INTRAVENOUS CYCLOPHOSPHAMIDE VERSUS MYCOPHENOLATE MOFETIL FOR INDUCTION THERAPY IN INCIDENT LUPUS NEPHRITIS: DATA FROM A MULTI-ETHNIC, MULTINATIONAL LATIN AMERICAN COHORT GLADEL 2.0

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Background

Lupus nephritis (LN) is one of the most severe complications of patients with systemic lupus erythematosus.
As induction treatment, cyclophosphamide (CYC) or mycophenolate mofetil (MMF) are used; however, comparative outcome data in Latin American populations remain limited.

Methods

Patients from the Grupo Latinoamericano de Estudio de Lupus (GLADEL) cohort 2.0 with incident LN were evaluated. LN diagnosis was based on kidney biopsy and/or 24-hour proteinuria (24-HP) or urine protein-creatinine ratio (UPCR) >0.5 g. All patients included had to have data on 24-HP/UPCR, serum creatinine level and estimated glomerular filtration rate (eGFR) at baseline, 6th month, and 12th month. Complete renal response (CRR) was defined as 24-HP or UPCR 0.7 g combined with eGFR ≥60ml/min/1.73m^2 or absence of a confirmed eGFR decrease greater than 20% from baseline, whereas partial renal response (PRR) was defined as ≥50% reduction of 24-HP or UPCR. Both CRR and PRR were evaluated at 6th month, and 12th month from baseline. Sociodemographic features (sex, age, ethnicity, socioeconomic status, and educational level), tobacco use, cumulative dose of glucocorticoid, antimalarial use, antiproteinuric drug use, disease activity, biopsy class, and type of induction treatment (CYC or MMF) were recorded. Univariable (UV) and multivariable (MV) logistic regression models were used to evaluate the association between induction therapy (MMF or CYC) and CRR, adjusting for relevant baseline confounders.

Results

A total of 76 patients were included. Female sex and Mestizo ethnicity were more frequent (66 [86.8%] and 55 [72.4%], respectively). At 6th month, 44 (57.9%) and 8 (10.5%) patients achieved CRR and PRR, respectively, whereas at 12th month (n=69), 49 (71.0%) and 5 (7.2%) achieved CRR and PRR, respectively (Table 1). Although not statistically significant, a numerically higher proportion of CYC users achieved CRR compared with MMF users at both time points (6th month: 25 [56.8%] vs 19 [43.2%], p=0.660; 12th month: 30 [61.2%] vs 19 [38.8%], p=0.613, Table 1). In both UV and MV analyses, no baseline variables were significantly associated with CRR at 6th month, and 12th month (Table 2). At 12th month, there was only one death in CYC group and there was no difference in infections and serious infections rates between CYC and MMF users (Table 3).

TABLE 1.
Sociodemographic features of incident LN patients at baseline and according to renal response on the 6th and 12th month

VARIABLES*	ALL PATIENTS (n=76)	CRR (n=44)	PRR (n=8)	NO RESPONSE (n=24)	p^
			BASELINE		
Sex					0.471
Female	66 (86.8)	38 (86.4)	6 (75.0)	22 (91.7)	
Male	10 (13.2)	6 (13.6)	2 (25.0)	2 (8.3)	
Age at diagnosis (years)^	26.0 (20.8–32.2)	27.0 (22.0–35.2)	30.5 (26.5–35.0)	21.5 (19.0–27.5)	**0.031**
Ethnicity					**0.014**
White	18 (23.7)	12 (27.3)	0	0	
Mestizo	55 (72.4)	32 (72.7)	4 (50.0)	19 (79.2)	
ALA	3 (3.9)	0	0	3 (12.5)	
Socio-economic status					0.336
High/Middle-high	13 (17.1)	7 (15.9)	2 (25.0)	4 (16.7)	
Middle	26 (34.2)	18 (40.9)	3 (37.5)	5 (20.8)	0.429
Middle-low/Low	35 (46.1)	17 (38.6)	3 (37.5)	15 (62.5)	
Educational level (years)^	13.0 (11.0–15.0)	13.0 (11.0–16.0)	14.5 (13.2–15.5)	12.0 (11.5–14.5)	**0.001**
Tabacco use					0.239
Never	64 (84.2)	38 (86.4)	4 (50.0)	22 (91.7)	
Past	3 (3.9)	1 (2.3)	0	2 (8.3)	
Current	3 (3.9)	2 (4.5)	1 (12.5)	0	
LN Class					0.164
I	1 (1.3)	0	1 (12.5)	0	
II	3 (3.9)	2 (4.5)	0	1 (4.2)	
III	10 (13.2)	9 (20.5)	0	1 (4.2)	
IV	39 (51.3)	22 (50.0)	3 (37.5)	14 (58.3)	
V	7 (9.2)	4 (9.1)	1 (12.5)	2 (8.3)	
III + V	9 (11.8)	3 (6.8)	3 (37.5)	3 (12.5)	
IV + V	2 (2.6)	1 (2.3)	0	1 (4.2)	
Proteinuria (g)^	2.4 (1.2–4.5)	2.2 (0.9–4.4)	6.4 (4.1–7.9)	1.9 (1.5–3.2)	**0.008**
Nephrotic proteinuria	28 (36.8)	16 (36.4)	6 (75.0)	6 (25.0)	**0.047**
Creatinine level (mg/dl)^	0.8 (0.7–1.1)	0.8 (0.7–1.1)	0.7 (0.5–0.8)	0.8 (0.7–1.1)	0.235
Severe disease^	14 (18.4)	4 (9.1)	1 (12.5)	9 (37.5)	**0.022**
			6TH MONTH		
Proteinuria (g)^	0.6 (0.3–2.1)	0.3 (0.2–0.5)	1.2 (0.9–2.2)	2.6 (1.2–3.2)	**0.001**
Creatinine level (mg/dl)^	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.7 (0.6–0.7)	0.8 (0.6–1.1)	0.189
Cumulative dose of GC (mg/d)^	2710.0 (1800.0–4537.5)	3007.5 (1800.0–4537.5)	2325.0 (1700.0–3076.2)	2710.0 (1980.0–5062.5)	0.723
Antimalarial use	24 (31.6)	17 (38.6)	3 (37.5)	4 (16.7)	0.178
Antiproteinuric drug use	52 (68.4)	30 (68.2)	5 (62.5)	17 (70.8)	0.515
Induction treatment					0.660
Cyclophosphamide	45 (59.2)	25 (56.8)	4 (50.0)	16 (66.7)	
Mycophenolate mofetil	31 (40.8)	19 (43.2)	4 (50.0)	8 (33.3)	
VARIABLES*	**ALL PATIENTS (n=69)**	**CRR (n=49)**	**PRR (n=5)**	**NO RESPONSE (n=15)**	**p^**
			12TH MONTH		
Proteinuria (g)^	0.5 (0.3–1.2)	0.4 (0.2–0.7)	3.0 (2.5–5.6)	1.7 (0.7–3.5)	**0.001**
Creatinine level (mg/dl)^	0.8 (0.6–0.9)	0.8 (0.5–0.9)	0.8 (0.7–0.8)	0.7 (0.6–1.0)	0.969
Cumulative dose of GC (mg/d)^	2700.0 (1365.0–4150.0)	3075.0 (1620.0–4500.0)	3035.0 (2400.0–3795.0)	2325.0 (400.0–2669.0)	0.147
Antimalarial use	24 (34.8)	16 (32.7)	2 (40.0)	6 (40.0)	0.840
Antiproteinuric drug use	41 (87.2)	29 (87.9)	4 (100.0)	8 (80.0)	0.779
Induction treatment					0.613
Cyclophosphamide	40 (58.0)	30 (61.2)	2 (40.0)	8 (53.3)	
Mycophenolate mofetil	29 (42.0)	19 (38.8)	3 (60.0)	7 (46.7)	

***ALA**: African Latin American, **CI**: Confidence interval, **CRR**: Complete renal response, **GC**: Glucocorticoids, **LN**: Lupus nephritis, **PRR**: Partial renal response.*
**All data are shown in numbers and percentages, except where otherwise indicated.*
^Chi-Square test, Fisher's exact test, and Wilcoxon test, as appropriate.
**Values are median and interquartile range (IQR).*
**Severe disease was defined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) >12.*

TABLE 2.
Univariable and multivariable analyses of achieving CRR on the 6th and 12th months

VARIABLE	UNIVARIABLE ANALYSIS OR (95% CI)	p	MULTIVARIABLE ANALYSIS OR (95% CI)	p
		6TH MONTH		
Sex				
Female	Ref		Ref	
Male	1.01 (0.26, 3.96)	0.985	0.70 (0.16, 3.13)	0.641
Age at diagnosis	1.03 (0.98, 1.08)	0.302	1.03 (0.97, 1.08)	0.337
Ethnicity				
White	Ref		Ref	
Mestizo	0.70 (0.23, 2.13)	0.524	1.06 (0.29, 3.88)	0.925
Educational level	1.06 (0.93, 1.20)	0.370	1.05 (0.91, 1.21)	0.508
Proteinuria	0.89 (0.74, 1.07)	0.215	0.91 (0.74, 1.11)	0.354
Antimalarial use	1.98 (0.70, 5.63)	0.200	1.89 (0.57, 6.23)	0.294
Severe disease*	0.34 (0.09, 1.29)	0.114	0.44 (0.09, 2.03)	0.290
Induction treatment				
Cyclophosphamide	Ref		Ref	
Mycophenolate mofetil	1.69 (0.63, 4.53)	0.298	1.9 (0.67, 5.38)	0.226
		12TH MONTH		
Sex				
Female	Ref		Ref	
Male	0.38 (0.08, 1.92)	0.243	0.38 (0.06, 2.31)	0.294
Age at diagnosis	1.01 (0.96, 1.06)	0.716	1.00 (0.94, 1.05)	0.946
Ethnicity				
White	Ref		Ref	
Mestizo	0.24 (0.05, 1.19)	0.08	0.31 (0.05, 1.73)	0.18
African Latin American	0.13 (0.01, 1.45)	0.096	0.22 (0.02, 3.18)	0.266
Educational level	0.98 (0.86, 1.13)	0.799	0.98 (0.84, 1.15)	0.832
Proteinuria	0.81 (0.66, 0.99)	0.038	0.83 (0.66, 1.05)	0.117
Antimalarial use	0.73 (0.25, 2.13)	0.562	0.72 (0.19, 2.83)	0.643
Severe disease*	0.35 (0.08, 1.64)	0.183	0.20 (0.03, 1.65)	0.136
Induction treatment				
Cyclophosphamide	Ref		Ref	
Mycophenolate mofetil	0.63 (0.22, 1.81)	0.393	0.77 (0.21, 2.79)	0.692

CI: Confidence interval, OR: Odds ratio.
**Severe disease was defined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) >12.*

TABLE 3.
Adverse events and mortality at 12th month

VARIABLE*	TOTAL (N=69)	CYCLOPHOSPHAMIDE (N=40)	MYCOPHENOLATE (N=29)	p^
Death	1 (1.4)	1 (2.5)	0	1.000
Infections	20 (29.0)	11 (27.5)	9 (31.0)	0.793
Serious infections	1 (1.4)	1 (2.5)	0	1.000
Leukopenia	6 (8.7)	3 (7.5)	3 (10.3)	0.678

**All data are shown in numbers and percentages.*
^Chi-Square test, Fisher's exact test, and Wilcoxon test as appropriate.

Conclusion

Contrary to reports from other populations indicating superior efficacy of MMF, this study found no evidence of MMF superiority over CYC as induction therapy in achieving CRR among patients with incident LN in this multi-ethnic Latin American cohort. Although a numerically higher response was observed with CYC, these findings should be interpreted cautiously given the sample size.

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Disclosures

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