Tacrolimus in Steroid Resistant and Steroid Dependent Childhood Nephrotic Syndrome

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Objective: *To evaluate the efficacy of tacrolimus (Tac) in steroid resistant and steroid dependent nephrotic syndrome (NS) in children.*
Material and Method: *Retrospective chart reviews of 18 children from outpatient clinic at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital were diagnosed with steroid resistant (SR) and steroid dependent (SD) NS during 2002-2008 were enrolled in the present study.*
Results: *The boy to girl ratio was 2:1. The mean age at diagnosis was 6.0 years (1-14.4 years). There were nine SR and nine SDNS. Nine patients had focal segmental glomerulosclerosis (FSGS), 4 IgM nephropathy and two had minimal change diseases (MCD). Three children did not receive renal biopsy. All patients received prednisolone at the start of Tac. The average time from the diagnosis to initiation of Tac was 3.5 years (0.2-14 years). The mean duration of Tac treatment was 1.3 year (0.3-6.2 years). The average Tac trough blood level was 4.09 mcg/L (1.3-9.9 mcg/L). The average dosage of Tac was 0.09 mg/kg/day (0.03-0.2 mg/kg/day). Thirteen (72.2%) children achieved complete response (CR). Five (27.8%) children did not respond to Tac. Nine (69.2%) children could stop prednisolone whereas four (30.8%) could lower prednisolone doses. The mean time to achieve CR was 24.6 days (0.1-3 months). The mean follow up period was 3.1 years (0.2-6.4 years). There was no change in an estimation of glomerular filtration rate (eGFR). In SRNS, there were CR in four (44.4%) and five (55.6%) children that FSGS did not respond to Tac. In SDNS, all responded to Tac and four (44.4%) children relapsed while on Tac and had upper respiratory tract infection (URI).*
Conclusion: *Tac is well-tolerated and effective treatment for SR and SDNS.*

Keywords: *Steroid resistant, Steroid dependent, Nephrotic syndrome*

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Idiopathic nephrotic syndrome (INS) is the most common NS in children. Histopathological abnormalities of the kidney include minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), IgM nephropathy, and diffuse mesangial proliferation (DMP). After receiving steroid treatment, patients can turn into remission, steroid resistant (SR), steroid dependent (SD), frequent relapse, or non-frequent relapse NS. SRNS has the worst prognosis among INS. After a follow-up of a 10-year period, 30 to 40% of children with SRNS develop end stage renal disease (ESRD)[1,2]. FSGS is responsible for the majority of cases of SRNS and 20 to 40% of FSGS progress to ESRD[2-4]. SR and SD patients subject to prolong and repeat use of steroid therapy, which place the risk of cushingoid appearance, obesity, growth retardation, hypertension, infections, osteoporosis, and psychological problems. Various steroid sparing agents such as levamisole[5], cyclophosphamide (CPM)[6], cyclosporine A (CsA)[7,8], mycophenolate mofetil (MMF)[9-13], sirolimus[14], and more recently rituximab[15,16] have been used to treat patients with SR and SD in order to achieve responses and reduce the side effects of steroid therapy. CsA came out as a first line therapy for SRNS and after alkylating agents or MMF in patients with relapses or who have steroid side effects[17-19]. However, treatment with CsA has faced relapses after withdrawal, toxicity, and secondary resistance[20,21].

Tacrolimus (Tac) is a macrolide immuno-suppressant that inhibits calcineurin similar to CsA and blocks the translocation of the cytosolic component of

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the nuclear factor of activated T cells (NF-AT)[22]. Tac has been shown to be more potent in suppressing cytokine and it has lower cosmetic side effects[23]. These make Tac preferable over CsA in renal transplantation. The data using Tac in pediatric NS is limited. The center has been using Tac in pediatric NS since 2002. The purpose is to evaluate the efficacy of Tac in SR and SDNS in children.

Material and Method

Data collection

Eighteen children with SR and SDNS received Tac during our study. These samples were collected over seven years, between January 2002 and December 2008, from the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University. Under the studies of a retrospective and descriptive of age groups, sex, renal biopsy results, steroid responsiveness, duration of disease prior to start of Tac, episodes of relapse NS, urinalysis includes urine protein and creatinine ratio (UP/CR), urine sugar, blood urea nitrogen, and serum creatinine. On follow-up visit, each patient received clinical examination, including height, weight, and blood pressure measurement. All patients had a history of receiving prednisolone and CPM 2 to 3 mg/kg/day for 8 to 12 weeks. One patient received prednisolone, CPM, and azathioprine (AZA). One patient received prednisolone, CPM, and intravenous pulse methylprednisolone (IVMP). CPM was added to the authors' treatment after prednisolone used due to difficult to treat NS. Renal biopsy was performed in 15 patients. Three patients did not receive renal biopsy due to families' reasons. There was no evidence of hypertension or renal impairment in these patients. At the start of Tac, all patients received prednisolone at 0.5 to 1 mg/kg/day. Each patient was informed about potential use and side effects of Tac. However, this medication had not been approved for the use in childhood NS. The present study was approved by the ethics committee at our institution.

Definitions

NS: the presence of signs and symptoms, including edema, hypoalbuminemia (serum albumin less than 3.0 g/dl), hypercholesterolemia, and urine protein (mg/dl)/creatinine (mg/dl) (UP/CR) more than 2[4].

Complete response (CR) to tacrolimus: UP/CR less than 0.2 and/or a negative urine dipstick for protein for three days[4,24]. Partial response (PR) to tacrolimus: persistent non-nephrotic range proteinuria (UP/CR between 0.2 and 2.0) after three months of therapy. No response (NR) to tacrolimus: persistent nephrotic range proteinuria (UP/CR more than 2.0) after three months of therapy[4].

Steroid resistance: no clinical response after eight weeks of daily prednisolone at 60 mg/m^2/day (maximum dose 60 mg/day). Steroid dependent: two consecutive relapses during tapering of steroid therapy or within 14 days of cessation of treatment. A relapse: urine dipstick of equal and more than 3+ with no previous proteinuria and with clinical evidence of edema or dipstick of equal and more than 2+ proteinuria for three days[24].

Estimated glomerular filtration rate (eGFR) was calculated by using the Schwartz formula[25-27].

Treatment

Tac was given at 0.1 mg/kg/day divided into two doses. The target for the trough Tac level was 3-7 mcg/L. Tac dose was adjusted according to trough Tac level. Tac levels were measured via the ARCHITECT i1000SR analyzer utilizing the immunoassay (Abbott Laboratories, Ill., USA). Before starting Tac, with the exception of prednisolone, all immunosuppressant agents were discontinued. For SRNS patients, enalapril 0.1-0.3 mg/kg per day was continued at the same doses and no doses adjustment during the present study. None of angiotensin receptor blocker was prescribed. For the patients who went into CR and PR (primary outcome variable), prednisolones were tapered over a 3-6 months period. The secondary outcome variables included Tac dosing and levels, time to achieve CR or PR, time to prednisolone free, relapse while on and off Tac, UP/CR and renal function during treatment.

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 software. Data are presented as descriptive statistics such as mean, standard deviation (std), median (range), frequency, and percentage. Wilcoxon Signed Ranks test was performed to compare UP/CR before and after receiving Tac and eGFR before and after receiving Tac. A p-value of less than 0.05 was considered to be statistically significant.

Results

Eighteen patients participated in this study and included 12 males (66.7%). The mean age at diagnosis of NS was 6.0 years (range 1-14.4 years). Patients were divided as nine SR and nine SDNS. There

were nine FSGS, four IgM nephropathy, two MCD, and the remaining three did not received renal biopsy. Of these three patients, there were one SR and two SDNS. All patients received prednisolone at starting of Tac. The average time from the diagnosis to initiation of Tac was 3.5 years (range 0.2-14 years). The mean follow-up period was 3.1 years (range 0.2-6.4 years). Table 1 displays the full details of the presented patients.

In Table 2, individual patients are fully displayed with their Tac's result. Here the mean duration of treatment with Tac was 1.3 year (range 0.3-6.2 years). The average Tac trough blood level was 4.09 mcg/L (range 1.3-9.9 mcg/L). The average dosage of Tac was 0.09 mg/kg/day (0.03-0.2 mg/kg/day). Thirteen (72.2%) children achieved CR and five (27.8%) children did not respond to Tac. All patients who were in CR would do so within three months. The mean time to achieve CR was 24.6 days (0.1-3 months). In all CR, nine (69.2%) (nos. 4, 5, 9, 10, 12, 13, 14, 15, 18) patients could stop prednisolone after Tac was started at average time of 4.1 months (range 0.5-6 months) and four (30.8%) (nos. 3, 11, 16, 17) patients could taper down prednisolone. Five (38.5%) (nos. 12, 13, 15, 16, 18) patients had relapses while on Tac and had upper respiratory tract infection. Eight (61.5%) (nos. 3, 4, 5, 9, 10, 11, 14, 17) patients had no relapse since Tac had been started. Among these, four (nos. 4, 5, 10, 17) patients still received Tac and four (nos. 3, 9, 11, 14) patients could stop Tac. However, two of them (nos. 9, 11) got relapses. Of the 13 children who attained CR, eight (61.5%) patients were off steroid and Tac and only three (nos. 3, 12, 14) patients achieved sustained remission. The other five (38.5%) (nos. 4, 5, 10, 17, 18) patients are still on Tac therapy. Five (nos. 1, 2, 6, 7, 8) children did not respond to Tac. Prednisolone and Tac were discontinued within three to six months in three patients. Two (nos. 2, 6) patients received Tac longer than six months without clinical nephrotic picture even though they still had nephrotic ranges proteinuria.

In the group of SRNS as shown in Fig. 1, there was CR in four patients (44.4%) (nos. 4, 9, 11, 12). Three patients could stop prednisolone on average at five months (range 3-6 months) since Tac had been started but one patient relapsed three times while on

Table 1. General data for individual 18 patients

Patient	Gender	Age (year) at onset	Duration* (year)	Biopsy results	Respond to steroid	Previous therapies
1	F	14.4	0.6	FSGS	SR	P, CPM
2	F	7.6	0.2	FSGS	SR	P, CPM
3	M	2.2	8.0	FSGS	SD	P, CPM, IVMP
4	F	10.1	1.0	FSGS	SR	P, CPM
5	M	1.3	0.8	FSGS	SD	P, CPM
6	F	12.5	2.2	FSGS	SR	P, CPM
7	M	8.0	6.1	FSGS	SR	P, CPM
8	M	7.0	2.0	FSGS	SR	P, CPM
9	F	4.0	1.6	FSGS	SR	P, CPM
10	M	2.0	7.0	MCD	SD	P, CPM
11	M	2.0	4.8	MCD	SR	P, CPM
12	M	2.1	0.8	None	SR	P, CPM
13	M	1.0	1.3	None	SD	P, CPM
14	F	12.0	0.8	None	SD	P, CPM
15	M	5.0	14.0	IgM nephropathy	SD	P, CPM
16	M	11.0	1.7	IgM nephropathy	SD	P, CPM, AZA
17	M	2.0	2.7	IgM nephropathy	SD	P, CPM
18	M	3.9	7.2	IgM nephropathy	SD	P, CPM

FSGS = focal segmental glomerulosclerosis; MCD = minimal change disease; SR = steroid resistant; SD = steroid dependent; P = prednisolone; CPM = cyclophosphamide; IVMP = intravenous pulse methylprednisolone; AZA = azathioprine; Duration* = duration of disease prior to start tacrolimus

Table 2. Tacrolimus's results for each patient

Patient/diagnosis on each patient	Duration on Tac (months)	Mean Tac level (mcg/L)	Dose of Tac (MKD)	Time to response (days)	From response to prednisolone free (months)	Number of relapses since Tac started	Number of relapses since Tac off
1/FSGS*	3	8.1	0.08	None	None	No CR/PR	No CR/PR
2/FSGS*	21	4.2	0.20	None	None	No CR/PR	No CR/PR
3/FSGS	4	2.0	0.03	10	Not yet	0	0
4/FSGS	29	1.9	0.08	60	6.0	0	Not yet
5/FSGS	23	2.6	0.15	8	2.0	0	Not yet
6/FSGS*	10	3.3	0.07	None	None	No CR/PR	No CR/PR
7/FSGS*	3	ND	0.12	None	None	No CR/PR	No CR/PR
8/FSGS*	6	ND	0.11	None	None	No CR/PR	No CR/PR
9/FSGS	4	1.3	0.09	7	6.0	0	3
10/MCD	74	4.6	0.12	90	0.5	0	Not yet
11/MCD	3	3.5	0.10	8	Not yet	0	2
12/none	24	5.5	0.08	7	3.0	3	0
13/none	24	3.6	0.10	30	3.0	1	1
14/none	30	2.0	0.09	3	3.0	0	0
15/IgM nephropathy	17	1.3	0.07	30	6.0	1	1
16/IgM nephropathy	29	9.9	0.04	7	Not yet	3	4
17/IgM nephropathy	6	5.3	0.09	30	Not yet	0	Not yet
18/IgM nephropathy	36	6.4	0.03	30	4.0	4	Not yet

* None response to tacrolimus
ND = no data; CR = complete response; PR = partial response; Not yet = patient still was on prednisolone or on Tac

Tac and had URI. Five (55.6%) children did not respond. All of them were FSGS. Renal biopsies were done in eight patients resulted in seven FSGS and one MCD. One Patient (no. 12) did not receive renal biopsy due to parents' concern. This patient went to CR within seven days after Tac treatment. In steroid-resistant FSGS group, two patients (28.6%) were in CR.

In the group of SDNS as shown in Fig. 2, all nine patients were in CR with Tac. Renal biopsies were done in seven patients resulted in four IgM

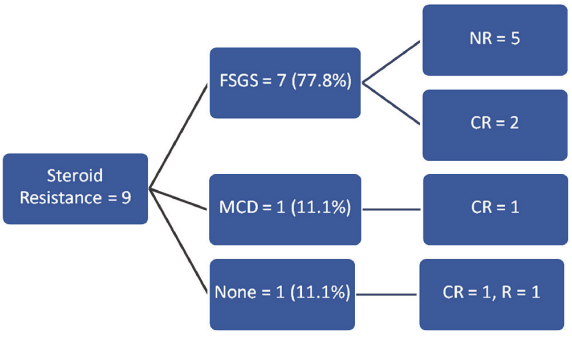

Fig. 1 Outcome of patients with steroid-resistance group. FSGS = focal segmental glomerulosclerosis; MCD = minimal change disease; None = patient did not received renal biopsy; NR = no response; CR = complete response to tacrolimus; R = relapse

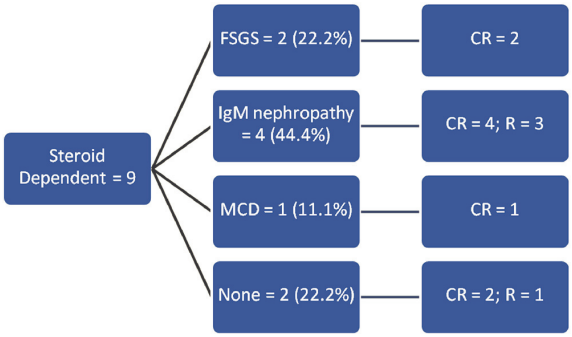

Fig. 2 Outcome of patients with steroid-dependent group. FSGS = focal segmental glomerulosclerosis; MCD = minimal change disease; None = patient did not received renal biopsy; CR = complete response to tacrolimus; R = relapse

nephropathy, two FSGS, and one MCD. Renal biopsies were not performed in two patients. Four (44.4%) (nos. 13, 15, 16, 18) patients relapsed while on Tac and had URI. Three of them were IgM nephropathy. Six (66.7%) (nos. 5, 10, 13, 14, 15, 18) patients could stop prednisolone within average 3.1 months (range 0.5-6 months) after remission. In both figures 1 and 2, response rates are fully displayed.

In nine SR, the estimated median (range) values for UP/CR are significantly reduced from 8.00 (2.68-18.00) to 2.31 (0.11-6.27) with p-value = 0.011. The estimated median (range) values for eGFR before and after receiving Tac were 194.67 (29.25-250.00) and 125.00 (31.57-269.50). There was no difference between eGFR before and after receiving Tac (p-value = 0.374). In nine SD, the estimated median (range) values for UP/CR are significantly reduced from 6.63 (0.16-38.00) to 0.17 (0.05-0.33) with p-value = 0.008. The estimated median (range) values for eGFR before and after receiving Tac were 189.00 (128.40-246.00) and 186.50 (155.00-238.00). There was no difference between eGFR before and after receiving Tac (p-value = 0.859).

Discussion

Apart from single case reports[28,29], there are a few single center studies of SR and SDNS in children with Tac therapy[30-33]. The present study found a complete response to be 72.2%. This estimated value is in a similar level when compared to the finding of 81.3% from Loeffler et al's study[31].

In SRNS group: Table 3 displayed published data compared to our study. CR in our study achieved within three months. This result was comparable to other studies which CR occurred an average of two to four months[4,31-33]. The present study has lower CR rate compared to other studies[4,31-33]. This could be from higher portion of FSGS (77.8%) in our SRNS group and the authors did not identify SRNS from genetic causes, which might have been accounted in the present study population. Furthermore, the authors' target Tac blood level was 3 to 7 mcg/L, which was lower compared to 5 to 10 mcg/L in other studies. In SR FSGS group: Paik et al[3] reported three different treatment regimens in patients with SR FSGS. CR in patients who were treated with IVMP, CPM, and CsA was 25, 20.8, and 33.3% respectively. An increase in the initial serum creatinine and resistance to treatment were independent risk factors for chronic renal failure. The result in the present study is not different compared to the results in other treatments and previous studies[3,4,34]. However, much better results were found in a study from Loeffler et al[31] in which all five patients who had SR FSGS achieved CR and from Butani et al[33], which seven of eight children (87.5%) with SR FSGS achieved CR.

In SDNS group: nine SDNS who previously received steroid and CPM, all were in CR. The role of URI in exacerbating NS had been reported[35]. Loeffler et al[31] reported the use of Tac in eight children with SDNS, which were seven FSGS and one MCD. Seven (87.5%) children achieved CR and one went into PR. Six of seven children who had FSGS achieved CR. Patients turned CR within an average of 1.9 months (range 0.5-4 months). At last follow-up, six of eight SDNS were off steroid. From our and other studies, all

Table 3. Published data compare to our study on tacrolimus treatment in children with SRNS

Author	SRNS (%FSGS)	Previous failed treatment	Outcome
Roberti et al.[4]	19 (52.6%), lost follow-up =1	MMF, CPM, CsA, rituximab	CR = 8 (42.1%), PR = 2 (10.5%), NR = 4 (21.1%), ESRD = 4 (21.1%)
McCauley et al.[30]	4 (100%)	CPM, CsA	CR = 1 (25%), PR = 1 (25%), NR = 2 (50%)
Loeffler et al.[31]	7 (71.4%)	CsA, MMF, chlorambucil	CR = 6 (85.7%), PR = 1 (14.3%)
Gulati et al.[32]	22 (50%), withdrawn = 3	CPM, CsA	CR = 16 (84.2%), PR = 2 (10.5%), NR = 1 (5.3%)
Butani et al.[33]	16 (50%)	CPM, CsA, chlorambucil	CR = 15 (93.8%), ESRD = 1 (6.2%)
Bhimma et al.[34]	20 (100%)	CPM	CR = 8 (40%), PR = 9 (45%), NR = 3 (15%), ESRD = 2 (10%)
The present study	9 (77.8%)	CPM	CR = 4 (44.4%), NR = 5 (55.6%)

FSGS = focal segmental glomerulosclerosis; MMF = mycophenolate mofetil; CPM = cyclophosphamide; CsA = cyclosporine A; NR = no response

data showed that irrespective of histopathology if patients had SDNS they trend to response well to Tac. At the start of Tac, all patients received prednisolone at 0.5 to 1 mg/kg/day. CR may result from prednisolone and/or Tac. However, the benefit of Tac helped us to discontinue prednisolone in majority of SDNS (66.7%).

Compare to CsA: Sinha et al[36] reported the use of Tac in 10 children (9 MCD and 1 FSGS) with severe SDNS who were previously treated with CPM and CsA. The median relapse rate in CsA and Tac treatment was two and one relapse per year. There were no significant differences in efficacy, cumulative steroid dosage, renal function, or statural growth between CsA and Tac therapies. Hamasaki et al[7] reported 35 SRNS treated with 12-month course of CsA. There were 23 MCD, five DMP, and seven FSGS. Remission was achieved in 23 of 28 (82.1%) patients in MCD and DMP group and in six of seven (85.7%) patients in FSGS group. Ehrich et al[37] reported 66 SRNS in combination therapy using CsA, prednisolone and IVMP or CsA and prednisolone. Forty of 52 (76.9%) idiopathic FSGS and all 14 MCD went into CR. However, Shatat et al[8] reported nine SRNS and seven SDNS patients with primary FSGS, only two of nine (22.2%) SRNS were CsA responsive whereas all SDNS were CsA responsive. The study showed a similar result compared to the present study, which reported seven SRNS and two SDNS with primary FSGS. Two of seven (28.6%) SRNS were Tac responsive whereas all SDNS were Tac responsive.

The authors conclude that Tac is well tolerated and shows an effective treatment for SR and SDNS. SDNS has a much better respond rate to Tac. SR FSGS provides the worst respond rate to Tac. Tac is as effective as CsA in treatment children with SRNS, SR FSGS and SDNS. There was no significant change in renal function. A long-term study and well-designed randomized control study should be pursued.

Potential conflicts of interest

None.

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ผลของยาทาโครลิมุสในผู้ป่วยเด็กกลุ่มอาการเนโฟรติกที่ดื้อต่อยาสเตียรอยด์และต้องพึ่งยาสเตียรอยด์

สุโรจน์ ศุภเวคิน, วันทนี สุรไพฑูรย์กร, ฐิติมา คุรุพงศ์, ธนพร ไชยภักดิ์, นันทวัน ปิยะภาณี, อนิรุธ ภัทรากาญจน์, อัจฉรา สัมบุณณานนท์

วัตถุประสงค์: *เพื่อศึกษาผลการตอบสนองของยาทาโครลิมุสในการรักษาผู้ป่วยเด็กเนโฟรติก*
วัสดุและวิธีการ: *ศึกษาข้อมูลผู้ป่วยทั้งหมด 18 ราย จากเวชระเบียนผู้ป่วยนอก ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ที่ได้รับการวินิจฉัยว่าเป็นเนโฟรติกที่ดื้อต่อยาสเตียรอยด์และต้องพึ่งยาสเตียรอยด์ ระหว่างปี พ.ศ. 2545-2551*
ผลการศึกษา: *สัดส่วนเพศชายต่อเพศหญิงเท่ากับ 2:1 อายุเฉลี่ยขณะได้รับการวินิจฉัย 6.0 ปี (1-14.4 ปี) เป็นผู้ป่วยที่ดื้อต่อยาสเตียรอยด์ 9 ราย ต้องพึ่งยาสเตียรอยด์ 9 ราย เป็นชนิด focal segmental glomerulosclerosis (FSGS) 9 ราย IgM nephropathy 4 ราย และ minimal change disease (MCD) 2 ราย ผู้ป่วย 3 ราย ไม่ได้รับการตรวจชิ้นเนื้อไต ผู้ป่วยทุกคนได้รับการรักษาด้วยยาเพรดนิโสโลนในขณะที่เริ่มยาทาโครลิมุส ระยะเวลาตั้งแต่ได้รับการวินิจฉัยจนกระทั่งได้รับการรักษาด้วยยาทาโครลิมุสเฉลี่ยคือ 3 ปี 6 เดือน (0.2-14 ปี) ผู้ป่วยได้รับยาทาโครลิมุสเป็นระยะเวลาเฉลี่ย 1 ปี 4 เดือน (0.3-6.2 ปี) ระดับยาเฉลี่ย 4.09 ไมโครกรัม/ลิตร (1.3-9.9 ไมโครกรัม/ลิตร) โดยใช้ขนาดยาเฉลี่ย 0.09 มก./กก./วัน (0.03-0.2 มก./กก./วัน) ผู้ป่วย 13 ราย (ร้อยละ 72.2) มีผลการตอบสนองที่ดี ผู้ป่วย 5 ราย (ร้อยละ 27.8) ไม่ตอบสนองต่อยาทาโครลิมุส ผู้ป่วย 9 ราย (ร้อยละ 69.2) สามารถหยุดยาเพรดนิโสโลน ผู้ป่วย 4 ราย (ร้อยละ 30.8) สามารถลดขนาดยาเพรดนิโสโลน ช่วงเวลาการตอบสนองที่ดีใช้เวลาเฉลี่ย 24.6 วัน (0.1-3 เดือน) ช่วงเวลาการติดตามผู้ป่วยเฉลี่ย 3 ปี 1 เดือน (0.2-6.4 ปี) ไม่พบการเปลี่ยนแปลงของอัตราการกรองที่หน่วยไต ผู้ป่วยที่ดื้อต่อยาสเตียรอยด์ 9 ราย มีการตอบสนองที่ดี 4 ราย (ร้อยละ 44.4) ไม่ตอบสนองต่อยาทาโครลิมุส 5 ราย (ร้อยละ 55.6) โดยทั้งหมดมีผลการตรวจชิ้นเนื้อไตเป็น FSGS ในผู้ป่วยที่ต้องพึ่งยาสเตียรอยด์ 9 ราย ทุกรายมีผลการตอบสนองที่ดีต่อยาทาโครลิมุส ในจำนวนนี้ 4 ราย มีอาการเนโฟรติกกำเริบขณะได้รับทาโครลิมุสและมีการติดเชื้อทางเดินหายใจส่วนบน*
สรุป: *ยาทาโครลิมุสมีประสิทธิผลดีในการรักษาผู้ป่วยเด็กเนโฟรติกที่ดื้อต่อยาและที่ต้องพึ่งยาสเตียรอยด์*