

Short-Term Outcome of Sub-Saharan Africans with Proliferative Lupus Nephritis Treated with Cyclophosphamide Versus Mycophenolate Mofetil

Mansour Mbengue¹, Serigne Fall¹, Jatt Tсахabayembi¹, Idrissa Sall¹, Mohamed Diouf¹, Niakhaleen Keita¹, Maria Faye², Ahmed Tall Lemrabott², El Hadji Fary Ka², Abdou Niang¹

¹Nephrology Department, Cheikh Anta Diop University of Dakar, Dalal Jamm Hospital, Dakar, Senegal

²Nephrology Department, Cheikh Anta Diop University of Dakar, Aristide Le Dantec Hospital, Dakar, Senegal

Email: fallserigne498@gmail.com, mansourmbengue92@gmail.com

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Abstract

Introduction: Proliferative classes of lupus nephritis are the most frequently reported in the literature, with a prevalence ranging from 40% to 80% of cases. These classes are clearly associated with the poorest medium-term prognosis. This study was conducted to assess the progression of proliferative lupus nephritis following induction therapy in Sub-Saharan African patients. **Patients and Methods:** A retrospective and descriptive study was performed over a 10-year period, from January 1, 2007, to December 31, 2016, in the nephrology department of Aristide Le Dantec Hospital in Dakar. Patients diagnosed with proliferative lupus nephritis were included. The diagnosis was based on renal biopsy findings consistent with proteinuria exceeding 0.5 g/24h or active urinary sediment, classified according to the 2003 ISN/RPS classification (Classes III or IV, with or without Class V). Epidemiological, clinical, biological, histological, therapeutic, and outcome data were collected. Glomerular Filtration Rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula. Nephrotic proteinuria was defined as >3 g/24h. Patients received either intravenous cyclophosphamide (1 g/m²/month) or mycophenolate mofetil (2 g/day), combined with methylprednisolone (15 mg/kg for 3 days) followed by prednisone (1 mg/kg/day), alongside hydroxychloroquine. Follow-up lasted 6 months, with remission and resistance defined per EULAR/ERA/EDTA criteria. **Results:** Among 64 Black patients with lupus nephritis, 44 cases of proliferative glomerulonephritis were identified, representing a prevalence of 68.7%. The mean age was 31.8 ± 11.2 years, with 33 women and 11 men (sex ratio: 0.3). Renal edema was present in 36 patients (81.8%),

and hypertension was noted in 22 patients (mean systolic blood pressure 141 mmHg, mean diastolic blood pressure 91 mmHg). Mean serum creatinine was 24.2 mg/L \pm 23.2, with renal failure in 45.5% of patients. Mean proteinuria was 3.9 g/24h \pm 2.7, and nephrotic syndrome was observed in 72.7% of cases. Histological classification included Class III in 11.3%, Class IV in 27.3%, Class III + V in 43.2%, and Class IV + V in 18.2%. Cyclophosphamide was administered to 22 patients, and mycophenolate mofetil to 10 patients. Of the 44 patients, 35 were followed for 6 months, with 9 lost to follow-up. Remission rates (complete and partial) were 36.8% for cyclophosphamide and 66.6% for mycophenolate mofetil, with resistance rates of 63.2% and 33.4%, respectively. Five deaths occurred due to pulmonary embolism, bacterial meningitis, pulmonary tuberculosis, and indeterminate causes in two cases. Chronic renal failure developed in 8 patients. Infectious complications affected 38.6% of patients, with cutaneous (32%), urogenital (24%), and pulmonary (16%) localizations being the most common. Conclusion: The risk of progression to chronic renal failure was relatively high. Patients treated with mycophenolate mofetil exhibited a higher remission rate compared to those treated with cyclophosphamide. The hypothesis of an ethnic influence on therapeutic response warrants further investigation.

Keywords

Proliferative Lupus Nephritis, Cyclophosphamide, Mycophenolate Mofetil, Remission

1. Introduction

Proliferative classes of lupus nephritis are the most commonly reported in the literature, with a prevalence ranging from 40% to 80% of cases [1]-[3]. These classes are the most severe, often associated with kidney failure and nephrotic syndrome. Induction treatment typically involves corticosteroid therapy combined with immunosuppressive agents, such as cyclophosphamide or mycophenolate mofetil. Although biologics have not yet proven effective for this indication, emerging protocols suggest improved remission rates following induction therapy and potential corticosteroid-sparing benefits for patients. These forms are unequivocally linked to the poorest outcomes in the medium term [4], particularly when accompanied by significant extracapillary proliferation or advanced interstitial fibrotic lesions. Renal prognosis varies substantially by ethnic background, with Black patients exhibiting a less favorable outcome and a long-term risk of progression to end-stage renal disease ranging from 40% to 60%.

2. Patients and Methods

A retrospective and descriptive study was conducted over a 10-year period, from January 1, 2007, to December 31, 2016, in the nephrology department of Aristide

Le Dantec Hospital in Dakar, Senegal. Patients diagnosed with proliferative lupus nephritis were included. The diagnosis was established based on renal biopsy findings consistent with proteinuria exceeding 0.5 g/24h or active urinary sediment, and classified according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification (Classes III or IV, with or without Class V) [5].

For each patient, epidemiological, clinical, biological, histological, therapeutic, and outcome data were recorded. The estimated Glomerular Filtration Rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Nephrotic proteinuria was defined as nephrotic-range proteinuria (>3 g/24h). Treatment regimens included intravenous cyclophosphamide (1 g/m²/month) or oral mycophenolate mofetil (2 g/day), both combined with methylprednisolone (15 mg/kg for 3 days) followed by prednisone (1 mg/kg/day). All patients received hydroxychloroquine as adjunctive therapy. Patients were followed for 6 months.

Treatment allocation was not randomized. The choice between cyclophosphamide and Mycophenolate Mofetil (MMF) was guided by drug availability, patient financial resources, and clinical considerations. Cyclophosphamide was generally available through the hospital pharmacy, while MMF required out-of-pocket purchase. MMF was more frequently prescribed to patients with sufficient means, particularly to young women in whom fertility preservation was a clinical concern.

Remission and resistance were defined according to EULAR/ERA/EDTA criteria [6]:

- Complete remission: Proteinuria < 0.5 g/24h and normal eGFR or within 10% of baseline.
- Partial remission: Reduction in proteinuria by >50% to <3 g/24h, with near-normal eGFR (preferably within 6 months, but not beyond 12 months of induction).
- Resistance: Lack of improvement within 3 - 4 months or absence of partial remission after 6 months of treatment.

Data were entered and analyzed using Sphinx version 5.1.0.2 software.

3. Results

Among 64 Black patients with lupus nephritis, 44 cases of proliferative glomerulonephritis were identified, yielding a prevalence of 68.7%. The mean age was 31.8 ± 11.2 years, with 33 women (75%) and 11 men (25%), resulting in a sex ratio of 0.3. Renal edema was present in 36 patients (81.8%). The mean systolic blood pressure was 141 mmHg, and the mean diastolic blood pressure was 91 mmHg, with hypertension observed in 22 patients. The mean serum creatinine level was 24.2 mg/L ± 23.2, and renal failure was noted in 20 patients (45.5%). Mean serum albumin was 25.1 g/L ± 25.4, and mean serum protein was 55.3 g/L ± 9.07. The mean proteinuria was 3.9 g/24h ± 2.7, with nephrotic syndrome in 32 patients

(72.7%), of which 25 cases (56.8%) were non-pure nephrotic syndrome. Immunological testing was not systematically performed due to resource limitations. Anti-nuclear antibodies (ANA) were positive in all 8 patients tested, anti-ENA antibodies were positive in 16 of 18 tested patients, and native anti-DNA antibodies were positive in 7 of 16 tested patients (43.7%). Complement levels (C3 and CH50) were decreased in two patients, while C4 levels remained within normal range in all tested individuals. These results must be interpreted cautiously given the limited number of patients tested. Histological classification revealed Class III in 5 cases (11.3%), Class IV in 12 cases (27.3%), Class III + V in 19 cases (43.2%), and Class IV + V in 8 cases (18.2%).

These various results described above are summarized in **Table 1**.

Table 1. Comparative table between CYC and MMF—patients' profile.

Category	Variable	CYC (N=22)	MMF (N=22)	p
Demography	Age (year, average \pm standard deviation)	32.8 \pm 12.0	25.8 \pm 10.6	0.314
	Feminine (%)	78.9%	70%	0.319
	Masculin (%)	21.1%	30.0%	
Background	HTA (%)	5.3%	0.0%	-
	Diabetes (%)	5.3%	0.0%	
Clinic	Gross hematuria	0%	10%	-
Renal function	Creatinine level (mg/l, average \pm standard deviation)	26.6 \pm 26.6	17.3 \pm 14.7	0.261
	DFG (ml/min, average \pm ecart type)	64.1 \pm 54.2	93.4 \pm 56.7	0.175
	PU 24H (g/L)	3.55 \pm 2.11	3.91 \pm 2.94	0.765
Hematology	Hemoglobin (g/dL)	8.5 \pm 1.9	9.2 \pm 1.4	0.402
	White blood cells (/mm ³)	7300 \pm 4200	6520 \pm 3502	0.785
Proteins	Proteinemia (g/L)	50.6 \pm 7.0	60.5 \pm 11.5	0.028
	Albuminemia (g/L)	19.2 \pm 4.9	20.9 \pm 9.1	0.569
Immunology	AAN positif (%)	21.1%	40%	0.084
	DNA natif positif (%)	15.8%	10.0%	0.156
	Anti ECT (%)	31.58%	30%	0.326
Histology	Classe III (%)	15.8%	20.0%	0.407
	Classe III + V (%)	47.4%	40.0%	
	Classe IV (%)	26.3%	30.0%	
	Classe 4IV + V (%)	10.53%	10%	

Treatment included cyclophosphamide for 22 patients and mycophenolate mofetil for 10 patients. Of the 44 patients, 35 were followed for 6 months, with 9 lost to follow-up. Remission rates (complete and partial) were 36.8% for cyclophosphamide and 66.6% for mycophenolate mofetil, with resistance rates of 63.2% and 33.4%, respectively (**Table 2**). Five deaths were recorded, attributed to pulmonary embolism, bacterial meningitis, pulmonary tuberculosis, and indeterminate causes

in two cases. Chronic renal failure developed in 8 patients (**Table 3**). Infectious complications occurred in 17 patients (38.6%), with cutaneous (32%), urogenital (24%), and pulmonary (16%) localizations being the most frequent. The distribution of infected sites is detailed in **Table 4**.

Table 2. Distribution of patients according to the therapeutic protocol and the evolutionary modalities.

	Cyclophosphamide (n=22)	Mycophenolate mofetil (n=9)
Remission (complete and partial)	36.8%	66.6%
Resistance	63.2%	33.4%

Table 3. The different complications related to the disease.

Complications	Absolute frequency	Percentages
Chronic Kidney Disease (CKD)	8	66.7
CKD stage V	5	
CKD stage III	3	
Thromboembolic	3	25.0
Inferior vena cava thrombosis	2	
Thrombophlebitis	1	
Tamponade	1	8.3
Total	12	100.0

Table 4. The different sites of infectious complications.

Infectious Complications	Absolute frequency	Percentages (%)
Pulmonary	4	16
Pneumopathies	3	
Tuberculosis Pulmonary	1	
Cutaneous	8	32
Shingles	4	
Facial abscess	1	
Furunculosis	1	
Erysipelas	1	
Cellulitis	1	
Digestive	3	12
Gastroenteritis	3	
Urinary	3	12
Lower urinary tract infections	2	
Pyelonephritis	1	
Genitales	3	12
Vaginitis	2	
Genital herpes	1	

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Osteoarticular	1	4
Spondylodiscitis	1	
Neurological	2	8
Bacterial meningitis	2	
Ophthalmological	1	4
Herpetic keratitis	1	
Total	25	100

4. Discussion

In this cohort, the mean Systolic Blood Pressure (SBP) was 141 mmHg, and the mean Diastolic Blood Pressure (DBP) was 91 mmHg, values consistent with those reported by Ayodele [7], Korbet [8], and Nossent [9], who documented SBP/DBP of 146/90, 142/88, and 135/85, respectively. This hypertension is multifactorial, with glomerular damage from lupus as the primary cause, exacerbated by renal failure and corticosteroid therapy [10].

The mean serum creatinine level of 24.2 mg/L in our study aligns with findings from Ayodele [7], Okpechi [11], and Korbet [8], who reported values of 16, 17, and 19 mg/L, respectively. However, Moroni, Nossent, and Mok reported lower values (11, 10, and 12 mg/L, respectively) [9] [12] [13]. The higher creatinine levels in our Black patient cohort compared to studies on Caucasian populations may reflect the greater severity of lupus nephritis in Black patients [14]. Previous studies, such as Contreras' work in the USA and the LUMINA study (Lupus in Minorities, Nature vs. Nurture), have similarly highlighted more severe disease in Black patients, potentially linked to the HLA-DRB1*1503 (DR2) allele [14].

The remission rate (complete and partial) appeared higher with Mycophenolate Mofetil (MMF) than with Cyclophosphamide (CYC) in our study (66.6% vs. 36.8%). The ASPREVA trial [5] confirmed MMF's efficacy as an induction therapy for proliferative lupus nephritis, with remission rates comparable to CYC (56% vs. 53%). However, studies by Chan, Sahay, and Mendonça [15]-[17] reported similar initial remission rates for both treatments in predominantly non-Black populations (Table 5), suggesting a potential ethnic influence in our findings. A secondary analysis of the ASPREVA study [18] supported this, showing comparable CYC and MMF remission rates in Asians (53.2% vs. 64.9%) and Caucasians (56% vs. 54.2%), but lower CYC efficacy in Black (40% vs. 53.9%) and Hispanic (38.8% vs. 60.9%) patients. This may indicate limitations in the NIH protocol, widely used in our cohort. Our findings are consistent with other studies in Sub-Saharan Africa. In South Africa, Mbanya *et al.* reported a 69.6% partial or complete remission rate at 6 months among 131 patients with proliferative or membranoproliferative lupus nephritis. High baseline serum creatinine was the strongest predictor of poor outcome [19]. Similarly, in Ethiopia, a multicenter cohort of 200 patients treated primarily with MMF and prednisone showed a 66.5% complete and 18% partial remission rate. Non-response was associated with high

disease activity, leukopenia, comorbidities, and induction therapy exceeding six months [20].

Table 5. Remission rates reported by some studies according to the therapeutic protocol.

Authors	Cyclophosphamide	Mycophenolate mofetil
ASPREVA	53	56.2
Mendonca	85.95	88.24
Chan	90	95
Sahay	72.5	72.8
Our series	36.8	66.6

A systematic review by Okpechi *et al.* covering 16 African studies found mortality rates up to 34.9%, with widespread use of corticosteroids and cyclophosphamide [21]. In our series, the remission rate observed with MMF (66.6%) is comparable, while the mortality rate (11%) and high burden of infectious complications underline the ongoing challenges in treatment access, monitoring, and socioeconomic support in African settings.

The incidence of infectious complications in our study (38.6%) falls within the reported range of 26% to 78% [22], aligning with the 40% reported in France [23], but exceeding rates in Canada (25%) [24] and India (26.5%) [25]. Infections predominantly affected the lungs, skin, and urogenital tract (>70% of cases) [26] [27], with rarer involvement of osteoarticular, central nervous system, or endocardial sites. Lupus predisposes to infections due to immunosuppression from impaired chemotaxis and phagocytosis, functional asplenia [28], hypocomplementemia (due to excessive C3 and C4 consumption or congenital deficiencies) [27], elevated Fc gamma III and GM-CSF levels, reduced CD8+ T-cell cytotoxicity, and decreased production of protective cytokines (IL-1, IL-2, interferons) [29]. Renal impairment, hypogammaglobulinemia in nephrotic syndrome, lymphopenia, and immunosuppressive therapies further increase this risk [24] [29].

5. Limitations

This study has several limitations. First, the retrospective design and non-randomized treatment allocation introduce potential selection bias. Treatment choice depended on real-life factors such as drug availability, clinician preference, contraindications, and the patient's ability to afford MMF. Cyclophosphamide was generally more accessible through hospital supply, whereas MMF was prescribed when financially feasible, especially in young women due to concerns about gonadal toxicity.

Second, 9 patients (20.5%) were lost to follow-up and excluded from outcome analysis. Their baseline characteristics suggest moderate to severe disease, and their absence may have influenced remission estimates.

Third, immunological testing was incomplete due to resource limitations, re-

stricting our capacity to assess immunologic predictors of treatment response and limiting external comparability.

6. Conclusion

The risk of progression to chronic renal failure was relatively high in this cohort. Mortality was associated with infectious and thromboembolic complications. Patients treated with mycophenolate mofetil demonstrated a higher remission rate compared to those treated with cyclophosphamide. The potential role of ethnicity in therapeutic response remains a subject for further debate and investigation.

Ethical Statement

This study was approved by the local ethics committee.

Informed Consent

Informed consent was obtained from all human participants involved in this research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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