patients With Cutaneous or Systemic Lupus Erythematosus

Characteristic	No. (%) CLE (n = 4)	SLE (n = 28)
Age, median (IQR), y	40 (34-45)	40 (31-55)
Sex		
Female	4 (100)	24 (86)
Male	0	4 (14)
Ethnicity[a]		
Hispanic or Latino	2 (50)	5 (18)
Race		
Asian	1 (25)	1 (4)
Black	1 (25)	10 (36)
White	1 (25)	12 (43)
Unknown[b]	1 (25)	3 (11)
Other[c]	0	2 (7)
Time since diagnosis, y		
<1	0	2 (7)
1 to <5	2 (50)	2 (7)
5 to <10	0	2 (7)
≥10	2 (50)	22 (79)
History of lupus nephritis	NA	10 (36)
cSLEDAI, median (IQR)	NA	4 (2-6)
Mucocutaneous	NA	25 (89)
Fever	NA	1 (4)
Musculoskeletal	NA	7 (25)
Vasculitis	NA	1 (4)
Renal	NA	1 (4)
CLASI-Activity, median (IQR)	10 (6-16)	17 (11-23)[d]
CLASI-Damage, median (IQR)	5 (3-10)	10 (8-22)[d]
Main indication for anifrolumab		
Refractory skin manifestations	4 (100)	25 (89)
Acute CLE	0	3 (11)
Subacute CLE	0	4 (14)
Discoid LE	3 (75)	22 (79)
Bullous	0	1 (4)
Panniculitis	2 (50)	0
Refractory joint manifestations	0	2 (7)
Refractory fever	0	1 (4)
Other treatments		
Hydroxychloroquine	2 (50)	19 (68)
Prednisone dose, median (IQR)	0 (0-2)	0 (0-8)
Immunosuppressants[e]	2 (50)	15 (54)

Abbreviations: CLE, cutaneous lupus erythematosus; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity; cSLEDAI, Clinical Systemic Lupus Erythematosus Disease Activity Index 2000; NA, not applicable; SLE, systemic lupus erythematosus.

[a] Race and ethnicity data were self-reported by participants.

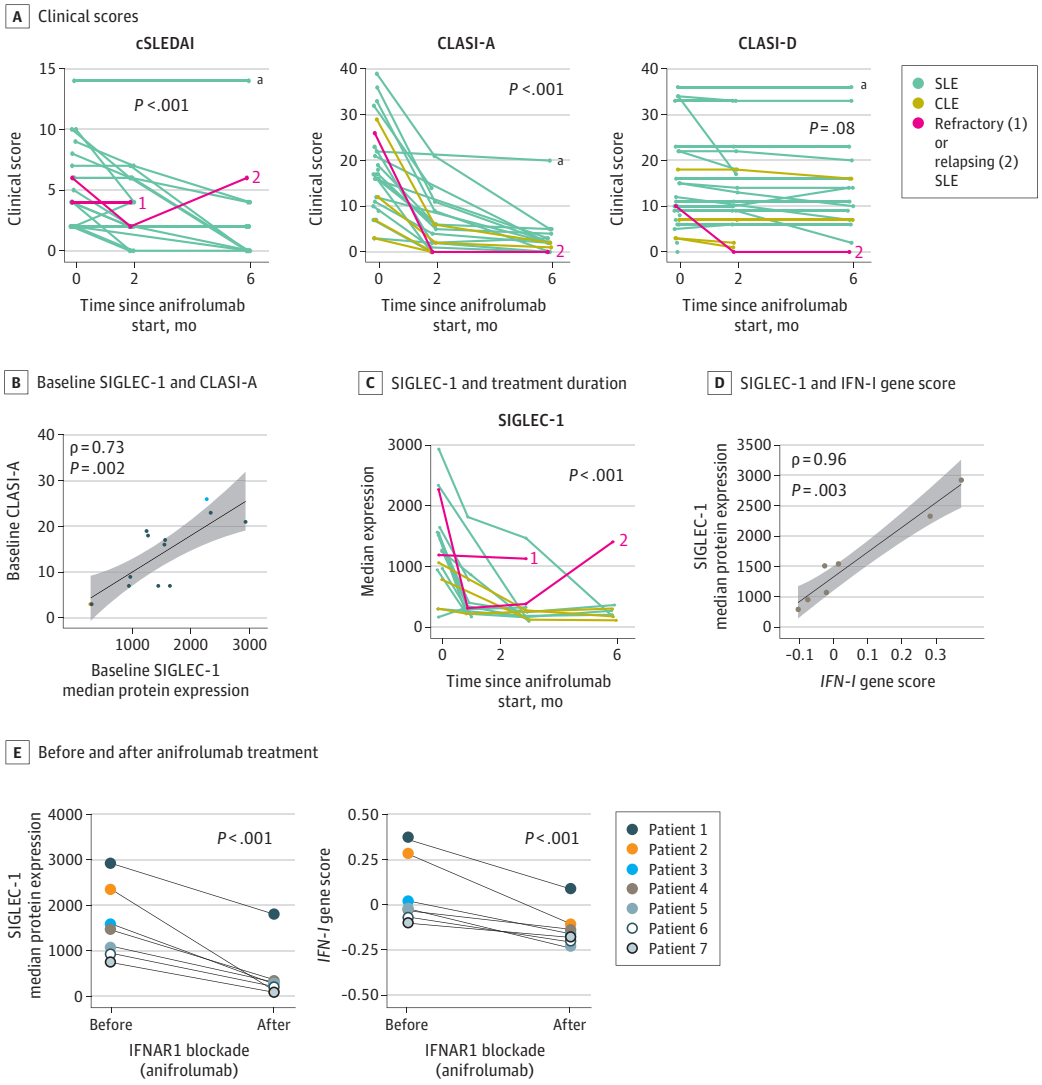
[b] All participants who did not report race are of Hispanic ethnicity.

[c] Patients selected the "other" category when reporting their race.

[d] n = 25 patients with skin manifestations.

[e] Includes lenalidomid (n = 4), methotrexate (n = 3), azathioprine (n = 3), mycophenolate mofetil (n = 10), and belimumab (n = 2, stopped prior to anifrolumab).

Figure. Changes in Disease Characteristics and SIGLEC-I Expression in Patients With Lupus Treated With Anifrolumab



A, Clinical systemic disease activity (cSLEDAI; N = 28, 21, and 14 at baseline, 2 months, and 6 months), cutaneous activity (CLASI-Activity; N = 29, 19, and 16 at baseline, 2 months, and 6 months) and cutaneous damage (CLASI-Damage; N = 29, 19, 16 at baseline, 2 months, and 6 months) before and during treatment with anifrolumab. B, Correlation between baseline CLASI-Activity score and SIGLEC-1 median protein expression measured on CD14-positive monocytes by flow cytometry (N = 15). The gray shading represents 95% CI. C, SIGLEC-1 median protein expression before and during treatment with anifrolumab (N = 18, 13, 12, 8 at baseline, 1 month, 3 months, and 6 months). D, Baseline correlation between SIGLEC-1 expression and IFN-I gene score based on 21 IFN-I–induced genes measured in paired samples from 7 patients with lupus treated with anifrolumab. The gray shading represents 95% CI. E, SIGLEC-1 expression and in IFN-I gene score before and after anifrolumab treatment. Colors correspond to individual patients and are consistent across both panels. Statistical significance was determined using a mixed-effect model including patient as a random effect (A and C), and using Spearman correlation (ρ) (B, D, and E).

CLE indicates cutaneous lupus erythematosus; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity; cSLEDAI, Clinical Systemic Lupus Erythematosus Disease Activity Index 2000; IFN-I, type I interferon; SLE, systemic lupus erythematosus.

[a]The patient did not adhere to treatment.

patients with blood samples, baseline SIGLEC-1 correlated with CLASI-Activity (ρ = 0.73; *P* = .002; Figure, B), CLASI-Damage (ρ = 0.66; *P* = .02), and cSLEDAI (ρ = 0.50; *P* = .03). Notably, 2 patients showed persistent (patient 1) or increased (patient 2) SIGLEC-1 despite full adherence (Figure, C). Patient 1 had refractory joint-predominant involvement; anifrolumab was discontinued due to lack of benefit and patient preference. Patient 2 achieved rapid and sustained cutaneous remission but developed synovitis and pericarditis with parallel increase in SIGLEC-1 (Figure, C). Results were reproducible in patients with discoid or subacute LE without other skin manifestations. Baseline SIGLEC-1 correlated with IFN-I gene score (ρ = 0.96; *P* = .003) and paralleled changes in IFN-I gene score following anifrolumab therapy (Figure, D-E).

Discussion | Our findings support the value of anifrolumab in moderate to severe skin-predominant LE[2] and nominate SIGLEC-1 as a candidate biomarker for monitoring response,

showing correlation with cSLEDAI, CLASI-Activity, and IFN-I-signature. Additionally, the lack of improvement in skin damage supports the need for early intervention. Despite the overall success of anifrolumab in this cohort, 2 patients exhibited persistent or increased SIGLEC-1 expression, coinciding with refractory or relapsing nonskin disease.

Limitations include the study's single-center design, small sample size, and skin-predominant LE cohort. Whether SIGLEC-1 levels influence response kinetics requires further study. To our knowledge, SIGLEC-1 measurement is not yet routinely available in commercial diagnostic laboratories. However, SIGLEC-1 can be readily assessed by flow cytometry, a tool widely available globally. The assay has already been implemented in several academic institutions (eg, Nationwide Children's Hospital in the US; Lausanne University Hospital in Switzerland) and is internationally recognized as a potential biomarker in autoimmune diseases.[6] Thus, SIGLEC-1 shows promise as a real-time biomarker of IFN-I activity, which may guide use of IFN-I–targeted therapies.

Alice Horisberger, MD
Katharina S. Shaw, MD
Rochelle Castillo, MD, MS
Eilish Dillon, BS
Kathryne E. Marks, PhD
Ifeoluwakiisi Adejoorin, BS
Emily G. Oakes, BA
Heather L. Roland, BS
Julia Caldropoli, BS
Karen H. Costenbader, MD, MPH
Avery LaChance, MD, MS
Ruth Ann Vleugels, MD, MPH, MBA
Deepak A. Rao, MD, PhD

Author Affiliations: Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Horisberger, Castillo, Dillon, Marks, Adejoorin, Oakes, Roland, Caldropoli, Costenbader, LaChance, Vleugels, Rao); Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland (Horisberger); Department of Dermatology, School of Medicine, University of Pennsylvania, Philadelphia (Shaw).

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Corresponding Author: Deepak A. Rao, MD, PhD, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Rd, Room 6002R, Boston, MA 02115 (darao@bwh.harvard.edu).

Author Contributions: Drs Horisberger and Castillo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Horisberger, Shaw, and Castillo contributed equally to this work as co–first authors. Drs Vleugels and Rao contributed equally to this work as co–senior authors.

Concept and design: Horisberger, Shaw, Castillo, Marks, Costenbader, Vleugels, Rao.
Acquisition, analysis, or interpretation of data: Horisberger, Castillo, Dillon, Marks, Adejoorin, Oakes, Roland, Caldropoli, Costenbader, LaChance, Vleugels, Rao.
Drafting of the manuscript: Horisberger, Shaw, Castillo, Vleugels, Rao.
Critical review of the manuscript for important intellectual content: Horisberger, Castillo, Dillon, Marks, Adejoorin, Oakes, Roland, Caldropoli, Costenbader, LaChance, Vleugels, Rao.
Statistical analysis: Horisberger, Shaw, Costenbader, Vleugels.
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