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EFFICACY OF CYCLOSPORINE-A FOR THE TREATMENT OF STEROID RESISTANT NEPHROTIC SYNDROME

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Abstract:

Aim: *To evaluate the efficacy and safety of cyclosporin A, which is the basis for the treatment of complete and sustained remission in steroid resistant nephrotic syndrome in children.*

Project: *A hospital based descriptive study (case series).*

Place and duration: *In the department of pediatric Nephrology, Children Hospital Lahore for one-year duration from January 2019 to January 2020.*

Patients and methods: *Twenty-nine patients with steroid resistant nephrotic syndrome (focal segmental glomerulosclerosis in 13 cases, minimal change in disease in 8 cases, mesangoproliferative glomerulonephritis in 4 cases, membranoproliferative glomerulonephritis in 3 and crescentic glomerulonephritis in 1) with normal renal function and glomerular filtration rate, were treated with Cyclosporine-A and Enalapril for 12 months along with low dose alternate day Prednisolone tapered over six to nine months.*

Results: *The average age of 29 patients (20 boys and 9 girls) was 8.3 (range: 2.7-14). The mean age at the beginning of the nephrotic syndrome and the beginning of the cyclosporin-A study was 4.3 years (range 1.7-12) and 8 years (range: 2.5-14), respectively. Seven (24.1%) cases had "early steroid resistance" and 22 (75.8%) had "late steroid resistance". At the end of the 12-month treatment, 17 (58.6%) patients were mostly in full and continuous remission with focal segmental glomerulosclerosis (9 of 13 cases) and minimal lesion disease (6 of 8 cases). Eight (27.5%) patients continued to have proteinuria in the nephrotic range. This group initially included only 6 cases in which partial remission was achieved, and then 2 cases that stopped responding to cyclosporin-A after a period of full remission. Four (13.7%) cases did not undergo remission from the very beginning. The median time to achieving "full remission" and "partial remission" after the start of the cyclosporin-A study was 2.2 months (range 1 to 3.5) and 3 months (range 2-5), respectively. The correlation of early remission with longer and total remission time was significant. Recurrence of pyuria was demonstrated in 4 (13.7%) and bacterial peritonitis in 2 cases. Hirsutism was reported in 22 (75.8%) patients. Three (10.3%) patients went on to end-stage renal disease.*

Conclusion: *Cyclosporin-A is highly effective and safe to achieve full remission lasting at least 12 months in approximately 60% of cases of steroid-resistant nephrotic syndrome in children, especially when it leads to early remission.*

Keywords: *Nephrotic syndrome, steroid resistance, cyclosporin-A.*

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INTRODUCTION:

The clinical management of steroid-resistant nephrotic syndrome (SRNS) is very difficult, often difficult, and sometimes quite annoying. There is no consensus as to when a patient should be marked as a non-reactive steroid due to the lack of a precise and universally accepted definition of steroid resistance. However, no response to oral prednisolone 60 mg / m2 / day or 2 mg / kg / day for at least 6-8 weeks will be marked as steroid resistance. these cases. those who were initially sensitive to steroids for a variable time, but stopped responding at a later stage. Clinical experience has shown that long-term aggressive treatment with various combinations of steroids with alkylating agents and alternative drugs such as cyclosporin A (CY-A) can cause complete or partial remission in 20-80% of cases. It is said that even a partial response improves long-term prognosis and results, but only a limited number of cases will achieve long-term, accurate and lasting remission using current treatment protocols. CY-A, one of the calcineurin inhibitors, has become the second most commonly used second-line drug in many centers, based on the first observation of approximately 20-30% of cases. Pediatric SRNS responds particularly to CY-A in patients with focal segmental glomerulosclerosis as the underlying disease. The theoretical concern based on the lipophilic nature of CY-A is that a much higher plasma concentration may be necessary to achieve adequate tissue concentration in the presence of severe hypercholesterolemia. Another difficult question is when to discontinue CY-A treatment and when to announce a refractory patient. A trial period of at least six months is recommended. In this study, CY-A was used as the basis for SRNS in children to evaluate the following goals.

1. Assess the efficacy of CY-A in inducing remission.
2. Investigate the full and partial remission time caused by CY-A.
3. Assess safety for negative effects on CY-A.

PATIENTS AND METHODS:

This descriptive study (series of cases) was at the department of pediatric Nephrology, Children Hospital Lahore for one-year duration from January 2019 to January 2020. SRNS, irrespective of the underlying histology, up to 14 years of age with normal renal function and glomerular filtration rate were selected to undergo CY-A trial according to the following criteria.

1. Early resistance: cases that have not responded to oral treatment with 2 mg / kg / day or 60 mg / m2 / day for at least two months or longer with prednisolone.
2. Delayed resistance: cases that initially remained susceptible to steroids for a variable period of time, but then did not respond to treatment in case of relapse.

Children with SRNS with renal impairment were excluded from the study and histological classification was made prior to the start of the CY-A study. When performing a kidney biopsy in the ward using a modified Menghini "SURECUT" biopsy needle in mild sedation and local anesthesia, 3 patients had already received a histological diagnosis during recruitment. job. As shown in Figure 1, patients had 13 cases of focal segmental glomerulosclerosis (FSGS), 8 cases of minimal lesion disease (DCM), 4 cases of mesangiroliferative glomerulonephritis (Moon PGN), 3 cases of diffuse tumor-proliferative glomerulonephritis (DMPGN) and 1 crescent glomerulonephritis (DMPGN) and 1 crescent glomerulonephritis (DMPGN). A biopsy of a CGN patient suggested crescent formation in 15 to 20% of the glomeruli. Hypertension and nephrotic gap are manifested by proteinuria, but with normal serum creatinine and GFR. Before entering the study, it was prepared daily with 12 doses of 30 mg / kg in pulse therapy with methylprednisolone. No patient has ever been exposed to CY-A. In all cases, there was no clinical or laboratory evidence of systemic diseases such as vasculitis, hepatitis B, systemic lupus erythematosus or malignancy. Each patient has been documented to have a normal glomerular filtration rate (GFR), serum urea, creatinine and electrolytes. Estimated GFR was obtained based on appropriate serum creatinine levels and patient survival height. In all cases, parental leave was accepted in writing. The most likely drug-related results and side effects were explained to parents before starting the CY-A study. CY-A (Neoral, Novartis Pharma) was administered orally at a dose of 5-10 mg / kg / day in two separate doses during the first 6 months, then reduced to 2-5 mg / kg / day during maintenance therapy. Each patient in serum was also given a single dose of Enalapril 0.5 mg / kg / day and prednisolone 1 mg / kg on an alternative day after breakfast. The latter has been reduced to 6 to 9 months. Response to CY-A was assessed every 6-8 weeks until the end of the 12-month study. Each subsequent visit; In addition to the detailed physical examination, weight, standing height and blood pressure were documented. Images of urine, peripheral blood, serum urea, creatinine, electrolytes, calcium, phosphate, alkaline phosphatase and lipid profile images were examined for albumin, pyuria and microscopic hematuria. Unless otherwise stated, serum CY-A levels were recorded every two months. Important details have been reported for the treatment

of infection, ascites and hypertension. Twelve cases required blood and plasma transfusions at various stages of the study.

Pearson's correlation was determined between the onset of remission and its duration. The various terms used in research are defined as follows:

1. Total and continuous remission: serum albumin levels increased to over 2.5 grams / dL for at least 12 months with edema and albuminuria.
2. Partial remission: persistent albuminuria from 1 to 2+ in the bayonet test, but without swelling and maintained serum albumin (over 2.5 grams / dl).
3. No remission or CY-A resistance: persistent edema, severe albuminuria (more than 2 in the test strip) and hypoalbuminaemia (less than 2.5 grams / dl) or re-occurrence of these results for at least six months of complete or partial remission.
4. Early remission: Complete remission was achieved in the first eight weeks of the CY-A study.
5. Delayed remission: Complete remission is achieved after the first eight weeks of treatment.

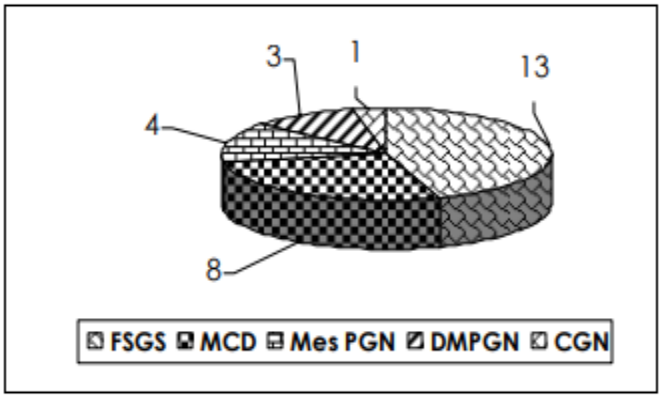

Fig 1: Histology distribution of 29 patients.

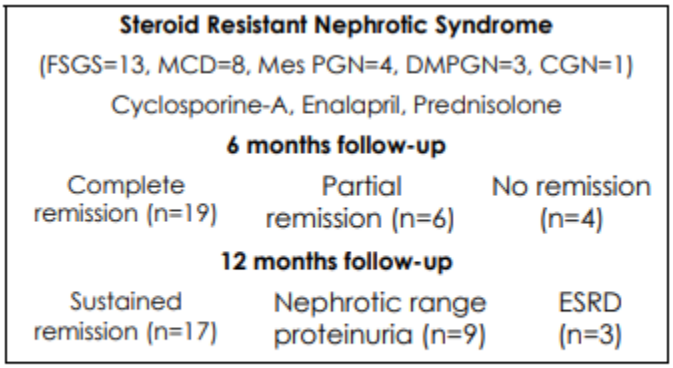

Fig. 2: Treatment protocol, follow-up and outcome.

RESULTS:

During the four years 29 children with SRNS were detected. In the current documentation of five patients, while poorly variable cyclophosphamide treatment was observed for various periods, 2 received pulse therapy with methylprednisolone for at least 5 to 18 months before enrolling in the study, but had to stop treatment for internal reasons. Twenty of the 29 patients selected for the study had 20 boys and 9 girls aged 2.7-14 years. The mean age at the beginning of the nephrotic syndrome and the beginning of the CY-A study was 4.3 years (between 1.7-12) and 8.0 (between 2.5-14), respectively. The median time of documented steroid resistance before induction in the study was 14 months (range: 3-48). 7 (24.1%) cases had "early resistance to steroids" and 22 (75.8%) had "late resistance". At the end of 6 months of CY-A treatment, 19 (65.5%) patients had complete remission, 6 (20.6%) patients had a partial response, and 4 (13.7%) showed no signs of remission. The mean time to complete and partial remission after starting the CY-A study was 2.3 (range 1-3.5) and 3

(range 2-5) months, respectively. In the histopathological classification of cases of complete remission of FSGS in 10 patients, MCD, PGN, DMPGN and CGN in 6 patients, each was detected in 1 patient. FSGS dominated in this group (10 of 13 cases: 76.9%), followed by DCM (6 of 8 cases: 75%). In 6 patients (FSGS, DCM and PGN month: 2 cases each), "partial remission" lasted 5.5 months on average (range 2-10). A group of 4 "non-responding" patients (13.7%) were FSGS: 1, Ay PGN: 1 and DMPGN: 2. In a 12-month follow-up period 17 (58.6%) cases (FSGS: 13 of 13 (69.2)%), DCM: 6 out of 8 (75.0%), Moon PGN: 1 and DMPGN: 1) were in full and continuous remission. . (Figure 2). It should be noted that 17 (89.4%) of 19 full remission cases achieved "early remission" and all were able to achieve full remission at the end of the 12-month CY-A study. Therefore, it was found that the early onset of CY-A-induced remission was strongly associated with a longer total remission time (Pearson correlation, r = 0.01). Nine (31.0%) patients (FSGS: 3, MCD: 2, Ay PGN: 3 and CGN: 1) containing 6 partial remission groups have already returned to nephrotic proteinuria. Three (10.3%) patients went on to end stage renal disease (ESRD) from "partial remission" 1 (FSGS) and 2 from "no remission" (DMPGN). Infections were reported in 7 (24.1%) cases classified as recurrent pyuria in 4, lobular pneumonia in 1 and bacterial peritonitis in 2. Hypertensive encephalopathy developed in one patient at the beginning of the study period, but responded well to supportive and antihypertensive treatment. Two (6.8%) patients had pruritus and moderate hyperuricemia requiring allopurinol treatment, but no arthritis symptoms were observed. Hirsutism was very stressful and was reported in 22 (75.8%) of 29 patients. Hyperlipidemia has been documented in 12 patients (41.3%), but the corresponding serum CY-A levels did not justify any change in CYA dose. There were no deaths during the study period associated with SRNS or CY-A. Parental cooperation and patient compliance remained satisfactory.

Table I shows a comparison of different clinical-pathological features and results in the groups of "complete remission" and "partial / non-responding".

TABLE I: Comparison of clinical features, histology and outcome at 12 months

Features	Complete remission (n=17, 58.6%)	Partial or no remission (n=12, 41.3%)
Age at onset	4.9 years (range: 1.7-6.9)	3.7 years (2.3-10)
Age at treatment	8.1 years (range: 3.7-14)	7.9 years (2.5-11.5)
Male: female	12:5	8:4
Steroid resistance	13.6 months (range: 3-36)	15.5 months (5-48)
Time to remission	2.2 months (range: 1-3.5)	3 months (25)
FSGS	9	4
MCD	5	3
Mes PGN	2	2
DMPGN	1	2
CGN	-	1
Hypertensive Encephalopathy	1	-
Recurrent pyuria	1	3
Peritonitis	1	1
Lobar pneumonia	-	1
Hyperuricemia	-	2
Hyperlipidemia	9	3
Hirsutism	15	7

DISCUSSION:

About 10% of all pediatric nephrotic syndromes are likely to be resistant to steroids and have been described as chronic progressive disease10. The transition to ESRD is unavoidable in cases with severe and refractory nephrotic syndrome. Although the ultimate goal of treatment in this subset of patients is kidney transplantation, a disease like FSGS has been

reported in approximately 25% of kidney transplants. The aim of this study was to assess induced persistence and CY-A-targeted remission in SRNS. The results of this CY-A study are consistent with the latest literature that within 12 months of treatment, approximately 60% of patients may experience complete and well-maintained remission, characterized by a low acceptable frequency of very worried side effects. nephrotoxicity. CY-A is a well-tested, promising immunosuppressant and is used in organ transplant programs, but in patients with nephrotic syndrome, therapeutic use of CY-A began in 1985. The effectiveness of this drug has been documented. SRNS, steroid-induced nephrotic syndrome (SDNS) and many other glomerular diseases. Despite initial concerns about CY-A-associated nephrotoxicity, CYA and alternative daytime steroids were used to treat SRNS patients when post-treatment biopsy showed low renal toxicity. important discovery. CY-A significantly increased the number of children providing complete remission compared with placebo or without treatment. Despite their potential chronic nephrotoxicity, Etlo and Mello VR reduce corticosteroids in patients with steroid toxicity symptoms, especially on alternative days, the combination of prednisolone is effective in the treatment of CYNS and SDNS and in patients with steroid toxicity symptoms. In a 1998 Indian study, it was found that CYA could be considered a possible treatment option for patients with NSDS and SRNS with renal impairment. The results indicate that longer CY-A treatment is probably required in these cases. Osmani and Farooqui concluded that CY-A monotherapy is a rational and important option in the treatment of patients with nephrotic syndrome whose classic treatment regimen fails. CY-A was successfully used in combination with steroid-resistant FSGS in combination with prednisone each day and earlier for 8 weeks of pulse therapy with methylprednisolone. No progressive evidence of interstitial disease was observed in post-treatment control renal biopsies. A six-month CY-A treatment protocol has been shown to effectively maintain remission in patients with NSDS and SRNS with renal histology suggesting DCM, in combination with low daily steroid doses. Our findings confirm the data from these studies and guarantee the combined use of low-dose steroids and CY-A to achieve full and continuous remission, especially in cases of FSGS and DCM. A Japanese study confirms the concept that long-term treatment with moderate doses of CY-A is effective in patients with NSDS and SRNS and has a low incidence of histologically confirmed nephrotoxicity. Long-term use of CY-A appears to reduce the SDNS coefficient and reactivity after steroids in SRNS. Gauthier and Trachtman reported that CY-A causes complete remission in 85% of children and 79% of adults with NSDS and 67% of children and 61% of adults with SRNS. CY-A has been shown to be an effective and well-tolerated drug in children with SRNS, and especially those with FSGS may have a reduced risk of early end ineffectiveness. In a study of 22 children in 1996, it was found that CY-A can be used to terminate SRNS and maintain remission in cases of SDNS, and also has constant expectations for remission after stopping treatment. CY-A was used to maintain and prolong remission in young children with SRNS, where remission is induced by pulsed methylprednisolone therapy at an average of 24 doses over approximately 4 weeks. CY-A treatment has also been reported to be effective in patients with RNSS caused by membrane-permeable glomerulonephritis in children and adults who do not respond to other treatment protocols. In our study, one patient with 3 cases of DMPGN was in full and continuous remission after 12 months, while the other two ended ESRD. In a randomized controlled trial comparing 26-week CY-A treatment with placebo plus low-dose prednisolone and prednisone, 49 adults with confirmed biopsy SRNS and FSGS responded significantly to the CY-A / prednisolone protocol. Despite the high relapse rate, a significant reduction in proteinuria and maintenance of filtration function have been observed in a significant number of patients. According to our study, 69.2% of FSGS cases and 62.5% of MCD SRNS ensure complete and continuous remission over 12 months of treatment while maintaining normal renal function. Butt and Ahmed used CY-A only in 10 cases of SRNS and only for 12 weeks. Due to the small sample size and very short CY-A treatment, it is difficult to draw any conclusions compared to the results of the present study. Scientists have expressed concerns about secondary CY-A resistance in children with SDNS and SRNS. Secondary resistance is defined as complete and sustained initial remission with CY-A followed by a relapse after treatment discontinuation and incomplete or poor response to drug relocation. They concluded that the presence of FSGS increases the risk of secondary resistance, and that some of these cases may rapidly switch to ESRD. Evidence for the treatment of interstitial fibrosis and atrophy of the CY-A tubules in patients with NSDS and SRNS has been documented and reported in several studies and has significant incidence potential.

CONCLUSION:

Even in the absence of standardized guidelines for the dose and duration of treatment, CY-A appears to be a highly rational therapeutic agent for patients with SRNS, especially patients with FSGS, along with

alternative low dose steroids and enalapril. DCM with low risk of nephrotoxicity when used in well-selected patients.

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