British Journal of Medicine & Medical Research
12(6): 1-8, 2016, Article no.BJMMR.21806
ISSN: 2231-0614, NLM ID: 101570965

SCIENCEDOMAIN *international*
www.sciencedomain.org

Efficacy of Tacrolimus in Treating Nephrotic Syndrome Children

Sijan Thapa[1] and Hongzhu Lu[1*]

[1]Department of Pediatrics, Clinical Medical College, Yangtze University, Pediatric Research Institute of Yangtze University, China.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/21806
Editor(s):
(1) Toru Watanabe, Department of Pediatrics, Niigata City General Hospital, Japan.
Reviewers:
(1) Anonymous, Sindh Institute of Urology and Transplantation, Pakistan.
(2) Pietro Scicchitano, Hospital "F. Perinei", Italy.
(3) Nitin Gupta, Ivy Hospital, India.
Complete Peer review History: http://sciencedomain.org/review-history/12282

Review Article

Received 4th September 2015
Accepted 9th October 2015
Published 12th November 2015

ABSTRACT

Nephrotic Syndrome (NS) is primarily a pediatric disorder, common in pre-schooler and school aged children. Immunosuppresive drugs like prednisolone, cyclophosphamide, cyclosporine A (CsA) has been the main treatment regimen in the management of Nephrotic syndrome. This has remain still the same therapy which is not satisfactory in the management of nephrotic syndrome children. The management of children with idiopathic Steroid-Resistant Nephrotic Syndrome (SRNS) and Steroid-Dependent Nephrotic Syndrome (SDNS) are difficult to treat but there is no consensus on the most appropriate treatment therapy. Pneumonia and urinary tract infection are also a challenge in the management of NS. The main goal of treatment is complete or partial remission of proteinuria, which is the most important marker of long term outcome. Calcineurin inhibitors (CNIs) are used to avoid steroid toxicity in children with NS. There are limited data on the relative efficacy and safety of calcineurin inhibitors and alkylating agents for NS in children. There are different immunosuppressant drugs but tacrolimus can be used in the treatment of childhood NS which is less expensive, have less cosmetic side effects and easy to administered. In this review we discuss the safety and efficacy of tacrolimus, a new drug which can be administered orally as a twice daily dose in the management of childhood NS. Some study suggests that application of tacrolimus can be a new turning point for the treatment of nephrotic syndrome.

**Corresponding author: E-mail: lucas215@163.com;*

Keywords: Tacrolimus; Nephrotic Syndrome (NS); Steroid-Resistant Nephrotic Syndrome (SRNS); Steroid-Dependent Nephrotic Syndrome (SDNS).

1. INTRODUCTION

Nephrotic syndrome is also called nephrosis. NS usually begins between the age of 2 and 5 years. It is characterized by proteinuria, hypo-albuminimia, hyperlipidemia and edema. A condition in which the kidneys leak large and abnormal amounts of protein into the urine. With the loss of protein in the urine, this leads to puffiness of the eyelids, feet and ankles, and eventually the abdomen. Main reason of NS is still unclear. Idiopathic nephrotic syndrome (INS) is the most frequent form of Nephrotic syndrome in children representing more than 90 percent of cases between 1 and 10 years of age and 50 percent after 10 years of age [1]. Majority of patient with minimal change disease >90% are sensitive to long term steroid therapy. However, 50% of mesengial proliferation and 30% of focal segmental glomerulosclerosis response to steroid therapy [2]. Most of the children respond very well to steroid treatment. Remission can be achieved with in two weeks. Most children will have at least one relapse or recurrence of protein in the urine. Around 10% of children have secondary nephrotic syndrome with significant lesions. Some children doesnot respond to steroid and considered as SRNS while some children relapse after lowering dose or stopping steroid and considered as SDNS. In practice immunosuppressant drugs such as Cyclophosphamide and CsA has been used as a second line drug who doesnot respond with steroid alone. However these immune-suppressant drugs like CsA have high remission rate but they also have high relapse rate and high resistant rate nowadays. So this has become a troublesome for the patients and doctors too. CNIs such as tacrolimus can be an alternative drug as it has high remission and low relapse rate.

2. INDICATION

Tacrolimus is widely used as an immuno-suppressant for malignancy (lymphomas and leukemias), organ transplants (liver, kidney) and severe inflammation of gastro-intestional tracts (ulcerative colitis) and skin condition such as atopic dermatitis. With the advances of medical technology and research in different parts of the world scientist and medical doctors have developed possibilities and efficacy of tacrolimus in treating children with severe form of Nephrotic Syndrome i,e Steroid Resistant Nephrotic Syndrome (SRNS) and Steroid Dependant Nephrotic Syndrome (SDNS). Different studies suggest that tacrolimus is much more potent and effective than other immune suppressive agent like CsA and Cyclophosphamide with minimum side effect and high remission rate. Tacrolimus is less expensive, less cosmetic side effects and easy to administered.

3. MANAGEMENT OF NEPHROTIC SYNDROME WITH TACROLIMUS

Most cases of idiopathic nephrotic syndrome are responsive to corticosteroids. Prednisolone has been used as first drug of choice in treating Nephrotic syndrome. KDIGO guidelines recommends to treat initial episode of steroid sensitive nephrotic syndrome with corticosteroid therapy (prednisone or prednisolone) be given for at least 12 weeks. It recommends that oral prednisone be administered as a single daily dose starting at 60 mg/m2/d or 2 mg/kg/d to a maximum 60 mg/d. Initially daily oral prednisone be given for 4–6 weeks followed by alternate-day as a single daily dose starting at 40 mg/m2 or 1.5 mg/kg (maximum 40 mg) and continued for 2–5 months with tapering of the dose. Different research are included in the treatment of severe form of nephrotic syndrome with tacrolimus. Although tacrolimus does not appear to have a theoretical superiority to CsA for use in any disease but there are some aspects in favour of tacrolimus. In this prospective study by Wang W et al comparative study of tacrolimus with CsA was done. In terms of short-term efficacy, tacrolimus was found more effective than CsA in children with steroid-resistant nephrotic syndrome with higher efficacy and lower renal toxicity [3]. Kim J and his co-workers conducted study comparing tacrolimus with other placebo where response rate was 96% and 65% respectively in treating SRNS and frequent relapse-SSNS [4].

Some study concluded that tacrolimus is more effective and safe for treating children with refractory case of CsA-resistant with no any serious toxicities [5]. A case report of a 9-year-old Japanese boy with nephrotic syndrome caused by focal segmental glomerulosclerosis, which was refractory case of CsA. CsA in his treatment regimen was replaced with tacrolimus, complete remission was achieved, with no futher side effects [6]. Choudary and his team conducted RCT where significantly high relapse

was observed in those receiving CsA with side effects such as nephrotoxicity, hypertrichosis, and gum hyperplasia compared to tacrolimus. Tacrolimus can be a promising alternative to CsA in view of the lower risk of relapses and lack of cosmetic side effects [7].

Although CsA is a well-established alternative immunomodulating agents. So far CsA is the oldest and best-studied CNI in nephrotic syndrome whereas some data suggest that tacrolimus may be a promising alternative to CsA both in SRNS and SDNS [8]. Unfortunately, prolonged use of CsA has been associated with interstitial fibrosis [9]. CsA can achieved a remission rate of 85% in children with SDNS, however, the risk of CNI-induced nephrotoxicity [10]. The early use of tacrolimus to control SDNS reduce relapses [11]. CsA treatment has serious problems including CsA toxicity and development of treatment resistant [7,11]. CsA directly affect podocyte structure and function according to Greenbaum and Benndorf [12]. A pilot trial of tacrolimus in steroid-resistant nephrotic syndrome by McCauley et al. [13] was the first report of seven patients who all responded positively despite being resistant to prior therapies with CsA. Ponticelli et al. suggest that CsA in patients with steroid-resistant may have good remission rate but has high relapse rate and it is prolonged, expensive, and requires monitoring for nephrotoxicity and other adverse effects [14,15].

As we know cyclophosphamide has been used as second line drug after prednisolone since last 30 years in treating nephrotic syndrome. Now, there are lot of resistant cases of cyclophosphamide. Dose-related toxicities of cyclophosphamide include bone marrow suppression, gonadal toxicity, alopecia, hemorrhagic cystitis. There is an increased risk of infection and viral diseases, particularly measles and chicken pox, are more severe during treatment with cyclophosphamide [16] and malignancies including acute leukemia and carcinoma of urinary bladder has been noted in some children [17]. Gulati et al. [18] concluded the first prospective, randomized, multicenter trial of intravenous cyclophosphamide versus tacrolimus in 131 children with SRNS. Consecutive patients aged 2–16 years with biopsy-confirmed minimal-change NS (MCNS), FSGS, or mesangioproliferative glomerulonephritis were stratified by early and late steroid resistance and randomized to 12 months of tacrolimus or 6 monthly infusions of cyclophosphamide. Each group received alternate-day prednisolone. The primary end point was the proportion of patients with complete or partial remission, on the basis of first-morning urine protein-to-creatinine ratios at 6 months. Complete or partial remission rates were higher in patients receiving tacrolimus (82.5%) versus cyclophosphamide (45.9%), and sustained remission or steroid-sensitive disease was higher in the tacrolimus group at 12 months (52.4% versus 14.8%). In contrast, treatment withdrawal due to drug toxicity was higher among patients on cyclophosphamide (ten patients, eight because of serious infections) than tacrolimus (two withdrawals, both for nephrotoxicity). Notably, the most frequent adverse event with cyclophosphamide was serious infection (16 of 54 events), while the most common adverse event with tacrolimus was acute nephrotoxicity (9 of 45 events). The authors conclude that prescription of tacrolimus and prednisolone is effective, safe, and superior to intravenous cyclophosphamide as the initial therapy for children with SRNS [18]. Tacrolimus has also come into recent favor. Some studies have found cytotoxic treatment, especially intravenous cyclophosphamide, to be less effective in steroid resistant NS [19]. A clinical trail shows that Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis alternatively tacrolimus may be considered [20].

Tacrolimus has clear superiority over cyclophosphamide and give further evidence that in childhood SRNS are both easy and vital for improving the standard of care [21]. Another retrospective chart reviews of 18 children, received prednisolone at the start of tacrolimus. 72.2% children achieved complete response (CR), medicine was well tolerated and treatment was effective [22]. A clinical study suggest that the low dose tacrolimus and prednisone for 6 months, can achieved complete remission in 96.66% and partial remission in 3.33%. Over 85% of the patients achieved reduction in proteinuria, serum albumin improvement and serum lipid recovery which favors tacrolimus can be considerd as alternative to other immunosuppressive drugs [23]. So far largest study conducted by Gulati and his co-workers to evaluate the safety and efficacy of tacrolimus in SRNS suggest that tacrolimus can be an effective therapy who doesnot responce to Cyclophosphamide and CsA [24]. In a clinical study done in different pathological types of nephrotic syndrome treated with tacrolimus. The overall response rate was 91.67% within 2 months with 1 failure out of 12 cases [25].

Table 1. Characteristics and results included in this text

Authors	Type	Initially received	Clinical features	Dose of tacrolimus divided dose 12 hourly	Results	Side effects
Kim J et al. [4]	FSGS	Prednisolone	SSNS(22/23) SRNS(17/22)	0.1 mg/kg per day	CR-96%SSNS CR-77% SRNS	No any side effects
Aizawa-Yashiro T et al. [5]	Minimal change disease	CyclosporinA	SDNS(9/14) SRNS(5/14)	0.1 mg/kg per day	CR-40% (All SDNS & 2 SRNS)	1 patient developed end stage reanal disease
Loeffler K et al. [11]	FSGS-13 MCD-1 IgA Nephropathy-2 Mean age -11.4 years	Prednisolone	SRNS (13/16)	0.1 mg/kg per day	CR-81% PR-13%	Anemia, seizure was Observed in 2 patient
Tsugawa K et al. [6]	FSGS Age- 9 years	Methylprednisolone plus with CsA	SDNS(1/1)	0.1 mg/kg per day	CR (100%)	No side effects
Choudhry S et al. [7]	MCD & FSGS	Prednisolone	SDNS(21/41)	0.1-0.2 mg/kg per day	CR 18(85.7%)	Nephrotoxicity in 4.7%
Westhoff TH et al. [8]	MCD & FSGS	Prednisolone	SDNS (5/10) (4/10)	0.1 mg/kg per day	CR 50% PR 40%	1 patient was resistant to tacrolimus
Bhimma R et al. [31]	FSGS Mean age-4.7 years	Prednisolone	SRNS	0.2-0.4 mg/kg/day	CR-40% PR-45% Nonresponsive-15%	Sepsis-2 Diarrhea-2 Anemia-4
Butani L et al. [29]	FSGS-8 MCD-7 Membranous Nephropathy-1 Mean age-5.2years	Prednisolone & Oral CPM	SRNS (15/16)	0.1 mg/kg per day	CR-94%	2 patient developed bacterial infection 1 patient developed viral infection.

Authors	Type	Initially received	Clinical features	Dose of tacrolimus divided dose 12 hourly	Results	Side effects
Gulati S et al. [24]	FSGS-11 MCD-9 Diffuse mesangial hypercellularity-2 Mean age-5.9 years	Prednisolone	SRNS (16/19)	0.1mg/kg per day	CR-84% PR-10.5% Nonresponsive-1	TAC had to be withdrawn in 3 children because of its side effects
Supavekin S et al. [22]	FSGS-9 MCD-2 IgM Nephropathy-4 Mean age-6 years	Prednisolone	SRNS-9 SDNS-9	0.09 mg/kg/day	CR-72.2% Nonresponsive-27.80%	URTI was observed In SD group
Yao SH et al. [27]	MCD-6 FSGS-4 IgM Nephropathy-5 Mesengial proliferative-1	Prednisolone	SRNS	0.1 to 0.15 mg/kg per day	CR-68.75% PR-31.25%	No side effects
Roberti I [28]	FSGS-10 C1q nephropathy-4 MCD-2 Membranous nephropathy-2 Membranoproliferative-1 Immunoglobulin A nephropathy- Mean age-10 years	Prednisolone	SRNS	0.1mg/kg per day	CR-58% PR-32% Nonresponsive-9%	1 case acute kidney injury &3 cases of hyperglycemia

Keywords- FSGS (Focal Segmental Glomerulosclerosis), MCD (Minimal Change Disease), CR (Complete Remission), PR (Partial Remission), CPM (Cyclophosphamide), SRNS (Steroid Resistant Nephrotic Syndrome), SDNS (Steroid Dependant Nephrotic Syndrome)

However, some clinical trails conducted to treat steroid resistance and steroid dependent with tacrolimus suggest response rate of 90% [26]. In the retrospective longitudinal study of SRNS children received oral tacrolimus with low-dose steroids shows reliable effects with minimum side effects [27].

Roberti and Vyas [28] conducted study between January 2000 and July 2008 for SRNS and concluded in a retrospective single-center study, tacrolimus induced CR in 58% and PR in 32% within 8 weeks. According to Butani L and Ramsamooj R [29] study in 16 children with SRNS, 15 went into CR after a median of 120 days of therapy. Nine children were able to stop steroids, while the others were on tapering doses with tacrolimus therapy. Children who suffer from SRNS require aggressive treatment to achieve remission. However some patients with SRNS will progress to end-stage renal disease if remission is not achieved. Therefore, tacrolimus can be promising treatment therapy in such cases [30].

Tacrolimus, a calcineurin inhibitor that inhibits interleukin-2-driven T-cell activation, has shown promising results in various single-centered studies [11,24,28,29]. Loeffler et al. [11] reported the use of tacrolimus in seven children with SRNS; six children achieved CR and one went into PR after a mean duration of 2 months of therapy. Five of the seven children were off steroids on follow-up, although the steroid-free duration was quite short. Gulati et al. [24] describe CR rate of 84% in a cohort of North Indian children treated with tacrolimus and steroids. Lastly Bhimma et al. [31] subsequently reported a CR rate of 40% and a PR rate of 45% in 20 South African children with SRNS from idiopathic FSGS who received a 12-month course of tacrolimus. At last follow-up, only five (25%) remained in CR. Long term use of tacrolimus in these children was associated with relatively little observed toxicity. These research results further support that CNIs as tacrolimus work best when used in combination with steroids.

4. ADVERSE EFFECT OF TACROLIMUS

Some study suggest that tacrolimus is well tolerated by the children. There are only few adverse effect reported. The most common side effects were diarrhea and hyperglycemia induced by tacrolimus treatment [24,31]. Tacrolimus induced HUS were seen with tacrolimus therapy within one month but improved after 2 weeks of stopping tacrolimus [32]. Insulin dependent diabetes mellitus were observed in some children diagnosed with SDNS [33]. Rarely children have new onset hypertension, seizure and sepsis [11,29]. Nephrotoxicity were observed in SRNS but was reversible [11]. Urinary tract infection and pneumonia are the major side effects observed but reported cases are very low. Other non specific symptoms like body aches, flu symptoms, sores in your mouth and throat are observed. All of the symptoms are mild and can be controlled.

5. CONCLUSION

NS is a chronic disease that has numerous associated comorbid conditions. The treatment of complex, corticosteroid-resistant NS continues to be a difficult challenge. Doctors are still using the old therapy to treat childhood nephrotic syndrome with drugs like cyclophosphamide and CsA. Treatment of SRNS and SDNS has become a more troublesome. From the different therapeutic study and research trial done in different parts of the world, we came to know that calcineurin inhibitors (CNIs) as FK 506 (Tacrolimus) can be the drug of choice in SRNS and SDNS. Different therapeutic trial has shown that tacrolimus efficacy with low dose prednisolone is superior than other immune-suppresive drugs like cyclophosmamide and CsA with 80-85% remission rate. Nephrotic syndrome children who were initially relapsed with prednisolone alone or with combination with cyclophosphomide and CsA achieved high remission after initiation of tacrolimus.

Since the adverse effect of prednisolone like short stature, obesity, osteoporosis, cataract could be serious issue and dose can be minimized with the introduction of drugs like tacrolimus. Older medications like cyclo-phosphamide and CsA can be replaced with new ones such as tacrolimus with good outcome and less side effect profiles. The treatment of refractory cases with combination therapy is also promising. Prolonged tacrolimus treatment at a low blood concentration can alleviate the illness persistently with a low recurrence rate and gratifying safety. Tacrolimus can be well tolerated by the children. Although use of tacrolimus in treating nephrotic syndrome in children is not used widely like cyclo-phosphamide and CsA but it could be a best and effective promising drug of choice for childhood nephrotic syndrome. Tacrolimus can be a new

turning point in the management of nephrotic syndrome. Lowest possible dose of tacrolimus to maintain remission be used in children with SDNS and SRNS.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int. 1978;13(2):159–165.
2. Barnett HL, Edelmann CM, Greifer I. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the international study of kidney disease in children. J Pediatr. 1981;98(4):561–564.
3. Wang W, Xia Y, Mao J, Chen Y, Wang D, Shen H, et al. Treatment of tacrolimus or cyclosporine A in children with idiopathic nephrotic syndrome. Pediatr Nephrol. 2012; 27(11):2073-9.
4. Kim J, Patnaik N, Chorny N, Frank R, Infante L, Sethna C. Second-line immuno-suppressive treatment of childhood nephrotic syndrome: A single-center experience. Nephron Extra. 2014;4(1):8-17.
5. Aizawa-Yashiro T, Tsuruga K, Watanabe S, Oki E, Ito E, Tanaka H. Novel multidrug therapy for children with cyclosporine-resistant or –intolerant nephrotic syndrome. Pediatr Nephrol. 2011;26(8):1255-61.
6. Tsugawa K, Tanaka H, Nakahata T, Ito E. Effective therapy of a child case of refractory nephrotic syndrome with tacrolimus. Tohoku J Exp Med. 2004; 204(3):237-41.
7. Choudhry S, Bagga A, Hari P, Sharma S, Kalaivani M, Dinda A. Efficacy and safety of tacrolimus versus cyclosporine in children with steroid-resistant nephrotic syndrome: A randomized controlled trial. Am J Kidney Dis. 2009;53(5):760-9.
8. Westhoff TH, Schmidt S, Zidek W, Beige J, van der Giet M. Tacrolimus in steroid-resistant and steroid-dependent nephrotic syndrome. Clin Nephrol. 2006;65(6):393-400.
9. Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. Nat Med. 2008; 14(9):931-8.
10. Niaudet P, Habib R. Cyclosporine in the treatment of idiopathic nephrosis. Nephrol. 1994;5:1049–1056.
11. Loeffler K, Gowrishankar M, Yiu V. Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome. Pediatr Nephrol. 2004;19(3): 281-7.
12. Greenbaum LA, Benndorf R, Smoyer WE. Childhood nephrotic syndrome-current and future therapies. Nat Rev Nephrol. 2012; 8(8):445-58.
13. McCauley J, Shapiro R, Ellis D, Igdal H, Tzakis A, Starzl TE. Pilot trial of FK 506 in the management of steroid-resistant nephrotic syndrome. Nephrol Dial Transplant. 1993;8(11):1286-90.
14. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis Kidney Int. 1999;56(6): 2220-6.
15. Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E, Rinaldi S, et al. A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. Kidney Int. 1993;43(6):1377-84.
16. Bernatsky S, Clarke AE, Suissa S. Hematologic malignant neoplasms after drug exposure in rheumatoid arthritis. Arch Intern Med. 2008;168(4):378-81.
17. Pryor BD, Bologna SG, Kahl LE. Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. Arthritis Rheum. 1996;39(9):1475-82.
18. Gulati A, Sinha A, Gupta A, Kanitkar M, Sreenivas V, Sharma J, et al. Treatment with tacrolimus and prednisolone is preferable to intravenous cyclo-phosphamide as the initial therapy for

children with steroid-resistant nephrotic syndrome. Kidney Int. 2012;82(10):1130-5.
19. van Husen M, Kemper MJ. New therapies in steroid-sensitive and steroid-resistant idiopathic nephrotic syndrome. Pediatr Nephrol. 2011;26(6):881-92.
20. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatr Nephrol. 1996;10(5):590-3.
21. Becknell B, Greenbaum LA, Smoyer WE. A new 'tac' for childhood nephrotic syndrome. Kidney Int. 2012;82(10):1049-51.
22. Supavekin S, Surapaitoolkorn W, Kurupong T, Chaiyapak T, Piyaphanee N, Pattaragarn A, et al. Tacrolimus in steroid resistant and steroid dependent childhood nephrotic syndrome. J Med Assoc Thai. 2013;96(1):33-40.
23. Miao L, Sun J, Yuan H, Jia Y, Xu Z. Combined therapy of low-dose tacrolimus and prednisone in nephrotic syndrome with slight mesangial proliferation. Nephrology (Carlton). 2006;11(5):449-54.
24. Gulati S, Prasad N, Sharma RK, Kumar A, Gupta A, Baburaj VP. Tacrolimus: A new therapy for steroid-resistant nephrotic syndrome in children. Nephrol Dial Transplant. 2008;23(3):910-3.
25. Xia Z, Liu G, Gao Y, Fan Z, Fu Y, Zhang LF, et al. FK506 in the treatment of children with nephrotic syndrome of different pathological types. Clin Nephrol. 2006;66(2):85-8.
26. Westhoff TH, Van der Giet M. Tacrolimus in the treatment of idiopathic nephrotic syndrome. Expert Opin Investig Drugs. 2007;16(7):1099-110.
27. Yao SH, Mao JH, Xia YH, Wang DY, Chen YF, Fang CQ, et al. Clinical application of tacrolimus with low-dose prednisone in 21 children with steroid-resistant nephrotic syndrome. 2011;49(11):825-8.
28. Roberti I, Vyas S. Long-term outcome of children with steroid-resistant nephrotic syndrome treated with tacrolimus. Pediatr Nephrol. 2010;25(6):1117-24.
29. Butani L, Ramsamooj R. Experience with tacrolimus in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2009; 24(8):1517-23.
30. Kang HG. Treatment of steroid-resistant pediatric nephrotic syndrome. Korean J Pediatr. 2011;54(8):317-21.
31. Bhimma R, Adhikari M, Asharam K, Connolly C. Management of steroid-resistant focal segmental glomerulo-sclerosis in children using tacrolimus. Am J Nephrol. 2006;26(6):544-51.
32. Pandirikkal VB, Jain M, Gulati S. Tacrolimus-induced HUS: An unusual cause of acute renal failure in nephrotic syndrome. Pediatr Nephrol. 2007;22(2): 298-300.
33. Dittrich K, Knerr I, Rascher W, Dötsch J. Transient insulin-dependent diabetes mellitus in children with steroid-dependent idiopathic nephrotic syndrome during tacrolimus treatment. Pediatr Nephrol. 2006;21(7):958-61.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/12282