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# Clinical Profile and Therapeutic Level of Tacrolimus in Children withSteroid Resistant Nephrotic Syndrome-A Single Centre Retrospective Study

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## Abstract:

**Background:** Nephrotic Syndrome is a chronic kidney disease in children.Majority of the children usually respond to standard steroids treatment and achieve complete remission of proteinuria but 10-15% of these patients do not respond to steroid. This condition is categorized as steroid resistant nephrotic syndrome (SRNS) and treated with Calcineurin inhibitors. The Tacrolimus is one of the important Calcineurin inhibitor prescribed for thetreatment of SRNS. The aim of this study is tostudy Clinical profile and therapeutic level of Tacrolimus in Children with Steroid Resistant Nephrotic Syndrome.

**Method:** A retrospective study of follow up patients referred to Drug Assay Lab was done. Therapeutic drug monitoring of tacrolimus was done for the SRNS patients from January, 2021 to April, 2021.The clinical profile 55 children with steroid resistant nephrotic syndrome were assessed. Data was evaluated on the basis of laboratory report of tacrolimus and hospital patient's card of these patients.

**Results:** 55 patients were studied. Mean age at onset of Nephrotic syndrome was 5.45±3.79. Gender distribution ration was 2.43:1. Kidney Biopsy results showed thatmost common histological diagnosis was minimal change disease (47.27%**)** followed by Focal Segmental Glomerulosclerosis (34.54%).Themean trough concentration of tacrolimus at follow up visit after one year was found 6.41 ng/mL and 61.81% achieved a remission and 30.90% patients showed partial remission.

**Conclusion:**61.81% patients achieved a complete remission and 30.90% patients showed partial remission.Clinical profile and trough level of tacrolimus of children showed a better treatment outcome with tacrolimus therapy.

**Keyword:** Steroid Resistant Nephrotic Syndrome (SRNS); Tacrolimus; Nephrotic Syndrome, Calcineurin inhibitors.

**Introduction**: Nephrotic Syndrome is a common glomerular disorder in children characterised by combination of massive proteinuria, hyperlipidemia, hypoalbuminemia and edema. The prevalence of childhood nephrotic syndrome (NS) varies in different population from 12–16/ 100000 children [1]. It affects all ages and ethnic background. The reported incidence of nephrotic syndrome is 2-3/100,000 children in western countries, slightly higher in 2- 7/100,000 in south Asian origin [2].The majority of patients of Nephrotic syndrome are idiopathic while a small proportion of cases may be secondary or congenital [3]. The common causes of nephrotic syndrome in children consist of minimal change disease (MCD), Focal segmental glomerulosclerosis (FSGS), IgA nephropathy and membranous nephropathy. The patients of nephrotic syndrome are treated with multiple immunosuppressive therapies which include calcineurin inhibitors (cyclosporine and tacrolimus), cyclophosphamide, Mycophenolatemofetil and Rituximab [4, 5].

**Steroid Resistant Nephrotic Syndrome (SRNS)**: Most of the children with Nephrotic

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Syndrome initially respond to steroids and achieve remission of proteinuria following 4-6 weeks of treatment with prednisolone, however 10-15% patients do not achieve complete remission and classified as steroid resistant nephrotic syndrome (SRNS) [6]. Recent studies have indicated significant increase in the number of steroid resistant Nephrotic syndrome particularly in south east Asia.Management of Steroid Resistant Nephrotic Syndrome requires combination of immunosuppressants, angiotensin converting enzyme inhibitor, low dose steroids and statin etc. Failure of immunosuppressive medications leads to a high risk of developing end stage renal disease (ESRD). The management of SRNS is a challenging task for nephrologists due to various side effects related to immunosupression such as infections, nephrotoxicity, cytopenia neurotoxicity and malignancies. Regular therapeutic monitoring of calcineurin inhibitor drug are important and the choice of immunosuppressant primarily depends upon their efficacy and safety of drugs. Tacrolimus and cyclosporine are important drugs primarily prescribed for the treatment of SRNS. The aim of this study is to evaluate clinical profile and therapeutic level of Tacrolimus in children receiving treatment of with Steroid Resistant Nephrotic Syndrome.

**Material and Methods:** A retrospective study of all patients referred to Drug Assay Lab at Kalawati Saran Children's Hospital (KSCH) for therapeutic drug monitoring of Calcineurin Inhibitor was done. Chart review of 55 children in the age group of 1–18 years of age, attended Nephrology Clinic from January 2021 to March, 2021 was performed. The study was approved by the Institutional Ethics Committee of LHMC & Associated Hospitals vide letter no LHMC/IEC/2021/01. Trough concentration of tacrolimuswas evaluated in children with steroid resistant nephrotic syndrome receiving treatment from Kalawati Saran Children's Hospital, New Delhi.KSCH is a tertiary care children hospital which provides a comprehensive care and facility for diagnosis, treatment and management of pediatric patients. Our hospital runs special clinic for patients with nephrotic syndrome every Tuesday and Saturday. Regular follow-up and laboratory monitoring of all patients is done. The patients are examined by specialist medical practitioners. Hospital has a dedicated Drug Assay Laboratory provide facility for therapeutic drug monitoring for various important drugs. Therapeutic drug monitoring is also available for Calcineurin inhibitors like tacrolimus and cyclosporine. Tacrolimus level are done on Indiko$^{TM}$(Thermo Fisher) fully automated clinical chemistry analyzer using particle enhanced turbidimetric immunoassay (PETIA) Technology. Clinical Data of duly registered patients of Nephrotic Syndrome like clinical history, treatment, laboratory reports of patients was evaluated. All analyses were carried out using statistical software, SPSS, after data collection.

**Inclusion Criteria:**

- Children in the age group of 1–18 years were included in the study. Nephrotic Syndrome was diagnosed as per the ISPN guidelines (nephrotic range proteinuria 40 mg/m$^{2/}$ hr or >1000 mg/m$^2$ /day; spot Up/Uc>2 mg/mg; 3-4+ by dipstick; with spot hypoalbuminemia (albumin <3.0 g/dL; and edema.

**Exclusion criteria:**

- Children with secondary causes of nephrotic syndrome were excluded from the study.

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• Children whose records were not complete were excluded from the study

**Box I Definitions Related to Nephrotic Syndrome [7]**

| | |
|---|---|
| Nephrotic syndrome | Nephrotic range proteinuria (40 mg/m2/hr or >1000 mg/m2/day; spot Up/Uc>2 mg/mg; 3-4+ by dipstick); hypoalbuminemia (albumin <3.0g/dL); and edema. |
| Steroid sensitivenephrotic syndrome | Complete remission within 6-weeks' treatment with prednisolone at a dose of 60 mg/m2/ day (2 mg/kg/day; maximum 60 mg/day) |
| Initial steroid-resistance | Failure to achieve complete remission after 6-weeks initial therapy with prednisolone (as defined above) |
| Late (secondary) steroid-resistance* | Initially steroid-sensitive; steroid resistance in a subsequent relapse |
| Complete remission | Urine protein nil-trace by dipstick for 3 consecutive days, Up/Uc<0.2, or 24-hr protein <100 mg/m2/day |
| Partial remission | Urine protein 1+/2+ (dipstick), Up/Uc between 0.2-2, or 24-hr urine protein 100-1000 mg/m2/day; serum albumin ≥3.0 g/dL; and absence of edema |
| Non-response | Urine protein 3+/4+ (dipstick), Up/Uc>2, or 24-hr urine protein >1000 mg/m2/day; albumin <3.0 g/dlL or edema |
| Relapse | Urine albumin 3+/4+ for 3 consecutive days, Up/Uc>2, or 24-hr protein >1000 mg/m2/day, in a patient previously in partial or complete remission |
| Monogenic disease | Pathogenic or likely pathogenic variation, defined by American College of Medical Genetics and Genomics, in a gene associated with nephrotic syndrome |
| CNI-resistant disease | Non-response to cyclosporine or tacrolimus, given in adequate doses and titrated to blood levels, for 6-months |
| Allograft recurrence of nephrotic syndrome | Persistent proteinuria (Up/Uc>1) if previouslyanuric;or increase of Up/Uc>1 if proteinuria at time of transplant (in absence of other apparent causes) |

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CNI Calcineurin inhibitor; Up/Uc urine protein to creatinine ratio (mg/mg)
*Patients with steroid toxicity may receive daily prednisolone for 4 weeks, followed by alternate-day therapy for 2 weeks. All above definitions are as per ISPN guidelines*

**Results:**55 patients were studied. Mean age at onset of Nephrotic syndrome was 5.45±3.79 and mean age of all patients undertaking treatment in different age group was 7.65±4.42. Gender distribution ration was 2.43:1. Kidney Biopsy results showed that most common histological diagnosis was minimal change disease (47.27%**)** followed by Focal Segmental Glomerulosclerosis (34.54%). mean trough concentration of tacrolimus at follow up visit after one year was found 6.41 ng/mL. After one year, 61.81% showed a remission and 30.90% patients showed partial remission.

**Table 1: Demographic Profile of Patients with Steroid Resistant Nephrotic Syndrome**

| **Variable** | **Number** | **Percentage** | **Mean±SD** |
|---|---|---|---|
| Age in years (SRNS) Patients | | | |
| 1–3 | 5 | 9.09 % | 7.65±4.44 |
| 3–6 | 22 | 40 % | |
| 6–9 | 11 | 20 % | |
| 9–12 | 6 | 10.9 % | |
| 12–15 | 5 | 9.09 % | |
| 15-18 | 6 | 10.9 % | |
| **Sex** | | | |
| Male | 39 | | 70.90% |
| Female | 16 | | 29.09% |
| **Rural/Rural** | | | |
| Rural | 14 | | 25.45% |
| Urban | 41 | | 74.54% |

Majority of children receiving treatment of SRNS were in age group of 3-6 years (40%). Male children were higher (71%) and female children were 29% and most of the children were from urban area.

**Table 2: Age at onset of Nephrotic Syndrome (in Years)**

| **Age in years** | **Number** | **Percentage** | **Mean±SD** |
|---|---|---|---|
| 1–3 | 16 | 29.00 | 5.57±3.63 |
| 3–6 | 21 | 38.18 | |
| 6–9 | 08 | 14.54 | |
| 9-12 | 06 | 10.90 | |

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| | | | |
|---|---|---|---|
| 12-15 | 03 | 05.45 | |
| 15-18 | 01 | 01.81 | |

**Table 3: Duration of SRNS Treatment**

| Duration in Years | Number | Percentage | Mean±SD |
|---|---|---|---|
| 1-2 | 32 | 58.18 | 2.2±1.00 |
| 2-3 | 11 | 20.00 | |
| 3-4 | 07 | 12.72 | |
| 4-5 | 05 | 9.00 | |

**Table 4: Treatment Outcomes in SRNS Patients**

| Variable | Number | Percentage |
|---|---|---|
| Full Remission | 34 | 61.81 |
| Partial Remission | 17 | 30.90 |
| No Remission | 05 | 09.00 |

**Table 5: Histological findings on renal biopsy-Histological diagnosis**

| Variable | Number | Percentage |
|---|---|---|
| Minimal Change Disease (MCD) | 26 | 47.27% |
| Focal Segmental Glomerulosclerosis (FSGS) | 19 | 34.54% |
| Biopsy not done/Report not available | 10 | 18.18% |

Most of the patients were in treatment duration of 1-2 years and 5 patients ( 9%) were taking treatment from 4-5 years due to multiple relapse. After one year, around 62% achieved complete remission, 31% showed partial remission and around 9% indicated no remission. Histopathology report indicated Minimal Change Disease (MCD) in 47%, Focal Segmental Glomerulosclerosis (FSGS) in 34% and biopsy were not done in 18% cases.

**Table 6: Complication in SRNS Patients**

| **Diseases/Condition** | Number | Percentage |
|---|---|---|
| Urinary Tract Infection | 8 | 14 |
| Hypertension | 2 | 3.6 |
| Pneumonia | 3 | 5.45 |
| Tuberculosis | 2 | 3.6 |

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| | | |
|---|---|---|
| Hypothyroidism | 1 | 1.81 |
| COVID-19 infection | 1 | 1.81 |
| MRKH with Cholelithiasis | 1 | 1.81 |
| No major diseases/complication | **37** | **67** |

**Table 6: Trough level of Tacrolimus after one year of Tacrolimus Therapy**

| level of Tacrolimus | Number | Percentage | Mean±SD |
|---|---|---|---|
| 0- 4 ng/ mL | 15 | 27.27 | 6.41±4.31 |
| 4- 8 ng/ mL | 27 | 49.09 | |
| 8- 12 ng/ mL | 09 | 16.36 | |
| 12-16 ng/mL | 02 | 3.63 | |
| 16-20 ng/mL | 01 | 1.81 | |
| 20-30 ng/mL | 01 | 1.81 | |

**Table 6: Laboratory Parameter in Patients**

| Laboratory Parameters | Total Number | Mean Reported Value |
|---|---|---|
| Urea | 42 | 29 |
| Creatinine | 40 | 0.4 |
| UP:CR | 35 | 1.53 |

**Discussion:**In our study, most common histological diagnosis was minimal change disease (47.27%**)** followed by Focal Segmental Glomerulosclerosis (34.54%) which is in contrast to a study by Bhutani et al. which reported FSGS as a common histopathological finding as 50-60% in children with SRNS [8]

Tacrolimus has gained acceptance for treatment of SRNS yet it was found that pharmacokinetics date and correlation is very limited regarding therapeutic efficacy. There is serious dearth of target concentration for children with SRNS and treatment of SRNS is done on the basis of therapeutic concentration applied in organ transplantation.

In this study, mean trough concentration of tacrolimus was found 6.41 ng/mL.The desirable $C_0$ of tacrolimus in pediatric transplant immediately after transplant are 10-12 ng/mL and 5-10 ng/mL subsequently to prevent rejection of organ.[9] On the basis of transplant data, suitable target concentration of tacrolimus in SRNS is considered from 5ng/mL to 10 ng/mL in most of the studies[10].In our study we found a significant correlation of trough concentration of tacrolimus with other studies.The average value of blood urea reported in 42 patients was 29 mg/dL and average creatinine level was found 0.4 mg/dl. The average UP:CR was found 1.53 in

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35 patients.The male children were higher in number as compare to female. The mean age group of children at the onset of treatment was5.45±3.79 and maximum children were in age group of 3-6 years and maximum patients were belonging to urban background. In our study the 3-6 years age group indicated maximum number.

**Conclusion:** Clinical profile of children showed a better treatment outcome with tacrolimus. The similarity was found with other studies in age of children at onset of nephrotic syndrome. Mean Trough concentration of tacrolimus and clinical profile of children was similar with typical steroid resistant nephrotic syndrome in children. However, long-term follow-up with more number of patients is required to substantiate the findings.

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**Conflict of Interest**: None

**Ethical Approval**: Study was approved by the Institutional Ethics Committee of LHMC & Associated Hospitals vide letter no LHMC/IEC/2021/01

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**Abbreviations:**
NS- Nephrotic syndrome,
SDNS- steroid dependent nephrotic syndrome,
SRNS- steroid resistant nephrotic syndrome,
CR- complete remission,
PR- partial remission,
NR- no remission,
MCD- Minimal change disease,
FSGS- Focal segmental glomerulosclerosis,