Published in final edited form as:

Am J Med Sci. 2011 December ; 342(6): 467–473. doi:10.1097/MAJ.0b013e3182199214.

Lupus Nephritis. A Retrospective Analysis of Clinical Presentation and Outcomes from a single center

Sandeep Singh, MD¹, Xin J. Zhou², Chul Ahn³, and Ramesh Saxena, MD, PhD¹

¹Department of Internal Medicine, Division of Nephrology, UT Southwestern Medical Center, Dallas, Texas, USA

²Department of Pathology, UT Southwestern Medical Center, Dallas, Texas, USA

³Department of Clinical Science, UT Southwestern Medical Center, Dallas, Texas, USA

Abstract

Background and Objectives—Lupus nephritis (LN) is an ominous complication of Systemic lupus erythematosus (SLE) and the risk factors for the disease progression are not very well characterized.

Design, Setting, Participants and measurements—In a retrospective study, we evaluated the mode of presentation and outcomes of 163 consecutive patients with biopsy proven LN, who presented to our center between January 1999 and September 2008. Using stepwise logistic regression analysis we assessed risk factors independently associated with response to treatment as well as to progression to end stage renal disease (ESRD) in proliferative LN (PLN).

Results—Ninety percent of our patients belonged to minority population. Among 122 patients with class III and IV LN (PLN), 76 patients received intravenous cyclophosphamide (IVC) and 38 mycophenolate for induction while 34 patients received IVC, and 63 mycophenolate for maintenance. Thirty six (30%) patients with PLN progressed to ESRD and 3 patients died over a mean follow-up of 37.5 months. On multivariate analysis, chronicity index (CI) ($p=0.0007$) and hypertension ($p=0.042$) positively correlated with progression to ESRD and death and CI was associated with increased probability of non-response to treatment ($p=0.001$). Additionally, mycophenolate as maintenance agent was associated with increased likelihood of sustained complete remission and partial remission [$p=0.045$].

Conclusions—In patients with LN, Hypertension and a high CI are independent risk factors for progression to ESRD or death. Furthermore, a high CI is associated with poor response and mycophenolate as a maintenance agent may improve the response to treatment.

Keywords

lupus nephritis; outcomes; lupus; SLE; LN

Correspondence to: Ramesh Saxena MD, PhD, Division of Nephrology, UT Southwestern Medical Center, 5323 Harry Hines Blvd., H5:122, Dallas, TX 75390-8856, Office: 214-648-2681, Fax: 214-648-2071, Ramesh.saxena@utsouthwestern.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Lupus nephritis (LN) is one of the common manifestation of systemic lupus erythematosus (SLE), occurring in about 50–70% of patients, and is a major cause of morbidity and mortality in the SLE population¹. The clinical course of LN is heterogeneous and varies from mild subclinical disease to an aggressive course that may rapidly progress to end-stage renal disease (ESRD)¹. In fact, LN is the most common secondary glomerulonephritis leading to ESRD². The nature and severity of the clinical features of LN do not always predict the underlying histological severity^{3–5}. Nevertheless, certain histological and clinical parameters have been associated with poor renal survival^{6–24}. However, results have been diverse due to differences in the population studied, sample size, selection criteria and outcome variables chosen in different studies.

About 15% of patients will develop ESRD despite treatment, with a higher frequency among minority patients^{24,25}. Early diagnosis and prompt treatment of LN are of paramount importance to reduce morbidity and mortality¹⁴. While there has been significant improvement in patient and renal survival over the past years, the current immunosuppressive regimens still achieve suboptimal results, with unacceptable high rates of progression to ESRD, disease relapse rate and treatment related complications. Moreover, most of the recent clinical trials exclude severe LN patients (patients with serum creatinine > 3.5 mg/dl or patients with rapidly progressive glomerulonephritis) from their recruitment^{26–29}. Furthermore, barring a few recent studies, the majority of clinical trials in LN patients have not included patients from minority populations. Indubitably, given the high incidence of severe LN in minority populations, there is an urgent need to decipher the risk factors associated with disease progression as well as safer and more effective therapies to improve the outcome of LN in this disproportionately affected group. This prompted us to conduct a retrospective review of biopsy proven lupus nephritis patients at our institution. The purpose of this study was to define the patient population, their clinical presentation, response to treatment and to investigate the risk factors associated with progression of lupus nephritis (LN) in our high risk patient population, predominantly consisting of African Americans (AA) and Hispanics of Mexican origin.

Material and Methods

Study Population

In the present study, we included all the patients with SLE who had a kidney biopsy during the period from January 1999 to September 2008 at our institution. SLE patients with clinical manifestations of LN but without a kidney biopsy were excluded. Medical records were reviewed for demographic, clinical, histological and treatment data. Renal pathology was assessed by our renal pathologist, Xin Jin Zhou, MD, and reported using the International Society of Nephrology/Renal Pathological Society (ISN/RPS) classification³⁰.

Kidney biopsies done prior to 2005 using old WHO classification were re-evaluated and re-classified using ISN/RPS classification. Activity Index (AI) and Chronicity Index (CI) were calculated using well-established guidelines for all patients exhibiting proliferative class III or IV LN⁶.

The patients with PLN were treated with either 500 to 1000 mg per meter square of cyclophosphamide using NIH protocol or were given MMF (mycophenolate mofetil) or MPS (mycophenolate sodium). The dosing generally ranged from 1500 mg to 3000 mg per day of MMF or 1080 mg to 2160 mg of MMS per day.

The endpoints of the study consisted of 1) the composite of progression to ESRD or death and 2) response to treatment in the form of complete remission, partial remission, non response and relapses.

Definitions

ESRD group comprised of patients whose disease progressed to the level requiring renal replacement therapy.

Complete remission (CR) was defined by all of the following.

Normalization of serum creatinine as evidenced by either serum creatinine less than or equal to the upper limit of normal range of laboratory values or serum creatinine $\leq 15\%$ greater than baseline, if baseline creatinine is within the normal range of the laboratory values. In addition, the patients should have urinary protein to creatinine ratio < 0.5 .

Partial remission (PR) was defined as by serum creatinine $\leq 15\%$ above baseline value and either 50% improvement in urinary protein to creatinine ratio, if the baseline urinary protein to creatinine ratio is ≤ 3.0 , or a urine protein to creatinine ratio of ≤ 3.0 if baseline protein to creatinine ratio is > 3.0 .

Those patients who did not achieve complete or partial remission were classified as non responders (NR).

Relapse or renal flare was defined by either a sudden increase in serum creatinine of at least 30% over the last value, associated with nephritic urinary sediment or doubling of proteinuria if at last visit proteinuria was in sub-nephrotic range or an increase in proteinuria by at least 2 grams if value at last visit was in the nephrotic range.

The definitions used to describe various end points were modified from the criteria used in the recently conducted ALMS (Aspreva Lupus Management Study)²⁷ and LUNAR (Lupus Nephritis Assessment with Rituximab)²⁶ trials.

Patient was determined to be non adherent to treatment if it was indicated in physician's progress notes.

Hypertension was diagnosed if the blood pressure (BP) was consistently $\geq 140/90$ mm Hg on two or more occasions or if the patient was on anti hypertensive medications.

Significant co-morbidities were compared to see if there was any difference in their number among patients achieving various end points. The co-morbidities included for comparison were anemia (Hemoglobin less than 9 gm/dl), coronary artery disease, cerebrovascular accident, congestive heart failure, dyslipidemia, hypothyroidism, pancreatitis, diabetes mellitus, hypertension, asthma, chronic obstructive lung disease, malignancies, depression, deep venous thrombosis and pulmonary embolism.

The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center (UTSW).

Statistical Methods

Student's *t*-tests were used to examine if there were significant differences in continuous variables between two groups of patients. Chi square or Fisher's exact tests were conducted to investigate if there were significant differences in categorical variables between two groups. Stepwise logistic regression analyses were used to identify independent significant

risk factors for primary and secondary endpoints. The risk factors described in Table 1 were included as independent variables for stepwise logistic regression analyses. A *p* value less than 0.05 was considered significant. Statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Inc, Cary, NC).

Results

Between January 1999 and September 2008, 277 new patients with lupus nephritis were seen at UTSW affiliated hospitals and clinics. On reviewing their charts, 163 patients were found to be eligible for inclusion. Among 114 patients who were excluded, 81 did not have a kidney biopsy and there was no follow up data on 33 additional patients. The patients' characteristics at time of initial presentation are shown in Table 1.

Of 163 patients biopsied, 18 (11%) had Class II, 59 (36%) class III, 63(38.6%) class IV, 22 (13.5%) class V and 1 patient was diagnosed with class VI LN. Despite treatment, 41 (25%) patients progressed to ESRD or death. None of the patients with class II or V progressed to ESRD while 1 patient with Class V LN died. The one patient with class VI LN needed renal replacement therapy. Since the majority of patients who progressed to ESRD or death belonged to class III and IV LN, we examined the risk factors for non-response and progression to ESRD and death in the 122 patients with proliferative (Class III and IV) lupus nephritis (PLN). The cause of death in patient with class V LN was unclear. Differential diagnosis included pulmonary embolism versus GI perforation. The etiologies of death in 3 PLN patients were massive CVA, diffuse alveolar hemorrhage and septic shock respectively. Among 122 patients with PLN, 76 patients received IV cyclophosphamide (IVC), 38 mycophenolate, 5 patients received other agents and 3 patients received no treatment for induction. For maintenance, 34 patients received IVC, 63 Mycophenolate, 11 received other agents and 14 received no maintenance therapy. Mean and Median durations of follow-up were 37.5 and 30.0 months respectively. Thirty (25%) patients were considered to be non adherent to treatment during follow up period. (Table 1). The reason for non-adherence to treatment was mainly non-compliance with medication intake. Whether medication side effects played a significant role in inducing non-compliance was unclear.

Risk factors for progression to ESRD or death

Among 122 patients with PLN, 36 (30%) patients progressed to ESRD and 3 patients died. Of 39 individuals who progressed to ESRD or died, 26 (67%) had class IV LN and 13 (33%) had Class III LN. Eight (21%) of the 39 patients were male (Table 2). Mean serum creatinine and mean 24-hour proteinuria at presentation were significantly higher in the group with ESRD and deaths (2.2 ± 1.6 vs. 1.5 ± 1.5 , $p=0.031$; and 5011 ± 3977 mg/24 hrs vs. 3595 ± 3014 mg/24 hrs, $p=0.035$ respectively) (Table 3). In addition, chronicity index (CI) was significantly higher in ESRD and death group (3.9 ± 2.2 vs. 2.3 ± 1.2 , $p=0.0011$). On the other hand, there was no significant difference in the activity index (AI) between the two groups (12.3 ± 3.4 vs. 11.5 ± 4.0 , $P=0.350$) (Table 3). More AA (59%) progressed to ESRD as compared to Hispanics (36%) but the difference was not statistically significant ($p=0.218$). Thirty seven of the 39 patients who progressed to ESRD or died had HTN as a co morbidity compared to 54 out of 83 patients with proliferative LN who were alive and free of dialysis ($p=0.0004$) (Table 2). Moreover, patients who progressed to ESRD or died had more co-morbidities compared to those who remained alive and free of dialysis [31(79%) vs. 51(61%) respectively, $p=0.044$] (Table 2). There was no statistically significant difference in age at the time of diagnosis of LN (Table 2). The incidence of relapses between the two groups and the mean follow up in both groups (31.1 ± 25.9 months in ESRD and death group vs. 38.4 ± 27.6 months in others, $p=0.166$), were similar (Table 3).

Multivariate analysis using stepwise logistic regression was conducted to identify significant independent risk factors of ESRD and death. Chronicity index ($p=0.0007$, Odds ratio 1.771) and HTN ($p=0.042$, Odds ratio 5.425) positively correlated with progression to ESRD and death. There was 77.1% increased risk of progression to ESRD or death with each 1 unit increment in CI and patients with HTN were more than 5 times likely to progress to ESRD or die as compared to those without HTN (Table 4).

Risk factors for non response to treatment

Of the 122 patients with PLN, 59 achieved CR or PR while 63 patients did not respond to the treatment. Compared to the patients who achieved CR or PR, the patients who did not respond to treatment had significantly higher incidence of hypertension [54(86%) vs. 37(63%), $p=0.0035$], more comorbidities [50(79%) vs. 32(54%), $p=0.0094$] and a higher rate of non adherence with treatment [22(35%) vs. 8(14%), $p=0.0062$] (Table 2). It was also found that mean chronicity index was higher among non responders compared to those who achieved CR or PR (3.4 ± 2.0 vs. 2.1 ± 1.3 respectively, $p=0.0001$) (Table 3). Again, there was no significant difference in age, race, gender or incidence of relapses between those who achieved CR/PR and the non-responders. (Tables 2 and 3).

On stepwise logistic regression it was observed that higher chronicity index was associated with increased probability of non-response to treatment ($p=0.001$, odds ratio 1.747) (Table 4). Furthermore, compared to IVC and other immunosuppressive agents, mycophenolate as maintenance agent was associated with increased likelihood of sustained CR and PR ($p=0.045$, odds ratio 0.396) (Table 4).

A unique opportunity arose for us to compare the efficacy of mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) due to a formulary switch at our county hospital in August 2005. Prior to August 2005, all the patients who were initiated or being maintained on mycophenolate received MMF. After August 2005, the patients started receiving MPS instead of MMF. The switch was made with 360 mg of MPS considered equivalent to 500 mg of MMF. Thus patients on 1000 mg of MMF twice a day were started on 720 mg of MPS two times a day. Hence, we had 2 groups of PLN subjects who received mycophenolate as induction (I) or maintenance (M) agent: Group 1 (pre switch group) who received MMF ($n= 19$ & 26 for I and M respectively) and a group 2 (post switch group) who received MPS ($n= 19$ & 37 for I and M respectively). A third group consisted of all PLN patients who received other immunosuppressive agents for induction and maintenance therapy ($n= 84$ & 59 respectively). Statistical analysis was performed to detect any significant difference in response to treatment between the three groups of patients.

There was no significant difference between the three groups in achieving CR or PR during the induction phase ($p=0.6572$). For the maintenance therapy, there was a significant difference between MPS (group 2) and other immunosuppressive agents (Group 3) for sustained CR and PR ($p=0.0258$). However, there was no significant difference between group 1 (MMF) and group 2 (MPS) for maintenance therapy (Table 5).

Relapses

Among 122 patients with class III and IV LN, 30 patients had at least 1 renal flare or relapse. On univariate analysis, lower age at the time of diagnosis of lupus nephritis was associated with higher risk of relapse ($P= 0.0035$). There was a trend towards higher risk of relapse in patients who had HTN [26(87% vs. 20(70%), $P=0.0802$]. Mean follow up time in months was higher in individuals who had a renal flare compared to those who did not have a flare (50.17 ± 26.9 vs. 31.42 ± 25.76 months, $p=0.0008$). In multivariate analysis, HTN was the only variable found to be an independent predictor for relapses (Table 4).

Discussion

This is a large retrospective study from a single center, which attempts to shed light on demographic features, clinical course and the prognostic factors associated with poor renal and patient survivals as well as non-response to treatment in patients with LN belonging mainly to Hispanic and AA ethnicities. This patient population has been shown to have high morbidity and mortality associated with Lupus in general and LN in particular in previous studies^{15, 31, 32}. Austin et al showed AA race increased the risk of progression of kidney disease in lupus nephritis³³. Similarly, Dooley studied 89 LN patients with diffuse proliferative glomerulonephritis (DPGN) and found that AA had less renal survival than Caucasians⁷. Other studies have reiterated the association of increased risk of progression of Lupus nephritis with AA race, which may be related to both genetic and environmental factors^{15, 31, 32}. There have been very few studies comparing outcomes of LN between AA and Hispanics^{12, 31, 32}. These studies have reported that Hispanics and AA are at equal risk of adverse outcomes in Lupus^{12, 32, 34–37}.

Contreras, et al studied the outcomes in AA and Hispanics with LN and found more chronic renal failure and deaths in AA and Hispanics of Cuban descent³¹.

Our study highlights the importance of various laboratory, biopsy and clinical parameters as prognostic indicators in a population comprising mainly of Hispanics of Mexican origin and African Americans. In concurrence with earlier reports,^{9,19,20,32,38} our study showed HTN and higher number of associated co-morbidities (two or more) to be significant predictor variables for progression to ESRD and death. This underscores the importance of aggressively treating hypertension and other co-morbidities in patients with LN to improve the outcome.

We also showed that higher serum creatinine and greater proteinuria at the time of renal biopsy were important predictors for poor outcomes of ESRD and death in our patient population. High serum creatinine and greater degree of proteinuria indicate either severe disease presentation or a delay in the diagnosis of the disease, further emphasizing that early diagnosis and prompt and aggressive treatment of PLN is essential to improve outcomes of LN.

Among biopsy features, higher chronicity index (CI) was associated with non response, poor renal survival and death in PLN patients. CI is an indicator of irreversible damage at the time of biopsy and hence portends poor prognosis as shown in previous studies.^{6,8,18,31,33} Activity index, though it depicts aggressive disease, did not stand out as a significant predictor variable for non response to treatment, since it is potentially reversible if promptly treated.

In a multivariable model, chronicity index and HTN predicted progression to ESRD or death and Mycophenolate as a maintenance agent was associated with improved remission rates. Hypertension is an added insult on top of severe glomerular inflammation in PLN and may hasten the disease progression. This corroborates the findings of previous studies^{13,32} and highlights the need for effectively treating this risk factor. Our study did not find any significant difference between IVC and mycophenolate when used as an induction agent but mycophenolate was found to be associated with higher remission rates when used as a maintenance agent. Several trials including a recent, large, multicenter, Aspreva Lupus Maintenance Study (ALMS) found no difference in efficacy of these 2 agents²⁷ though Ginzler et al found mycophenolate to be superior to IVC when used as an induction agent²⁹. This could be due to difference in exclusion criteria in the latter study since our patient population included 19 rapidly progressive glomerulonephritis (RPGN) patients who presented with creatinine of >3 mg/dl and showed good treatment response to IVC.

In our study, mycophenolate was found to be more effective in maintaining remission as compared to IVC. This supports the results of a randomized trial conducted by Contreras et al³¹ and suggests that mycophenolate can be used as an effective maintenance agent in treatment of LN. An interesting observation was made in our study when we separated the mycophenolate group into MMF and MPS groups and compared these 2 groups with a third group comprising mainly of cyclophosphamide and azathioprine (Table 5). MMF and MPS showed no statistical difference in maintaining remission when compared to each other but MPS was found to be superior to the third group. It is possible that this difference may be due to better adherence with MPS because of better gastro-intestinal tolerability. However, this needs to be examined further in randomized, prospective trials.

Age, race and gender were not shown to be significant risk factors of disease progression in our patient population consisting mainly of Hispanics and African Americans. In the previous studies, race difference has only been demonstrated when comparing AA with Caucasians or Hispanics with Caucasians^{24,33,39}. Compared to previous studies, our study showed a higher incidence of ESRD and death (25.1%) over mean follow up period of 34.5±25.3 months. This could be due to the fact that most of our patients belonged to a high risk category with low socio-economic status. Non-adherence to treatment must also have contributed to increased morbidity and mortality in this patient group as it was found to be a significant predictor variable of poor outcome in univariate analysis.

There are several limitations of our study. It has inherent flaws of a retrospective study. Only associations can be made by using statistical techniques. Furthermore, we may have excluded several other potential prognostic indicators from our study. For example, we did not look at socio-economic status of the patients as a specific variable. A vast majority of our patients belonged to low-socio-economic class, which has been associated with poor prognosis^{24,32,40}.

Notwithstanding limitations of our study, this study provides insight into several demographic, clinical, and laboratory features of LN and attempts to highlight various risk factors associated with unfavorable outcomes in this large, well-defined, high risk minority patient population with biopsy proven Lupus nephritis from a single center in the US.

Acknowledgments

This study was supported by a research grant (CERL080AUS73T) from Novartis Pharmaceutical Corporation, and a grant from the George M. O'Brien Kidney Research Core Center NIH P30DK079328.

References

1. Appel, GBRJ.; Radhakrishnan, J.; D'Agati, V. Secondary glomerular disease. In: Brenner, BM., editor. The Kidney. 8th edition. Philadelphia, PA: Saunders; 2008. p. 1067-1146.
2. USRDS. Annual data report 2010. www.usrds.org
3. Bajaj S, Albert L, Gladman DD, Urowitz MB, Hallett DC, Ritchie S. Serial renal biopsy in systemic lupus erythematosus. J Rheumatol. 2000; 27:2822–2826. [PubMed: 11128670]
4. Wada Y, Ito S, Ueno M, Nakano M, Arakawa M, Gejyo F. Renal outcome and predictors of clinical renal involvement in patients with silent lupus nephritis. Nephron Clin Pract. 2004; 98:c105–c111. [PubMed: 15627787]
5. Zabaleta-Lanz M, Vargas-Arenas RE, Tapanes F, Daboin I, Atahualpa Pinto J, Bianco NE. Silent nephritis in systemic lupus erythematosus. Lupus. 2003; 12:26–30. [PubMed: 12587823]
6. Austin HA 3rd, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. Kidney Int. 1984; 25:689–695. [PubMed: 6482173]

7. Dooley MA, Hogan S, Jennette C, Falk R. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. Glomerular Disease Collaborative Network. *Kidney Int.* 1997; 51:1188–1195. [PubMed: 9083285]
8. Nossent HC, Henzen-Logmans SC, Vroom TM, Berden JH, Swaak TJ. Contribution of renal biopsy data in predicting outcome in lupus nephritis. Analysis of 116 patients. *Arthritis Rheum.* 1990; 33:970–977. [PubMed: 2369432]
9. Lupus nephritis: prognostic factors and probability of maintaining life-supporting renal function 10 years after the diagnosis. Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL). *Am J Kidney Dis.* 1992; 19:473–479. [PubMed: 1585937]
10. Najafi CC, Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J. Significance of histologic patterns of glomerular injury upon long-term prognosis in severe lupus glomerulonephritis. *Kidney Int.* 2001; 59:2156–2163. [PubMed: 11380817]
11. Esdaile JM, Federgreen W, Quintal H, Suissa S, Hayslett JP, Kashgarian M. Predictors of one year outcome in lupus nephritis: the importance of renal biopsy. *Q J Med.* 1991; 81:907–918. [PubMed: 1808631]
12. Alarcón GS, McGwin G Jr, Bastian HM, et al. SLE in three ethnic groups XIII. the 'weighted' criteria as predictors of damage. *Lupus.* 2002; 11:329–331. [PubMed: 12090571]
13. de Castro WP, Morales JV, Wagner MB, Graudenz M, Edelweiss MI, Gonçalves LF. Hypertension and Afro-descendant ethnicity: a bad interaction for lupus nephritis treated with cyclophosphamide? *Lupus.* 2007; 16(9):724–730. [PubMed: 17728366]
14. Fiehn C, Hajjar Y, Mueller K, Waldherr R, Ho AD, Andrassy K. Improved clinical outcome of lupus nephritis during the past decade: importance of early diagnosis and treatment. *Ann Rheum Dis.* 2003; 62:435–439. [PubMed: 12695156]
15. Korbet SM, Schwartz MM, Evans J, Lewis EJ. Severe lupus nephritis: racial differences in presentation and outcome. *J Am Soc Nephrol.* 2007; 18:244–254. [PubMed: 17167111]
16. Moroni G, Pasquali S, Quaglini S, et al. Clinical and prognostic value of serial renal biopsies in lupus nephritis. *Am J Kidney Dis.* 1999; 34:530–539. [PubMed: 10469865]
17. Moroni G, Quaglini S, Maccario M, Banfi G, Ponticelli C. "Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. *Kidney Int.* 1996; 50:2047–2053. [PubMed: 8943489]
18. Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. *Kidney Int.* 1994; 45:544–550. [PubMed: 8164443]
19. Esdaile JM, Levinton C, Federgreen W, Hayslett JP, Kashgarian M. The clinical and renal biopsy predictors of long-term outcome in lupus nephritis: a study of 87 patients and review of the literature. *Q J Med.* 1989; 72:779–833. [PubMed: 2694209]
20. Petri M, Perez-Gutthann S, Longenecker JC, Hochberg M. Morbidity of systemic lupus erythematosus: role of race and socioeconomic status. *Am J Med.* 1991; 91:345–353. [PubMed: 1951378]
21. Donadio JV Jr, Hart GM, Bergstralh EJ, Holley KE. Prognostic determinants in lupus nephritis: a long-term clinicopathologic study. *Lupus.* 1995; 4:109–115. [PubMed: 7795613]
22. Appel GB, Cohen DJ, Pirani CL, Meltzer JI, Estes D. Long-term follow-up of patients with lupus nephritis. A study based on the classification of the World Health Organization. *Am J Med.* 1987; 83:877–885. [PubMed: 3674094]
23. Alarcon GS, McGwin G Jr, Petri M, Reveille JD, Ramsey-Goldman R, Kimberly RP. Baseline characteristics of a multiethnic lupus cohort: PROFILE. *Lupus.* 2002; 11:95–101. [PubMed: 11958584]
24. Contreras G, Lenz O, Pardo V, et al. Outcomes in African Americans and Hispanics with lupus nephritis. *Kidney Int.* 2006; 69:1846–1851. [PubMed: 16598205]
25. Bono L, Cameron JS, Hicks JA. The very long-term prognosis and complications of lupus nephritis and its treatment. *QJM.* 1999; 92:211–218. [PubMed: 10396609]
26. A Study to Evaluate the Efficacy and Safety of Rituximab in Subjects With ISN/RPS Class III or IV Lupus Nephritis (LUNAR).
<http://clinicaltrials.gov/ct2/show/NCT00282347?term=LUNAR&rank=1>

27. Appel GB, Contreras G, Dooley MA, et al. The Aspreva Lupus Management Study Group. Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis. *J Am Soc Nephrol*. 2009; 20:1103–1112. [PubMed: 19369404]
28. Chan TM, Tse KC, Tang CS, Lai KN, Li FK. Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide followed by azathioprine. *Lupus*. 2005; 14:265–272. [PubMed: 15864912]
29. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med*. 2005; 353:2219–2228. [PubMed: 16306519]
30. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol*. 2004; 15:241–250. [PubMed: 14747370]
31. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. *N Engl J Med*. 2004; 350:971–980. [PubMed: 14999109]
32. Barr RG, Seliger S, Appel GB, et al. Prognosis in proliferative lupus nephritis: the role of socio-economic status and race/ethnicity. *Nephrol Dial Transplant*. 2003; 18:2039–2046. [PubMed: 13679478]
33. Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. High-risk features of lupus nephritis: importance of race and clinical and histological factors in 166 patients. *Nephrol Dial Transplant*. 1995; 10:1620–1628. [PubMed: 8559480]
34. Alarcón GS, Roseman J, Bartolucci AA, et al. Systemic lupus erythematosus in three ethnic groups: II. Features predictive of disease activity early in its course. LUMINA Study Group. Lupus in minority populations, nature versus nurture. *Arthritis Rheum*. 1998; 41:1173–1180. [PubMed: 9663472]
35. Alarcón GS, McGwin G Jr, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups. VII [correction of VIII]. Predictors of early mortality in the LUMINA cohort. LUMINA Study Group. *Arthritis Rheum*. 2001; 45:191–202. [PubMed: 11324784]
36. Seligman VA, Lum RF, Olson JL, Li H, Criswell LA. Demographic differences in the development of lupus nephritis: a retrospective analysis. *Am J Med*. 2002; 112:726–729. [PubMed: 12079714]
37. Bastian HM, Roseman JM, McGwin G Jr, et al. LUMINA Study Group. LUpus in MInority populations: NAture vs nurture: Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus*. 2002; 11:152–160. [PubMed: 12004788]
38. Mok CC, Ying KY, Ng WL, et al. Long-term outcome of diffuse proliferative lupus glomerulonephritis treated with cyclophosphamide. *Am J Med*. 2006; 119:e325–e333. 335.
39. Neumann K, Wallace DJ, Azen C, et al. Lupus in the 1980s: III. Influence of clinical variables, biopsy, and treatment on the outcome in 150 patients with lupus nephritis seen at a single center. *Semin Arthritis Rheum*. 1995; 25:47–55. [PubMed: 8525390]
40. Fernández M, Alarcón GS, Calvo-Alén J, et al. LUMINA Study Group: A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. *Arthritis Rheum*. 2007; 57:576–584. [PubMed: 17471524]

Table 1

Presenting features of patients with lupus nephritis.

Features	All patients (n=163)	Class III and IV (n=122)
Gender*		
Female	138 (85%)	102 (84%)
Male:	25 (15%)	20(16%)
Race*		
African-American:	78 (48%)	56 (46%)
Hispanics	68 (42%)	55 (45%)
Caucasians	12 (7%)	8 (7%)
Others:	5 (3%)	3 (2%)
Age (Years) at LN diagnosis	32.3±11.4	31.4±11.2
Initial Presentation*		
LN	23 (14%)	16 (13%)
LN with others	41 (25%)	35 (29%)
Others	99 (61%)	71(58%)
Hypertension*	112 (69%)	91 (75%)
Anemia*	67 (45%)	55 (50%)
Proteinuria (mg/g)	3816.8±3459.6	4043.0±3395.7
Creatinine (mg/dl)	1.6±1.5	1.7±1.6
Number of co morbidities*		
0	21 (13%)	16 (13%)
1	31 (19%)	24 (20%)
2 or more	111 (68%)	82 (67%)
ISN/RPS class of LN*		
II	18 (11%)	
III	59 (36%)	59 (48%)
IV	63 (39%)	63 (52%)
V	22 (13.5%)	
VI	1 (1%)	
Treatment induction*		
Mycophenolate	54 (33%)	38 (31%)
Cyclophosphamide	77 (47%)	76 (62%)
None	12 (7%)	3 (2%)
OTHER	20 (12%)	5 (4%)
Maintenance*		
Mycophenolate	78 (48%)	63 (52%)
Cyclophosphamide	34 (21%)	34 (28%)
None	27 (17%)	14 (11%)
OTHER	24 (15%)	11 (9%)
Response*		

Features	All patients (n=163)	Class III and IV (n=122)
CR	62 (38%)	41 (34%)
PR	23 (14%)	18 (15%)
No response	37 (23%)	24 (20%)
ESRD	37 (23%)	36 (30%)
Death	4 (2%)	3 (2%)
Follow up (months)	37.5±28.3	36.0±27.2
Non adherence *	34 (21%)	30 (25%)
Relapses *	32 (20%)	30 (25%)

LN: Lupus, nephritis, ISN/RPS (International Society of Nephrology/ Renal Pathology Society),

* Indicates that the corresponding values for that feature will be expressed as the number (percent) of patients in each column.

Table 2

Comparison of categorical variables for response to treatment and progression to ESRD and death in patients with proliferative lupus nephritis.

Class III and IV patients	Alive, dialysis free (n=83)	ESRD or Death (n=39)	
<i>Variable</i>	<i>Number (%)</i>	<i>Number (%)</i>	<i>p-value</i>
Gender			0.3995
Female	71 (86%)	31 (79%)	
Male	12 (14%)	8 (21%)	
Race			0.2184[#]
African-Americans	33 (40%)	23 (59%)	
Hispanics	41 (49%)	14 (36%)	
Caucasians	6 (7%)	2 (5%)	
Others	3 (4%)	0 (0%)	
Hypertension	54 (65%)	37 (95%)	0.0004
Number of co-morbidities			0.0442[#]
0	15 (18%)	1 (3%)	
1	17 (20%)	7 (18%)	
2 or more	51 (61%)	31 (79%)	
Treatment (Induction)			0.0541[#]
Mycophenolate	29 (35%)	9 (23%)	
Cyclophosphamide	50 (60%)	26 (67%)	
Other	4 (5%)	1 (3%)	
None	0 (0%)	3 (8%)	
Treatment (Maintenance)			0.0875[#]
Mycophenolate	48 (58%)	15 (39%)	
Cyclophosphamide	21 (25%)	13 (33%)	
Other	8 (10%)	3 (8%)	
None	6 (7%)	8 (21%)	
Non-adherence	19 (23%)	11 (28%)	0.5250
Relapses	21 (25%)	9 (23%)	0.7902
Class III and IV patients	Complete or Partial Response(n=59)	No-response (n=63)	
<i>Variable</i>	<i>Number (%)</i>	<i>Number (%)</i>	<i>p-value</i>
Gender			0.0723
Female	53 (90%)	49 (78%)	
Male	6 (10%)	14 (22%)	
Race			0.3005[#]
African-Americans	25 (42%)	31 (49%)	
Hispanics	28 (47%)	27 (43%)	
Caucasians	3 (5%)	5 (8%)	
Others	3 (4%)	0 (0%)	
Hypertension	37 (63%)	54 (86%)	0.0035

Class III and IV patients	Alive, dialysis free (n=83)	ESRD or Death (n=39)	
Number of co-morbidities			0.0094
0	12 (20%)	4 (6%)	
1	15 (25%)	9 (14%)	
2 or more	32 (54%)	50 (79%)	
Treatment (Induction)			0.4734[#]
Mycophenolate	19 (32%)	19 (30%)	
Cyclophosphamide	38 (64%)	38 (60%)	
Other	2 (3%)	3 (5%)	
None	0 (0%)	3 (5%)	
Treatment (Maintenance)			0.1003
Mycophenolate	37 (63%)	26 (41%)	
Cyclophosphamide	14 (24%)	20 (32%)	
Other	4 (7%)	7 (11%)	
None	4 (7%)	10 (16%)	
Non-adherence	8 (14%)	22 (35%)	0.0062
Relapses	12 (20%)	18 (29%)	0.2913

[#] p values based on Fisher's exact test, the other p-values are based on chi-square test

Table 3

Comparison of continuous variables for response to treatment and progression to ESRD and death in patients with proliferative lupus nephritis.

Class III and IV patients	Alive, dialysis free	ESRD or Death	
<i>Variable</i>	<i>Mean±Std</i>	<i>Mean±Std</i>	<i>p-value</i>
Age (years)	31.6±10.8	31.0±12.0	0.788
S. Creatinine (mg/dL)	1.5±1.5	2.2±1.6	0.031
Proteinuria (mg/24 hour)	3595.3±3013.7	5011.1±3976.8	0.035
Follow-up (months)	38.4±27.6	31.1±25.9	0.166
Activity index (out of 24)	11.5±4.0	12.3±3.4	0.350
Chronicity Index (out of 12)	2.3±1.2	3.9±2.2	0.001
	Complete/Partial response	No Response	
<i>Variable</i>	<i>Mean±Std</i>	<i>Mean±Std</i>	<i>p-value</i>
Age (years)	32.4±10.6	30.5±11.7	0.335
S. Creatinine (mg/dL)	1.6±1.7	1.9±1.4	0.274
Proteinuria (mg/24 hour)	3645.5±3106.0	4447.4±3649.5	0.203
Follow-up (months)	37.0±26.2	35.1±28.2	0.695
Activity index (out of 24)	11.6±4.1	12.0±3.5	0.627
Chronicity Index (out of 12)	2.1±1.3	3.4±2.0	0.0001

Table 4

Multivariate analysis by stepwise logistic regression to assess independent risk factors associated with poor response to treatment, progression to ESRD or death and renal flares (relapses) in patients with Class III and IV (proliferative) lupus nephritis

Response	Risk Factor	Regression coefficient	P-value	Odds ratio	Lower95% CL	Upper 95% CL
No response	<i>Mycophenolate as maintenance agent</i>	-0.927	0.045	0.396	0.160	0.979
	<i>Chronicity index</i>	0.558	0.001	1.747	1.246	2.450
ESRD or Death	<i>Hypertension</i>	1.691	0.042	5.425	1.066	27.612
	<i>Chronicity index</i>	0.572	0.0007	1.771	1.273	2.464
Relapses	<i>Hypertension</i>	2.334	0.027	10.322	1.310	81.308

Table 5

Pair-wise comparison of various maintenance treatment groups for treatment outcomes in proliferative lupus nephritis. Mycophenolate sodium (MPS), when compared to the others [a group comprising cyclophosphamide and miscellaneous immunosuppressive agents excluding mycophenolate mofetil (MMF)] as a maintenance agent showed a significantly better complete and partial remission rates in proliferative lupus nephritis.

Outcome variable	Maintenance treatment group	p
No Relapse vs. Relapse	MPS vs. Others	0.7246
Alive and not on dialysis vs. ESRD or Death	MPS vs. Others	0.0777
CR or PR vs. Non-responders	MPS vs. Others	0.0258*
No Relapse vs. Relapse	MPS vs. MMF	0.2718
Alive and not on dialysis vs. ESRD or Death	MPS vs. MMF	0.6358
CR or PR vs. Non-responders	MPS vs. MMF	0.4089
No Relapse vs. Relapse	MMF vs. others	1.0
Alive and not on dialysis vs. ESRD or Death	MMF vs. others	0.2759
CR or PR vs. Non-responders	MMF vs. others	0.285

CR; complete remission, PR: partial remission,

* indicates statistically significant result.