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Tacrolimus Therapy Among Steroid-Resistant Nephrotic Syndrome Children: A Preliminary Study in West Java, Indonesia

Ahmedz Widiasta,[1,3] Kurnia Wahyudi,[2,4] Dedi Rachmadi[1,3]

[1]Department of Child Health, Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital Bandung, Indonesia
[2]Department of Public Health, Faculty of Medicine, Universitas Padjadjaran, Indonesia
[3]Genetic Research Center, Faculty of Medicine, Universitas Padjadjaran, Indonesia
[4]Community Health System Research Center, Faculty of Medicine, Universitas Padjadjaran, Indonesia

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Correspondence:
Ahmedz Widiasta,
Department of Child Health, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital Bandung, Indonesia
Email: ahmedzwidiasta@gmail.com

Abstract

Objective: To explore the outcomes of Tac therapy for Steroid-Resistant Nephrotic Syndrome (SRNS) and its implication in reducing the number of CKD events.

Methods: An open, prospective, cohort study was conducted at a tertiary hospital in Bandung, West Java, Indonesia. Children (age 1–18 years old) with steroid and cyclophosphamide resistant nephrotic syndrome were enrolled in this study. Blood pressure, urinary protein, serum ureum, and creatinine levels were measured every month, Tac and soluble urokinase plasminogen activator receptor (supaR) levels were assessed at the 0, third, and sixth months.

Results: Ten of fifteen subjects enrolled in this study got better within 3–6 months with a trend of decreasing suPAR level and proteinuria, as well as stable blood pressure and serum creatinine and ureum level. During treatment, no side effects of the subjects were found with the Tac level maintain safely.

Conclusion: Tac is an effective and safe agent in treating SRNS, especially for those do not respond well to an alkylating agent.

Keywords: Developing-country, soluble urokinase plasminogen activator receptor, steroid-resistant nephrotic syndrome, tacrolimus

Introduction

Steroid-resistant nephrotic syndrome (SRNS) is a significant issue in pediatric nephrology. It adversely affects children's quality of life, leading to stunted growth, chronic kidney disease (CKD), and potentially end-stage renal disease. In Indonesia, treatment primarily involves cyclophosphamide (CPA), an alkylating agent, or cyclosporine A (CyA), a calcineurin inhibitor, as these are the only drugs well-covered by Indonesian national insurance. The Kidney Disease Initiative Global Outcome (KDIGO) no longer recommends CPA for resistant steroid nephrotic syndrome.[1]
Calcineurin inhibitors (CNIs) are first-line agents recommended by KDIGO for treating SRNS. However, studies on the safety and efficacy of these agents in developing countries remain limited.[1] There is insufficient data from Indonesia regarding the treatment of steroid-resistant nephrotic syndrome with newer drugs like tacrolimus (Tac) or rituximab. As a CNI, Tac is known to be effective and has fewer side effects compared to other immunosuppressive agents. Both Tac and CyA have strong evidence supporting their use in treating SRNS, but some studies revealed that tacrolimus has fewer side effects.[2] Treatment with CyA presents challenges in developing countries, particularly in monitoring blood CyA levels, which should be routinely checked to avoid interstitial nephritis.

Compared to CyA, Tac is more potent in

cytokine suppression and appears to cause less renal toxicity.[1,2] Calcineurin inhibitors (CNIs) are commonly used as first-line agents in children with SRNS. Tac (FK506) acts by inhibiting calcineurin through its association with FK506-binding protein (FKBP). The initial rationale for using CNIs in SRNS stemmed from their immunomodulatory properties, and recent experimental evidence shows that calcineurin is expressed by podocytes. Furthermore, CNIs, or podocyte-specific inactivation of calcineurin, stabilizes the podocyte actin cytoskeleton and reduces proteinuria in response to glomerular injury.[3,4] Unfortunately, prolonged use of Tac has been associated with interstitial fibrosis. In a retrospective single-center study, Tac induced complete remission in 15 of 16 patients (94%) after a median of 120 days of therapy.[5,6]

Therapy with Tac, accompanied by a tapering dose of prednisolone, appears to yield quicker remission than treatment with CYC along with prednisone.[7]prospective cohort study enrolled Chinese adults with SD-MCNS. At the start of the study, we administered TAC or intravenous CYC together with prednisone (0.5 mg/kg/day However, the availability of this drug in some developing countries is limited for treating SRNS.

The best assessment of therapeutic efficacy involves conducting periodic laboratory tests of blood, urine, and kidney biopsy. Most parents of patients in Indonesia are reluctant to subject their children to repeated kidney biopsies, creating a need for alternative examinations that can effectively monitor kidney histology. Recent studies have highlighted the usefulness of soluble urokinase plasminogen activator receptor (suPAR) biomarker in estimating and distinguishing SRNS clinically.[8–12] SuPAR is the circulating form of a glycosylphosphatidylinositol-anchored three-domain membrane protein that is expressed on various cells, including immunologically active cells, endothelial cells, and podocytes.[13]and calcineurin inhibitors (CNIs

The authors aimed to determine the outcomes of tacrolimus administration as therapy for SRNS that did not respond to alkylating agents. To the authors' knowledge, there is still very limited research on this subject, with no such studies conducted in Indonesia.

Methods

This study was conducted as an open, prospective cohort study at a single medical center, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. The scientific and ethics committee of Hasan Sadikin General Hospital approved the study protocol. The potential risks associated with Tac were communicated to each subject, regardless of their enrollment status in the study.

The researchers enrolled children aged 1 to 18 years with steroid- and cyclophosphamide-resistant nephrotic syndrome, based on the presence of nephrotic-range proteinuria, hypoalbuminemia, and swelling. All patients were admitted to the nephrology department from January 2018 to December 2019. Steroid resistance was defined as a positive urinary protein for more than four weeks of treatment with prednisone or methylprednisolone. Cyclophosphamide (CPA) resistance was defined as persistent urinary protein after six intravenous pulses of CPA treatment. Exclusion criteria included systemic diseases and severe infections prior to Tac therapy. Patients were assigned to the Tac group (oral Tac in combination with oral prednisolone). Oral Tac treatment was initiated at a dose of 0.05 mg/kg/day, divided into two doses over 12-hour intervals, and subsequently adjusted according to the trough blood level, with a target of 4–8 ng/mL. A dosage of 32 mg/m^2 of methylprednisolone was also administeredto the subjects.

The primary outcome measures were complete remission (CR) and partial remission (PR). The secondary outcome measures included suPAR levels, renal function during treatment and follow-up, side effects, and Tac serum levels. Complete remission (CR) was defined as the loss of swelling and a return of proteinuria to the normal range (<0.3 g/day). Partial remission (PR) was defined as a loss of swelling with persistent non-nephrotic proteinuria (0.3–3.5 g/day). The time required for PR was calculated as the duration from the initiation of Tac treatment to the first day PR was observed.

The researchers performed follow-ups monthly for six months. At each visit, complete blood counts, serum levels of creatinine, albumin, alanine aminotransferase (ALT), and urinalysis were obtained, and Tac levels were measured every three months.

Results

Of the 15 enrolled subjects, ten were included in this study. All subjects underwent biopsy by a nephrologist, revealing eight (8) with

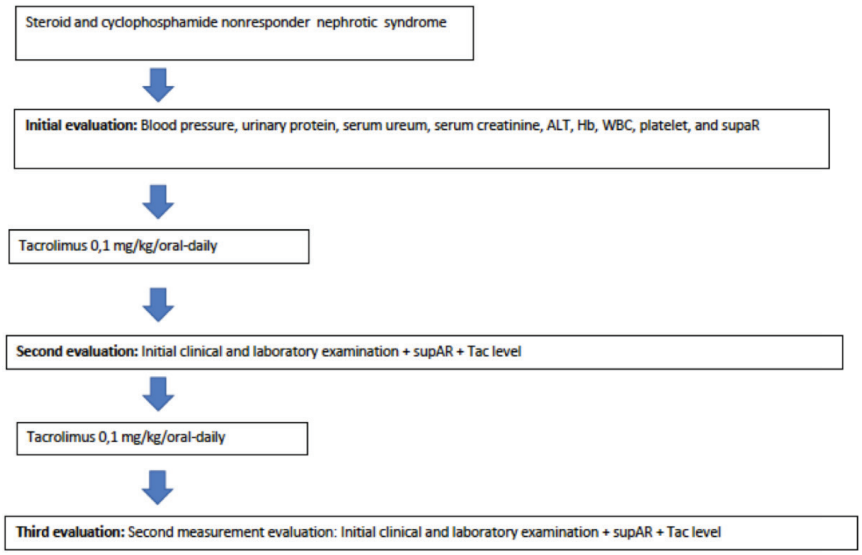

Fig. 1 The Study Flowchart

focal-segmental glomerulosclerosis (FSGS) and two subjects with membranoproliferative glomerulonephritis (MPGN). None of the 15 subjects responded to either steroids or the alkylating agent. Five subjects experienced severe infections during alkylating agent therapy prior to Tac therapy and were subsequently excluded. All ten subjects had suPAR serum levels measured at the initiation of Tac treatment and then again three and six months after treatment commenced. Blood pressure, swelling, proteinuria, complete blood counts, and serum creatinine levels were monitored monthly for six months (Table 1). High suPAR levels were observed at the initiation of Tac treatment, with a wide range of upper and lower limits. By the third month of Tac therapy, the levels decreased, and by the sixth month, they further declined with a narrower range (Fig. 2)

Tac levels at the 0, 3rd, and 6th months of therapy revealed a trend of increasing values,

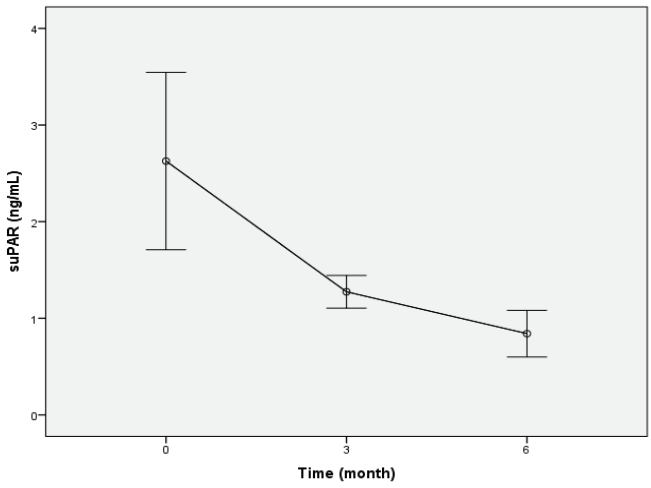

Fig. 2 SuPAR Level During 0, 3, and 6 Months of Tacrolimus Treatment

Table 1 Characteristic, Urinary Protein, Blood Pressure, and suPAR level

Subject Number	Characteristic		Initial			Second visit			Third visit		
	Age (years)	Gender (M/F)	Blood pressure	Urinary protein (g/day)	suPAR (ng/mL)	Blood pressure (3rd month)	Urinary protein (g/day)	suPAR	Blood pressure (6th month)	Urinary protein (g/day)	suPAR (ng/mL)
SRNS-Tac-1	9	M	Hypertension stage 2	3.6	5.18	Hypertension stage 2	3.0	1.67	Hypertension stage 2	2.5	1.66
SRNS-Tac-2	16	F	Normotensive	3.8	1.97	normotensive	2.0	1.32	normotensive	0.4	0.93
SRNS-Tac-3	8	M	Hypertension stage 2	3.6	2.44	normotensive	0.3	1.09	normotensive	0.1	1.02
SRNS-Tac-4	9	M	Hypertension stage 1	3.7	2.02	Hypertension stage 1	0.7	1.66	Hypertension stage 1	0.3	0.82
SRNS-Tac-5	9	M	Hypertension stage 2	3.8	1.94	normotensive	0.5	1.16	normotensive	0.2	0.53
SRNS-Tac-6	11	M	Hypertension stage 2	3.9	2.33	Hypertension stage 2	2.0	1.07	Hypertension stage 1	0.7	0.72
SRNS-Tac-7	12	M	Hypertension stage 2	3.7	1.89	normotensive	0.9	1.35	normotensive	0.6	0.79
SRNS-Tac-8	10	M	Hypertension stage 2	3.6	1.74	Normotensive	0.3	1.31	normotensive	0.1	0.41
SRNS-Tac-9	9	M	Hypertension stage 2	3.6	1.89	Normotensive	0.8	1.02	Hypertension stage 1	0.5	0.75
SRNS-Tac-10	2	M	Hypertension stage 1	3.7	4.87	hypertension stage 1	0.9	1.09	hypertensive stage 1	0.4	0.78
Mean				3.7	2.63		1.14	1.27		0.84	
Median				3.7	1.99		0.8	1.24		0.79	

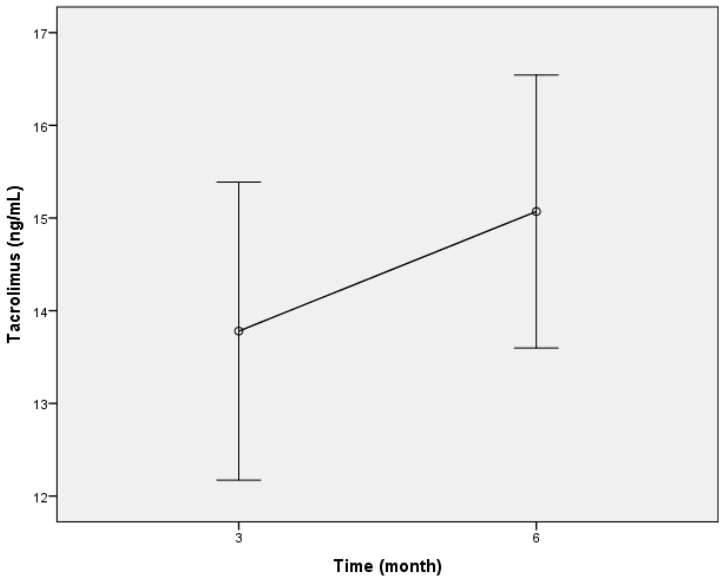

Fig. 3 Tac Level During Third and Sixth Months of Tac Treatment

remaining within the therapeutic range (Fig. 3)

During treatment, no side effects, including decreases in hemoglobin, white blood cell, or platelet counts, or increases in liver enzymes, were observed (Table 2). Monthly monitoring of serum Tac levels showed that no subjects experienced levels lower than 10 ng/mL or greater than 20 ng/mL (Fig. 2).

Discussion

This study reflects that Tac, as a CNI, is an effective agent in treating SRNS, which aligns with the KDIGO recommendation.[1] Some developing countries, such as Indonesia, have low economic resources, making it challenging for many individuals or health insurance plans to cover the costs of CNIs. In these countries, using CPA as an alkylating agent may offer a better solution that balances medical and economic aspects. Although the remission rate of an alkylating agent is lower than that of CNIs in treating SRNS, Indonesia has two CNIs—Tac and CyA—readily available. Previous studies indicate that both Tac and CyA positively impact SRNS, but Tac has a better cosmetic effect.[5] Falkiewicz *et al*. reported that Tac-treated patients recovered significantly faster from tubular phosphate reabsorption impairment compared with CyA-treated recipients. Tac-based immunosuppression also led to better kidney allograft function during a 2-year observation period.[14]

There were 15 subjects in the study; however, five were excluded due to severe infections while undergoing CPA therapy prior to Tac treatment. Four of these subjects experienced severe malnutrition and bronchopneumonia, and one patient died from severe bronchopneumonia. The remaining ten subjects had good nutritional status, excellent medication compliance, and no severe infections during Tac therapy. All patients showed improvement within 3–6 months without any side effects. Their CKD did not worsen, likely related to Tac's immunosuppressive effect on cytokine release.[15] . It may also stabilize the actin skeleton in podocytes and improve foot process motility, preventing podocyte-loss-related proteinuria by inhibiting the dephosphorylation of synaptopodin, which is an initial step for cathepsin-L-mediated degradation of synaptopodin.[16]

Tac is a macrolide antibiotic with immunosuppressive properties. Its mode of action is similar to that of CyA, although the two are structurally unrelated. Tac primarily affects gene expression in target cells by binding to an immunophilin, FK506 binding protein (FKBP). This complex inhibits calcineurin phosphatase, impeding calcium-dependent events such as interleukin-2 (IL-2) gene transcription, nitric oxide synthase (NOS) activation, cell degranulation, and

Table 2 Laboratory Profile During Tac Therapy

Subject Number	Initial						Third month					Sixth month				
	Hb (g/dL)	WBC (x10 mm^3)	Platelete (x10^3 mm^3)	Serum creatinine (mg/dL)	Serum ureum (mg/dL)	ALT (U/L)	Hb (g/dL)	WBC (x10 mm^3)	Serum creatinine (mg/dL)	Serum ureum (mg/dL)	ALT (U/L)	Hb (g/dL)	WBC (x10 mm^3)	Serum creatinine (mg/dL)	Serum ureum (mg/dL)	ALT (U/L)
SRNS-Tac-1	11.5	8.3	320	0.6	35	21	11.4	8.3	0.7	37	25	11.4	8.2	0.7	38	27
SRNS-Tac-2	11.2	9.1	220	0.9	39	31	11.3	9.0	0.8	41	32	11.2	9.0	0.9	40	34
SRNS-Tac-3	10.4	9.9	490	0.8	28	23	10.2	9.8	0.9	27	24	10.3	9.7	0.8	33	27
SRNS-Tac-4	13.2	9.1	470	0.9	39	34	13.0	9.1	0.8	38	37	12.9	9.2	0.8	40	38
SRNS-Tac-5	10.7	8.9	390	0.8	35	13	10.4	8.8	0.8	39	16	10.5	8.8	0.8	41	19
SRNS-Tac-6	11.7	8.8	450	0.9	40	15	11.5	8.7	0.7	38	18	11.3	8.6	0.8	39	20
SRNS-Tac-7	12.1	7.9	350	0.8	43	19	12.1	7.8	0.9	40	21	12.0	8.1	0.8	41	22
SRNS-Tac-8	11.9	9.4	500	0.7	46	24	11.8	9.5	0.8	45	27	12.0	9.4	0.9	45	29
SRNS-Tac-9	11.8	9.6	460	0.9	38	34	11.9	9.5	0.9	39	35	12.0	9.3	0.8	45	37
SRNS-Tac-10	10.7	9.3	370	0.8	35	19	12.0	9.4	0.8	39	21	11.6	9.5	0.8	44	21

apoptosis. Additionally, Tac enhances the actions of glucocorticoids and progesterone by binding to FKBPs within the hormone-receptor complex, preventing degradation. This agent may also enhance the expression of the transforming growth factor-β1 (TGFB1) gene in a manner analogous to CyA, inhibiting T-cell proliferation in response to T-cell receptor ligation. T cell-mediated cytotoxicity is impaired, while B cell growth and antibody production are indirectly affected by the suppression of T cell-derived growth factors; however, antigen presentation appears to be spared.[15,17]

This study revealed that all subjects experienced partial remission (PR) during three months of Tac therapy, after having been on a steroid in combination with CPA for six months without any remission prior to Tac therapy. Six subjects experienced improved blood pressure during the six months of Tac therapy, accompanied by angiotensin-converting enzyme inhibitor administration. All subjects showed a decrease in suPAR levels, indicating that their condition was less likely to progress to end-stage renal disease. SuPAR is a biomarker that may signify CKD progressivity.[13,18,19]

The outcomes observed in this study were consistent with reports from Gulati *et al.*[20] that Tac is superior to CPA in treating SRNS, and from Butani *et al*.[5] that Tac is superior to CPA in treating SRNS, and from Butani *et al*. that Tac is safe and effective in inducing remission in children with SRNS. However, the present study uniquely monitored clinical improvement using suPAR as a novelty. SuPAR was selected as a monitoring tool because its non-invasiveness offers a viable option for subjects who do not have parental permission for repeated kidney biopsies. Furthermore, previous studies have shown that podocyte αvβ3 integrin activity is low under normal conditions but can be enhanced by ligands on podocytes,[21] steroid and cyclophosphamide (CPA, such as suPAR or its soluble form, suPAR.[13] This results in the reorganization of the podocyte actin cytoskeleton and foot process effacement, leading to proteinuria—a hallmark of many primary glomerular diseases.[15]

Tac showed better outcomes because it resulted in earlier complete remission and lower treatment withdrawal rates than CPA. The suggestion is that calcineurin inhibitors (CNIs) are more effective in inducing complete remission in SRNS compared to alkylating agents. The patients in this study did not experience any side effects, which is consistent with other reports indicating that Tac is very safe and has a low risk of nephrotoxicity.[13] Tac level measurements were performed every three months due to the high cost of this examination, which is not well covered by Indonesian national health insurance. The results revealed that Tac levels at the start of therapy, the third month, and the sixth month remained within the therapeutic range. A wide upper and lower limit interval was observed at the initial stage, which narrowed in the third and sixth months, likely due to the variability in FKBP among subjects. The researchers administered a Tac dose of 0.1-0.15 mg/kg BW, along with an oral tapering dose of methylprednisolone. Other laboratory results were normal. This study demonstrated that Tac yields positive results in treating SRNS without any side effects, based on clinical and laboratory monitoring, whereas CPA can cause side effects such as bone marrow suppression, gonadal failure, and malignancy.[21] Patients maintained stable levels of hemoglobin, white blood count, platelet count, and liver enzymes, with some experiencing no cosmetic disturbances. However, some patients did experience cosmetic issues like hirsutism and striae, whichmight be caused by long-term steroid therapy. The most common complications of nephrotic syndrome in children are infections, arising from both the disease itself and immunosuppressive agents. All ten patients did not experience any infections during Tac treatment, whereas five excluded subjects had bronchopneumonia before starting Tac. Another benefit of using Tac for SRNS therapy is that patients have a more straightforward and cost-effective accommodation, as Tac is administered orally and does not require hospitalization. Indonesia has a heterogeneous geographic profile, making accommodation costs a significant barrier to successful treatment. All subjects successfully tapered off steroids and did not experience any relapses during the tapering process, while serum Tac levels were maintained within a therapeutic range, minimizing the risk of interstitial nephritis. In Indonesia, difficulties in achieving repeated kidney biopsies from parents are often encountered; hence, the suPAR measurement could serve as an alternative evaluation tool for assessing whether the SRNS is improving. This study enhances the evidence regarding Tac treatment in SRNS, particularly in developing countries, as previous studies on Tac in SRNS were mostly conducted in developed

countries, which have better drug availability and national insurance coverage.[2]

Tac, in combination with a steroid, is an effective and safe treatment for SRNS, even in cases that are unresponsive to steroid and CPA combinations. The time to achieve complete remission and the side effects of Tac are better than those of CPA; however, more funding and subjects are needed to continue this cohort study with a larger sample size. This report could provide strong evidence to propose Tac as the first-line option covered by Indonesian national insurance for the treatment of children with SRNS, and it may also be a first step toward conducting multicenter randomized controlled trials on the outcomes of SRNS treatment with Tac.

This study provides valuable information, especially for pediatric nephrologists in developing countries, as it demonstrates the success of using Tac in treating SRNS in children with a low risk of clinical toxicity.

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