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Medium-Term Outcome of Cyclosporine in Children with Steroid-Dependent Nephrotic Syndrome: Single Centre experience from Pakistan

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ABSTRACT

Objective: To determine the medium-term outcome of Cyclosporine in children with steroid-dependent nephrotic syndrome from a single centre in Pakistan

Study Design: Prospective longitudinal study

Place and Duration of Study: Pediatric Nephrology Department of Sindh Institute of Urology and Transplantation, Karachi Pakistan from Jan 2014 to Dec 2016.

Methodology: All consecutive patients with steroid-dependent nephrotic syndrome of either gender, between 1-12 years of age, were identified and included in this study, who relapsed post-Cyclophosphamide therapy and were prescribed Cyclosporine after renal biopsy.

Results: Seventy-five children with steroid-dependent nephrotic syndrome met the inclusion criteria. There were 55(74%) boys with a mean age of 4.3 ± 2.5 years, while the mean age at the start of Cyclosporine therapy was 6.5 ± 1.5 years. All patients were previously treated with Cyclophosphamide, and sustained remission was achieved for 37.6 ± 43.6 weeks. All patients underwent renal biopsy showing minimal change disease in 46(61.3%) subjects, focal segmental glomerulosclerosis in 12(16%), IgM nephropathy in 13(17.3%) and mesangioproliferative glomerulonephritis in 4(5.3%) children. At the last follow-up, 36(48%) patients were in complete remission, 26(35%) achieved partial remission, seven children (9.3%) did not achieve remission at all, 2(2.7%) were lost to follow-up, and 4(5.3%) patients expired. The mean estimated glomerular filtration rate at the start of Cyclosporine was 112.55 ml/min/1.73 m2, which declined to 107.77 ml/min/1.73 m2 at three years.

Conclusion: In the medium term, Cyclosporine effectively maintains remission and reduces steroid usage with minimal nephrotoxicity in steroid-dependent nephrotic syndrome.

Keywords: Children, Cyclosporine, Nephrotic syndrome, Steroid-dependent.

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INTRODUCTION

In almost half of the cases, children with steroid-sensitive nephrotic syndrome (SSNS) show a steroid-dependent pattern.[1] Steroid-dependent nephrotic syndrome (SDNS) represents a significant therapeutic challenge because prolonged use of steroids accrues serious side effects. Among the many steroid-sparing drugs available, alkylating agents and calcineurin inhibitors (CNIs) have better-proven efficacy.[2,3] Cyclophosphamide (CYP), an alkylating agent, has a long-established role in SDNS but with variable reported rates of sustained remission that lasts for two or more years. CNIs (Cyclosporine and Tacrolimus) are usually used after alkylating agents in SDNS.[4,5] These drugs function by down-regulating interleukin-2 (IL-2) driven T-cell activation.[6] The efficacy of these agents is dose-dependent. It correlates with the circulating blood levels, resulting in relapse after the drug is stopped. Hence, prolonged use of CNIs is required. The duration of remission following CNI therapy is also variable.[7] However, the long-term use is limited by the possible development of irreversible renal damage.[8] A 36% incidence of nephrotoxicity has been reported with the prolonged use of Cyclosporine A (CyA) in NS.[9] This presents a challenge for pediatric nephrologists regarding the management and duration of therapy while minimising the risk of nephrotoxicity.[10]

In this analysis, we aimed to determine the medium-term outcome of CyA use in SDNS patients who relapsed after an initial treatment course of CYP. The primary outcomes were achievement of complete or partial remission and no response to CyA. This study also determined if remission was affected by age at onset of disease, histopathological findings or duration of sustained remission following CYP treatment. The secondary outcome was the status of renal functions in terms of estimated Glomerular Filtration Rate (eGFR) at specific follow-up intervals.

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METHODOLOGY

The prospective longitudinal study included SDNS patients diagnosed from January 2014 and December 2016 at the Pediatric Nephrology Department of Sindh Institute of Urology and Transplantation (SIUT) Karachi. Study was approved by the Ethical Review Committee of the institute (SIUT-ERC-2020/A-202).

Inclusion Criteria: All patients between 1-12 years of age who were prescribed CyA for relapse following treatment with CYP were identified and included in this study.

Exclusion Criteria: Patients who had developed proteinuria while on CYP therapy or developed secondary steroid resistance were excluded.

Renal biopsy was done in all patients before starting CyA. After remission with induction dose in all patients, steroids were tapered to 1 mg/kg/every other day (maximum 40mg) and CyA at 5mg/kg/day in two divided doses. CyA was tapered to the minimum possible dose at which a state of complete or partial remission was maintained without causing more than a 30% increase in serum creatinine and maintaining a CyA trough level of 80-120ng/dl. 11 Similarly, steroids were further tapered and stopped once a steady state of remission, whether complete or partial, was obtained. All patients had normal serum creatinine for age at initiation of CyA therapy.

The population of SDNS patients in 3 years would be around 80 patients. Based on previous estimates at three years follow-up, complete remission was observed in 87.5% of patients.[7] With a margin of error of 5% and a 95% confidence interval, a sample size of 75 was calculated using the OpenEpi calculator. After reviewing the medical records with consecutive sampling techniques, 75 children with SDNS receiving CyA treatment were identified. Their demographic, clinical, laboratory and histopathological findings and treatment were recorded on a predesigned proforma. Laboratory investigations included serum creatinine and urinary dipstick for proteinuria.

The outcome was recorded at 12 weeks, one year, three years and the last available follow-up. Disease outcome was based on the classification of patients into either complete or partial remission or no response. Renal function at each follow-up was recorded and estimated Glomerular Filtration Rate (eGFR) was calculated using age and gender-appropriate modified Schwartz formula.[12,13]

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis All continuous variables were presented as mean with standard deviation and categorical variables as frequencies and percentages. The chi-square test was applied to determine the association between clinicopathologic features and achievement of remission. Estimated marginal means were used to plot the graph. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Seventy-five children with SDNS met the inclusion criteria and were enrolled in the study. There was a male predominance with 55(74%) boys, and age ranged from 1 to 12 years with a mean age of 4.3±2.5 years (Table-I). All patients were treated with CYP previously, with a mean duration of treatment being 12 weeks. Post-CYP sustained remission lasted for a mean duration of 37.6±43.6 weeks before relapse of NS. The mean age of patients at the start of CyA therapy was 6.5±1.5 years. All patients underwent renal biopsy before CyA therapy. The predominant pattern of histology was minimal change disease (MCD) in 46 (61.3%) patients, followed by focal segmental glomerulosclerosis (FSGS) and IgM nephropathy in 12(16%) and 13(17.3%) patients, respectively.

Table-I: Demographic, Treatment and Histopathological Characteristics of study patients (n = 75)

Parameters	n(%)
Gender	
Male	55(73%)
Female	20(26%)
Mean age at onset of NS (years)	4.3±2.5
Mean duration of CYP therapy (weeks)	12±5.88
Mean duration of post CYP relapse (weeks)	37.6±43.6
Age at the time CyA introduced (years)	6.5±1.5
Mean duration of CyA therapy (years)	3.2±1.4
Histopathology	
Minimal Change Disease	46(61.3%)
IgM Nephropathy	13(17.3%)
Focal Segmental Glomerulosclerosis	12(16%)
Mesangioproliferative Glomerulonephritis	4(5.3%)

All patients with post-CYP relapse were treated with CyA. The first follow-up was scheduled at 12 weeks when 66(88%) patients were found to respond and achieved complete remission, while 9(12%) still had nephrotic range proteinuria. No patient was noted to be in partial remission. At 1-year follow-up, 51(68%) patients were seen to maintain complete remission, 8(10.7%) had partial remission, 14(18.6%) showed no response, and 2(2.7%) patients had expired due to infection-related complications. At 3-year follow-up,

34(45%) patients showed complete remission, 27(36%) were in partial remission, and 9(12%) showed no response. Two (3%) patients were lost to follow-up, and one more died due to sepsis, with total expiries being 3(4%). The outcome at the last follow-up was complete remission seen in 36(48%) patients, partial remission in 26(35%), failure to achieve remission found in 7 patients (9.3%), loss of follow-up in 2(2.7%) children and death occurred in 4(5.3%) patients.

Table-II: Association of Clinicopathologic Parameters with the Status of Remission (n=69)

Parameter	Remission State			*p*-value
	Complete Remission	Partial Remission	No Remission	
Age				
<5 Years	24(34.8%)	21(30.4%)	5(7.2%)	0.7
>5 Years	11(16%)	6(8.7%)	2(2.9%)	
Gender				
Male	22(31.9%)	24(34.8%)	5(7.2%)	0.2
Female	13(18.8%)	3(4.3%)	2(2.9%)	
Histopathology				
Minimal change disease	21(30.4%)	18(26.1%)	4(5.8%)	0.6
Focal segmental glomerulosclerosis	5(7.2%)	6(8.7%)	-	
IgM nephropathy	7(10%)	2(2.9%)	2(2.9%)	
Mesangiopro-liferative glomerulonephritis	2(2.9%)	1(1.4%)	1 (1.4%)	
Duration of Post Cyp Remission				
<6 months	18(26.1%)	14(20.3%)	3(4.3%)	0.1
6 months-1 year	14(20.3%)	4(5.8%)	2(2.9%)	
>1 year	3(4.3%)	9(13%)	2(2.9%)	

In the study cohort, 20(26.7%) patients were switched to alternative regimes. Eighteen (24%) participants were given Tacrolimus, while 2(2.7%) were switched to a triple regime comprising lowdose steroids, Tacrolimus and Mycophenolate Mofetil. Association of clinicopathologic parameters with the status of remission is shown inTable-II).

The trend of renal functions during this period was determined by calculating eGFR and noted at the start of CyA therapy, 12 weeks, one year, and 3-year follow-up. The mean baseline eGFR was 112.55 ml/min/1.73m^2, and at 12 weeks was 111.29 ml/min/1.73m^2, which was almost the same. It was found to be 110.403 ml/min/1.73 m2 and 107.77 ml/min/1.73m^2 at one and 3-year follow-up. A marked decline in eGFR was observed after three years of CyA therapy, (Figure).

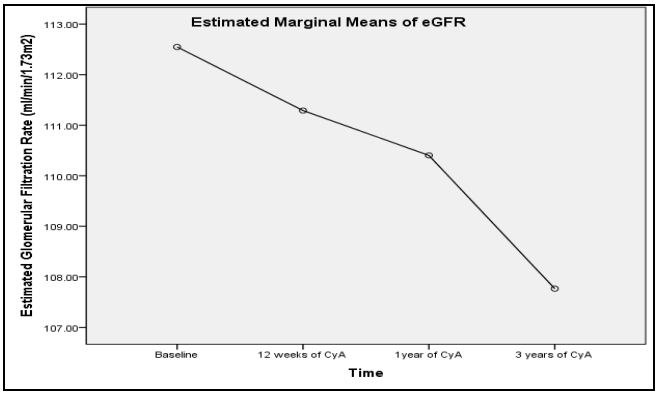

Figure: Trend of Renal Functions over three years of Cyclosporine usage

DISCUSSION

This study analysed the medium-term outcome of pediatric SDNS patients prescribed CyA after using CYP. Our study focused specifically on the role of CyA in SDNS patients in contrast to most other studies that have studied the efficacy of CyA in both SRNS and SDNS patients simultaneously or compared the response of CyA in SRNS with that of the response in SDNS. We determined if remission was achieved with CyA in SDNS patients and studied the trend of renal functions. We found CyA safe and efficacious in SDNS with a low side effect profile when used in low-maintenance doses.

Our study showed that the mean duration of sustained remission post-CYP was 37 weeks, consistent with previous studies.[12,13] The most common histological lesion in our study was MCD, followed by FSGS and IgM nephropathy, while a small percentage of patients had MesPGN. Similar findings were reported by Sadaf *et al.*[14] and another study done in northern Pakistan.15 There was no association of underlying histological diagnosis with the clinical outcome of SDNS in our study. Phadke and colleagues, 16 Niaudat *et al.* and Habib and his co-workers reported a similar observation. [17-18]

In the very short term, the outcome of CyA therapy was good, showing achievement of complete remission in sixty-six (88%) patients at the initial follow-up of 3 months when steroids were tapered and stopped. A similar result was found in a study by Saeed *et al*.conducted in Saudi children in which 87% of patients achieved complete remission. In comparison, 13.5% achieved partial remission at the 6-month follow-up.[19] A lower percentage (69%) of complete remission was seen in a Brazilian study, probably because of the ethnic and genetic variation in the study population.[20]

Relapses are common when CyA therapy is terminated. Only one patient from our study cohort remained in remission after cessation of CyA. The remaining relapsed with nephrotic range proteinuria whenever CyA was tapered with the intent of stopping therapy. This trend of CyA dependency is well known.[21] However, Hino *et al.* have demonstrated sustained remission, steroid independence as well as steroid dependence after cessation of 2-year therapy of CyA.[8] In contrast, Kemper *et al.*have reported severe steroid dependency in patients who had been on maintenance CyA for more than two years followed by a relapse. These children developed persistent proteinuria whenever steroids were tapered to alternate-day therapy of 40mg/m2/day, and other agents were then used to induce remission.[21] Our study corroborated the observation of Ponticelli *et al.*, who did not find any clinical or laboratory parameters that could predict the chances of remission in patients with SDNS.[2]

Our study found CyA in maintenance dose to be beneficial in maintaining remission, whether complete or partial, in more than 80% of the patients of SDNS. While there was a decline in eGFR, it remained within normal ranges, making CyA usage safe in the medium term.

LIMITATIONS OF STUDY

Nephrotoxicity due to CyA usage cannot be excluded completely by serum creatinine levels alone and needs renal biopsy for definitive diagnosis. The natural progression of the disease rather than the use of CyA causing a deterioration in renal functions cannot be excluded without a renal biopsy. Follow-up biopsy was not performed in our patients on maintenance doses of CyA, which was a limitation of our study.

CONCLUSION

This study concluded that CyA is beneficial in maintaining complete remission and reducing steroid usage with minimal nephrotoxicity in more than half of the patients with SDNS over the medium term. Further studies are required to assess the long-term outcome of CyA usage in SDNS while reducing the risk of nephrotoxicity.

Authors Contribution:

Following authors have made substantial contributions to the manuscript as under:

SK: & MA: Conception, study design, drafting the manuscript, approval of the final version to be published.

PK: & SUA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AAL: & SH: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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