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ORIGINAL ARTICLE

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Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome

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Abstract This is a retrospective analysis of 16 children started on tacrolimus with various types of treatment-resistant nephrotic syndrome. There are 13 patients with focal glomerulosclerosis, 1 minimal change disease, and 2 IgA nephropathy with nephrosis. The mean age of the children was 11.4 years (range 3.5–18.1 years) with a mean age at diagnosis of 5.6 years (range 1.6–13.3 years). All patients initially received prednisone 2 mg/kg per day. Other therapies for 15 of 16 included cyclosporine (*n*=15), chlorambucil (*n*=5), mycophenolate mofetil (*n*=5), levamisole (*n*=3), i.v. methylprednisolone (*n*=3), and cyclophosphamide (*n*=2). The major indication for the initiation of tacrolimus included treatment resistance/dependence (*n*=15) and intolerable side effects from other therapies (*n*=1). The average time from the diagnosis to initiation of tacrolimus was 5.3 years (range 0.3–13.3 years, median 6 years). The initial dosage of tacrolimus utilized was 0.1 mg/kg per day divided into two doses. The mean follow-up period was 6.5 months (range 2.5–18 months). Thirteen patients (81%) went into a complete remission within an average of 2 months (range 0.5–5.5 months), with 3 patients relapsing while on treatment. Three patients did not respond. Of these, 2 had partial remissions (13%) and 1 failed to respond. Adverse events included anemia (*n*=1), seizure (*n*=1), worsening or new-onset hypertension (*n*=5), and sepsis (*n*=1). All patients remain on tacrolimus. Tacrolimus is an effective, well-tolerated medication for treatment-resistant forms of nephrotic syndrome in children, with a complete remission rate of 81% and a partial remission rate of 13% (totaling 94%).

Keywords Focal segmental glomerulosclerosis · Treatment · Tacrolimus · Efficacy · Adverse events

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Introduction

Treatment-resistant forms of nephrotic syndrome (NS) [with focal segmental glomerulosclerosis (FSGS) as the most common entity] are the most common forms of NS associated with the development of renal failure [1, 2, 3, 4]. The total number of cases of FSGS has been increasing over recent years, although the absolute number of cases of NS has not [5]. Despite years of research, the pathophysiology and treatment strategies of this difficult group of diseases remain an enigma.

Therapeutic options for treatment-resistant forms of NS have included prednisone, levamisole, cyclosporine, i.v. methylprednisolone, alkylating agents, angiotensin-converting enzyme inhibitors (ACEI), plasmapheresis, and, most recently, mycophenolate mofetil [2, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. However, therapeutic success has only been as high as 60%, with the majority of therapies reporting less than 50% efficacy. In addition, if remission is not achieved and proteinuria continues, prognosis is poor and associated with a high incidence of progression to renal failure [11, 20, 21, 22, 23].

Tacrolimus is a macrolide antibiotic that has a relatively selective inhibitory action on CD4 helper cells. It differs from cyclosporine in being more potent in cytokine suppression and, therefore, potentially more potent in suppressing the "permeability" factor responsible for FSGS [24]. A pilot trial of tacrolimus in steroid-resistant NS by McCauley et al. [25] was the first report of seven

patients (of whom four were pediatric patients). All the patients responded positively to tacrolimus despite being resistant to previous therapies [25, 26]. Since then, there have been three more publications of successful treatment with tacrolimus, two involving pediatric patients [27, 28, 29]. The majority of these reports have been single to small series case reports, with the largest series reporting a remission rate of 75% among 25 adults [27]. Based on these experiences and the desperation these patients face when they fail conventional therapies, we embarked on a trial of tacrolimus in treatment-resistant forms of NS in children. There have been no randomized controlled trials comparing tacrolimus with other immunosuppressive therapies, and there is little knowledge of the long-term side effects and long-term efficacy of this medication for difficult cases of NS. To our knowledge, this is the largest case series to date describing tacrolimus therapy for treatment-resistant NS in children.

Materials and methods

Patient selection

We retrospectively reviewed 16 children from 1 January 2000 to 31 December 2002, with treatment-resistant NS on tacrolimus. Indications for initiation of tacrolimus included treatment resistance/dependence on steroids and/or other immunosuppressive treatments (defined as presence of nephrotic-range proteinuria after 3 months of treatment) and/or the presence of intolerable side effects of the present medications (i.e., diabetes, uncontrolled hypertension, gingival hyperplasia requiring gingivectomies).

Prior to receiving tacrolimus, all patients initially received prednisone at 2 mg/kg per day. Other forms of immunosuppressive therapy that were tried without success included cyclosporine, alkylating agents, i.v. methylprednisolone, mycophenolate mofetil, and levamisole [9]. ACEI were the treatment of choice for associated hypertension and were also used to aid with the reduction in proteinuria.

All renal biopsies were performed with 18-gauge biopsy needles via the percutaneous route under ultrasound guidance. All kidney samples were sent for routine light microscopy, immunofluorescence, and electron microscopy. The diagnoses of minimal change disease (MCD), FSGS, and IgA nephropathy (IgAN) were made by the renal pathologist according to standard histological classifications.

Each patient was informed that tacrolimus was a new type of immunosuppressant medication that had not yet been approved for the use in NS, although there were some preliminary publications reporting some success. The side effects profile was discussed with each patient and family. An informal verbal consent was obtained after discussions with the families and patient. The retrospective study review was approved by the ethics committee at our institution.

Definitions

NS was defined as a syndrome comprising hypoalbuminemia (<30 g/l), hyperlipidemia (cholesterol >upper limit of normal for age), edema, and proteinuria [urine protein/creatinine ratio (Pr/Cr) >200 mg/mmol]. Steroid resistance was defined as no clinical response after 8 weeks of daily steroids at 60 mg/m^2 per day (maximum dose 60 mg/day) [30]. Steroid dependency was defined as two consecutive relapses during tapering of steroid therapy or within 14 days of cessation of treatment [30]. Treatment resistance was defined as no clinical response after a 3-month trial of the index medication.

A relapse was defined as urine dipstick of $\geq$3+ with no previous proteinuria and with clinical evidence of edema or dipstick of $\geq$2+ proteinuria for 3 days [30]. Complete remission (CR) was defined as a normal spot urine Pr/Cr (2–20 mg/mmol) and/or a negative urine dipstick for protein for 3 days or more [30]. Partial remission (PR) was defined as a spot urine Pr/Cr ratio between 20 and 200 mg/mmol. Nephrotic-range proteinuria was defined as urine Pr/Cr ratio >200 mg/mmol and/or 24-h urine protein >3.5 g/1.73 m^2 per day.

Hypertension was defined as a systolic blood pressure or a diastolic blood pressure greater than the 95th percentile for age and sex measured on at least three separate occasions [31]. Creatinine clearance was calculated via the Schwartz formula [32].

Therapy

Tacrolimus was given at 0.1 mg/kg per day divided into two doses over 12-h intervals. The goal for the trough tacrolimus level was 5.0–10.0 μg/l [27, 28, 29]. All previous immunosuppressant agents (with the exception of prednisone) were discontinued prior to the start of tacrolimus. For patients who remained on steroids at the initiation of tacrolimus, the steroid dose was adjusted downwards once there was a reduction in urine protein excretion. For the patients who went into CR, the steroids were tapered over a 1- to 3-month period. For patients in PR, the steroids were slowly tapered over a course of 3–6 months. Patients who relapsed while on tacrolimus were treated with the standard dosing of prednisone (60 mg/m^2) until remission, followed by a gradual taper over 2 months.

Follow-up

Follow-up was arranged weekly initially for the first 4 weeks, followed by monthly visits. Blood was drawn for measurement of tacrolimus trough levels, creatinine, urea, electrolytes, albumin, and complete blood count 1 week after initiation of tacrolimus. This was followed by monthly measurements for 3 months until stable levels of tacrolimus were achieved. Tacrolimus levels were measured via the IMX analyzer utilizing the microparticle enzyme assay (MEIA) (Abbot Laboratories, Ill., USA).

Outcome variables

The primary outcome variable was the number of patients who went into a CR or PR. Secondary outcome variables included renal function during treatment, adverse events, tacrolimus dosing and levels, time to achieve remission, and maintenance of remission once achieved.

Results

Baseline clinical demographics

Table 1 displays the demographics and the biopsy results from the 16 study patients. The patients included 12 males and 4 females, with an average age of 11.4 years (range 3.5–18.1 years). The racial distribution included 9 Caucasian, 5 Aboriginal, 1 Asian, and 1 black patient. The mean duration of disease before initiation of tacrolimus was 5.6 years (range 0.3–13.3 years). The mean total duration of therapy ranged from 0.4 to 13 years. Biopsy results confirmed that 13 patients have FSGS, 1 has

Table 1 Patient demographics, biopsy results, and previous therapies (*C* Caucasian, *A* aboriginal, *E* East Indian, *B* black, *FSGS* focal segmental glomerulosclerosis, *IgAN* IgA nephropathy, *MCD* minimal change lesion, *SD* steroid dependence, *SR* steroid resistance, *CyA* cyclosporine, *L* levamisole, *A* chlorambucil, *MMF* mycophenolate mofetil, *M* i.v. methylprednisolone, *P* p.o. cyclophosphamide)[a]

Patient	Gender	Race	Age (years)	Age at onset (years)	Duration of disease prior to start of tacrolimus (years)	Biopsy results	Prednisone at start of tacrolimus	Steroid responsiveness	Previous therapies	Previous CyA responsive
1	M	C	10.8	7.5	2.6	FSGS	Yes	SR	CyA	Yes
2	M	A	13.7	13.3	0.4	IgAN	Yes	SR	CyA	No
3	F	C	14.3	2.3	12.0	FSGS	Yes	SD	CyA, L	Yes
4	M	E	13.5	2.7	10.7	FSGS	Yes	SD	A, CyA, MMF, L	Yes
5	F	C	17.2	3.3	13.3	FSGS	Yes	SD	A, CyA, MMF, L	Yes
6	M	A	12.9	11.3	1.4	FSGS	Yes	SR	CyA	No
7	F	A	3.5	1.6	2.9	FSGS	Yes	SR	CyA	Yes
8	M	C	4.1	3.3	0.3	MCD	Yes	SD	CyA	No
9	M	C	13.9	1.6	11.7	FSGS	Yes	SD	A, CyA, M, P	Yes
10	M	C	18.1	7.0	9.7	FSGS	Yes	SD	CyA, P	Yes
11	F	C	10.6	9.2	0.3	IgAN	Yes	SR	None	NA
12	M	A	16.0	14	1.5	FSGS	Yes	SD	CyA	Yes
13	M	C	8.7	2	8.4	FSGS	No	No[b]	CyA, MMF	No[c]
14	M	A	3.1	1.8	0.4	FSGS	Yes	SR	CyA	No
15	M	C	12.1	6.5	4.2	FSGS	Yes	SD	A, CyA, MMF, M	Yes
16	M	B	9.8	2.7	5.6	FSGS	Yes	SR	A, CyA, MMF, M	Yes
Median			12.5	3.3	3.5					
Mean			11.4	5.6	5.3					

[a] An angiotensin-converting enzyme inhibitor was added during the course of treatment to all patients
[b] Developed diabetes while on prednisone
[c] Developed acute renal failure while on CyA

MCD, and 2 have IgAN. All patients were nephrotic at the time of the biopsy and at the time of initiation of tacrolimus.

Other therapies

Prednisone therapy and responsiveness varied with each patient (Table 1). Only 1 patient was not on steroids at the time of initiation of tacrolimus, due to the development of steroid-induced diabetes. Of the other patients, 7 were steroid resistant and 8 were steroid dependent. Once the tacrolimus was initiated, the patients who were steroid resistant were placed on tapering doses of prednisone over a course of 1–3 months. Those who were steroid dependent were maintained on alternate-day steroids at doses of 0.5 mg/kg per dose until remission was achieved and then the steroids were tapered.

Cyclosporine was utilized previously in all patients with either FSGS or MCD (n=15) (Table 1). Of these patients, 10 were cyclosporine responsive during the initial treatment, but upon discontinuation of the cyclosporine after 1 year of remission, all patients relapsed. Despite retreatment with cyclosporine, all 10 patients continued to remain nephrotic or had frequent relapses, therefore necessitating other therapies.

Alkylating agents (cyclophosphamide and chlorambucil) were given early in the course of the diagnosis of NS for patients 4, 5, 9, 15, and 16 prior to the diagnosis of FSGS. The duration of treatment for alkylating agents ranged from 8 to 12 weeks. The initial biopsies for all these patients revealed a diagnosis of MCD. None of the patients who were diagnosed with biopsy-proven FSGS received alkylating agents.

Mycophenolate mofetil was attempted in 4 patients for a 3-month trial period, but was not found to be effective in reducing the steroid dose, relapse rate, or increasing the remission rate. Levamisole was also ineffective in the 3 patients. Intravenous methylprednisolone was given to 3 patients according to the Mendoza protocol [9]. There was no effect on patient 9. Patient 15 responded initially, but relapsed after 12 months of therapy. Patient 16 remains on i.v. methylprednisolone in remission, with plans for a slow tapering of the steroids while maintained on tacrolimus.

The 2 patients with IgAN (patients 2 and 11) both remained nephrotic despite a full trial of prednisone. Patient 2 received a trial of cyclosporine due to the initial assumption that he also had FSGS, as his brother had biopsy-proven FSGS. However, the subsequent biopsy revealed the diagnosis of IgAN and the patient was then switched to tacrolimus when there was no response to the cyclosporine. Within 2 weeks and 8 weeks of initiation of tacrolimus, patients 11 and 2 (respectively) responded with abrupt cessation of proteinuria and recovery from the NS.

Hypertension was controlled by different classes of antihypertensive medications, including ACEI, angiotensin receptor blockers (ARB), calcium channel blockers, and beta-blockers (Table 2). Twelve patients were on antihypertensive medications prior to institution of tacrolimus. Four patients (patients 1, 8, 11, and 14) had

Table 2 Blood pressure control pre and post tacrolimus (*ACEI* angiotensin-converting enzyme inhibitors, *CCB* calcium channel blockers, *ARB* angiotensin receptor blockers)

Patient	Pre tacrolimus blood pressure (mmHg)	Post tacrolimus blood pressure (mmHg)	Pre tacrolimus antihypertensives	Post tacrolimus antihypertensives
1	128/82	119/82	ACEI, CCB, minoxidil, β-blocker	ARB
2	119/81	122/64	CCB	CCB, ACEI
3	120/70	120/70	No	ARB
4	132/93	108/66	No	β-blocker
5	121/67	121/70	No	None
6	110/60	120/80	No	None
7	110/66	120/80	ACEI	ACEI[a]
8	124/86	109/53	ACEI, CCB	None
9	115/66	120/78	ACEI	Same
10	130/82	120/78	ACEI	Same
11	130/60	125/65	ACEI	None
12	115/79	114/51	ACEI	Same
13	98/42	105/61	ACEI, ARB	Same
14	115/80	98/48	ACEI, CCB	None
15	127/89	130/69	ACEI	Same
16	110/75	118/72	ACEI	ACEI, CCB

[a] Required double dosing of the ACEI post tacrolimus

Table 3 Response to tacrolimus therapy (*CR* complete remission, *PR* partial remission)

Patient	Current dose of tacrolimus (mg/kg per day)	Length on tacrolimus (months)	Mean tacrolimus level (μg/l)	Response to tacrolimus	Time to response (months)	Time to prednisone free (months)	Relapse since tacrolimus started	Urine Pr/Cr ratio		Creatinine clearance (ml/min per 1.73 m^2)[a]	
								Pre	Post[b]	Pre	Post[b]
1	0.20	10	7.9	CR	5.5	1	None	1398	18	61	131
2	0.12	4	8.5	PR	2	1	None	1835	164	93	133
3	0.17	3	7.0	PR	1.5	Not yet	None	1191	71	110	108
4	0.13	7	5.5	CR	0.75	Not yet	1	598	6	138	103
5	0.17	6	6.1	CR	4	1.2	None	315	5	138	136
6	0.23	2.5	12.8	CR	2	Not yet	1	649	9	229	204
7	0.14	8	4.4	CR	3	3	None	1445	31	499	221
8	0.17	6	5.9	CR	1.5	2	None	1320	15	300	118
9	0.18	3	7.0	CR	4	1	None	446	10	499	167
10	0.18	5	8.8	CR	0.5	3	None	242	13	120	147
11	0.12	13	13	CR	0.5	6	None	454	13	120	119
12	0.07	6	16	CR	1	4	None	788	11	235	171
13	0.19	3	7.3	No	NA	NA	NA	352	356	84	88
14	0.40	10	8.0	CR	3	3	None	357	20	158	109
15	0.18	18	6.8	CR	1.5	3	None	608	17	405	162
16	0.20	6	9.4	CR	3	Not yet	2	1090	15	148	185
Mean	0.18	6.8	8.4		2			818	48	208	143
Median	0.18	6.0	7.6		2			629	15	143	135

[a] Calculated via the Schwartz formula [32]
[b] Most-recent value at follow-up

significant improvement in blood pressure control, with reductions or elimination of antihypertensive treatment after tacrolimus was instituted. Five patients (patients 2, 3, 4, 7, and 16) required either an increase in the dosage or an additional antihypertensive medication after tacrolimus was started. Tacrolimus had no influence on blood pressure in the other 7 patients.

Renal response to tacrolimus

Tacrolimus was initiated at a dose of 0.1 mg/kg per day divided into twice daily dosing. The dose of tacrolimus was adjusted to maintain a therapeutic value between 5.0 and 10.0 μg/l. The mean dose of tacrolimus was 0.18 mg/kg per day divided into twice daily dosing and the mean trough tacrolimus level was 8.4 (4.4–12.8 μg/l) (Table 3). The mean time for response to tacrolimus for those who went into CR and PR was 2 months.

Thirteen patients went into CR after a median of 6 months following the initiation of tacrolimus therapy.

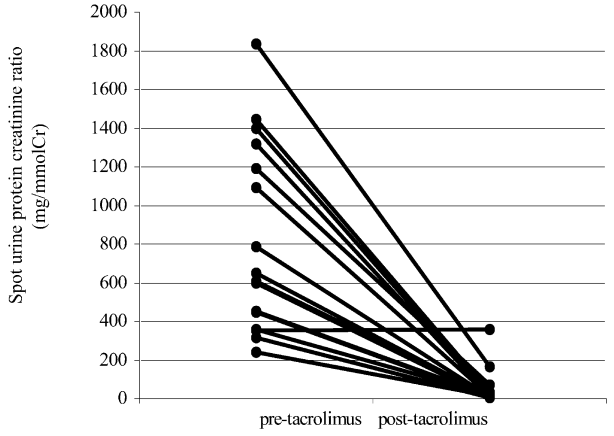

Fig. 1 Proteinuria pre and post tacrolimus use

Two patients are in PR with significant reductions in the urine Pr/Cr ratios. Three patients relapsed while on tacrolimus treatment. All relapses were precipitated by upper respiratory tract viral infections and responded with adjustments to the prednisone dose. Patient 16 had two relapses while on tacrolimus. This patient had severe non-responsive NS for the preceding 2 years despite all attempts at varying therapies. Within 3 months of initiating tacrolimus, patient 16 became protein free, but unfortunately developed relapses precipitated by upper respiratory tract viral infections. Both relapses resolved with the maintenance of therapy, which included prednisone and tacrolimus. Patient 13 is the only non-responder, but may have immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, thereby making this an atypical case of FSGS [33]. Figure 1 shows the level of proteinuria pre and post tacrolimus therapy.

The mean urine Pr/Cr ratio prior to the start of tacrolimus was 818 mg/mmol and decreased to 48 mg/mmol after tacrolimus was instituted. The mean creatinine clearance prior to the start of tacrolimus was 208 ml/min per 1.73 m^2, as calculated via the Schwartz formula [32]. This decreased slightly to 143 ml/min per 1.73 m^2 while on tacrolimus, likely reflecting more normal renal function without the state of hyperfiltration.

Toxicity

During our chart review, some adverse events were detected after the institution of tacrolimus. These included sepsis (patient 1), seizure (patient 8), anemia (patient 15), and new-onset hypertension (patients 3, 4). Hypertension also worsened in 3 patients that required a dose increase or an additional antihypertensive medication. All patients continue on tacrolimus therapy.

Patient 1 developed *Staphylococcus aureus* sepsis from an infected Portacath 1 month after tacrolimus therapy was started. Patients 3 and 4 developed new-onset hypertension 5 months and 2 months (respectively) after tacrolimus treatment, requiring therapy with antihypertensive medications. Patient 8 had a short 2-min generalized tonic-clonic seizure 1 month after starting tacrolimus that did not require any short-term or long-term anticonvulsant therapy. The tacrolimus level for this patient ranged between 4.8 and 10.5 μg/l. Patient 15 developed anemia 4 months after the initiation of tacrolimus that has improved on iron supplementation.

Discussion

In this retrospective review, we analyzed the efficacy and safety of use of tacrolimus in the treatment-resistant NS of 16 pediatric patients. This report is limited by its retrospective format but we hope that it will lead to prospective clinical trials. Treatment for refractory disease once cyclosporine and i.v. methylprednisolone are found to be ineffective is very limited, and often becomes limited to the use of ACEI and/or ARB. We believe that our report offers significant hope for this group of treatment-resistant children, where prognosis is poor, and confirms previous isolated case reports of the efficacy of tacrolimus in treatment-resistant NS.

In our experience, 94% of patients improved, with a CR rate of 81% within an average of 2 months of therapy. Only 1 patient has not responded, but this patient has other co-morbid conditions causing the etiology of the FSGS to be atypical and therefore less likely to respond to conventional therapies. These results are impressive in that prior to tacrolimus, for steroid- and cyclosporine-resistant forms of NS there was not much hope for any effective therapy, let alone one able to induce CR.

All patients with either FSGS or MCD were on prior steroids and cyclosporine. Of those who received cyclosporine, the initial response to cyclosporine did not influence the effects of tacrolimus. Two of the patients who were resistant to cyclosporine did respond with CR while on tacrolimus. Therefore, a lack of efficacy of cyclosporine should not preclude a trial of tacrolimus.

Two patients with IgAN also responded with complete resolution of their NS. IgAN is not classically placed within the same category with MCD and FSGS. However, both patients experienced the severe degree of nephrosis and complications that one would expect with idiopathic NS. Our attempt to utilize tacrolimus in these two situations was not based on previous reports, as there are none, but more on the hope that it might be useful in a generalized nephrotic state with differing etiologies. The abruptness with which the remissions occurred after the institution of tacrolimus made it less likely to be part of the natural history of IgAN and strongly suggested to us that it was the tacrolimus that was responsible for the remission.

Although we report some side effects experienced by some of the patients, all were treatable, and all patients remain on tacrolimus. There were no demonstrated deleterious effects on renal function in our cohort. There was also improvement in the creatinine clearance from a hyperfiltration state with a high glomerular filtration rate.

We are limited in this study in that we do not have histological evidence of the effects of tacrolimus on the kidneys, but we hope to gather these data with prolonged follow-up of our patients.

The mechanisms behind the efficacy of tacrolimus rather than cyclosporine in refractory NS are not known. There are some data to suggest that tacrolimus has differing effects on proteinuria in NS compared with cyclosporine [34, 35]. Maruyama et al. [36, 37] also demonstrated better inhibition of the vascular permeability factor cultured from patients with MCD with tacrolimus than with cyclosporine. Tacrolimus also has better cytokine suppression than cyclosporine, which may also influence the differing responses to therapy [24].

In our experience with treatment-resistant forms of NS, tacrolimus can be a very effective treatment in what was otherwise known as a disease without hope. We hope that this report will encourage larger prospective randomized trials of the use of tacrolimus as an alternative treatment in NS and help answer the important question of whether tacrolimus should be a first-line agent for use in steroid-resistant or -dependent forms of NS.

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