

# 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 Latino Americano 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) >0.5g. All patients included had to have data on 24-HP/UPCR, serum creatinine level and estimated glomerular filtration rate (eGFR) at baseline, 6<sup>th</sup> and 12<sup>th</sup> month. Complete renal response (CRR) was defined as 24-HP or UPCR ≤0.7g combined with eGFR ≥60ml/min/1.73m<sup>2</sup> 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 6<sup>th</sup> and 12<sup>th</sup> month from baseline. Sociodemographic features (sex, age, ethnicity, socioeconomic status, educational level), tobacco use, cumulative dose of glucocorticoid (GC), antimalarial use, antiproteinuric drugs use, disease activity, 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

Seventy-six patients were included. Female sex and Mestizo ethnicity were more frequent [66 (86.8%) and 55 (72.4%), respectively]. At 6<sup>th</sup> month, 44 (57.9%) and 8 (10.5%) patients achieved CRR and PRR, respectively, whereas at 12<sup>th</sup> month, 39 (56.5%) and 5 (7.3%) achieved CRR and PRR, respectively (Table 1). In both UV and MV analyses, no baseline variables were significantly associated with CRR at 6<sup>th</sup> and 12<sup>th</sup> month (Table 2). Although not statistically significant, a numerically higher proportion of CYC users achieved CRR compared with MMF users in both time points [6<sup>th</sup> month: 25 (56.8%) vs 19 (43.2%),  $p=0.660$ ; 12<sup>th</sup> month: 30 (61.2%) vs 19 (38.8%),  $p=0.613$ ] (Table 1). At 12<sup>th</sup> 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 (data not shown).

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

VARIABLES <sup>a</sup>	ALL PATIENTS (N=76)	CRR (N=44)	PRR (N=8)	NO RESPONSE (N=24)	p <sup>b</sup>
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) <sup>c</sup>	26.0 (20.8-32.2)	27.0 (22.0-35.2)	30.5 (26.5-35.0)	21.5 (19.0-27.5)	<b>0.031</b>
Ethnicity					<b>0.014</b>
White	18 (23.7)	12 (27.3)	0	0	
Mestizo	55 (72.4)	32 (72.7)	4 (50)	19 (79.2)	
ALA	3 (3.9)	0	0	3 (12.5)	
Socio-economic status					0.336
High/Middle-high	13 (17.6)	7 (16.7)	2 (25.0)	4 (16.7)	
Middle	26 (35.1)	18 (42.9)	3 (37.5)	5 (20.8)	0.429
Middle-low/Low	35 (47.3)	17 (40.5)	3 (37.5)	15 (62.5)	
Educational level (years) <sup>c</sup>	13.0 (11.0-15.0)	13.0 (11.0-16.0)	14.5 (13.2-15.5)	12.0 (11.5-14.5)	<b>0.001</b>
Tobacco use					0.229
Never	64 (91.4)	38 (92.7)	4 (80.0)	22 (91.7)	
Past	3 (4.3)	1 (2.4)	0	2 (8.3)	
Current	3 (4.3)	2 (4.9)	1 (20.0)	0	
LN Class					0.427
I	1 (1.4)	0	1 (12.5)	0	
Proliferative + membranous	42 (58.3)	23 (56.1)	3 (37.5)	16 (69.6)	
V	7 (9.7)	4 (9.8)	1 (12.5)	2 (8.7)	
II	3 (4.2)	2 (4.9)	0	1 (4.3)	
III	19 (26.4)	12 (29.3)	3 (37.5)	4 (17.4)	
Proteinuria (g) <sup>c</sup>	2.4 (1.2-4.5)	2.2 (0.9-4.4)	6.4 (4.1-7.9)	1.9 (1.5-3.2)	<b>0.008</b>
Nephrotic proteinuria	28 (36.8)	16 (36.4)	6 (75.0)	6 (25.0)	
Creatinine level (mg/dl) <sup>c</sup>	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 <sup>d</sup>	14 (19.2)	4 (9.8)	1 (12.5)	9 (37.5)	<b>0.022</b>
			<b>6<sup>TH</sup> MONTH</b>		
Proteinuria (g) <sup>c</sup>	0.6 (0.3-2.1)	0.3 (0.2-0.5)	1.2 (0.9-2.2)	2.6 (1.2-3.2)	<b>0.001</b>
Creatinine level (mg/dl) <sup>c</sup>	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) <sup>e</sup>	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 (86.7)	30 (83.3)	5 (83.3)	17 (94.4)	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)	
			<b>12<sup>TH</sup> MONTH</b>		
Proteinuria (g) <sup>c</sup>	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) <sup>c</sup>	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) <sup>e</sup>	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)	0.779
Antiproteinuric drug use	41 (87.2)	29 (87.9)	4 (100.0)	8 (80.0)	0.613
Induction treatment					
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)	

HDL-c=high-density lipoproteins  
 CRR: Complete renal response. PRR: Partial renal response. ALA: African Latin American. LN: Lupus nephritis. GC: glucocorticoids.  
<sup>a</sup> All data are shown in numbers and percentages, except where otherwise indicated.  
<sup>b</sup> Chi-Square test, Fisher's exact test and Wilcoxon test as appropriate.  
<sup>c</sup> Values are median and Interquartile range (IQR).  
<sup>d</sup> 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 6<sup>th</sup> and 12<sup>th</sup> months.

VARIABLE	UNIVARIABLE ANALYSIS OR (95% CI)	p	MULTIVARIABLE ANALYSIS OR (95% CI)	p
			<b>6<sup>TH</sup> MONTH</b>	
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 <sup>a</sup>	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
			<b>12<sup>TH</sup> MONTH</b>	
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 <sup>a</sup>	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

OR: Odds ratio.  
<sup>a</sup> Severe disease was defined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) > 12.

## CONCLUSIONS

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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