Comparison of Lupus Nephritis Induction Treatments in a Hispanic Population: A Single-center Cohort Analysis

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ABSTRACT. ***Objective.*** To evaluate response rates in an adult lupus nephritis (LN) cohort in Mexico City, Mexico.

Methods. We analyzed 165 patients with biopsy-proven LN histological International Society of Nephrology/Renal Pathology Society classes III, IV, or V, distributed by treatment drug in 3 groups: mycophenolate mofetil (MMF; dosage > 2 g/day per 6 mos, n = 63), intravenous cyclophosphamide (IVC; 0.7 g/m^2 body surface area monthly per 6 pulses, n = 66), or azathioprine (AZA; dosage > 1.5 mg/kg/day per 6 mos, n = 36). Median followup was 31 ± 18 months. The primary endpoint was the proportion of patients achieving complete renal response (CR). Secondary endpoints included the proportion of patients achieving renal response (complete or partial), renal flare–free survival, doubling of serum creatinine, and progression to endstage renal disease (ESRD).

Results. MMF induction was superior to IVC (HR 2.00, 95% CI 1.23–3.25, p = 0.005) and AZA (HR 2.12, 95% CI 1.23–3.66, p = 0.007) in the primary endpoint. Censored CR rates at 6, 12, 24, and 36 months were 32.6%, 56.1%, 76.6%, and 94.1% for MMF; 24.2%, 34.4%, 57.9%, and 62.1% for IVC; and 8.4%, 39.8%, 49.7%, and 49.7% for AZA. MMF was also superior in renal response to treatment and renal flare–free survival outcomes. There were no differences between groups in doubling of serum creatinine or progression to ESRD. The induction treatment with MMF (HR 2.04, 95% CI 1.25–3.33, p = 0.005) and absence of vascular lesions on renal biopsy (HR 2.05, 95% CI 1.25–3.37, p = 0.004) were associated with CR, whereas proteinuria at the time of presentation was negatively associated with CR (HR 0.91, 95% CI 0.84–0.98, p = 0.013).

Conclusion. MMF induction therapy is superior to IVC and AZA in patients with LN of Mexican-mestizo race. (J Rheumatol First Release September 15 2015; doi:10.3899/jrheum.150395)

Key Indexing Terms:
LUPUS NEPHRITIS CYCLOPHOSPHAMIDE MYCOPHENOLATE MOFETIL
AZATHIOPRINE MEXICAN-MESTIZO HISPANIC

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Lupus nephritis (LN) is present in almost 50% of patients with systemic lupus erythematosus (SLE)[1]. It is one of the main mortality predictors[2], and its remission significantly improves patient and renal survival[3]. Even with present therapeutic regimens, almost 10% to 20% of patients will eventually develop endstage renal disease (ESRD)[4]. It has been clearly demonstrated that Hispanic populations have an early onset of renal disease[5] and worse survival[6]; the latter has been attributed to lower socioeconomic conditions[7].

Current induction to remission therapeutic regimens for LN include a combination of immunosuppressive agents: mycophenolate mofetil (MMF), intravenous cyclophosphamide (IVC), azathioprine (AZA), and steroids[8]. The Aspreva Lupus Management Study (ALMS) suggested that Hispanic populations might benefit from the induction of MMF as compared with IVC[9].

In our present study, we retrospectively compared efficacy of LN induction with remission treatment regimens containing IVC, MMF, or AZA in a single-center cohort of patients with LN.

MATERIALS AND METHODS

Design. Our present study is a retrospective cohort analysis from a single center in Mexico City (Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán). This is a third-level teaching hospital with one of the largest SLE cohorts in Mexico.

Patients. All files from adult patients with biopsy-proven LN performed between January 2008 and April 2013 were analyzed (n = 319). Included patients had to have less than a 3-month lag between the performance of the renal biopsy and the initiation of induction therapy. A diagnosis of class III, IV, V, or mixed types of LN according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) was required. All biopsies were examined by a single expert nephropathologist; activity and chronicity scores were determined as described by Austin, *et al*[10] and vascular lesions described according to the ISN/RPS classification. Reasons for exclusion were participation in a clinical trial, treatment change prior to 6 months, incomplete followup to 6 months, incomplete records, combination therapies, or loss to followup. Excluded patients are detailed in Figure 1.

Demographic, clinical, and laboratory data at the time of LN diagnosis, renal histopathology, treatment, and followup variables were collected. Socioeconomic status was defined according to our local social worker evaluation and classified into 3 groups: (1) low income that included those patients with government subsidy on hospital expenses over 80% (patient paid 20% or less), (2) intermediate income with subsidy between 20% and 80% (patient payment between 20% and 80%), and (3) health insurance for those affiliated with a social security institution that covered 100% of hospital expenses (patients did not pay for institutional attention).

Induction to remission treatment groups. We divided our population into 3 groups according to the type of induction therapy that was prescribed: (1) IVC: intravenous monthly pulses of cyclophosphamide (CYC) according to the modified National Institutes of Health protocol (at least 6 monthly pulses) and a minimum 0.5 mg/kg starting dose of oral daily prednisone (PRED); (2) MMF: MMF for at least 6 months with a dose equal or superior to 2 g/day and a minimum 0.5 mg/kg starting dose of oral daily PRED; and (3) AZA: AZA for at least 6 months with a dose equal or above 1.5 mg/kg/day and a minimum 0.5 mg/kg starting dose of oral daily PRED. At our center, AZA was considered an alternative induction to remission treatment for women of childbearing age with apparent nonsevere LN who refused to receive CYC and could not afford MMF.

Maintenance treatment. Of the 66 patients in the IVC group, 42 (63.7%) were maintained with AZA and low-dose steroids (less than 10 mg PRED per day), and 24 (36.3%) with MMF and low-dose steroids. In the MMF group, 58 (92.0%) were maintained with MMF and low-dose steroids, and 5 patients (7.9%) with AZA and low-dose steroids. All 36 patients from AZA group were maintained with AZA and low-dose steroids.

Outcome and response criteria. The primary outcome of our study was to test whether any of the regimens showed superiority in the proportion of patients achieving complete renal response (CR). The response criteria used were the same as those considered in the Lupus Nephritis Assessment with Rituximab trial[11]. CR was defined as normal renal function, 24-h urinary protein to creatinine ratio (uPCR) < 0.5 g/g, and inactive urinary sediment. Partial response (PR) was defined as serum creatinine within 115% from baseline, 50% reduction of 24-h uPCR to < 1 g/g if initially subnephrotic or < 3 g/g if initially nephrotic, and at least 50% reduction of urinary sediment erythrocytes. Secondary endpoints included the proportion of patients achieving renal response to treatment (RTT), defined as either PR or CR; doubling of serum creatinine, defined as a persistent duplication of the lowest serum creatinine levels on the followup; progression to ESRD, defined as renal replacement therapy requirement; and renal flare–free survival. Renal flare, based on previously published European Consensus definitions[12], was defined as a persistent increase in uPCR to values higher than 0.5–1.0 g/day after a CR, doubling of proteinuria with values higher than 1.0 g/day after PR (proteinuric flare), or as an increase or recurrence of active urinary sediment with an increase of > 25% in serum creatinine (severe nephritic flare).

Patients were censored if any of the following occurred: endpoint achievement, loss to followup, change of induction drug, ESRD development, or death.

Statistical analysis. Base characteristics were compared with ANOVA, Kruskal-Wallis test, or chi-square as appropriate. Numerical variables with normal distribution are expressed by means ± SD, and those with non-normal

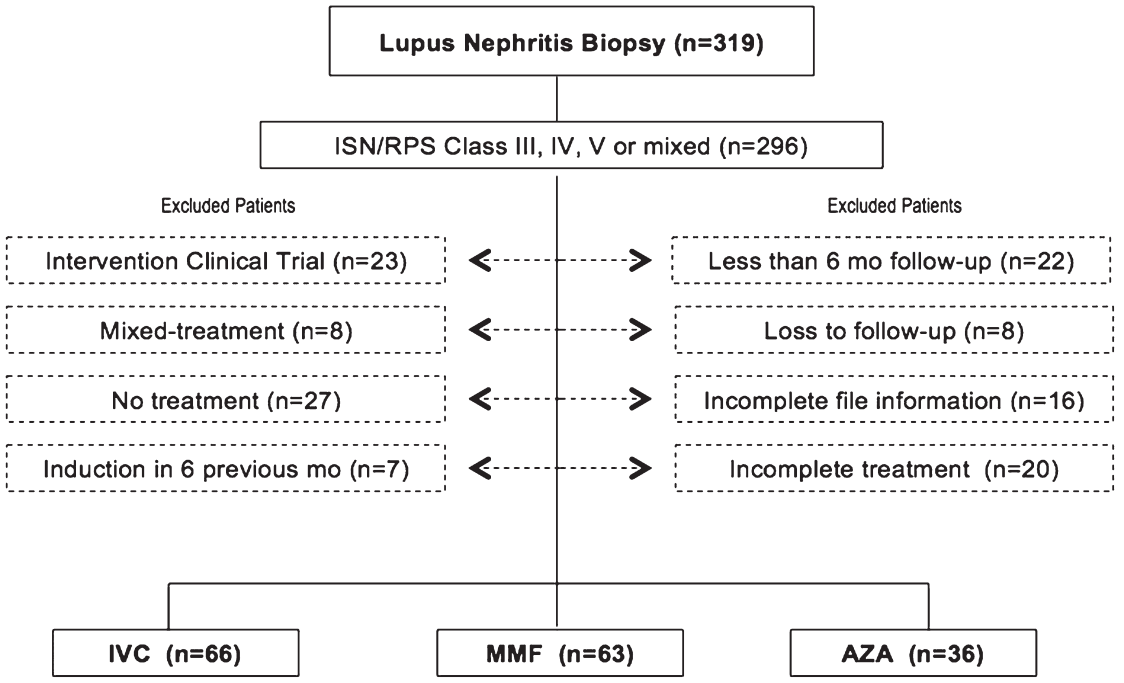


Figure 1. Patient selection. ISN/RPS: International Society of Nephrology/Renal Pathology Society; IVC: intravenous cyclophosphamide; MMF: mycophenolate mofetil; AZA: azathioprine.

distribution are expressed by median and interquartile ranges (IQR). For primary and secondary outcomes, treatment groups were compared with the use of Kaplan-Meier curve analysis. The magnitude of the differences in outcomes between induction groups was estimated by means of the HR obtained with an unadjusted Cox model. A multivariate model to predict CR was constructed with variables that were significantly associated with this outcome on univariate analysis using a backward-selection approach. Statistical analysis was performed using SPSS 20.0 software (SPSS Systat Inc.), and a 2-tailed p value = 0.05 was used as the threshold for significance.

RESULTS

Demographics and immunosuppressive therapies. Out of the 319 adult patients with renal biopsy–proven LN diagnosed between January 2008 and 2013, 165 were included for the analysis (Figure 1). There were no differences in age, sex, or previous medical history between groups, and the entire population race was Mexican-mestizo (Table 1). Patients in the AZA group presented more frequently as asymptomatic urinary abnormalities with less proteinuria, and fewer of them had a renal biopsy with ISN/RPS class IV + V LN. The IVC group had a higher proportion of patients classified as low-income economic status. Patients treated with IVC received a CYC cumulative dose of 4.25 ± 1.5 g/m^2 of body surface area through a median 6 monthly pulses (IQR 6–9), the MMF group received ≥ 2 g/day for a median 13 months (IQR 8–23), and the AZA group received a mean 1.99 ± 0.4 mg/kg dose during the 6-month induction phase. The AZA group had a slower PRED taper, with a median 6-month (IQR 3–8) taper to < 20 mg/day versus 4 months (IQR 3–6) and 5 months (IQR 3–6) in the IVC and MMF groups, respectively (Table 1). Mean followup for the whole cohort from the start of induction therapy was 31.8 ± 18.2 months.

Efficacy analysis. MMF was significantly superior to IVC (HR for CR 2.00, 95% CI 1.23–3.25, p = 0.021) and to AZA (HR 2.12, 95% CI 1.23–3.66, p = 0.007) in the primary outcome, proportion of patients achieving CR (Figure 2A). There was no statistically significant difference between the IVC and AZA groups for this outcome (HR 1.13, 95% CI 0.61–2.09, p = 0.69). Overall, 41 patients in the MMF group achieved CR (65.1%) compared with 32 patients in the IVC group (48.5%) and 15 in the AZA group (41.7%) during the observation period. Censored CR at 6, 12, 24, and 36 months was 32.6%, 56.1%, 76.6%, and 94.1% for MMF; 24.2%, 34.4%, 57.9%, and 62.1% for IVC; and 8.4%, 39.8%, 49.7%, and 49.7% for AZA. As shown in Figure 2A, median time to CR was 10 months for MMF and 19 months for IVC. Less than 50% of patients in the AZA group achieved CR on the observation period.

Both the MMF (HR 2.35, 95% CI 1.41–3.92, p = 0.001) and IVC groups (HR 1.79, 95% CI 1.09–2.94, p = 0.021) were superior to AZA in proportion of patients with RTT. There was no significant difference between the MMF and IVC groups (HR 1.33, 95% CI 0.86–2.04, p = 0.20) for this outcome (Figure 2B). Overall, RTT was achieved in 53 (84.1%), 53 (80.3%), and 20 patients (55.5%) in the MMF, IVC, and AZA groups, respectively. Censored RTT at 6, 12, 24, and 36 months was 67.3%, 80.0%, 87.5%, and 100% for MMF; 57.6%, 74.3%, 85.3%, and 85.3% for IVC; 30.9%, 56.0%, 56.0%, and 67.0% for AZA. As shown in Figure 2B, median time to RTT was 4 months for MMF, 5 months for IVC, and 9 months for AZA. The rate of change of uPCR during the first 6 months was –0.427 ± 0.52 g/g per month for MMF, –0.514 ± 0.58 g/g per month for IVC, and –0.151 ± 0.42 g/g for AZA (MMF vs IVC, p = 1.00; MMF vs AZA, p = 0.050; IVC vs AZA, p = 0.005).

To explore the lack of difference in CR rates between the IVC and AZA groups, we divided patients by histopathological ISN/RPS class. Of those with pure membranous (class V) LN (n = 15), 5 out of 6 patients (83.3%) in the AZA group achieved CR compared with 1 out of 4 in the MMF group (25%) and 3 out of 5 (60%) in the IVC group (log-rank p = 0.18). When we reanalyzed Kaplan-Meier survival curves excluding pure membranous LN (Figure 2C and 2D), MMF was superior to IVC (HR 2.01, 95% CI 1.23–3.30, p = 0.006) and AZA (HR 2.65, 95% CI 1.48–4.75, p = 0.001) in the proportion of patients achieving CR and was also superior to AZA (HR 2.68, 95% CI 1.55–4.62, p < 0.001) in the proportion of patients with RTT. There was a nonsignificant trend to a superior RTT in the MMF group compared with the IVC group (HR 1.45, 95% CI 0.93–2.25, p = 0.10). The IVC group was superior to AZA in the proportion of patients with RTT (HR 1.90, 95% CI 1.11–3.26, p = 0.020), but still not different from AZA in CR outcome (HR 1.46, 95% CI 0.75–2.86, p = 0.27).

We performed unadjusted and multivariate Cox regression analysis for CR endpoint (Table 2). Significant predictors of CR on unadjusted analysis were serum creatinine and proteinuria at presentation, chronicity variables on renal biopsy, absence of vascular lesions, and induction treatment with MMF. Upon multivariate analysis, MMF was superior to IVC (HR 2.04, 95% CI 1.25–3.33, p = 0.005) and AZA (HR 3.19, 95% CI 1.72–5.93, p < 0.001) in CR outcome. In this model, the absence of vascular lesions in the renal biopsy was a potent predictor of CR (HR 2.05, 95% CI 1.25–3.37, p = 0.004), whereas higher proteinuria at presentation was associated with an inferior CR rate (HR 0.91, 95% CI 0.84–0.98, p = 0.013).

Renal flare and renal survival. Patients in the MMF group were less likely to experience renal flares than the IVC (HR for renal flare 0.47, 95% CI 0.25–0.90, p = 0.024) and AZA groups (HR 0.36, 95% CI 0.13–1.00, p = 0.050). As shown in Figure 3, renal relapse rates at 12, 24, and 36 months (calculated from the date of RTT) were 7.3%, 28.3%, and 38.7% for MMF; 18.7%, 45.4%, and 63.1% for IVC; and 17.4%, 40.6%, and 64.3% for AZA.

There was no difference on the doubling of serum creatinine (p = 0.84; Figure 4B) or progression to ESRD (p = 0.62, Figure 4D) between treatment groups. Those patients who achieved CR or PR were less likely to double

Table 1. Demographics and baseline disease characteristics. Values are mean ± SD or median (IQR) unless otherwise specified.

Characteristics	MMF	IVC	AZA	p
Demographic				
Age, yrs	30.2 ± 10.5	30.9 ± 9.5	31.2 ± 10.0	0.890
Female, n (%)	54 (85.7)	58 (87.9)	33 (91.7)	0.683
BMI, kg/m^2	24.9 ± 5.4	24.3 ± 4.1	25.1± 4.4	0.639
Socioeconomic status, n (%)				
Low income	25 (39.7)	41 (62.1)	16 (44.4)	0.030
Intermediate income	34 (54.0)	24 (36.4)	19 (52.8)	0.095
Health insurance	4 (6.3)	1 (1.5)	1 (2.8)	0.325
History				
Time SLE diagnosis to symptoms, mos	23 (0–73)	26 (0–59)	27.5 (1.3–68)	0.629
Time symptoms to biopsy, mos	4 (2–13)	5.5 (1.8–16.3)	6 (2–12.8)	0.528
Previous renal activity, n (%)	12 (19)	13 (19.7)	10 (27.8)	0.550
Clinical presentation				
Glomerular syndrome, n (%)				
RPGN	1 (1.6)	6 (9.3)	2 (5.6)	0.172
Nephrotic	33 (52.4)	28 (42.4)	10 (27.8)	0.059
Nephritic	9 (14.3)	17 (25.8)	3 (8.3)	0.060
AUA	20 (31.7)	14 (21.8)	19 (52.8)	0.005
CKD	0 (0)	1 (1.5)	2 (5.6)	0.134
MAP, mmHg	96 ± 14	98 ± 15	94 ± 16	0.519
Creatinine, mg/dl	1.1 ± 0.6	1.4 ± 1.0	1.2 ± 0.9	0.234
eGRF, ml/min/1.73 m^2, n (%)	87.0 ± 35	72.0 ± 40	84.8 ± 41	0.071
≥ 90	30 (47.6)	25 (37.9)	18 (50.0)	—
≥ 60 to < 90	17 (26.9)	11 (17.2)	5 (13.9)	—
≥ 30 to < 60	13 (20.6)	19 (28.8)	8 (22.2)	—
< 30	3 (4.8)	11 (16.7)	5 (13.9)	—
Proteinuria, g/g	4.3 ± 3.2	5.3 ± 3.5	2.7 ± 2.0	0.004
Anti-dsDNA, IU/ml	318 ± 467	499 ± 800	191 ± 295	0.553
C3, × inferior limit	0.84 ± 0.4	0.84 ± 0.4	0.99 ± 0.5	0.250
C4, g/l	11.2 ± 7	11.4 ± 19	11.8 ± 6	0.980
Histopathology				
ISN/RPS LN class, n (%)				
Class III	3 (4.7)	6 (9.1)	3 (8.3)	0.615
Class IV	8 (12.7)	13 (19.7)	5 (13.9)	0.519
Class V	4 (6.3)	5 (7.6)	6 (16.7)	0.196
Class III + V	16 (25.4)	7 (10.6)	12 (33.3)	0.016
Class IV + V	32 (50.8)	35 (53.0)	10 (27.8)	0.036
Activity score	5.5 ± 3.3	7.9 ± 4.3	3.1 ± 2.2	0.234
Chronicity score	4.3 ± 2.3	4.1 ± 2.0	4.0 ± 2.3	0.715
Interstitial fibrosis, %	21 ± 18	19 ± 16	19 ± 19	0.825
Tubular atrophy, %	21 ± 19	19 ± 17	19 ± 19	0.902
No vascular lesions, n (%)	31 (49.2)	38 (57.6)	20 (55.6)	0.712
Arteriosclerosis, n (%)	31 (49.2)	27 (40.9)	15 (41.7)	0.681
TMA, n (%)	1 (1.6)	1 (1.5)	1 (2.8)	0.890
Treatment				
Cumulative dose, g/m^2 BSA	—	4.25 ± 1.5	—	—
MMF ≥ 2 g/day, mos	13 (8–23)	—	—	—
AZA, mg/kg/day	—	—	1.99 ± 0.4	—
Mos to PRED, < 20 mg	5 (3–6)	4 (3–6)	6 (3–8)	0.029

MMF: mycophenolate mofetil; IVC: intravenous cyclophosphamide; AZA: azathioprine; BMI: body mass index; SLE: systemic lupus erythematosus; RPGN: rapidly progressive glomerulonephritis; AUA: asymptomatic urinary abnormalities; CKD: chronic kidney disease; MAP: median arterial pressure; eGFR: estimated glomerular filtration rate (CKD-Epidemiology Collaboration equation); C3: complement factor 3; C4: complement factor 4; ISN/RPS LN: International Society of Nephrology/Renal Pathology Society lupus nephritis classification; TMA: thrombotic microangiopathy; BSA: body surface area; PRED: prednisone.

their serum creatinine than those without RTT (CR HR for serum creatinine doubling 0.02, 95% CI 0.01–0.05, p < 0.001 and PR HR 0.50, 95% CI 0.25–0.99, p = 0.047; Figure 4A). Interestingly, those patients who responded to treatment but

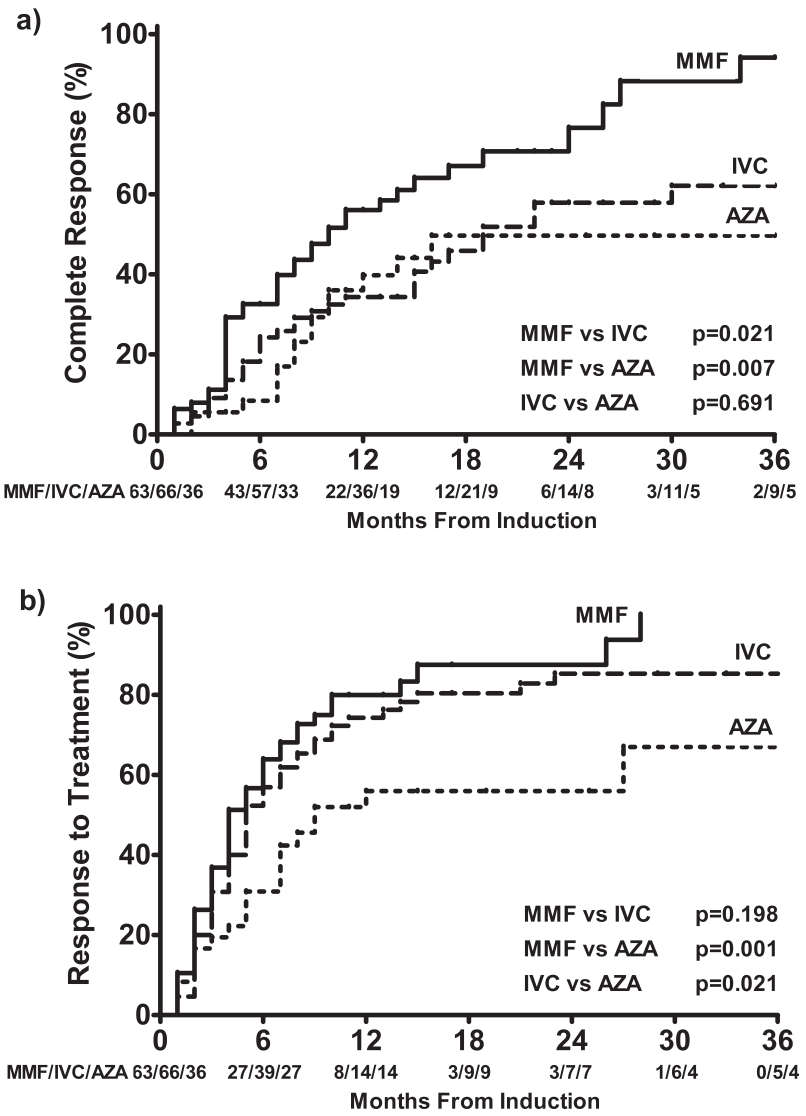


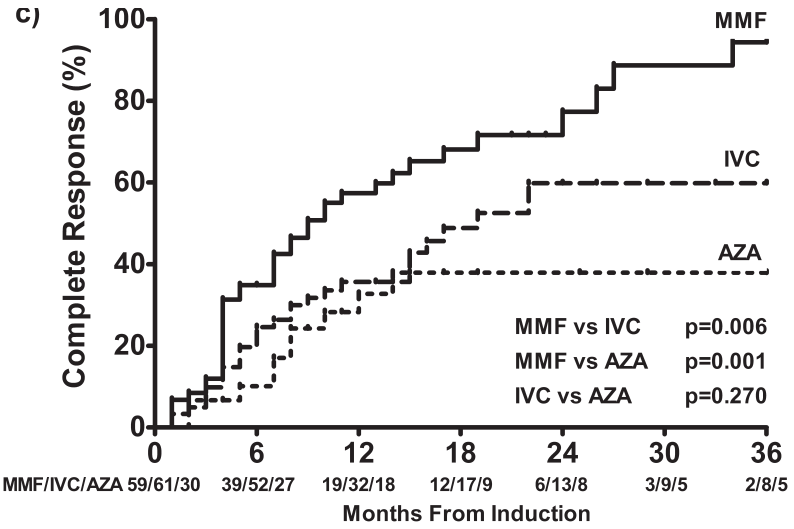
Figure 2. Probability of achieving CR (A and C) and RTT (B and D) by induction to remission treatment in all patients (A and B) and exclusively in proliferative ISN/RPS cases. CR: complete response; RTT: response to treatment; ISN/RPS: International Society of Nephrology/Renal Pathology Society; MMF: mycophenolate mofetil; IVC: intravenous cyclophosphamide; AZA: azathioprine.

did not achieve CR criteria (only PR) still progressed to ESRD without a significant difference with nonresponders (HR 0.50, 95% CI 0.24–1.21, p = 0.13; Figure 4C). On unadjusted analysis, the low-income economic status group had a higher risk of ESRD than the intermediate economic status group (HR 2.48, 95% CI 1.17–5.25, p = 0.018; Supplementary Figure 1 is available from the authors on request). On multivariate analysis, a higher chronicity score in renal biopsy (HR 1.27, 95% CI 1.07–1.49, p = 0.005) and low-economic status group (HR 2.64, 95% CI 1.19–5.85, p = 0.017) predicted ESRD development. We did not find any difference in other outcomes by patient economical status group.

DISCUSSION

Few clinical reports compare induction to remission regimens for LN in open clinical practice. Here we presented longterm clinical results of a 100% Mexican-mestizo cohort with variable grades of LN severity.

It has been shown from a subanalysis of the ALMS study[9] and a later metaanalysis[13] that race, ethnic, and socioeconomic differences condition responses to induction to remission regimens. The ALMS trial was a global study that included 28 Mexican-mestizo patients out of 54 categorized as "other race" (51.9%), and 131 (35.4%) self-reported their ethnicity as Hispanic. A posthoc analysis[9] suggested superiority of MMF over IVC induction on primary efficacy



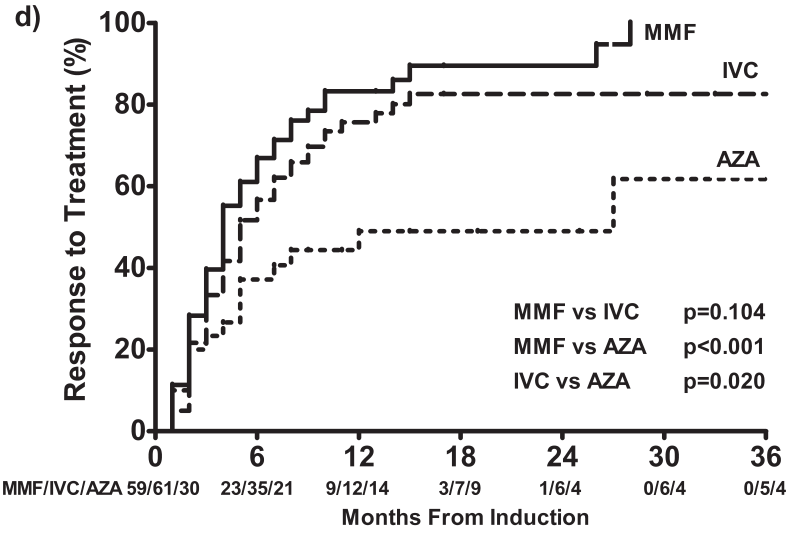


Figure 2. Continued.

endpoint at 24 weeks in a combined black and other race group (60.4% vs 38.5%, OR 2.4), in Hispanic ethnicity patients (60.9% vs 38.8%, OR 2.5), and in the Latin American region (60.7% vs 32.0%, p = 0.003, OR 3.4). These differences confirm a lower response rate to IVC in the "other race" group and in the Latin American region (only 32%).

We hereby demonstrate in our entire Mexican-mestizo population that MMF may be superior to IVC and AZA in inducing CR in patients with LN, and this difference persisted after adjusting for baseline characteristics.

At present, AZA induction is not considered a standard treatment. In a report by Austin, *et al*[14], a small group of 19 patients taking AZA was found to be numerically (but not statistically) inferior to IVC induction. We found AZA induction inferior to MMF and IVC in proliferative LN. Even then, it can still be considered a second-line treatment, particularly for women of childbearing age unable to tolerate or accept MMF or IVC.

It was previously reported in an ALMS subanalysis that "other race" patients halved their proteinuria faster in the MMF group[9]. Proteinuria reduction at 3 months and 6 months might predict a better renal outcome[15]. We did not find any differences in the rate of change in proteinuria at 6 months between the MMF and IVC induction groups. We found no differences in outcome for those who achieved CR earlier (data not shown), emphasizing that to date, the main goal of clinicians may still be to reach complete remission ahead of the promptness of the response.

Chronic histological variables as well as serum creatinine and proteinuria at presentation have been shown to be determinant factors to an inferior response to induction therapy[3]. One frequently underestimated variable is vascular affection,

Table 2. Univariate and multivariate Cox regression analysis for complete response.

Variables	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age, yrs	0.99 (0.98–1.02)	0.904	1.01 (0.99–1.04)	0.334
Male	0.79 (0.40–1.58)	0.506	0.67 (0.33–1.35)	0.264
Socioeconomic status				
Intermediate income	1.00, Reference	Reference		
Low income	0.98 (0.64–1.48)	0.907		
Serum creatinine at presentation, per mg/dl	0.62 (0.45–0.85)	0.002	0.83 (0.59–1.17)	0.287
Proteinuria at presentation, per g/g	0.92 (0.86–0.99)	0.017	0.91 (0.84–0.98)	0.013
Interstitial fibrosis, per % unit	0.98 (0.97–0.99)	0.010		
Tubular atrophy, per % unit	0.98 (0.97–0.99)	0.004		
Activity score, per unit	1.04 (0.99–1.09)	0.101		
Chronicity score, per unit	0.87 (0.79–0.96)	0.004	0.90 (0.81–1.01)	0.068
No vascular lesions	2.25 (1.44–3.52)	< 0.001	2.05 (1.25–3.37)	0.004
Induction regimen				
IVC	1.00, Reference	Reference	1.00, Reference	Reference
MMF	1.88 (1.18–3.00)	0.008	2.04 (1.25–3.33)	0.005
AZA	0.87 (0.47–1.61)	0.667	0.64 (0.34–1.21)	0.166

MMF: mycophenolate mofetil; IVC: intravenous cyclophosphamide; AZA: azathioprine.

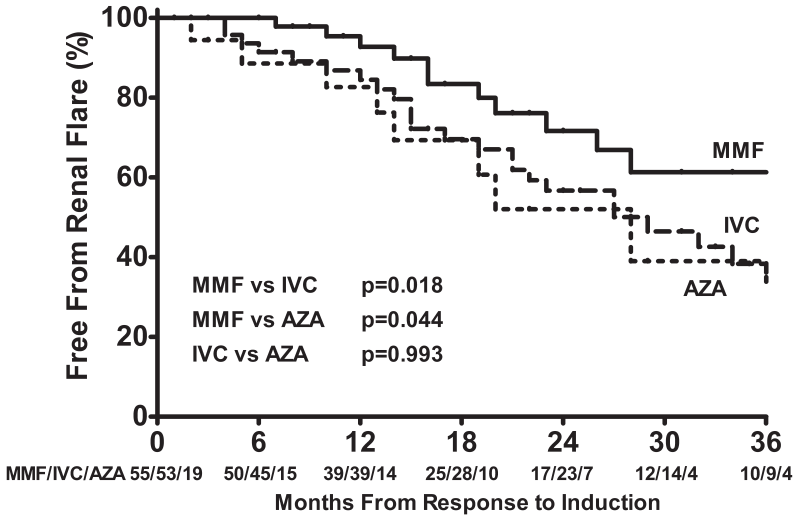


Figure 3. Renal flare survival curves by induction treatment. MMF: mycophenolate mofetil; IVC: intravenous cyclophosphamide; AZA: azathioprine.

in particular arteriolosclerosis, that may be an indicator of chronicity, and therefore of poor prognosis. Here we demonstrated that in addition to commonly used variables, the absence of vascular lesions in the renal biopsy might predict a good response to therapy (more than twice as probable to achieve CR in our report).

Patients with class V LN (pure membranous) behave differently from types III and IV proliferative ones[16]. In 2 small randomized clinical trials[17], MMF and IVC were found equivalent as induction therapy at a 24-week followup. Separately, Mok, *et al*[18] found a 67% complete remission rate with AZA and PRED treatment. We observed that this small subgroup of patients with class V LN had a different response than that observed in proliferative class III and IV LN, with an apparent better response to AZA/steroid treatment (83.3% CR rate), an intermediate response to IVC (66.7%), and worse response to MMF (25%), and yet this is a small subsample of type V LN to draw conclusions with. Nevertheless, it is important to consider that this subgroup should be analyzed separately in future trials.

The ultimate goal of treating LN is not only to achieve a response after induction therapy, but also the longterm preser-

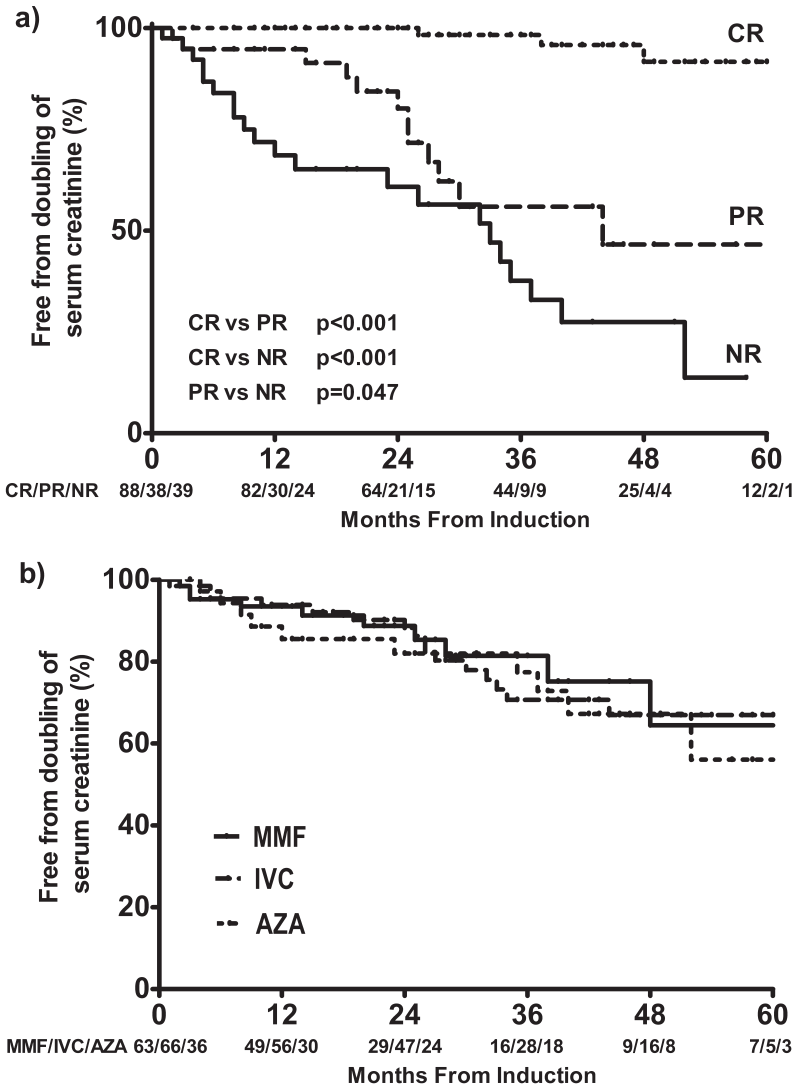


Figure 4. Doubling of serum creatinine (A and B) and progression to ESRD (C and D) survival curves by type of RTT (A and C) and by induction treatment groups (B and D). ESRD: endstage renal disease; RTT: response to treatment; CR: complete response; PR: partial response; NR: no response to induction; MMF: mycophenolate mofetil; IVC: intravenous cyclophosphamide; AZA: azathioprine.

vation of kidney function. Even with the high response rates observed in this cohort, 31.5% of patients presented a renal flare in this short observation period, and more importantly, these flares conditioned ESRD in 16.5% of patients (data not shown). Retrospective[19,20] and followup analysis of the ALMS[21] have shown greater failure to treatment (composite of flare, severe renal damage, or death), tendency to greater "residual" proteinuria, and higher ESRD and mortality in patients receiving IVC compared with MMF. We hypothesize that the lower flare rate observed in patients induced with MMF may be due to several factors: (1) a short IVC induction scheme was used that has been previously shown to be associated with more renal flares than a longer IVC scheme[22]; (2) CR has been shown to be a protective factor against renal flares[23,24,25] and a higher CR rate was observed in the MMF group; (3) MMF-maintained patients completed almost 17 months with MMF dose above 2 g/day; and (4) MMF-induced patients frequently continued the same drug as maintenance therapy while patients receiving IVC and AZA were commonly maintained with AZA; the different efficacy of these drugs for flare prevention has been suggested in previous reports[21].

In our study, we did not observe any differences between induction regimens for the doubling of serum creatinine or progression to ESRD, but it was clearly evident that those who achieved CR were less likely to develop these endpoints (Supplementary Figure 2 is available from the authors on request). In contrast, patients with PR (but no CR criteria) still

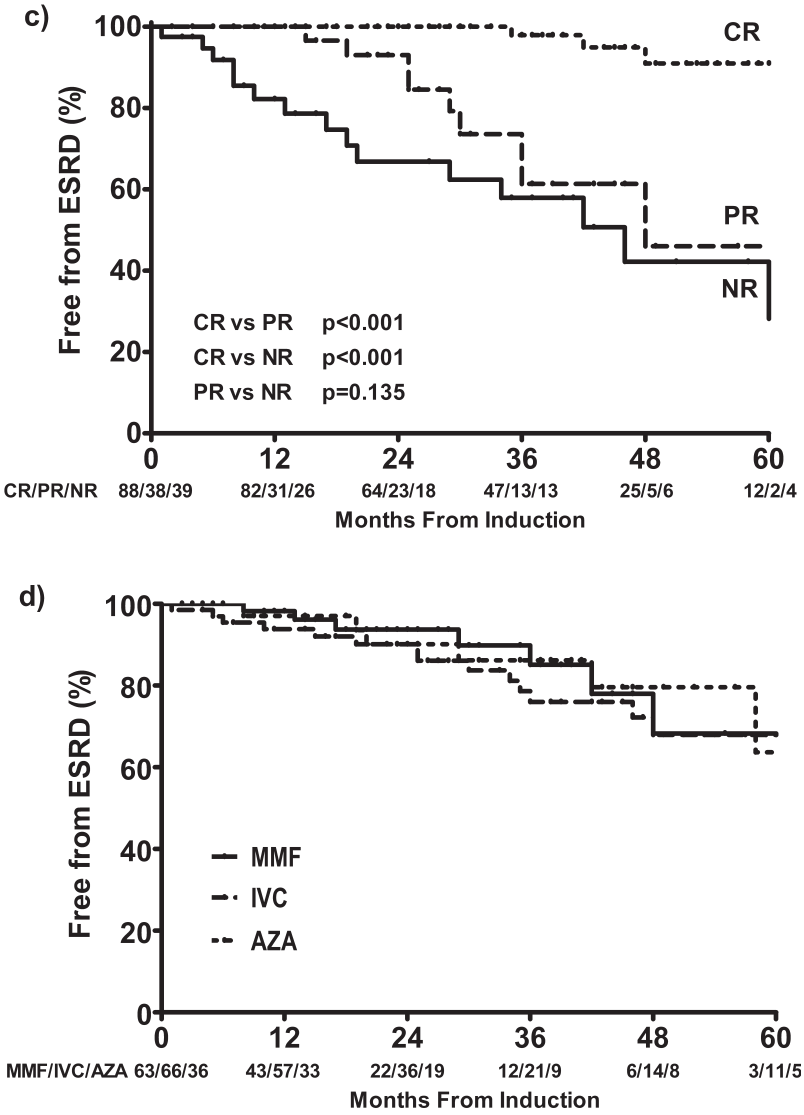


Figure 4. Continued

progressed to ESRD. As shown by Chen, *et al*[25], renal survival improves in PR patients, but 55% of them can still progress to ESRD in a 10-year followup. This may be because partial responders have worse serum creatinine, proteinuria, and chronicity score at presentation, and therefore are prone to more renal flares than complete responders (data not shown). Interestingly, low income was a potent risk factor (HR 2.64) to develop ESRD, but it did not condition response to therapy. This goes in line with the Lupus in Minorities description that the higher mortality might be influenced by economic status in addition to ethnicity[7].

There are several limitations in our present study. Our data are observational and treatment allocation was not randomized; therefore, treatment selection might be biased and variable by clinician selection. We did not register adverse events data on different treatment groups and treatment adherence was evaluated by medical records. We tried to establish rigid inclusion criteria to make the treatment groups homogeneous. We emphasize that 78.8% of the studied patients presented during their first LN episode and were naive to induction therapy. It has been suggested that LN flares may have a delayed RTT rather than the first LN activity episode.

Based on presented data, MMF induction therapy might be superior to IVC and AZA in the Mexican-mestizo population. AZA and steroids might still be an option for pure membranous LN, but this regimen is inferior to IVC and MMF when proliferative LN lesions are present. Treatment with MMF and absence of vascular lesions in renal biopsy predict a better RTT, whereas proteinuria at presentation conditions an inferior response. Vascular status in LN biopsy specimens should be added to histopathological reports.

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