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ANTI-C1Q AND ANTI-DSDNA ANTIBODIES CENTRALLY ASSESSED PREDICT RENAL INVOLVEMENT IN SLE PATIENTS FROM THE GLADEL 2.0 COHORT

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Background

Renal involvement remains one of the most severe manifestations of systemic lupus erythematosus (SLE). Although anti-dsDNA and anti-C1q antibodies play a pathogenic role in lupus nephritis (LN) and have been associated with renal disease activity, their predictive value has been variable across studies, partly due to inter-laboratory variability and differences in assay methodologies. Centralized assessment may improve prediction of renal activity and flares.

This analysis evaluated whether anti-C1q and anti-dsDNA antibodies centrally assessed predict active LN and renal flares in patients with SLE.

Methods

GLADEL 2.0 is a multicenter longitudinal cohort including SLE patients, categorized according to renal involvement: Group I (no history of LN); II (prevalent LN, currently inactive); III (prevalent LN, currently active) and IV (incident LN). Anti-C1q and anti-dsDNA antibodies were measured at the Werfen Autoimmunity headquarters & technology center. Anti-C1q antibodies were assessed using an ELISA assay (QUANTA Lite anti-C1q, CE-marked/RUO in USA), while anti-dsDNA antibodies were assessed using a chemiluminescence immunoassay (QUANTA Flash dsDNA) [Inova Diagnostics Inc., San Diego, USA]. Associations between biomarker levels and renal outcomes were evaluated, including active LN at cohort entry and the occurrence of renal flares during follow-up. Renal flare was defined as an increase in renal SLEDAI 2-K, worsening proteinuria (>0.5 g/24 h or increased urine protein-to-creatinine ratio), and/or the presence of active urinary sediment. Multivariable logistic regression models were used to identify factors associated with active LN at cohort entry. Cox proportional hazards models were used to evaluate predictors of time to first renal flare during follow-up. Models were adjusted for demographic, socioeconomic, and serologic variables.

Results

A total of 1,022 patients were included. Anti-C1q and anti-dsDNA levels increased progressively across LN groups, reaching the highest values in patients with incident LN (anti-C1q: 69.2, 103.1, 191.2 and 451.1 U; anti-dsDNA: 33.6, 36.5, 80.3 and 189.2 IU/mL across Groups I–IV, respectively; both p<0.001). During five years of follow-up, 573 patients developed a renal flare. At baseline, anti-C1q and anti-dsDNA antibody levels were significantly higher in these patients (191.6 vs 90.5 U and 81.0 vs 38.2 IU/mL, respectively; both p<0.001) (table 1). In multivariable logistic regression analyses, anti-C1q (OR 1.61, 95% CI 1.37–1.89) and anti-dsDNA antibodies (OR 1.41, 95% CI 1.22–1.62) were independently associated with active LN at cohort entry (table 2). In multivariable Cox regression models, anti-C1q (HR 1.38, 95% CI 1.23–1.55) and anti-dsDNA antibodies (HR 1.29, 95% CI 1.16–1.43) independently predicted time to first renal flare during follow-up (table 3).

TABLE 1.

Comparison of biomarkers according to renal flare during follow-up.

VARIABLE	TOTAL (n=1022)	RENAL FLARE DURING FOLLOW-UP: NO (n=449)	RENAL FLARE DURING FOLLOW-UP: YES (n=573)	*p*-value[a]
Anti-C1q antibodies, median (Q1-Q3)	124.3 (52.8-332.7)	90.5 (45.1-230.2)	191.6 (76.0-469.5)	0.001
Anti-dsDNA antibodies, median (Q1-Q3)	53.5 (23.1-166.1)	38.2 (20.3-98.5)	81.0 (29.3-264.7)	0.001
LN, n (%)				0.001
I (no LN)	416 (40.7)	354 (61.8)	62 (13.8)	
II (prevalent inactive)	214 (20.9)	129 (22.5)	85 (18.9)	
III (prevalent active)	231 (22.6)	53 (9.2)	178 (39.6)	
IV (incident LN)	161 (15.8)	37 (6.5)	124 (27.6)	

LN: lupus nephritis; [a]p-values correspond to the Wilcoxon test, Fisher's exact test, or the Chi-square test, as appropriate.

TABLE 2.

Logistic regression of active LN at cohort enrollment.

VARIABLE	UNIVARIATE MODEL: OR (95% CI)	UNIVARIATE MODEL: *p*-value	UNIVARIATE MODEL: OR (95% CI)	UNIVARIATE MODEL: *p*-value
Gender				
Male	Ref	<0.001	Ref	
Female	0.50 (0.33-0.75)	<0.001	0.60 (0.37-0.96)	0.034
Age at diagnosis	0.98 (0.96-0.99)		0.98 (0.97, 0.99)	0.007
Ethnicity				
Caucasians	Ref	0.010	Ref	
Mestizo	1.48 (1.10-2.00)	0.034	1.67 (1.18-2.35)	0.004
African Latin American	1.71 (1.04-2.82)		2.04 (1.13-3.66)	0.017
Socio-economic status				
High/Middle	Ref		Ref	
Middle	1.70 (1.20-2.42)	0.003	1.92 (1.28-2.90)	0.002
Middle low/Low	1.84 (1.30-2.59)	0.001	2.22 (1.44-3.45)	<0.001
Education	1.00 (0.97-1.04)	0.850	1.04 (0.99-1.09)	0.095
Anti-C1q+	2.07 (1.82-2.36)	<0.001	1.61 (1.37-1.89)	<0.001
Anti-dsDNA+	1.83 (1.64-2.05)	<0.001	1.41 (1.22-1.62)	<0.001

TABLE 3.

Cox regression: time to first renal flare[b] during follow-up.

VARIABLE	UNIVARIATE MODEL: HR (95% CI)	UNIVARIATE MODEL: *p*-value	UNIVARIATE MODEL: HR (95% CI)	UNIVARIATE MODEL: *p*-value
Gender				
Male	Ref		Ref	
Female	0.56 (0.42-0.74)	0.001	0.66 (0.49-0.90)	0.008
Age at diagnosis	0.98 (0.97-0.99)	0.001	0.98 (0.97-0.99)	0.005
Ethnicity				
Caucasians	Ref		Ref	
African Latin American	1.33 (1.04-1.45)	0.025	1.73 (1.15-2.60)	0.009
Mestizo	1.53 (1.04-1.56)	0.030	1.40 (1.08-1.80)	0.010
Socio-economic status			Ref	
High/Middle high	Ref		Ref	
Middle	1.46 (1.10-1.51)	0.010	1.51 (1.11-2.05)	0.009
Middle low/Low	1.57 (1.18-1.68)	0.002	1.77 (1.29-2.44)	0.001
Education	1.01 (0.98-1.04)	0.491	1.04 (1.01-1.07)	0.018
Anti-C1q+	1.70 (1.55-1.85)	0.001	1.38 (1.23-1.55)	0.001
Anti-dsDNA+	1.58 (1.46-1.71)	0.001	1.29 (1.16-1.43)	0.001

[b]*Time to first flare during follow-up was calculated as the time from baseline visit to the midpoint between the visit at which the flare was reported and the previous visit.*

Conclusion

Centrally measured anti-C1q and anti-dsDNA antibodies were independently associated with active LN and increased risk of future renal flares in this large, multiethnic Latin American SLE cohort. These findings support the clinical usefulness of these biomarkers for renal risk stratification and monitoring in patients with SLE.

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