ORIGINAL ARTICLE

TACROLIMUS DRUG LEVEL AND RESPONSE TO TREATMENT IN IDIOPATHIC CHILDHOOD STEROID RESISTANT NEPHROTIC SYNDROME

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Background: The management of Steroid Resistant Nephrotic Syndrome (SRNS) is an uphill task for paediatric nephrologists as immunosuppressive agents are the mainstay of treatment in these patients. Tacrolimus is used along with steroids. This study is conducted to see the relationship between the tacrolimus dose, drug level and response in the management of SRNS. **Methods:** This quasi experimental study was conducted at The Children's Hospital Lahore over a period of one year. Patients with SRNS of either sex and 1–10years of age were included and those with secondary nephrotic syndrome were excluded. Tacrolimus was given at a dose of 0.05–0.1 mg/kg/day in 2 divided doses along with steroids. The follow-up was done for six months with proteinuria monitoring and tacrolimus drug levels done two weeks after initiation of treatment. **Results:** Out of 42 patients, 27 (64.3%) were males and 15 (35.7%) were females. The most common histological diagnosis observed was mesangio-proliferative glomerulonephritis in 30 (71.4%) patients. The tacrolimus trough level range was 0.5–15.20 ng/ml with a mean value of 4.68 ng/ml±2.85. Forty-one (97.6%) children showed complete response to treatment while one patient showed partial response. **Conclusion:** This study suggests that tacrolimus is an effective drug for treatment of SRNS in paediatric patients and there is no linear relationship between the drug dose, response and drug level.

Keywords: Tacrolimus, steroid-resistant, nephrotic syndrome, drug level
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INTRODUCTION

Steroid Resistant Nephrotic Syndrome (SRNS) is considered when patients with nephrotic syndrome do not achieve remission after four weeks of full dose prednisone treatment.[1] About 10–20% cases of nephrotic syndrome do not show response to initial corticosteroidtherapy.[2] The management of SRNS is an uphill task for paediatric nephrologists. The treatment options in these patients are calcineurin inhibitors (tacrolimus, cyclosporine), cyclophosphamide, mycophenolate mofetil and IV methylprednisolone with angiotensin converting enzyme inhibitors (ACEIs)[3,4] and remission is achieved in about 50–60%. The prognosis is not good due to the risk of progression to chronic kidney disease as a result of persistent proteinuria.[5] The target of drug therapy in SRNS is to achieve remission, either complete or partial, which is the most important predictor of disease outcome.[6] During the last two decades cyclosporine has been used as the drug of choice for the management of SRNS and steroid dependent/frequently relapsing nephrotic syndrome.[7] The main issue with cyclosporine is nephrotoxicity and drug resistance if used for a long period of time as well also there are chances of relapse after discontinuation of treatment[8]. Because of limitations of availability of multiple second line drugs, tacrolimus is being used for treatment of different categories of nephrotic syndrome particularly SRNS.[9] It has shown response in SRNS in various studies[10,11], but the drug toxicity is similar to that of cyclosporine.

The exact relationship between tacrolimus dose and response to treatment in lieu of the drug level is not known in patients with SRNS. This study is conducted to determine the relationship between dose of drug, response to treatment and tacrolimus drug level in treatment of idiopathic SRNS in paediatric patients.

MATERIAL AND METHODS

This quasi experimental study was conducted in the Department of Paediatric Nephrology at The Children's Hospital and The Institute of Child Health Lahore over a period of one year from May 2014 to April 2015. Patients with SRNS showing histological pattern of minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis (MesangioPGN) were included in the study. Children of either sex between 1–12 years of age were selected while those with secondary nephrotic syndrome and hypocomplementemia were excluded. SRNS was labelled when failure of response was seen after four weeks treatment of oral prednisolone. Steroids were then tapered to 30 mg/m^2/day and tacrolimus added at an initial dose of 0.05–0.1 mg/kg/day in two divided doses. Patients visited for follow-up initially every

two weeks and then monthly with early morning proteinuria record monitored with urine dipstick. Complete remission was defined as detection of proteinuria being nil or trace, partial response was considered with proteinuria of 2+ on urine dip stick and no response if proteinuria ≥3+ persisted on urine dip stick. The patients were monitored for three months after initiation of therapy and in case of response (complete or partial) they were then followed for a total of six months. Blood pressure was measured on each visit along with regular monitoring of renal function tests, blood sugar, potassium, magnesium and uric acid levels to look for adverse effects of the drug. Tacrolimus trough levels were done after two weeks of starting the drug and the dose adjusted (increased to 0.2 mg/kg/day in case of no response. Patient data was collected and variables were recorded including age, sex, body surface area, blood pressure, proteinuria, serum albumin, serum cholesterol, blood urea nitrogen, serum creatinine, tacrolimus trough levels, histopathology, response to treatment and time interval from administration of tacrolimus to achievement of remission. Data was analysed by SPSS 20.0 and results were considered significant if *p*-value <0.05.

RESULTS

In this study a total of 42 patients diagnosed as SRNS were included out of which 27 (64.3%) were males and 15 (35.7%) were females. The age range of patients was 1.90–12 years with mean age of 6.76±3.08 years. The range of systolic blood pressure was between 90–120 mm Hg (mean=104.38±9.43) and the diastolic blood pressure was 50–90 mm Hg (mean=69.85±7.35). The minimum and maximum values of tacrolimus trough levels were 0.5 ng/ml and 15.20 ng/ml respectively (mean=4.68±2.85 ng/ml). The statistics of other variables like serum cholesterol, albumin, urea and creatinine are shown in table-1, while the frequency pattern of underlying aetiology of SRNS based on histological diagnosis is presented in table-2 by gender. Forty-one (97.6%) patients showed complete response after three months of initiation of treatment and were thus followed for a total of 6 months while only one (2.4%) child showed partial response. All male children went into complete remission while one female patient gave partial response. Patients with FSGS and MCD showed complete response to tacrolimus while one patient of MesangioPGN showed partial response to treatment. One patient relapsed at the end of six months of treatment presenting with septicaemia and expired. Patients who were started on treatment and showed response after initiation of tacrolimus treatment, there was no relationship between the initial tacrolimus trough level and the response (*p*-value=0.090 on chi-square test).

Table-1: Serum Levels of Cholesterol, Albumin, Urea, Creatinine, and Tacrolimus

Variables	(n)	Minimum	Maximum	Mean	SD
Cholesterol	42	205.00	786.00	387.6667	135.55139
Albumin	42	1.40	3.80	2.3048	.67893
Urea	42	12.00	90.00	29.9286	15.13741
Creatinine	42	0.20	4.00	.6929	.56542
Tacrolimus drug level	42	0.50	15.20	4.6881	2.85180

Table-2: Histopathology by Gender

Gender	Histology			Total
	FSGS	MCD	MesangioPGN	
Male	6	0	21	27
Female	4	2	9	15
Total	10	2	30	42

Table-3: Tacrolimus Drug Level

Total patients		42
Mean		4.6881
Median		4.2000
Mode		4.50
Range		14.70
Percentiles	20	2.6600
	40	3.8200
	60	4.5000
	80	5.5800

DISCUSSION

Tacrolimus is a macrolide antibiotic presumed to have inhibition action on activation and proliferation of CD4 T-Helper.[11] It is one of the calcineurin inhibitor being used recently for treatment of not only SRNS but also in patients with steroid dependence and steroid toxicity in order to achieve remission of disease.[12] It has been suggested recently that both podocytes and lymphocytes are involved in pathogenesis of idiopathic steroid resistant nephrotic syndrome.[13] The exact mechanism by which tacrolimus acts is not known but evidence suggests that it acts on actin cytoskeleton of podocytes and alters it resulting in a decrease in proteinuria.[14] According to recent Kidney Disease Improving Global Outcome (KDIGO)guidelines for treatment of SRNS, calcineurin inhibitors have been recommended as initial therapy.[15] There is no definite bioassay to monitor the efficacy of tacrolimus in children with SRNS but tacrolimus trough levels can be done to avoid the adverse effects of the drug particularly nephrotoxicity. It is assumed that drug level correlates clinically directly with its efficacy.[16] Though tacrolimus has been used in treatment of SRNS and steroid dependent nephrotic syndrome, no study has definitively showed relationship of drug level with response and outcome.[17]

Before initiation of the study it was presumed that upper range of therapeutic tacrolimus trough level was associated with complete response

and it may lead to short duration of therapy but patients also monitored for nephrotoxicity. Though the mean tacrolimus drug level was within the therapeutic range as described in literature,[18] patients even with low tacrolimus trough levels responded well and showed complete response with no relation of drug level to time for achieving remission. Due to financial constraints tacrolimus trough levels in our patients were not repeated on follow-up visits but they were monitored for proteinuria as well as the drug toxicity. In our study no patient relapsed except one who relapsed and presented with septicaemia. A study by Gulati S *et al*[18] concludes that out of 22 patients with SRNS given tacrolimus, 84% showed complete response while 10.5% went into partial remission and 4.55% patients showed no response at all in contrast to our study showing 97.5% patients achieving complete response and only 2.5% going into partial remission. In the former study tacrolimus was given initially at a dose of 0.1 mg/kg/day in two divided doses maintaining the drug trough levels between 5.0–10.0 ng/ml by adjusting the dose but the relationship of drug levels and response to treatment could not be established.

In another retrospective study of 16 patients by Loeffler K *et al*,[19] 81% went into complete remission while 13% and 6% showed partial and no response respectively. The tacrolimus trough levels were maintained between 5–10 ng/ml for drug response. In a symposium on Paediatric Nephrology, Sinha A *et al*[20] recommended tacrolimus trough levels in the range of 4–7 ng/ml for monitoring of toxicity in management of SRNS. Another study showing comparison of different drugs in SRNS, the tacrolimus trough levels were maintained at 5.8±1.9 ng/ml and remission (complete or partial) was achieved in 82.5% patients.[21] One study by Choudhry S *et al*[7] compares the efficacy of tacrolimus with cyclosporine in which remission was achieved in 85.7% patients receiving tacrolimus and drug level was kept between 5–10 ng/ml. Peyser K *et al*[22] looked retrospectively at the relationship of tacrolimus level and response to treatment and failed to see relationship between the starting dose and drug level. Also there was no association found of high dose of tacrolimus with response to treatment in regard to tacrolimus trough level. But they found significant (p<0.02) direct correlation during treatment between patient relapse/month and average tacrolimus trough level. Similarly in our study we could not relate the response to treatment with tacrolimus drug levels. Overall there was no inverse relationship found between tacrolimus drug levels and proteinuria.

Thus on the basis of our study, the target tacrolimus trough level could not be defined to predict which patients will respond to treatment and achieve remission, as we had financial limitations regarding regular monitoring of tacrolimus levels and only one drug level could be performed. About 80th percentile of our patients drug levels were less than 6 ng/ml and 97.5% patients showed complete response at the end of six months - this drug level is consistent with the results of the study conducted by Peyser K *et al*.[22] Our results also suggest that this is upper threshold pattern of drug level and beyond this drug level there may not be any benefit of increasing drug dose or drug level.

CONCLUSION

This study is so far the largest in terms of number of patients included for the drug response and trough level in children with SRNS. We conclude that tacrolimus is an effective therapeutic option for SRNS in paediatric patients and that children with even low drug trough levels respond to treatment with no linear relationship between the drug response and level.

AUTHOR'S CONTRIBUTION

SS: Data collection, data analysis, article writing, FH: Supervisor, NA: Article review

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