Efficacy of tacrolimus in steroid dependent and steroid resistant childhood nephrotic syndrome - A retrospective study

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Abstract

Introduction: Nephrotic syndrome is a common renal disease in children. Majority of the children usually responds to steroids without any long term effects on kidney function. However about 10-20% of children are usually steroid dependent or steroid resistant and require multiple additional immunosuppressive medications such as cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil and Rituximab. All these drugs are associated with specific adverse effects and lack of response to the drug can result in slow decline in renal function and development of end stage renal disease.

Material and Methods: A retrospective study was done to determine the efficacy of tacrolimus in steroid dependent and steroid resistant nephrotic syndrome (SDNS and SRNS). 40 children with SDNS and SRNS were included in the study. All patients were observed for complete remission, partial remission, decline in renal function and adverse effects of the drug.

Results: Study included 40 patients of SDNS (n=19) and SRNS (n=21) with 18 boys and 22 girls with mean duration of follow up of 24 months. Renal biopsy of patients showed minimal change disease (MCD) in 23, focal segmental glomerulosclerosis (FSGS) in 13, IgM nephropathy in 3 and mesangioproliferative glomerulonephritis (MPGN) in 1. Complete remission was achieved in 14 children in SDNS group and 11 children in SRNS group. 3 children in SDNS group and 4 children in SRNS group did not achieve any remission despite treatment for 6 to 12 months. Adverse effects of the drugs included infections, tremors and hyperglycemia and were similar in both the groups.

Conclusion: Tacrolimus is efficacious in inducing and maintaining remission in children with steroid dependent and steroid resistant nephrotic syndrome with minimal adverse effects.

Keywords: Steroid resistant nephrotic syndrome, Calcineurin inhibitor, cyclosporine, tacrolimus, minimal change disease.

Introduction

Nephrotic syndrome (NS) is characterized by proteinuria, edema, hypoalbuminemia and hyperlipedemia. It's commonly seen in children with age group of 2 -15 years. Common causes of idiopathic nephrotic syndrome include minimal change disease (MCD), Focal segmental glomerulosclerosis (FSGS), IgA nephropathy and membranous nephropathy. Most of the children respond to steroids (80-90%), however few patients have frequent relapses (40-60%) or develop steroid resistance (10-20%).[1] Steroid dependent nephrotic syndrome(SDNS) and steroid resistant nephrotic syndrome(SRNS) are treated with multiple immunosuppressive medications which include cyclophosphamide, calcineurin inhibitors (cyclosporine and tacrolimus), Mycophenolate mofetil and Rituximab.[2,3] Recent studies have shown increase in the number of steroid resistant NS especially in south a east Asia.[2]

Management of SRNS includes combination of immunosuppressants, angiotensin converting enzyme inhibitor, low dose steroids and statin. Majority of patients respond partially to immunosuppressive medications and have risk of developing end stage renal disease (ESRD).[4-6] These children are also at risk of developing side effects related to immunosupression such as infections, neurotoxicity, nephrotoxicity, cytopenia and malignancies. Therefore choice of immunosuppressant depends upon their efficacy and safety. Calcinuerin inhibitors are the first line drugs in treating steroid dependent and steroid resistant nephrotic syndrome. Among calcineurin inhibitors tacrolimus is usually preferred over cyclosporine due to its potency and side effects.[7] However there is paucity of data regarding efficacy and safety of tacrolimus in south Indian children with steroid resistant NS.

Tacrolimus is a calcinuerin inhibitor which is used as immunosuppressant in multiple conditions including organ transplant, autoimmune disease and malignancies. It inhibits the production of interleukin 2 (IL-2) which is required for the activation of T cells.[8] Oral tacrolimus is slowly absorbed through gastrointestinal tract with bioavailability of 20-25%. In the blood, tacrolimus is mainly bound to erythrocytes (95%) and partly (5%) in the plasma which is bound to plasma proteins. Its absorption is delayed by foods rich in fat and maximum blood concentration (Cmax) is achieved after 2-3 hours of oral intake. It's metabolized by liver CYP3A4 and excreted in feces as inactive metabolite. Biological half life is around 46 hours in healthy individuals and 12-16 hours in transplant recipients.

Material and Methods

A retrospective study was conducted from July 2010- June 2018 at K S Hedge charitable hospital

which is tertiary care hospital for nephrology services. The study included children (age < 18 years) with kidney biopsy proven steroid dependent (SDNS) and steroid resistant nephrotic syndrome (SRNS) who received tacrolimus with minimum of one year follow up. Children with secondary nephrotic syndrome, congenital nephrotic syndrome, previous exposure to cyclosporine or mycophenolate mofetyl, estimated glomerular filtration rate (eGFR) of < 60 ml/min/1.73m^2 and irregular follow up were excluded from the study. All the case definitions used in the study was based on KDIGO (kidney disease improving global outcome) 2012 guidelines (table 1). All included patients were seen in outpatient department on a monthly interval. At each outpatient visit their height, weight, blood pressure, urine analysis were recorded. Blood pressure was recorded using an appropriately sized cuff and a mercury sphygmomanometer.[9] Qualitative urinalysis was performed for evidence of proteinuria (recorded as negative, trace, 1+, 2+, 3+ and 4+) and measurements of plasma creatinine, plasma albumin and trough blood tacrolimus levels were carried out at 6 months interval or whenever clinically indicated.

All patients were treated as per our centre protocol. The protocol includes trial of cyclophopshamide (oral or IV) for 3 to 6 months (oral and IV respectively) after diagnosis of SDNS and SRNS. Children with persistent relapse were started on tacrolimus 0.1 mg/kg/day on two divided doses. Further changes to tacrolimus dose was made on the basis of 12 h trough blood levels of 5–10 mcg/L and drug levels were measured at least 6 monthly interval. Tcarolimus blood levels were analyzed on the Abbott IMX analyzer. The IMX Tacrolimus II assay is based on microparticle enzyme immunoassay technology.

Table 1: KDIGO case definition

Classification	Definition
Nephrotic syndrome	Edema, uPCR>2000mg/g or >300mg/dl or 3+ protein on urine dipstick and hypoalbuminemia (<2.5gm/dl)
Complete remission	uPCR < 200mg/g or <1+ protein on urine dipstick on 3 consecutive days
Partial remission	Proteinuria reduction of 50% or greater from presenting value and uPCR between 200mg/g and 2000mg/g
No remission	Failure to reduce urine protein excretion 50% from baseline or persistent excretion of uPCR> 2000mg/g
Steroid resistance	Failure to achieve complete remission after 8 weeks of steroid therapy
Relapse	uPCR> 2000mg/g or 3+ protein on urine dipstick for 3 consecutive days
Infrequent relapse	One relapse within 6 months of initial response or 1-3 relapse in any 12 months period
Frequent relapse	Two or more relapse within 6 months of initial response or 4 or more relapse in any 12 months period
Steroid dependence	Two consecutive relapses during steroid therapy or within 14 days of ceasing therapy

(uPCR- urinary protein creatinine ratio)

All patients underwent renal biopsy before initiating tacrolimus and whenever clinically indicated. GFR was calculated using Schwartz formula.[10]All patients were analyzed for response to tacrolimus in terms of complete remission (CR), partial remission (PR), no remission (NR) and number of relapses during treatment or after withdrawal of the drug.

Statistical analysis

The paired Student's t test was used to compare initial and follow-up laboratory data and the unpaired t test was used to analyze the effect of different variables on outcome. Analyses were performed using SPSS software ver. 20.0(SPSS, Chicago, IL). A p value of<0.05 was considered to be statistically significant. The study was approved by the Institutional ethics committee.

Results

Study included 40 patients of SDNS (n=19) and SRNS (n=21) with 18 boys and 22 girls with mean duration of follow up of 24 months. All the baseline characteristics were similar in both the groups except for higher degree of proteinuria in SRNS group (Table 2). Renal biopsy of patients showed minimal change disease (MCD) in 23, focal segmental glomerulosclerosis (FSGS) in 13, IgM nephropathy in 3 and mesangioproliferative glomerulonephritis (MPGN) in 1(Table 3). Children in both the group received tacrolimus as per protocol and small dose of steroid (prednisolone 5 to 10 mg/day). The mean duration of

tacrolimus therapy was 24±4 months. The average tacrolimus trough level was 4.88mcg/L. Complete remission was achieved in 14 children in SDNS group and 11 children in SRNS group (Table 4). 3 children in SDNS group and 4 children in SRNS group did not achieve any remission despite treatment for 6 to 12 months. There was slow decline in estimated glomerular filtration rate in both the group, however SRNS group had significant decline in eGFR at the end of follow up (Table 5). Adverse effects of the drugs were similar in both the groups (Table 6).

Table 2: Demographic profile and baseline characteristic of SDNS and SRNS children on tacrolimus

Features	Total	SDNS (n=19)	SRNS (n=21)
Boys/girls	18/22	8/11	10/11
Age at onset (months)	96.24 ± 44.37	97.38±43.27	98.23±44.27
eGFR (ml/min/1.73m^2)	110.88±10.28	111.12±9.88	109.33±10.88
Proteinuria (grams)	12.17±8.88	10.88±7.87	13.88±9.76
Serum albumin (gram/dl)	1.56±1. 98	1.86±1.76	1.22± 1.54
Total cholesterol(mg/dl)	438.33±165.39	411.34±154.87	453.76±167.54
Triglycerides (mg/dl)	283.44±67.44	265.56±54.67	298.32±76.44

Table 3: Histological findings on renal biopsy

Histological diagnosis	SDNS (n=19)	SRNS (n=21)
Minimal change disease	13	10
Focal segmental glomerulosclerosis	5	8
IgM Nephropathy	1	2
Mesangioproliferative glomerulonephritis		1

Table 4: Response to tacrolimus therapy on follow up

Response	SDNS (n=19)	SRNS (n=21)	P value
At 6 months			
CR	9	7	0.9
PR	5	8	0.5
NR	5	6	0.9
At 12th month			
CR	11	9	0.8
PR	5	7	0.6
NR	4	5	0.8
At 24 months			
CR	14	11	0.9
PR	2	6	0.8
NR	3	4	0.5
Relapses after stopping tacrolimus	10	16	0.02

(CR- Complete remission, PR- Partial remission, NR- No remission)

Table 5: eGFR of SDNS and SRNS children on follow up

Variables	SDNS (n=19)	SRNS (n=21)	p value
Baseline eGFR	111.12±9.88	109.33±10.88	0.6
Decline in eGFR at 6 months	-10.2±7.6	-11.2±8.7	0.2
Decline in eGFR at 12 months	-20.4±10.2	-22.5±8.8	0.4
Decline in eGFR at the end of follow up	-35.6±14.6	-36.55±17.6	0.3

Table 6: Adverse effects of tacrolimus

Adverse events	SDNS (n=19)	SRNS (n=21)	p value
Infections (number of episode)	5	6	0.3
Gum hyperplasia	0	1	0.9
Anemia	2	1	0.8
Hyperglycemia	0	1	0.2
Diarrhea	1	2	0.2
seizures	0	1	0.3
Tremors	0	1	0.9

Discussion

In our retrospective study on children with SDNS and SRNS, we looked at the efficacy of tacrolimus in inducing complete and partial remission. Tacrolimus treatment is associated with complete remission in 14 children (73.68%) in SDNS group (n=19) and 11 children (52.38%) in SRNS group (n=21) at the end of 24 months of follow up. However 3 children (15.78%) in SDNS group and 4 children (19.04%) in SRNS group did not show any response at the end of follow up. In a pilot trail of tacrolimus in children with SRNS done by McCauley et al showed good response to the drug despite patients being resistant to cyclosporine.[11]A study conducted by Kim J et al in children with SRNS and steroid sensitive frequently relapsing NS showed remission in 96% and 65% respectively.[12] In a similar study done by Aizawa-Yashiro T et al concluded that tacrolimus is more effective and has fewer adverse effects in children with SRNS who are intolerant to cyclosporine.[13] In a randomized control trial done by choudhry et al comparing tacrolius and cylcosporin in SRNS patients, showed remission in 85.7% in tacrolimus group and 80% in cyclosporine group after 6 months of treatment and concluded that tacrolimus is similar in efficacy to cyclosporine and is associated with less adverse effects.[14] In our study we found 84.21% remission rate (CR and PR) in SDNS group and 80.95% (CR and PR) remission rate in SRNS group which is similar to the outcome observed by choudhry et al. In a randomized multicenter study done by Gulati et al, tacrolimus was compared to cyclophosphamide in treating SRNS children showed 82.5% remission in tacrolimus group and 45.9% remission in cylcophosphamide group which is consistent with our study.[15]

The mechanism of action of tacrolimus in SRNS appears to be due to its immunosupressive effects and direct action on podocyte cytoskeleton.[16,17] Tacrolimus is a more potent drug compared to cyclosporine and suppresses cytokine production, interleukin-18 (IL-18) and IL-12, decreases mRNA levels of granulocyte macrophage colony stimulating factor, tumor necrosis factor alpha, interferon and c-myc in activated T cells. Tacrolimus affects growth and differentiation of T and B lymphocytes resulting in potent immunosupression.

Relapse of NS after tacrolimus withdrawal was common especially in SRNS group (76.19%). Each episode of relapse was managed with steroids and re-initiation of tacrolimus. Tacrolimus dependency was common after reinitiation of the drug and children were maintained in the lowest tacrolimus dose with small dose of steroids.

In our study, most common histological diagnosis was minimal change disease followed by FSGS which is consistent with epidemiological data in children with nephrotic syndrome. FSGS was more common in SRNS group (38.09%) compared to SDNS group. Both MCD and FSGS are podocytopathies resulting from progressive podocyte loss due to immunological and non immunological causes. FSGS is less responsive to steroids compared to MCD and can progress to ESRD.

Tacrolimus treatment was associated with slow decline in eGFR at the end of follow up. However we calculated GFR based on creatinine, which may be less accurate. Tacrolimus is associated with nephrotoxicity resulting from interstial fibrosis, which is common at higher therapeutic drug level. As all of our patients were on regular dose monitoring with tacrolimus trough levels, nephrotoxicity seems less likely although renal biopsy is required to demonstrate the nephrotoxicity of tacrolimus. Other possible causes for decline in GFR could be due to diuretics and angiotensin converting enzyme inhibitors (ACEi) such as enalapril.

Tacrolimus treatment was associated with few adverse effects in both the groups. However there was no significant difference in adverse effects, as both the group received similar cumulative dosage of the drug on follow up. Common adverse events noted during the study were opportunistic infections, tremors and hyperglycemia. Among infections, skin and respiratory infections were common and responded well to antibiotics. In case of recurrent or refractory infections, tacrolimus dose was reduced. In a retrospective study done by Yao SH et al in SRNS children receiving oral tacrolimus with low dose steroids reported minimal side effects of tacrolimus.[18]In a study done by Bhimma R et al tacrolimus and low dose steroids in SRNS children was associated with diarrhea and hyperglycemia.[19]Other studies on tacrolimus in SRNS have reported less common adverse effects such as seizure, new onset of hypertension and sepsis.[20]

Our study has few limitations such as retrospective study design, single center study with small sample size, short follow up, lack of genetic screening for nephrotic syndrome and lack of renal biopsy on follow up. Despite these limitations, our study provides reasonable evidence of efficacy of tacrolimus in SDNS and SRNS children with minimal side effects.

Conclusion

Tacrolimus is efficacious in inducing and maintaining remission in children with steroid dependent and steroid resistant nephrotic syndrome with minimal adverse effects.

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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,
MPGN- Mesangioproliferative glomerulonephritis,
ESRD- End stage renal disease,
eGFR- estimated glomerular filtration rate,
IV- Intravenous,
ACEi- Angiotensin converting enzyme inhibitors,
uPCR – urinary protein creatinine ratio.

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