Tacrolimus for children with refractory nephrotic syndrome: a one-year prospective, multicenter, and open-label study of Tacrobell®, a generic formula

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Original article

Background: **Cyclosporine A and tacrolimus (TAC) are often used as a second-line treatment for children with refractory nephrotic syndrome (NS). This study was undertaken to investigate the efficacy and safety of Tacrobell®, a locally produced generic form of TAC.**

Methods: **This study was a one-year prospective, open-label, single-arm, multicenter trial. Fourty-four children with steroid-dependent NS (SDNS) and 33 children with steroid-resistant NS (SRNS) were enrolled. The primary endpoints were defined as the remission rates, whereas the secondary endpoints were recognized as the duration of remission and adverse effects of TAC.**

Results: **After one-year treatment, 34 (77.3%) of the 44 patients with SDNS were in complete remission, and 6 (13.6%) were in partial remission. Nineteen (43.2%) patients did not relapse during the study; for those who did relapse, the mean duration of remission was 4.6±2.9 months. The number of relapse episodes during the study period (0.90 per patient-year) was significantly lower than that in the preceding year (2.8 per patient-year). After treatment for 3 and 6 months, 12 (36.4%) of the 33 patients with SRNS were in remission, and after treatment for 12 months, the number of patients had increased to 13 (39.4%). The mean time to achieve remission was 4.0±3.2 months. After remission (duration, 3.7±2.7 months), 12 (54.5%) of 22 patients relapsed. The fasting blood glucose and blood pressure levels during the therapy were similar to those at the time of study entry.**

Conclusions: **Treatment with Tacrobell® was effective and safe for children with refractory NS. The efficacy of this generic form of TAC was better than that of the original TAC formula.**

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Key words: **generic drugs; nephrotic syndrome; tacrolimus**

Introduction

Nephrotic syndrome (NS) is the most common glomerulopathy in children. Usually it is responsive to steroid treatment; however, about 40% of patients suffer from frequent relapse (frequently relapsing NS, FRNS) or steroid dependency (steroid-dependent NS, SDNS).[1] Repeated and prolonged use of steroids may result in obesity, poor growth, hypertension, cataracts, and osteoporosis.[2] About 10%-15% of patients have NS that does not respond to steroid treatment (steroid-resistant NS, SRNS);[1,3] their persistent proteinuria can significantly progress to chronic renal failure.[4] Thus, refractory NS requires alternative therapy to reduce steroid toxicity and to achieve remission.[5] Various immunosuppressive agents, such as alkylating agents, calcineurin inhibitors (CNIs), and mycophenolate mofetil, are used, though these second- or third-line therapies have their own adverse events, including bone marrow suppression with alkylating agents[4,6] and nephrotoxicity with CNIs.[4,7,8]

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Tacrolimus (TAC) is an immunosuppressive macrolide of the CNI group. It is more potent than cyclosporine (CsA) of the same group in cytokine suppression, and is widely used in allograft transplantation. Similarly to CsA, TAC has been found to be effective in maintaining remission in patients with refractory NS,[9,10] and does not have cosmetic side effects.[7,11-13] Moreover, it is more effective for SRNS than CsA.[14,15] TAC for NS has not yet been approved by the Korean Food and Drug Administration (FDA), and it is more costly than CsA. Alternatively, Tacrobell® (Chong Kun Dang Pharmaceutical Corp., Seoul, Korea), a generic, is a less expensive form of TAC that has been shown to be equivalent to the original product.[16] In this study, the efficacy and safety of Tacrobell® for refractory NS were evaluated in a one-year prospective open-label, single-arm, multicenter trial.

Methods

Patient selection

From June 2010 to August 2013, children with refractory NS were enrolled in this one-year prospective study, which was conducted at three centers in Korea after obtainment of informed consent. The criteria for enrollment were as follows: 1) SDNS, indicative of two or more relapses during tapering or within 14 days of stopping steroid therapy; 2) FRNS, more than four relapses within one year or at least two within six months; and 3) SRNS, absence of remission after four weeks of steroid therapy. The criteria for exclusion were as follows: 1) known secondary causes of NS; 2) estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m^2; and 3) active infectious disease. The study was approved by the Institutional Review Boards of all the participating centers as well as the Korean FDA. It was conducted according to the principles of the *Declaration of Helsinki*.

Treatment protocol and follow-up

Tacrobell® was administered in two equal doses of 0.1 to 0.2 mg/kg per day (every 12 hours). The dosage was adjusted to maintain the trough blood level between 5 and 10 ng/mL. No additional immunosuppressive agents except for steroids were used during the study period. For patients with SDNS or FRNS, TAC was introduced after appearance of remission, and an oral dose of glucocorticosteroid was adjusted according to the status of NS. For patients with SRNS, TAC was introduced at the time of enrollment; patients were allowed to discontinue TAC at any time if there was no response after three months of treatment. Relapsed patients were treated with 60 mg/m^2 of prednisolone per day until appearance of remission, followed by 40 mg/m^2 per day on alternate days for four weeks, with gradual tapering over two months. Angiotensin-converting enzyme inhibitors, other antihypertensive or lipid-lowering agents were added to the regimen when necessary.

Patients were followed up 2 weeks after treatment and then every month for 12 months in terms of physical examination, urinalysis, serum chemistry and complete blood counts. The TAC trough level was measured biweekly during the first month and then every three months. If the serum creatinine (sCr) level increased by more than 25%, the TAC dose was reduced by 25% onsuspicion of TAC nephrotoxicity; if the s+Cr level did not recover despite dose reduction, TAC was discontinued. eGFR was calculated at the first and last visit according to the revised Schwartz formula.[17]

Outcomes

The primary endpoints were defined as the remission rate at the end of the one-year treatment for SDNS/FRNS and at 3, 6, and 12 months of treatment for SRNS. The secondary endpoints included the duration of remission and the frequency of relapse for SDNS/FRNS, the time to remission for SRNS, change of renal function, and side effects of TAC. For patients with SDNS, the relapse rates and cumulative steroid doses while on TAC treatment were compared with those during the year before enrollment. Complete remission (CR) was defined as the absence of proteinuria, a urine protein/creatinine ratio (UP/C) less than 0.2 g/g creatinine, or negative results of a urine albumin test by dipstick for three consecutive days. Partial remission (PR) was defined as subnephrotic proteinuria ($0.2 \leq UP/C < 2$) or resolution of edema and an increment in serum albumin concentration to more than 2.5 g/dL. Relapse was defined as the reappearance of albuminuria more than 2+ (by dipstick) for three consecutive days. Duration of remission was defined as the duration from the remission on the enrollment or the first remission achieved while on the trial, to the subsequent relapse.

Statistical analysis

Data were analyzed on an intention-to-treat basis. Results were presented as the mean±standard deviation. Continuous variables were analyzed using the independent-sample *t* test, and categorical variables were analyzed using Fisher's exact test or the Chi-square test. The Kaplan-Meier method was used to estimate relapse-free survival. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 77 patients (male:female=54:23), 44 with SDNS/FRNS and 33 with SRNS, were enrolled in this study. The baseline characteristics of all the patients are shown in Table 1. Their average age of the patients was 9.9 years (range: 1.5-18.9 years). The mean duration of disease before initiation of TAC administration was 4.8 years (range: 0.2-16.0 years). Diseases diagnosed pathologically included minimal change disease (MCD; 29 patients), focal segmental glomerulosclerosis (FSGS; 17 patients), C1q nephropathy (4 patients), and mesangial proliferation (2 patients). Biopsy was not performed in 25 patients. As shown in Table 1, all of the patients except one had previously been treated with at least one kind of second-line therapy as a steroid-sparing agent in addition to corticosteroids. Sixty-four patients (43 in SDNS/FRNS and 22 in SRNS) were in remission at enrollment. Four SDNS patients and six SRNS patients withdrew from the study due to adverse effects; two SDNS patients and three SRNS patients withdrew due to poor response or unwillingness to remain in the study.

Response to therapy

Of the 44 patients with SDNS/FRNS, 34 (77.3%) patients were in CR and six (13.7%) patients were in PR at the end of the 12-month treatment period. In the course of TAC therapy, remission was sustained in 19 (43.2%) patients without subsequent relapse (Table 2), as shown on the relapse-free survival curve (Fig.). Twenty-five patients experienced one or more episodes of relapse, after a mean duration of remission of 4.6±2.9 months. The mean number of relapses was significantly reduced with treatment, from 2.8±1.3 episodes per year before TAC to 0.9±1.0 episodes per year after TAC treatment (P=0.001).

Of the SRNS patients (n=33), 12 (36.4%) were in CR, 11 (33.3%) in PR, and 10 showed no response at three months. At 6 months, 12 (36.4%) patients were still in CR and 6 (18.2%) were in PR, with an overall response rate (CR or PR) of 54.5%. At the end of 12-month treatment, 13 (39.4%) of the patients showed CR and 10 (30.3%) PR, with an overall response rate (CR or PR) of 69.7%. Table 3 shows the relationship between pathologic findings and response

Table 1. Baseline characteristics of the patients

Variables	SDNS group (n=44)	SRNS group (n=33)
Age at onset of disease (y), mean±SD	5.2±3.5	5.0±3.4
Age at enrollment (y), mean±SD	11.4±4.2	7.9±4.2
Duration of disease (y), mean±SD	6.2±3.7	2.9±2.6
Gender (male/female)	35/9	19/14
Histology, n		
MCD	16	13
FSGS	0	17
Mesangial proliferative GN	0	2
C1q nephropathy	3	1
Relapse episodes		
Preceding 1 y (episodes per y), mean±SD	2.8±1.3	NA
Cumulative steroid dose		
Preceding 1 y (mg/kg per y), mean±SD	108.5±67.8	199.7±232.3
Previous treatment regimen, n		
Cyclophosphamide	26	10
Cyclosporine	40	25
Levamisole	9	0
Bredinin	12	10
Azathioprine	2	0
Mycophenolate mofetile	1	0
Rituximab	1	0

SDNS: steroid-dependent nephrotic syndrome; SRNS: steroid-resistant nephrotic syndrome; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; GN: glomerular nephritis; SD: standard deviation; NA: not applicable.

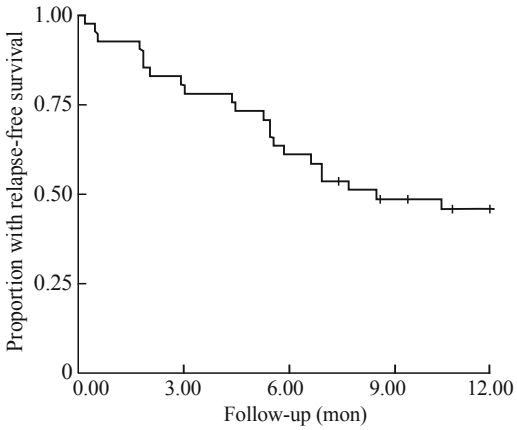

Fig. Relapse-free survival in steroid-dependent nephrotic syndrome patients treated with tacrolimus.

Table 2. Responses to TAC therapy

Syndromes	Outcomes
SDNS (n=44)	
Complete remission at 12 mon, n (%)	34 (77.3)
Sustained complete remission at 12 mon, n (%)	19 (43.2)
Mean duration of remission (mon), mean±SD	4.6±2.9
Calculated relapse rate (episodes/y), mean±SD	0.9±1.0
SRNS (n=33)	
Complete remission	
at 3 mon, n (%)	12 (36.4)
at 6 mon, n (%)	12 (36.4)
at 12 mon, n (%)	13 (39.4)
Mean time to remission (mon), mean±SD	4.0±3.2
Mean duration of remission (mon), mean±SD	3.7±2.7

TAC: tacrolimus; SDNS: steroid-dependent nephrotic syndrome; SRNS: steroid-resistant nephrotic syndrome; SD: standard deviation.

to treatment in SRNS patients. Diseases diagnosed histopathologically with complete remission included MCD (6 patients), FSGS (5), mesangial proliferative glomerular nephritis (1), C1q nephropathy (1) at the end of the 12-month treatment. Remission was achieved in 4.0±3.2 months (range: 0.5-9.6 months) after TAC treatment. In the 22 patients who had achieved CR, 12 experienced subsequent relapse during the treatment by 3.7±2.7 months (Table 2).

Other outcome variables

Laboratory findings of the study subjects upon completion of the 12-month treatment revealed that the levels of proteinuria, serum albumin and cholesterol had improved significantly compared with the baseline levels. Although the serum creatinine level had increased and the eGFR decreased, they were still within normal ranges. Neither fasting blood glucose level nor blood pressure was significantly different before and after the trial. The cumulative steroid dose during the study year was 102.2±120.8 mg/kg per year, whereas during the preceding year it was 139.7±151.9 (P=0.052; Table 4).

Adverse effects

Renal function decreased with TAC in 4 of the SRNS patients, whose proteinuria were unresponsive. Other adverse events including gastrointestinal trouble (n=1), headache (n=2), dizziness (n=1), and hand tremors (n=2) resulted in withdrawal of the patientsfrom the study. One patient complained of an itching sensation, which spontaneously ceased. Transient hyperglycemia was observed in one patient, and 11 patients (8 SRNS, 3 SDNS) showed transient glycosuria without hyperglycemia. Neither diabetes nor new-onset hypertension was observed during the trial.

Table 3. Responses to TAC therapy according to pathology of SRNS

Diseases	3 mon		6 mon		12 mon	
	CR	PR	CR	PR	CR	PR
MCD (n=13)						
Remission at enrollment (n=11)	5	4	7	2	6	5
No remission at enrollment (n=2)	-	-	-	-	-	-
FSGS (n=17)						
Remission at enrollment (n=9)	6	2	5	1	5	2
No remission at enrollment (n=8)	-	3	-	2	-	3
Mesangial proliferative GN (n=2)						
Remission at enrollment (n=1)	-	1	-	1	1	-
No remission at enrollment (n=1)	-	1	-	-	-	-
C1q nephropathy (n=1)						
Remission at enrollment (n=1)	1	-	1	-	1	-

TAC: tacrolimus; SRNS: steroid-resistant nephrotic syndrome; CR: complete remission; PR: partial remission; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; GN: glomerular nephritis. "-": none.

Table 4. Clinical and laboratory parameters before and after TAC therapy, mean±SD

Parameters	Baseline	12 mon	P value
Cumulative steroid dose (mg/kg per y)	139.7±151.9	102.2±120.8	0.052
Blood pressure (mmHg)			
Systolic	104.6±30.6	105.8±27.5	0.730
Diastolic	63.6±14.3	66.0±14.2	0.317
Urine protein/creatinine ratio (mg/mg)	3.6±11.3	0.8±1.4	0.047
Serum albumin (g/dL)	3.4±0.9	3.8±0.8	0.002
Serum creatinine (mg/dL)	0.5±0.2	0.6±0.2	0.001
Serum cholesterol (mg/dL)	306.8±145.5	209.7±97.0	0.001
Serum glucose (mg/dL)	99.1±25.2	92.6±13.1	0.070
Estimated GFR (mL/min/1.73 m^2)	124.7±45.4	104.8±38.9	0.001

TAC: tacrolimus; GFR: glomerular filtration rate; SD: standard deviation.

Discussion

In this study, Tacrobell®, a locally produced generic form of TAC, was proven to be effective and safe as administered for refractory NS. The pharmacokinetic parameters for Tacrobell® had been shown to be not significantly different from those for the original product, Prograf® (Astellas Pharma Inc, Tokyo, Japan), in healthy Korean adults;[16,18,19] the efficacy and safety of Tacrobell® for kidney transplant recipients, furthermore, also has been reported.[18] The efficacy of TAC for NS has been known since its first report in 1990[14] and the first pilot study in 1993,[15] and the same can be said for pediatric NS.[7,10,12,20-22] One of these studies reported a significantly lower relapse rate during treatment than for CsA (TAC group, 11%; CsA group, 50%),[7] and a second study noted a higher efficacy and lower renal toxicity in refractory NS.[12] A recent study reported that the response rate was 96% and 77% for SDNS and SRNS, respectively.[23] In our study, the overall response rate at a 12-month follow-up (SDNS, 90.9%; SRNS, 69.7%) was comparable to previous reports.[7,23] Transient hyperglycemia was observed in one patient; however, diabetes or new-onset hypertension was not observed in our study. Other side effects including nephrotoxicity were similar to those from previous investigations.[7,24] This is the first report on the efficacy of locally produced generic TAC in NS, indicating that generic form of TAC was not inferior to the original formula of TAC.

The rate of nephrotoxicity or the long-term effect of CNI is known to be similar or lower in TAC versus CsA treatment.[7,12,25-27] In our study, decreased renal function was found in four patients, two of whom had progressed to end-stage renal disease. Since none of them responded

to TAC therapy, we are not sure whether their renal impairment was due to the nephrotoxicity of TAC or a mere reflection of the natural course of SRNS. Another concern regarding TAC is the risk of diabetes,[28-31] the incidence of which in children reportedly is 2.6%-7.1% after kidney transplantation.[32,33] Transient or persistent diabetes also has been observed in NS children undergoing TAC treatment,[27-29,34] and is usually dose-dependent.[35,36] Therefore, while administering TAC, regular blood sugar monitoring is necessary.[29,35] In the present study with regular blood sugar monitoring, none of the patients showed new-onset diabetes, whereas some of them manifested transient glycosuria.

This study has several limitations. First, although it was a prospective study, it was not a randomized controlled study comparing the patients' clinical findings before and after TAC treatment. Second, in an assessment of CNI toxicity, we did not examine the pathology but used surrogate markers such as blood pressure or serum chemistry (total CO_2, uric acid, etc.). Third, the follow-up period was not long enough, which could lead to bias in the evaluation of the efficacy and safety of TAC for children with refractory NS. This study demonstrated improved clinical results as those previously reported in TAC treatment.

In conclusion, treatment with Tacrobell®, a generic, less expensive form of TAC, is safe and effective for children with refractory NS. Its efficacy for NS patients is certainly not inferior to that of the original TAC regimen.

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Ethical approval: This study was approved by the Institutional Review Board of Seoul National University Hospital (No. 0911-027-300).

Competing interest: None.

Contributors: Kang HG contributed to the concept and design; Lee ST, Cho HY, Lee JH, Park YS and Cheong HI contributed to the acquisition of data; YEM drafted the manuscript; Choi HJ revised the manuscript for important intellectual content; Kang HG and Ha IS supervisedthe study and the writing of manuscript.

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