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Case Report

The Art of Management of Children with Steroid-Resistant and Cyclophosphamide-Resistant Nephrotic Syndrome in Indonesia

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ABSTRACT

Background: Steroid resistant nephrotic syndrome (SRNS) in Indonesia contributes to chronic kidney disease (CKD). Data from several teaching hospitals in Indonesia states that the incidence of CKD which originates from inadequate therapy nephrotic syndrome and steroid resistant nephrotic syndrome is around 60 – 70%.
Case Presentation t: This figure is much higher than in developed countries. One of the causes is that the main treatment for SRNS is with a calcineurin inhibitor, namely cyclosporin A, which is not yet available. This case report discuss the management of SRNS with cyclosporine A as an effort to prevent CKD at one of the provincial referral hospitals in Indonesia.
Conclusion: Administration of CyA is the therapy of choice for SNRS, because it has a higher remission rate than CPA. The speed of achieving remission was also higher in CyA than CPA. There are several obstacles in providing CyA to pediatric SNRS patients in Indonesia currently, the main obstacle is cost.

INTRODUCTION

Nephrotic syndrome (NS) is a collection of symptoms and clinical manifestations characterized by massive proteinuria, hypoalbuminemia, edema, with or without hyperlipidemia. The incidence of NS is around 5 per 100,000 children aged 1 – 18 years with significant variations between different ethnic groups. [1] Administration of corticosteroids in various regimens is the basis of treatment and response to treatment. A good response to corticosteroid administration influences the long-term prognosis of NS.[1,2] Based on the response to

corticosteroid therapy, NS can be classified as Steroid Sensitive Nephrotic Syndrome (SSNS), Frequent Relapse Nephrotic Syndrome, Steroid Dependent Nephrotic Syndrome, or Steroid Resistant Nephrotic Syndrome (SRNS).

Steroid-Resistant Nephrotic Syndrome is defined as persistent proteinuria after eight weeks of corticosteroid administration at a dose of 60mg/m^2/day or at a dose of 2mg/kg/day.[4] Histopathological changes are common in SNRS, including minimal-change disease (MCD), mesangial proliferative glomerulonephritis, and focal segmental glomerulosclerosis (FSGS).[3] The prognosis of patients who do not respond to initial steroid therapy is poor and 50% or more of children develop chronic kidney disease (CKD) within three years. The histological picture of FSGS is most often found in patients with SRNS, characterized by histopathological features showing sclerosis and damage to the glomerular capillaries, IgM deposition on staining, and loss of podocytes. FSGS disease has a rapid progression to terminal kidney failure, namely within 5 – 10 years.[3]

Initial therapy for NS is by administering prednisone at a dose of 60 mg/m^2/day or 2 mg/kgBW/day for four weeks followed by a dose of 40mg/m^2/day or 1.5 mg/kgBW/day alternately (alternate dose) for 4 week.[5] In patients who do not obtain remission after administering prednisone at the appropriate dose, SRNS children can be given a combination of immunosuppressive drugs such as cyclophosphamide (CPA), cyclosporin A (CyA), Tacrolimus (Tac), Rituximab (RTX) or mycophenolate mofetil (MMF).[5]

CASE REPORT

A boy aged three years and four months came to the pediatric emergency department (IGD) with complaints of swelling all over his body (both eyes, stomach and legs) since 10 days before entering the hospital. Complaints accompanied by abdominal pain. The patient had previously been treated at the regional hospital for four days and received albumin transfusions three times totaling 175 mL. The patient was discharged with a discharge albumin level of 1.6 g/dL. Complaints are not accompanied by fever or vomiting. Urination in the last 3 days is said to be small (total urine is not collected).

The patient was first diagnosed as NS in November 2019 by a pediatrician at RSUD. The patient received prednisone therapy for two months, but the protein result was still +4. The patient was then referred to the province referred hospital at nephrology clinic for further treatment. The patient received methylprednisolone treatment 16 mg 1-0-0 (daily intervals) ~ equivalent to 2 mg/kgBW/day. After that the patient did not return to control. The patient was then controlled and treated at the provincial referral hospital again in June 2020 and received CPA chemotherapy.

The patient underwent CPA chemotherapy every month seven times and finished in December 2020. After chemotherapy, urine protein was still +4. The patient was sent home with CyA 2x25 mg, methylprednisolone 16 mg 1-0-0 (equivalent to 1 mg/kgBW/day), and captopril 2x6.25 mg. The patient took CyA for one month and then found urine protein (-), but the patient did not continue CyA treatment again due to cost constraints.

On physical examination, he was moderately ill, with vital signs showing hypertension with a blood pressure of 140/90 mmHg. Anthropometric examination was within normal limits. Another physical examination of the conjunctiva was anemic, palpebral edema was present, the abdomen was convex and soft, fluid waves were present, abdominal circumference was found to be 61 cm. Warm acral, pretibial and dorsum pedis edema are present. Other physical examinations were within normal limits.

On supporting examinations there were blood laboratory results of hemoglobin 11.6 g/dL, hematocrite 37.6%, leukocytes 8,860/mm^3, platelets 526,000/mm^3, type count 0/3/0/50/39/8 urea 20.7 mg/ dL, creatinine 0.19 mg/dL, albumin 0.38, urinalysis showed

protein +4, urine erythrocytes +2, leukocyte esterase (-), bacteria (-).

Based on these data, the working diagnosis for this patient is SRNS + Hypertension Stage II + Cushing Syndrome + Stage I CKD. The treatment given is 20% albumin transfusion 70 mL IV, methylprednisolone 40 mg/m^2/day ~ methylprednisolone 16 mg 1-0-0 (alternate dose), captoril 2x6.25 mg orally, CyA 2x25 mg orally, calcium carbonas 1x500mg, calcitriol 1x0.5mcg orally.

RESULT AND DISCUSSION

The problem raised in this case report is the use of cyclosporin A (CyA) therapy in SNRS patients. There are four classic characteristics of nephrotic syndrome (SN), namely proteinuria, hypoalbuminemia, edema, hyperlipidemia. Nephrotic syndrome can be caused by many factors, but has the same pathophysiology, namely loss of large amounts of protein in the urine due to defects in glomerular filtration. Proteinuria is a consequence of two mechanisms: abnormal transglomerular passage of proteins due to increased permeability of the glomerular capillary wall and subsequent impaired reabsorption by the epithelial cells of the proximal tubule.[6]

Van de Berg and Weening have suggested that there is an expression of immune and permeability factors such as interleukins, i.e IL-1β, IL-1ra (IL-1 receptor antagonist), IL-2, IL-4, IL-5, IL-9, IL-10, IL- 13, tumor necroting factor-alpha (TNF-α), and interferon gamma (IFN-γ) by peripheral blood monomuclear cells (PBMCs) from patients with minimal change disease during relapse and remission and from a control group of patients with NS are mainly caused by endogenous changes in the glomerular filter, for example, mutations in the genes coding for nephrin and podocytes.[7]

One form of NS is steroid resistant nephrotic syndrome (SRNS) which is defined as the absence of remission despite four weeks of therapy with daily prednisone at a dose of 2 mg/kg/day. Patients with SNRS have proven more difficult to treat, with 36–50% progressing to end-stage kidney disease (ESKD) within 10 years.[8]

Children with SNRS usually require treatment with second-line drugs and Calcineurin Inhibitors (CNIs) such as cyclosporine (CyA) are currently recommended as initial therapy.9 Cyclosporine is a cyclic protein with 11 amino acids, obtained from the fungus Tolypocladium inflatum. Cyclosporin A is a lipophilic peptide so it can easily pass through cell membranes. Initially, CyA is in an inactive form which then interacts with cyclophilin (a cytosolic protein) and thereby suppresses the production of interleukin (IL)-2 by inhibiting the movement of complex transcription factors within the cell, thereby inhibiting the enzymatic activity of calcineurin (Figure 1). Calcineurin is a target molecule that is inhibited by the cyclosporine/cyclophilin complex, playing a role in influencing the production of signals triggered by T cells. Calcineurin, which is an enzyme that binds to calmodulin and calcium, also has serine/threonine phosphatase qualities.[10]

Calcineurin plays a role in the dephosphorylation process, kinase activity, phosphatase activity, and protein expression. Dephosphorylation occurs on target molecules in cells as a result of the binding of cyclosporine / cyclophilin to calcineurin, and as a result, there is inhibition of the IL-2 gene and other cytokine genes. Thus, IL-2 production is blocked, and T cell proliferation signals disappear.[10] Cyclosporine has 2 mechanisms in eradicating proteinuria, an immunosuppressive mechanism which is demonstrated by directly influencing the release of glomerular permeability factors, the second mechanism is a non-immunological effect on glomerular permeability selectivity.[10]

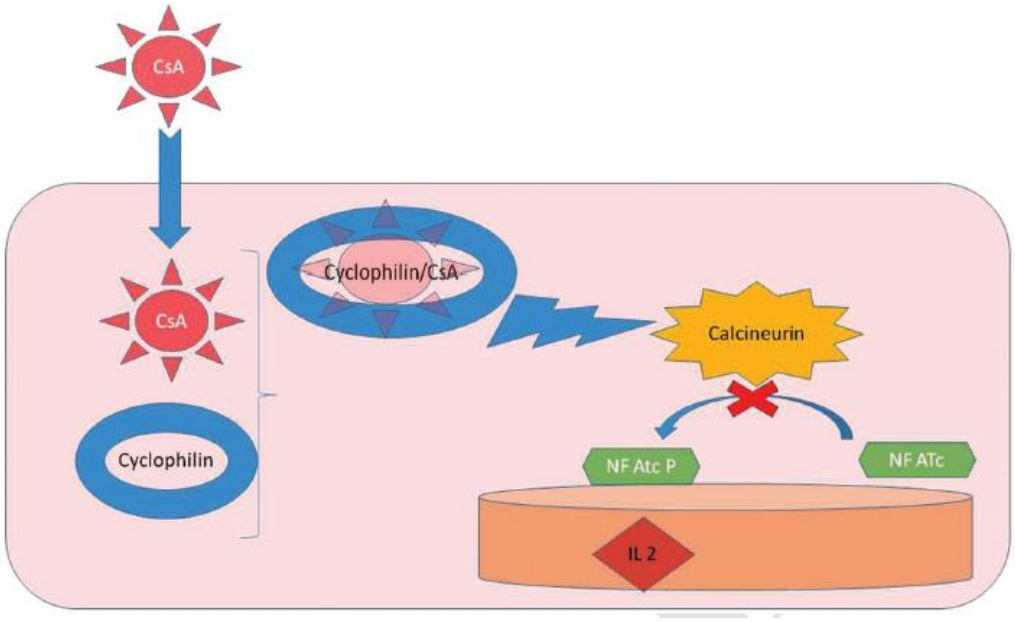

Figure 1. *Mechanism of action of cyclosporine: Cyclosporine (CyA); nuclear factor of activated T-cells (NF-A); Interleukin-2 (IL-2)*[10]

The study conducted by Khemani and Moorani showed that the response to cyclosporine was superior to cyclophosphamide in the induction of remission in nephrotic syndrome. Complete remission was significantly higher (78.5%) in the CyA group compared with cyclophosphamide (34.2%). Resistance was found to be high against CPA (17.7%) compared to CyA (2.5%).11 Based on research by Prasad, et al. CNIs are highly effective in inducing and maintaining remission in cyclophosphamide-SRNS patients. Tacrolimus and cyclosporine A have the same effectiveness. 12 However, CyA and Tac have a narrow therapeutic window so that their use can cause chronic toxicity, especially nephrotoxicity in children.[13]

Apart from the advantages of CyA as the main choice for second-line treatment, there are also various side effects. Nephrotoxicity was the most important side effect (Figure 2). The main effect of CyA is vasoconstriction in the glomerular afferent arterioles. In an experimental study, thromboxane B2, a potent vasoconstrictor was found in urine and production of the vasoconstrictor prostaglandin E2 was decreased. With calcineurin inhibition, along with IL-2, other ILs, transforming growth factor-β, endothelin (ET1), nitric oxide synthase, and other proteins that protect cells from apoptosis are also inhibited. This effect provides immunosuppression which also triggers renal toxicity. The most frequently seen electrolyte abnormalities are hyperkalemia, hyperuricemia, and hypomagnesemia. Urinary magnesium loss occurs due to downregulation of CyA and paracellin. Cyclosporine A (CyA) can cause stone formation by causing calciuria. While acute nephrotoxicity can be clinically asymptomatic, it manifests as increases in serum creatinine and blood pressure. This appears after a while after taking the drug and can return within a short time after the drug consumption is stopped.[10].

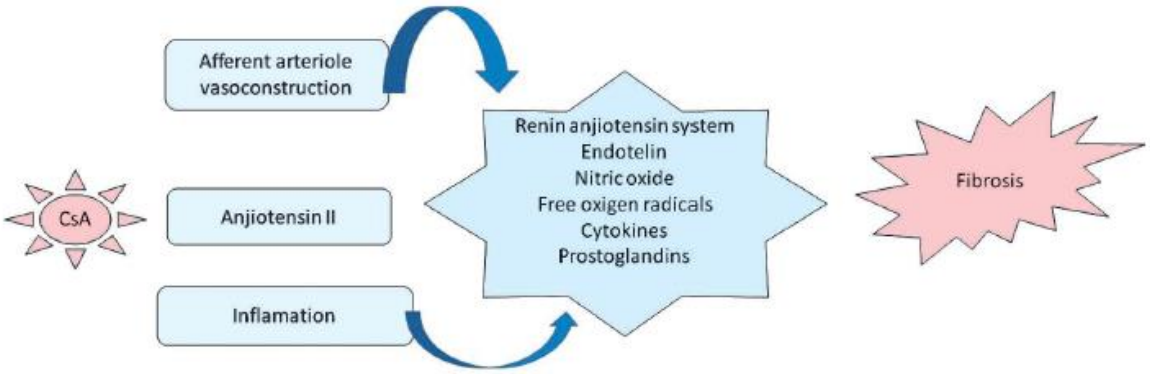

Figure 2. *Nephrotoxicity of cyclosporine (CyA)*[10]

Hypertension is reported as the most common side effect of cyclosporine. The process of inhibiting neural calcineurin can increase catecholamine levels as well as increase nitric oxide and endothelial-1 production, causing vascular resistance as a result of endothelial dysfunction. Hemolytic uremic syndrome (HUS) can be triggered by CyA after transplantation. Cyclosporine causes endothelial cell injury, but the mechanism is still not completely understood. CO levels with cyclosporine are more significant in predicting dyslipidemia.[10]

Gum hyperplasia and hypertrichosis are cosmetic side effects of cyclosporine. This causes problems, especially in adolescent patients, resulting in decreased medication compliance. When hypertrichosis and gingival hyperplasia are detected in patients, cyclosporine should be replaced with tacrolimus which has fewer side effects.[10] This is in line with studies conducted by Shah and Hafeez showing tacrolimus is more effective in achieving complete remission compared to cyclosporine with far less cosmetic side effects less.[14]

The exact mechanism of cyclosporine-induced gingival hypertrophy is unknown, although several factors have been implicated, such as upregulation in the expression of salivary inflammatory cytokines, including interleukin (IL)-1α, IL-6, and IL-8; increased proliferation of gingival fibroblasts and keratinocytes; and inhibition of gingival cell apoptosis.[15]

Cyclosporine-induced gingival hypertrophy is clinically characterized by papillary enlargement, which is more pronounced in the labial gingiva compared with the lingual and palatal gingiva. Oral hygiene, dose and duration of CyA therapy, CyA levels in blood and tissues, concomitant medications, patient age and underlying medical conditions may also modulate the incidence and severity of gingival hypertrophy.[15]

The pathogenesis of cyclosporine-induced hypertrichosis is unknown, but the literature explains that it is caused by a side effect that is most frequently observed in children in the first six months of treatment. Xu et al. stated that CyA induces the anagen phase and inhibits the catagenic phase of hair follicles. It was observed in animal model experiments that the drug stimulates hair growth by encouraging matrix cell proliferation, in addition to increasing the expression of growth factors such as Vascular Endothelial Growth Factor (VEGF). Based on research by Ponticelli et al. attributed this to a possible induction in the activity of the alpha-reductase enzyme, which is responsible for the conversion of androgens to dihydrotestosterone in tissues.[16]

Blood concentrations of cyclosporine should be monitored, usually at 2 hours post-dose and the dose should be adjusted within target levels (lowest level: 60–100 ng/mL; C2 level: 300–700 ng/mL). Nephrotoxicity is also problematic with an increased risk after prolonged use of the drug for 2 years or more.

17 The International Pediatric Nephrology Association (IPNA) recommends an initial dose of cyclosporine A of 3 – 5 mg/kg/day (maximum starting at 250 mg/day) given orally two times a day.[18]

Comparison of immunosuppressive agents on SNRS remission rates

The meta-analysis conducted by Jiang et al. stated in the form of a ranking in terms of complete or partial remission tacrolimus and cyclosporine were ranked as the best and second best therapeutic agents for inducing complete or partial remission (rank probability = 0.50 for tacrolimus and 0.48 for cyclosporine). [19] Results of meta-analysis by Li H, et al. showed that the CyA group had a higher total remission than the cyclophosphamide group. The CyA group had a higher complete remission rate than the cyclophosphamide group. In the CyA group with Tacrolimus there was no significant difference in remission in the two groups. 20 based on research by Li S, et al. Complete remission rates were obtained in various treatment groups: CyA (88.7%), Tac (86.4%), rituximab-Cyc (82.8%), MMF (59.8%), intravenous cyclophosphamide (44.8%), leflunomide (31.5%), chlorambucil (28.6%), azathioprine (28.6%), and oral cyclophosphamide (24.2%).[21]

CONCLUSION

The administration of Cyclosporin A (CyA) as immunosuppressant therapy in patients with SNRS-Cyclophosphamide can be considered, this is supported by research that reports good patient outcomes after administration of CyA. Currently, the therapy of choice for SNRS-cyclophosphamide with CNI, taking into account the cost factor until the therapy is completed, giving CyA is more considered in the BPJS era and developing countries compared to giving Tacrolimus with efficacy and safety results that are not much different.

Administration of CyA is the therapy of choice for SNRS, because it has a higher remission rate than CPA. The speed of achieving remission was also higher in CyA than CPA. There are several obstacles in providing CyA to pediatric SNRS patients in Indonesia currently, the main obstacle is cost. As a rational step, giving CyA to SNRS patients will really need to be considered in SNRS patients who do not respond to CPA.

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