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Clinical Characteristics of Children with Membranous Lupus Nephritis: The Childhood Arthritis and Rheumatism Research Alliance Legacy Registry

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Abstract

Objective: The objective of this article is to describe and compare clinical features, treatment, and renal outcomes of children with membranous lupus nephritis (MLN), through analysis of a national multicenter registry.

Methods: Patients with pediatric systemic lupus erythematosus (SLE) and MLN from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry were included. Demographic, disease and medication-related data were collected between 2010 and 2014 from 59 CARRA Legacy Registry sites.

Results: A total of 132 subjects had MLN, either in isolation or in combination with proliferative LN. Seventy-four subjects had pure class V LN. The proportion of subjects with daily corticosteroid treatment was similar among groups (96%, 91%, and 96%, for class III+V, IV+V, and V, respectively, $P=0.67$). Proportion of subjects exposed to mycophenolate was significantly different among groups, with a trend toward more frequent mycophenolate exposure in the pure class V group (83%, 74%, 92% for class III+V, IV+V, and V, respectively, $P=0.045$). Proportion of subjects exposed to any disease-modifying antirheumatic drug (DMARD) or biologic was similar among the three groups. Proportion of subjects with decreased glomerular filtration rate (less than 90 ml/min/1.73m²) was significantly different among groups (4%, 38%, and 4%, for class III+V, IV+V, and V, respectively, $P<0.0001$).

Conclusion: This is the largest reported cohort of children with MLN. More research is needed to understand treatment practices for pediatric MLN, particularly decisions related to pharmacologic treatment of pure MLN. More work is also needed to identify prognostic factors and predictors of outcome for pediatric MLN. Future observational studies will be a first step toward understanding and formulating a standardized approach to treatment of pediatric

membranous LN and allowing for the initiation of prospective comparative effectiveness studies and interventional trials.

Lupus nephritis (LN) is a common problem for children and adolescents with systemic lupus erythematosus (SLE), and 40–70% of pediatric SLE patients have kidney involvement.^{1–5} Prognostic assessments and treatment decisions for LN are guided in large part by kidney biopsy, as graded by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification.⁶ Patients with membranous lupus nephritis (MLN) make up 8–30% of pediatric LN cases.^{2, 7–11} MLN can manifest as isolated subepithelial immune deposits (pure class V LN) or in combination with proliferative glomerulonephritis.

For patients diagnosed initially with pure class V LN, risk of progression to proliferative LN is difficult to ascertain, given variable treatment practices and the limited availability of data from repeat renal biopsies. A study of 66 adult patients with pure MLN who were treated primarily with only steroids found that the rate of development of proliferative lesions was 35% at 10 years of follow-up.¹² A more recent study of 30 patients with pure pediatric class V LN found that 14% of patients had proliferative lesions on repeat renal biopsy, with median follow-up for re-biopsied patients of 5.3 years.⁹ Although outcomes for pure class V LN are generally thought to be favorable, renal insufficiency and end-stage renal disease (ESRD) do occur, with reported rates of ESRD ranging from 3–28% across adult studies and 0–25% in pediatric studies.^{2, 4, 9, 11–19} Reliable predictors of ESRD for patients with pure class V LN have not been identified.

Although consensus guidelines for management of LN have been formulated, these recommendations are based on evidence from adult studies, and treatment of pediatric LN is largely empirical.^{20–22} Consensus guidelines for treatment of pure class V LN suggest prednisone and/or immunosuppressive therapy for only those patients with nephrotic-range proteinuria. Additionally, the consensus guidelines recommend that patients without nephrotic-range proteinuria receive steroids and immunosuppressant medications as dictated only by extra-renal manifestations. We do not know if treatment for patients with pediatric class V LN should reflect the published consensus guidelines for management of adult LN. Similarly, the degree of variability in current treatment practices for patients with pediatric class V LN is largely unknown.

The objective of this study was to determine the clinical features, current treatment practices, and renal outcomes of children with MLN followed in pediatric rheumatology centers in the United States. We utilized data from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) observational registry of pediatric rheumatology patients to describe demographic, clinical, and treatment characteristics in this cohort.

Patients and Methods

Study Population

The CARRA Legacy Registry (CR) is an observational longitudinal data capture study that encompasses all major pediatric rheumatic diseases. Fifty-nine active CARRA clinical sites participated in the CR and represented the majority of pediatric rheumatology centers from

all major geographic regions of the United States. Patients with pediatric SLE were eligible for recruitment into the CR if they met revised 1997 ACR classification criteria for diagnosis of SLE, they developed pediatric SLE at 18 years of age, and their enrollment into the CR occurred at 21 years of age.²³ After obtaining Institutional Review Board approval, we analyzed clinical and demographic data from CR patients with biopsy-confirmed class V lupus nephritis as per ISN/RPS classification criteria. We used de-identified data from all active clinical sites from the start of the CR in May 2010 through July 2014.

Data Collection

Clinical data and demographic information were collected from the subjects/guardians and medical providers using both general and pediatric lupus-specific case report forms at the time of enrollment in the CR. Parental information, chart review, and physician recall were utilized in data collection. Clinical data were collected prospectively at six-month interval CR follow-up visits. De-identified data were pooled and stored in a secure centralized electronic database. Clinical data from the time period prior to patient enrollment in the CR was not included in the CR, and therefore this data was not available for analysis.

Disease Characteristics

Data regarding glomerular filtration rate (GFR), hematuria, proteinuria, physician global assessment (PGA) scores, patient global assessment scores, hypocomplementemia, and other disease data were collected at each CR visit. Patients for whom specific data was unavailable in the CARRA Registry were excluded from pertinent analyses. Estimated GFR was calculated using the Schwartz formula.^{24, 25} Renal survival was defined as absence of end stage renal disease (ESRD) requiring either chronic dialysis or renal transplant. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scoring was calculated according to the revised SLEDAI-2000 (2K) modification.²⁶ PGA scores and patient global assessment scores were scored on a 0–10 scale. Quantitative data regarding the level of proteinuria was not collected in the CR. Rather, data regarding proteinuria was collected with binary survey questions assessing for presence of urine protein/creatinine ratio > 0.5 (e.g. “Has the patient had a protein/creatinine ratio >0.5 in the last 10 days? Yes or No.”) Similarly, quantitative data regarding the level of hematuria was not available. Rather, binary survey questions were utilized to assess for >5 RBC/hpf on urinalysis. Data regarding complement levels were collected with binary survey questions to assess for C3 or C4 levels “below the lower limit of normal.”

Statistical Analysis

Statistical Analysis was conducted using Stata Software, version 14.1 (Statacorp). Descriptive analysis was performed for all variables. All data analyses were preceded by extensive data checking and verification to identify and resolve reasons for missing data and out of range values. Chi-square and Fisher Exact Test was used to evaluate associations between histologic LN class and categorical variables, as appropriate. Kruskal-Wallis was used to evaluate associations between histologic class and continuous variables. All tests were 2-sided and *P* values less than 0.05 were considered significant.

Results

Demographic features and disease characteristics

A total of 9522 pediatric rheumatology subjects were enrolled in the CR from May 2010 through July 2014, and 982 of these were subjects with SLE. Of these, 473 (48%) had biopsy confirmed LN. One-hundred and thirty two (28%) of these subjects had MLN, either in isolation or in combination with proliferative LN. Seventy-four (16%) of the total subjects with LN had pure MLN.

Demographic and disease characteristics are reported in Table 1. Length of follow-up in the CARRA Registry was variable, with the total number of CARRA Registry visits ranging from 1 to 6, corresponding to 0–3 years of follow-up. Of the 132 subjects with MLN, 61% had more than one CR visit. Groups defined by renal histopathology were similar with respect to gender, age at SLE onset, race and ethnicity. There was a trend toward differences in the median SLE duration (3.2, 3.1, and 4.8 years for class III+V, IV+V, and V, respectively, $P=0.070$). Groups were significantly different with regard to median LN duration (2.1, 1.7 and 2.9 years, $P=0.006$.)

Proportions of subjects who had proteinuria (random urine protein/creatinine >0.5) at any time during the study were similar between groups defined by renal histopathology (65%, 57%, and 55%, for class III+V, IV+V, and V, respectively, $P=0.71$). Proportion of subjects with proteinuria at the last study visit (LV) was similar for groups, with a trend toward less frequent proteinuria in the pure class V group (52.2%, 51.4%, and 32.9%, $P=0.09$). Proportion of subjects with hematuria (>5 RBC/hpf) at any time during the study was significantly different among groups (52%, 37%, and 22%, $P=0.01$). Proportion of subjects with hematuria at LV was significantly less in the pure class V group (30%, 29%, 11%, $P=0.03$).

Proportions of subjects with low serum complement levels or positive anti-double stranded DNA (anti-dsDNA) antibodies were similar among groups. Maximum and LV physician's global assessment scores were similar among groups, as were maximum and LV patient's global assessment scores. Maximum and LV Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores were also similar among groups.

Medication Exposures

Data regarding medication use are reported in Table 2. Proportion of subjects reporting hydroxychloroquine exposure (past or current) were significantly different among groups (96%, 86% and 99%, for class III+V, IV+V and V, respectively, $P=0.01$). Proportion of subjects reporting daily treatment with corticosteroids was similar among groups (96%, 91%, and 96%, $P=0.67$). Proportion of subjects exposed to mycophenolate was significantly different among groups, with a trend toward more frequent mycophenolate exposure in the pure class V group (83%, 74%, 92%, $P=0.045$). Cyclophosphamide exposure was more frequent in the class IV+V group (39%, 63%, 32%, $P=0.01$). Proportion of subjects exposed to any DMARD or biologic was similar among groups (82.6%, 91.4%, 94.6%, $P=0.189$).

Disease characteristics for groups distinguished by LN duration

For the purposes of these analyses, patients with LN duration <0.5 years were excluded. For subjects with pure class V LN, proportion of subjects with proteinuria at LV was significantly higher for LN duration <2 years versus LN duration >2 years (47% vs. 20%, respectively, $P=0.023$). Proportion of subjects with hematuria at LV were similar for subjects with pure class V LN, irrespective of LN duration. Proportion of subjects with hypocomplementemia, subject SLEDAI scores, physician global assessment scores, and subject global assessment scores were similar for subjects with pure class V LN, irrespective of LN duration.

For subjects with membranous plus proliferative LN (class III+V or class IV+V), proportion of subjects with hematuria at LV was significantly higher for LN duration <2 years versus LN >2 years (46% vs. 0%, respectively, $P<0.001$). Proportion of subjects with proteinuria at LV were similar for subjects with membranous plus proliferative LN, irrespective of LN duration. Proportion of subjects with hypocomplementemia, subject SLEDAI scores, physician global assessment scores, and subject global assessment scores were similar for subjects with membranous plus proliferative LN, irrespective of LN duration.

Renal insufficiency, dialysis use, and repeat kidney biopsy

Six patients had missing serum creatinine data and were excluded from analysis of GFR. Proportion of subjects with estimated glomerular filtration rate (GFR) <90 ml/min/1.73m² was significantly different among groups defined by renal histopathology (4%, 38%, and 4% for class III+V, IV+V, and V, respectively, $P<0.0001$) and this difference persisted after excluding subjects with LN duration <0.5 years (6%, 24%, 4%, $P=0.01$) (Table 1). For subjects with pure class V LN, none of the patients with disease duration <2 years had GFR <90 ml/min/1.73m². However, three patients (4%) with disease duration >2 years had GFR <90 ml/min/1.73m². For subjects with membranous plus proliferative LN, proportion of subjects with GFR <90 ml/min/1.73m² was similar for subjects with LN duration <2 years vs. >2 years (18.2% vs. 17.2%, $P=1$). For patients with LN duration >0.5 year, renal survival at time of LV was 100%, 100%, and 97% for class III+V, IV+V, and V, respectively.

Demographic and disease characteristics for the three subjects with pure class V LN and GFR <90 ml/min/1.73m² are reported in Table 3. None of the patients in this group had a repeat kidney biopsy. Two of these subjects required dialysis treatment. For patients with LN duration >0.5 year, renal survival at time of LV was 100%, 100% and 97% for class III+V, IV+V, and V, respectively.

None of the three patients with pure class V LN and GFR <90 ml/min/1.73m² had a repeat kidney biopsy. Two of these patients required dialysis treatment. Seven subjects (5.3%) had more than one kidney biopsy. Five of these subjects had pure class V LN on the first biopsy, and the repeat biopsy again showed class V LN for four of these subjects. The fifth subject's repeat biopsy revealed class IV+V LN. One subject had class III+V LN on the first biopsy and had two subsequent biopsies, showing class V and class III+V, in succession. One subject had class IV+V on initial and repeat kidney biopsy.

Discussion

To date, this is the largest reported cohort of children with membranous LN. Overall prevalence of LN, as well as prevalence of membranous LN in particular, was similar to previously reported cohorts of pediatric LN.^{1, 2, 7-9} Age at SLE onset and gender distribution were also similar to previous reports.^{1, 27} Distribution of race was similar to previously reported North American pediatric LN cohorts, with increased frequency of MLN in black patients compared to white patients.⁵

In comparison to patients with pure class V LN or class III+V LN, significantly more patients with class IV+V LN had renal insufficiency at their last study visit, even after excluding patients with LN <0.5 years. Notably, three patients (4.3%) with pure class V LN had renal insufficiency, and two of these subjects had ESRD and were on dialysis. Proportion of subjects with proteinuria at last visit was similar among groups, while hematuria at last visit was significantly more common in subjects with class III+V and IV+V LN. Maximum and last visit PGA scores and SLEDAI scores (measures of generalized SLE activity) were similar among groups. These measures are also influenced by extra-renal disease activity, suggesting that extrarenal activity was similar among groups.

To examine trends in outcome measures over time, we divided the cohort into subgroups based on LN duration, with a cut-off of 2 years. As our aim was to understand treatment outcomes, we excluded newly diagnosed patients with duration of disease < 0.5 years. For patients with pure class V LN, significantly fewer patients with disease duration >2 years had protein/creatinine ratio >0.5 at last visit, compared to patients with LN duration <2 years (20% vs. 47%, $P=0.02$). This finding is consistent with previously reported studies in children and adults, which suggest that a return of protein/creatinine ratios to levels <0.5 can be a gradual and lengthy process, even for patients who demonstrate an early decrease in the level of urinary protein excretion and who achieve favorable long-term renal outcomes.^{9, 28, 29}

For patients with class III+V and class IV+V LN, we found no difference in urinary protein excretion over time. However, we did observe a significant difference in hematuria <5 RBC/hpf for patients with LN duration >2 years, compared to those with LN duration <2 years (0% vs 45%, $P<0.001$). A possible explanation for these findings may be that proliferative LN predisposes to chronic renal injury or tubulointerstitial fibrosis and resultant chronic proteinuria, even in the absence of active nephritis.^{30, 31} Future studies, in which hematuria and proteinuria can be quantified and followed prospectively, will allow for further elucidation of these trends. Future studies will also be needed to confirm observed trends from the adult LN literature, particularly the observation that hematuria has been a poor predictor of renal outcome in two long-term, adult LN trials.^{32, 33}

Daily corticosteroid exposure was reported for >90% of patients irrespective of LN class. Previously reported rates of daily corticosteroid use for pediatric pure class V LN are similar, with 93% of the cohort reported by Hugel *et al.* being treated with prednisone.⁹ Notably, we found that 96% of pure class V LN patients in this cohort had exposure to additional DMARD and/or biologic medications. This stands in contrast to the cohort

reported by Hugle *et al.*, in which only 33% of patients treated with steroids received additional immunosuppressive medication treatment, with median follow-up time of 4.7 years. This relatively low rate of treatment with additional immunosuppressive therapies reported by Hugle *et al.* may reflect the treatment practices of a single center, whereas the CARRA Registry may reflect trends toward more frequent immunosuppressive use for these patients in a multi-center cohort. Cyclophosphamide exposure was significantly higher in the group with class IV+V LN. This likely reflects a belief on the part of many physicians that more severe LN mandates therapy with cyclophosphamide.³⁴

Quantification of proteinuria was not available in the CARRA Registry data, and data regarding presence or absence of nephrotic range proteinuria was not available. Additionally, retrospective data regarding extra-renal lupus manifestations (occurring prior to CR enrollment) was not available. As a result, we are unable to draw definite conclusions regarding whether treatment of patients with pure class V LN reflects current practice guidelines. These guidelines specify that patients without nephrotic-range proteinuria receive steroids and immunosuppressant medications as dictated by extra-renal disease.^{20–22} However, in the pediatric cohort reported by Hugle *et al.*, 43% of patients had nephrotic range proteinuria, while in the adult LN literature, reported prevalence of nephrotic syndrome in pure MLN is between 50–69%.^{9, 12} If we assume that the rate of nephrotic proteinuria in this cohort was similar to previously published cohorts, then the data from this cohort suggests that physicians are not limiting treatment with steroids and immunosuppressant medications to only those patients with nephrotic proteinuria. This may be because frequent extra-renal disease mandates such treatment, or it may be due to real-world practice habits that do not reflect the published guidelines. Three patients (4%) with pure MLN in this study had renal insufficiency. This statistic highlights the risk of poor renal outcome for patients with pure class V LN, which has been reported elsewhere.^{2, 9, 12–15} This risk may explain the use of more aggressive treatment for patients with pure MLN, even in the absence of nephrotic-range proteinuria.

This study was inherently limited due to its retrospective design. Additionally, as noted above, the nature of the CR data set did not allow for quantification of proteinuria and hematuria, limiting their utility as outcome measures. Additionally, because diagnosis of LN preceded enrollment in the CR for many of the patients included in our analysis, clinical data collected at first presentation with lupus or lupus nephritis were not available. Specifically, data regarding complement levels, presence or level of anti-dsDNA antibody, measures of hematuria, proteinuria, and serum creatinine were not available for time points preceding CR enrollment. Data regarding timing of medication exposures preceding CR enrollment were also not available. Given the variable length of time for each patient between diagnosis of LN and enrollment in the CR, analysis at a unified time point for all patients was not possible. Nor was it possible to do a survival analysis for time to outcome. Variable diagnostic and treatment practices among physicians may have led to center-dependent differences in patient characteristics. Assessment of inter-reader variability in biopsy interpretation and identification of additional prognostic biopsy features also were not possible in our retrospective analysis.

While many of the observations in this study are consistent with previously described cohorts of patients with pediatric membranous LN, this is the largest such cohort to date. Additionally, our observations regarding medication exposure suggest that treatment practices may vary among centers and may not reflect the published LN consensus treatment guidelines. More work will be needed to confirm the trends observed in this analysis of the CARRA Legacy Registry data. Surveys of physicians and detailed observational studies will to elucidate actual treatment practices. Collaboration between pediatric rheumatologists and pediatric nephrologists will be integral in formulating a standard approach to treatment of pediatric MLN and allowing for the initiation of prospective comparative effectiveness studies and interventional trials.

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Significance and Innovations

- This study reports clinical features, treatment, and renal outcomes of three groups of class V LN patients (class III+V, IV+V, and V), in the largest reported cohort of children with MLN.
- 96% of patients with pure class V LN were exposed to daily corticosteroid treatment, and 95% of patients with pure class V LN were exposed to additional DMARD or biologic therapy.
- Three patients (4%) with pure class V LN in this study had renal insufficiency, consistent with previously reported risk of poor renal outcome for patients with pure class V LN.

Table 1:

Demographic features and disease characteristics of subjects with class V lupus nephritis

	class III+V (n=23)	class IV+V (n=35)	class V (n=74)	P
female:male (% female)	18:5 (78)	31:4 (88)	57:17 (77)	0.395
Age at SLE onset, yrs, median (IQR)	12.4 (11.1,14.2)	13.5 (10.9,14.7)	12.7 (10.1,14.5)	0.345
length of follow up in CARRA Registry, yrs, median (IQR)	0.6 (0.0,1.7)	0.0 (0,1.1)	1.0 (0,1.7)	0.043
White, n (%)	7 (30)	15 (42)	29 (39)	0.630
Black	13 (56)	12 (34)	34 (46)	0.237
Asian	4 (17)	3 (9)	9 (12)	0.602
Hispanic or Latino	6 (26)	15 (43)	18 (24)	0.130
SLE duration at 1st renal biopsy, yrs, median, (IQR)	0.6 (0.2,2.1)	0.4 (0.1,2.6)	0.8 (0.2,2.5)	0.172
duration of SLE, yrs, median, (IQR)	3.2 (2.1,4.5)	3.1 (1.3,7.2)	4.8 (2.8,7.0)	0.070
duration of LN, yrs, median, (IQR)	2.1 (0.4,2.4)	1.7 (0.4,3.5)	2.9 (1.8, 5.4)	0.006
duration of LN 0.5 yrs, n (%)	16 (70)	25 (71)	69 (93)	0.003
eGFR at LV <90ml/min/1.73m ² , n (%)	1 (4)	12 (38)	3 (4)	<0.001
eGFR at LV <90ml/min/1.73m ² , >6 m LN duration	1 (6)	6 (24)	3 (4)	0.014
use of dialysis, within 6 m of LV	0 (0)	2 (6)	2 (3)	0.632
use of dialysis, within 6 m of LV, 0.5 yrs LN duration	0 (0.0)	0 (0.0)	2 (3)	1.000
proteinuria (Up/c > 0.5) at LV, n (%)	12 (52)	18 (51)	24 (33)	0.093
proteinuria at any time during study	15 (65)	20 (57)	41 (55)	0.706
hematuria (> 5 RBC/hpf) at LV, n (%)	7 (30)	10 (29)	8 (11)	0.026
hematuria at any time during study	12 (52)	13 (37)	16 (22)	0.014
SLEDAI at last visit, median, (IQR)	4 (2,8)	4 (0,8)	2 (2,8)	0.368
highest SLEDAI at any time	6 (4,11)	5 (2,12)	6 (2,10)	0.518
hypocomplementemia at LV, n (%)	9 (39)	21 (62)	30 (41)	0.094
hypocomplementemia, any time during study	11 (48)	21 (62)	37 (50)	0.459
positive anti-dsDNA antibody, any time during study	18 (78)	23 (66)	46 (65)	0.472
Physician's global assessment score, highest at any time median, (IQR)	4 (2,6)	3 (1,4)	2 (1,4)	0.128
Physician's global assessment score, at LV	2 (1,4)	1 (0,4)	2 (0,3)	0.380
Subject's global assessment score, highest at any time median, (IQR)	4 (3,6)	2 (1,5)	3.5 (2,7)	0.347
Subject's global assessment score, at LV	3 (0,5)	2 (0,4)	2 (1,4)	0.086

IQR = interquartile range; SLE = systemic lupus erythematosus; yrs = years; LN = lupus nephritis; eGFR = estimated glomerular filtration rate; LV = last CARRA Registry visit; RBC/hpf = red blood cells/high-power field; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

Table 2:

Medication exposures (past or current)

Medication (n, %)	class III+V (n=23)	class IV+V (n=35)	class V (n=74)	P
Hydroxychloroquine	22 (95.7)	30 (85.7)	73 (98.7)	0.013
Azathioprine	4 (17.4)	5 (14.3)	10 (13.5)	0.898
Mycophenolate	19 (82.6)	26 (74.3)	68 (91.9)	0.045
Cyclophosphamide	9 (39.1)	22 (62.9)	24 (32.4)	0.010
Rituximab	4 (17.4)	8 (22.9)	23 (17.4)	0.590
Tacrolimus	3 (13.0)	4 (11.4)	4 (5.4)	0.380
Cyclosporine	2 (8.7)	0 (0)	8 (10.8)	0.134
IV pulse corticosteroid	14 (60.9)	25 (71.4)	42 (56.8)	0.340
Daily corticosteroids	22 (95.7)	32 (91.4)	71 (96.0)	0.670
any DMARD or biologic use *	19 (82.6)	32 (91.4)	70 (94.6)	0.189

* Any DMARD or biologic use includes azathioprine, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate, and rituximab. (Excludes hydroxychloroquine and methotrexate). DMARD = disease-modifying antirheumatic drug.

Table 3:

Clinical features of patients with pure class V LN and with renal insufficiency

	patient #1	patient #2	patient #3
gender	female	male	female
race	Black	Black	Asian
age at SLE onset (yrs)	15.07	12.32	15.56
SLE duration (yrs)	6.29	2.58	2.55
LN duration (yrs)	5.71	2.58	2.55
length of follow-up in registry (yrs)	2.43	0.63	2.17
eGFR at subsequent visits (ml/min/1.73m ²)	114, 90, 67, 69	33, 16	47, 41, 33, 8
repeat biopsy	N	N	N
DMARD or biologic exposure *	AZA, CTX, MMF, RTX	MMF	MMF
hematuria at LV †	N	–	Y
proteinuria at LV †	N	–	N
low complement at LV	N	N	N
dialysis	N	Y	Y

* Any DMARD or biologic use includes azathioprine, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate, and rituximab. (Excludes plaquenil, methotrexate).

† data not reported for patient #2

SLE = systemic lupus erythematosus; LN = lupus nephritis; yrs = years; eGFR = estimated glomerular filtration rate; DMARD = disease-modifying antirheumatic drug; AZA = azathioprine; CTX = cyclophosphamide; MMF = mycophenolate; RTX = rituximab; LV = last CARRA Registry visit.