TREATMENT OUTCOMES OF PEDIATRIC LUPUS NEPHRITIS CLASS III AND IV IN NATIONAL CHILDREN'S HOSPITAL

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Treatment of lupus nephritis (LN) remains challenging. A prospective observational study on the children with newly diagnosed LN class III and IV from 9/2019 to 9/2021 intended to examine the efficacy of MMF with corticosteroids as induction therapy for pediatric lupus nephritis class III and IV. All patients received 3 days of pulse methylprednisolone followed by a tapering course of oral prednisone therapy in combination with Mycophenolate mofetil (MMF) 1200mg/m2/day (max 2g/day). Those with urine protein-creatinine ratio (uPCR) > 200mg/mmol and normal renal function after 1-month treatment received MMF and low dose Calcineurin Inhibitors (CNI). There were 57 children who were 75.4% females, 42.1% of children in class III, and 57.9% in class IV. The mean age was 10.88. 82.5% of patients r eceived Corticosteroid and MMF, and 10 children were treated with Corticosteroid, MMF, and CNI. Early responses at week 12 were achieved by 71.9%. The overall response was seen in 93.3% of patients after 6 months of therapy (42.2% complete response and 51.1% partial response). 2 patients (3.5%) had infections. MMF is effective in the treatment of children with proliferative lupus nephritis in induction therapy.

Keywords: Lupus Nephritis, serum Albumin, urine protein-creatinine ratio, Mycophenolate mofetil.

I. INTRODUCTION

Childhood-onset systemic lupus erythematosus (cSLE) has an incidence of 0.3 to 0.9 per 100,000 children-years and a prevalence of 3.3 - 8.8 per 100,000 children with higher prevalence rates in non-white populations including Asians.[1] About 10 - 20% of cases of SLE are diagnosed during childhood with a median age of onset of 11 - 12 years, and these patients have increased disease severity and lower survival rates.[2] Renal disease occurs in 50 - 75% of all cSLE patients, mostly within the first two years of diagnosis.[2]

Children with lupus nephritis, especially diffuse proliferative and membranous glomerulonephritis, may necessitate potent immunosuppressive medications such as cyclophosphamide (CYC) or mycophenolate mofetil (MMF).[3] In the last 30 years of the last century, randomized clinical trials performed primarily at the National Institutes of Health demonstrated that regimens using cyclophosphamide with corticosteroids were superior to corticosteroids alone for the treatment of proliferative lupus nephritis. However, the success of cyclophosphamide regimens comes with the burden of adverse events. The incidence of amenorrhea is significantly increased, ranging from 45 to 71% in patients who receive cyclophosphamide for 6 months. In addition, the incidence of herpes zoster infection is significantly increased, ranging from 25 to 33% with the use of cyclophosphamide. Hemorrhagic cystitis is seen primarily with the long-term use of oral cyclophosphamide with an incidence ranging from 14 to 17%.[4]

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In the past decade, the immunosuppressive agent mycophenolate mofetil (MMF) has been used in the treatment of lupus nephritis. The efficacy of MMF was demonstrated in rodent models of lupus nephritis. The meta-analysis of Moore and Derry that evaluated MMF in lupus nephritis, pooling five induction trials, showed that MMF was superior to cyclophosphamide. Combined partial and complete remission was significantly more frequent with MMF (66%) than with cyclophosphamide (54%), Serious infections, leucopenia and Amenorrhea occurred less frequently with MMF than with cyclophosphamide.[5] Experience in the pediatric population is quite limited. And there is currently no data on response to MMF treatment for pediatric lupus nephritis in Vietnam. The aim of this study was to examine the efficacy of MMF with corticosteroids as induction therapy for pediatric lupus nephritis in children.

II. MATERIALS AND METHODS

1. Study Design

The prospective observational, single-center-based study was performed at the Nephrology and Dialysis Department in Vietnam National Children's Hospital, from 9/2019 to 9/2021. All children younger than 18 with presented clinical features of LN were recruited. SLE was diagnosed using the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria for SLE classification.[6] We defined LN as the 24-hour urinary protein ≥ 500 mg (or uPCR ≥ 0.5g/mmol) or the appearance of red blood cell casts in urine (> 5 RBC/HPF by manual analysis of the urine sediment). Then all patients who underwent renal biopsy to determine LN class III or IV were recruited. These children received 3 days of pulse methylprednisolone followed by a tapering course of oral prednisone therapy in combination with MMF 1200mg/m^2/day (max 2g/day). Some of them who had high urine protein-creatinine ratio (uPCR > 200mg/mmol) and normal renal function after 1-month treatment with MMF were used MMF and low dose CNI. They were followed up for at least 3 months and patients who switched therapies or received other modalities were excluded.

2. Clinical and Laboratory Dataset

For each participant, the following laboratory data were collected at 3 time points at diagnosis, 12 and 24 weeks after treatment, including: full blood count, immuno-biological tests (blood glucose, serum albumin, serum protein, serum C-reactive protein, serum double-stranded DNA (dsDNA), and serum C3 and C4 levels, urine analysis, urine protein/creatinine rate, estimated glomerular filtration rate (eGFR). Clinical parameters (age, sex, skin lesions, rheumatism, neurological lesion, and heart lesion, edema, hypertension) were also documented for each subject. The systemic lupus erythematosus disease activity index (SLEDAI) was calculated for all patients to determine SLE activity levels.[6] Hypertension is defined as blood pressure higher than the 95th percentile value of healthy people of the same age and sex.[7] The eGFR was calculated based on the Schwartz formula.[8] An eGFR < 60 ml/min per 1.73 m^2 was moderate chronic kidney disease. We defined nephrotic syndrome as uPCR ≥ 200 mg/mmol and serum albumin < 30 g/L.

The indications of kidney biopsy were proteinuria > 0.5 g/ 24 hours (uPCR > 50mg/mmol) plus hematuria, defined as 5 RBCs per hpf, or plus cellular casts; or proteinuria > 1g/24 hours (uPCR > 100mg/mmol); or rising serum creatinine[9]. Renal biopsies were done by a Tru-Cut semi-automated renal biopsy gun. The trained pathologists at our hospital examined all renal biopsy specimens. Histopathology classification of lupus nephritis was performed

using six classes (i.e., I to VI) as the criteria of the International Society of Nephrology and the renal pathology society (ISN/RPS) in 2003 revised in 2018.[10]

Outcome measures were defined as per the Kidney Disease: Improving Global Outcomes guidelines.[11] Complete response (CR) was defined as return of renal function to normal and uPCR < 50 mg/mmol or < 500 mg/g, or < 0.5 g/24 h. Partial response (PR) was ≥ 50% decrease in proteinuria, to at least sub-nephrotic levels, plus stabilization or improvement of serum Creatinine.

3. Statistical Analyses

We represented continuous data by the mean and standard deviation (with normal distribution data) or median and interquartile range (with non-normal distribution). In addition, categorical data using frequency and percentage.

4. Ethical Approval

This study was approved by the Ethical Committee of Vietnam National Children's Hospital (no:1271/QĐ-BVNTƯ) and Hanoi Medical University (no:477/GCN-HĐĐĐNCYSH-ĐHYHN). All human research procedures followed the committee's ethical standards responsible for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008.

III. RESULTS

A total of 57 proliferative LN children, 43 (75.4%) were females and the average age was 10.88 ± 2.105 years. In this proliferative LN patients, 24 (42.1%) were class III and 33 were (57.9%) class IV. At week 24, 45 (79%) patients remained in the study and 4 (7%) patients withdrew from the study because of the covid 19 epidemic. During the study period from September 2019 to September 2021, there were 8 children (14%) treated for 3 months.

The most common symptom was skin lesion (75.4%) followed by rheumatism (43.9%) and fever (17.5%). Most patients had systemic lupus erythematosus disease activity index (SLEDAI) scores in high and very high activity (75.4% and 8.8% respectively).

Table 1. Clinical and laboratory characteristics of lupus nephritis patients before treatment

Some Characteristics of Lupus Nephritis	Frequence (N = 57)
Edema	37 (64.9%)
Hypertension	18 (31.6)
Hematuria	40 (70.2%)
uPCR < 200 mg/mmol	18 (31.6%)
uPCR ≥ 200 mg/mmol	39 (68.4%)
Serum albumin < 30 g/l	37 (64.9%)
Serum albumin ≥ 30 g/l	20 (35.1%)
eGFR 60 - < 90 ml/min/1.73 m^2	15 (26.3%)
eGFR < 60 ml/min/1.73 m^2	8 (14%)

(uPCR: urine protein-creatinine ratio, eGFR: estimated glomerular filtration rate)

As shown in **table 1**, those with clear LN with edema, hematuria and hypertension accounting for 64.9%, 70.2% and 31.6% of all participants respectively. Up to 68.4% of patients had an increase in uPCR ≥ 200 mg/mmol. The rate of hypoalbuminemia was high too with 64.9% of children. There was 40.3% children that had eGFR < 90 ml/min/1.73 m^2, in which 8 participants (14%) had eGFR < 60 ml/min/1.73 m^2.

Table 2. Treatment outcomes of lupus nephritis at National Children's Hospital.

Outcomes		12 weeks (n = 57)	24 weeks (n = 45)
uPCR (mg/mmol)	< 200	43 (75.4%)	42 (93.3%)
	≥ 200	14 (24.6%)	3 (6.7%)
Serum albumin (g/l)	< 30	4 (7%)	1 (2.2%)
	≥ 30	53 (93%)	44 (97.8%)
eGFR (ml/min/1.73 m^2)	60 - < 90	3 (5.3%)	3 (6.7%)
	< 60	1 (1.7%)	0
Overall remission	Overall remission	41 (71.9%)	42 (93.3%)
	complete response	16 (28.1%)	19 (42.2%)
	partial response	25 (43.8%)	23 (51.1%)
No response		16 (28.1%)	3 (6.7%)

As shown in **table 2**, the rate of hypoalbuminemia had dramatically decreased from 64.9% at start therapy to 7% at 3 months and 2.2% at 6 months. At 3 months, the proportion of patients with uPCR > 200mg/mmol decreased more than 2.5 times compared to the time of diagnosis and only 3 out of 45 patients (6.7%) at 6 months had uPCR > 200 mg/mmol. 4 out of 57 children in this study had eGFR < 90 ml/min/1.73 m^2, in which 1 patient had eGFR < 60 ml/min/1.73 m^2 after 3 months of treatment. At 12 weeks, 41(71.9%) patients had response and 16 of the 57 patients had complete remission. The rate of no response was quite high (28.1%). At 24 weeks, total respone increased in 93.3%. Partial remission occurred in 23 of 45 patients (51.1%) and CR reached to 42.2%. The number of no response children decreased to 3 (6.7%). In this study, there were 4 patients who dropped out of treatment as they could not come to our hospital because of the covid-19 pandemic.

In our study, 2 (3.5%) of the total patients had infections. 1 patient was lower respiratory tract infection, 1 child was urinary tract infection. No patients had leucopenia, diarrhea, or alopecia. Steroid-related adverse reactions seen in 3 participants with "moon face".

IV. DISCUSSION

cSLE is an autoimmune disease that causes multi-system damage and LN is one of its most important complications. Childhood LN is often more serious than LN onset in later adulthood.[12] Therefore, early diagnosis, timely treatment, and reasonable management are essential to improving the prognosis of children with LN. In our study, the epidemiological characteristics and

clinical manifestations were similar to previous reports. Of the 57 children with LN included in this study, 14 were males (24.6%) and 43 were females (75.4%), with a male:female ratio of 1:3.4. The mean age at diagnosis was 10.88 ± 2.105 years. Of initial non-renal manifestations, rash and rheumatism were the most common (75.4% and 43.9%, respectively), while patients with fever accounted for 10.6%. The average SLEDAI score is up to 14.69 point.

The initial manifestation of kidney involvement was mainly proteinuria. Kidney biopsy data in this study showed that the number of patients with class IV LN was more than one with class III LN (57.9% and 42.1% respectively). These findings were consistent with those of another study that class IV LN was the most common pathological type. Clinical manifestations of LN also had a certain relationship to the pathological type of LN. For example, urine protein level was significantly higher in class IV LN than in class III LN, and kidney function was better in pure class V LN than in proliferative LN. Carrying out a study on 57 children with class III and IV LN, we found that kidney lesions' clinical and subclinical symptoms were evident with 64.9% edema, 34.1% hypertension and 70.2% hematuria. Various studies reported that hypertension accounts for 30 to 50%.[2] Nearly 70% of patients had an increase in uPCR ≥ 200 mg/mmol and the rate of hypoalbuminemia was high too with 64.9% children. In our study, the ratio of patients with nephrotic syndrome was 49.1%, similar to Batinic et al[13]treatment and outcome of 37 Croatian children with biopsy-proven lupus nephritis seen over a 30-year period. The mean age at lupus nephritis presentation was 12.11 ± 2.59 years (range 4.66-17.0. But 14% of patients had eGFR < 60 ml/min/1.73 m^2.

Over the past decade several randomised controlled trials (RCTs) have been conducted for class III and IV LN, both in the induction and maintenance phase. Consequently, the guidelines are uniform in their recommendations for induction treatment: intravenous cyclophosphamide (ivCYC) or MMF (2-3 g total daily dose) in combination with oral glucocorticoids with or without three pulses of intravenous methylprednisolone (MP) at start of induction treatment. As per the ACR recent recommendation for class III/IV LN, MMF and glucocorticoids (GC) can be used as induction agents for African-American and Hispanic patients, whereas Cyc and GC remain the first choice for White populations[9]. Meta-analyses of smaller studies have suggested that more patients respond to MMF than to IVC, and the results from the large and racially diverse population of Gerald B. Appel's study indicate that these drugs in combination with prednisone have similar efficacy in short-term induction therapy.[14] We apply the treatment regimen of proliferative LN under the guidance of KDIGO, ACR, CARA. All patients received 3 days of pulse methylprednisolone (30 mg/kg/dose up to 1000 mg/dose) followed by a tapering course of oral prednisone therapy in combination with MMF 1200mg/m^2/day (max 2g/day). CNI-based regimens have been studied in Asia, and often combine MMF and steroids with a CNI ('multitarget therapy'). A large Chinese randomized trial reported improved rates of complete and partial renal remission at 24-weeks in patients treated with low-dose MMF, tacrolimus, and steroids compared to monthly IV-CYC and steroids for induction of proliferative LN.[15] Therefore, in this study, 10 patients (17.5%) who had high urine protein-creatinine ratio (uPCR > 200mg/mmol) and normal renal function after 1-month treatment with MMF were used multitarget therapy of prednisolon MMF and low dose CNI.

In our study, there were 4 patients who dropped out of treatment as they could not come to our hospital because of the covid-19 pandemic, 8 of 57 children has been treated for 3 month, and 45 patients were followed for 6 months. At 3 months, the proportion of patients with uPCR > 200mg/mmol decreased more than 2.5 times compared to the time of diagnosis and only 3 out of 45 patients (6.7%) at 6 months had uPCR >200 mg/mmol. Moreover, the rate of hypoalbuminemia had dramatically decreased from 64.9% at start therapy to 7% at 3 months and 2.2% at 6 months. Before treatment, there was 40.4% children that had eGFR < 90 ml/min/1.73 m^2, in which 8 participants (14%) had kidney failure. But, after 3 months of treatment, 4 out of 57 children in this study had eGFR < 90 ml/min/1.73 m^2, in which 1 patient had eGFR < 60 ml/min/1.73 m^2. At 12 weeks, 41(71.9%) patients had response and 16 of the 57 patients had complete remission. The rate of no response was quite high (28.1%). At 24 weeks, total response increased in 93.3%. Partial remission occurred in 23 of 45 patients (51.1%) and CR reached to 42.2%. This result was similar to previous study **(table 3**)

Table 3. Comparison with other studies

Study	Ginzler et al[16]	Xuebing Feng et al[17]	Our stydy
Year	2005	2014	2021
N	71/140	30/90	57
CR + PR at 12 weeks	78%	90% (CR: 24%)	71.9%(CR:28.1%)
CR + PR at 24 weeks	52.1%(CR: 22.5)	72%	93.3%(CR:42.2)

(CR: complete response, PR: partial Response)

In our stdudy, 2 (3.5%) of the patients had infections. 1 patient was lower respiratory tract infection; 1 child was urinary tract infection. No patients had leucopenia, diarrhea, or alopecia. Steroid-related adverse reactions seen in 3 participants with “moon face”.

Limitation: The study was limited to 24 weeks of follow-up.

V. CONCLUSIONS

Mycophenolate Mofetil is effective in the treatment of children with proliferative lupus nephritis in induction therapy.

REFERENCES

1. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. *Nat Rev Rheumatol*. 2010; 6(9): 538-546. doi:10.1038/nrrheum.2010.121.

2. Levy DM, Kamphuis S. Systemic Lupus Erythematosus in Children and Adolescents. *Pediatr Clin North Am*. 2012; 59(2): 345-364. doi:10.1016/j.pcl.2012.03.007.

3. Almutairi A, Alkathiri Z, Al-Mayouf SM. Combination of tacrolimus and mycophenolate mofetil in persistent proteinuria due to refractory childhood lupus nephritis. *Int J Pediatr Adolesc Med*. 2018; 5(3): 99-102. doi:10.1016/j.ijpam.2018.08.001.

4. Contreras G, Sosnov J. Role of Mycophenolate Mofetil in the Treatment of Lupus Nephritis. *Clin J Am Soc Nephrol*. 2007; 2(5): 879-882. doi:10.2215/CJN.02740707.

5. Moore RA, Derry S. Systematic review and meta-analysis of randomised trials and cohort studies of mycophenolate mofetil in

lupus nephritis. *Arthritis Res Ther*. 2006; 8(6): R182. doi:10.1186/ar2093.

6. Dahlström Ö, Sjöwall C. The diagnostic accuracies of the 2012 SLICC criteria and the proposed EULAR/ACR criteria for systemic lupus erythematosus classification are comparable. *Lupus*. 2019; 28(6): 778-782. doi:10.1177/0961203319846388.

7. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *PEDIATRICS*. 2004; 114(2): 555-576. doi:10.1542/peds.114.2.S2.555.

8. Schwartz GJ, Muñoz A, Schneider MF, et al. New Equations to Estimate GFR in Children with CKD. *J Am Soc Nephrol JASN*. 2009; 20(3): 629-637. doi:10.1681/ASN.2008030287.

9. Sinha R, Raut S. Pediatric lupus nephritis: Management update. *World J Nephrol*. 2014; 3(2): 16-23. doi:10.5527/wjn.v3.i2.16.

10. Pinheiro SVB, Dias RF, Fabiano RCG, Araujo S de A, Silva ACS e. Pediatric lupus nephritis. *J Bras Nefrol*. 2019; 41(2): 252-265. doi:10.1590/2175-8239-JBN-2018-0097.

11. Sahay M, Saivani Y, Ismal K, Vali PS. Mycophenolate versus Cyclophosphamide for Lupus Nephritis. *Indian J Nephrol*. 2018; 28(1): 35-40. doi:10.4103/ijn.IJN_2_16.

12. Sato V a. H, Marques IDB, Goldenstein PT, et al. Lupus nephritis is more severe in children and adolescents than in older adults. *Lupus*. 2012; 21(9): 978-983. doi:10.1177/0961203312443421.

13. Batinić D, Milošević D, Čorić M, Topalović-Grković M, Jelušić M, Turudić D. Lupus nephritis in Croatian children: clinicopathologic findings and outcome. *Lupus*. 2015; 24(3): 307-314. doi:10.1177/0961203314563133.

14. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis. *J Am Soc Nephrol JASN*. 2009; 20(5): 1103-1112. doi:10.1681/ASN.2008101028.

15. Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med*. 2015; 162(1): 18-26. doi:10.7326/M14-1030.

16. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med*. 2005; 353(21): 2219-2228. doi:10.1056/NEJMoa043731.

17. Feng X, Gu F, Chen W, et al. Mizoribine versus mycophenolate mofetil or intravenous cyclophosphamide for induction treatment of active lupus nephritis. *Chin Med J (Engl)*. 2014; 127(21): 3718-3723.