

## Immunosuppressive therapy in children with steroid-resistant nephrotic syndrome: single center experience

Tratamento com imunossupressores em crianças com síndrome nefrótica resistente a corticosteróide: experiência de um único centro

### Autores

Catalina Velez Echeverri<sup>1</sup>  
Gustavo Adolfo Zuluaga  
Valencia<sup>2</sup>

Lina Maria Serna Higuaita<sup>1</sup>

Ana Katherina Serrano  
Gayubo<sup>3</sup>

Carolina Lucia Ochoa<sup>3</sup>

Luisa Fernanda Rojas  
Rosas<sup>3</sup>

Laura Carolina Muñoz<sup>3</sup>

Javier Sierra<sup>3</sup>

Jhon Jairo Zuleta<sup>2</sup>

Juan José Vanegas Ruiz<sup>1</sup>

<sup>1</sup> Hospital Pablo Tobon Uribe  
Antioquia University.

<sup>2</sup> Hospital Pablo Tobon  
Uribe.

<sup>3</sup> Antioquia University.

Data de submissão: 28/02/2013.

Data de aprovação: 28/05/2013.

### Correspondência para:

Lina Maria Serna Higuaita.  
Pablo Tobón Uribe Hospital.  
Antioquia University.  
Pablo Tobón Uribe Hospital:  
Calle 78B # 69 - 240 Medellín,  
Colombia.  
Phone: + 57 - 4 - 4459902.  
Antioquia University: Calle 67  
# 53 - 108, Medellín, Colombia.  
E-mail: lm.serna@hotmail.com

DOI: 10.5935/0101-2800.20130032

### ABSTRACT

**Introduction:** Nephrotic syndrome is one of the most frequent glomerular diseases among children, and steroid therapy remains as the treatment choice. In spite of this, 10 to 15% of the patients are steroid-resistant, and the best therapy for such cases has never been defined. Mycophenolate acid (MA) is one of the treatments used in such situations. **Objective:** To describe the clinical behavior of children diagnosed with steroid-resistant nephrotic syndrome (SRNS) and to assess the therapeutic response to MA. **Methods:** This was a retrospective and descriptive study. **Results:** 26 clinical records of patients with SRNS; 70% male and 30% female. All patients underwent kidney biopsies, which showed a predominance of focal segmental glomerulosclerosis (FSGS). The immunosuppressive drugs used were: Mycophenolate mofetil (MMF) 100%, Cyclosporine 69.2%, Cyclophosphamide 23.1%, and Rituximab 23%. One month after treatment initiation with MMF 61.5% achieved remission. The median of relapses per year for the patients was 3 (p25: 2.75 - p75: 4). This median became 1 (p25: 1 - p75: 3.25) after using this medication ( $p = 0.08$ ). Furthermore, prior to the start of the MMF treatment, the median of the steroid dose was 1 (p25: 0.5 - p75: 1.62) mg/k/day. After using MMF, this median became 0.07 (p25: 0 - p75: 0.55) mg/k/day ( $p < 0.001$ ), in 8 patients prednisolone was stopped. **Conclusion:** In our experience, treatment with MMF showed positive results such as decrease in the frequency of relapses, less proteinuria, and reduction in the dose of steroids administered without deterioration of glomerular filtration rates. However, more studies are needed to assess efficacy, safety, and optimal dosage.

**Keywords:** immunosuppressive agents; kidney failure, chronic; mycophenolic acid; nephrotic syndrome.

### RESUMO

**Introdução:** A síndrome nefrótica é uma das mais frequentes doenças glomerulares em crianças e o tratamento com corticosteróides ainda é o tratamento de escolha. Apesar disso, 10 a 15% dos pacientes são resistentes a corticosteróides, e o melhor tratamento para tais casos ainda não foi definido. O ácido micofenólico (AM) é um dos tratamentos usados em tais situações. **Objetivo:** Descrever o comportamento clínico de crianças diagnosticadas com síndrome nefrótica resistente a corticosteróide (SNRC) e avaliar a resposta terapêutica ao AM. **Métodos:** Esse foi um estudo retrospectivo e descritivo. **Resultados:** 26 registros de pacientes com SNRC; 70% homens e 30% mulheres. Todos os pacientes foram submetidos a biópsias renais, o que mostrou predominância de glomeruloesclerose segmentar focal (GESF). Os medicamentos imunossupressores utilizados foram: Mofetil Micofenolato (MMF) 100%; Ciclosporina 69,2%; Ciclofosfamida 23,1%; e Rituximabe 23%. Um mês após início do tratamento com MMF, 61,5% tiveram remissão. A mediana das recidivas por ano para os pacientes foi de 3 (p25: 2,75 - p75: 4). Essa mediana se tornou 1 (p25: 1 - p75: 3,25) após o uso da medicação ( $p = 0,08$ ). Além disso, antes do início do tratamento com MMF, a mediana da dose de corticosteróide foi de 1 (p25: 0,5 - p75: 1,62) mg/k/dia. Após a utilização do MMF, essa mediana se tornou 0,07 (p25: 0 - p75: 0,55) mg/k/dia ( $p < 0,001$ ), em 8 pacientes a prednisolona foi interrompida. **Conclusão:** em nossa casuística, o tratamento com MMF mostrou resultados positivos, tais como a redução na frequência de recidivas, menos proteinúria, e redução da dose de corticosteróide administrada sem deterioração nas taxas de filtração glomerular. Entretanto, mais estudos são necessários para se avaliar a eficácia, segurança e otimização da dosagem.

**Palavras-chave:** agentes imunossupressores; insuficiência renal, crônica; síndrome nefrótica; ácido micofenólico.

## INTRODUCTION

Nephrotic syndrome (NS) is one of the most frequent glomerular diseases among children. It is characterized by structural or functional defect in the glomerular filtration barrier<sup>1</sup> resulting in excessive loss of protein through the urine.<sup>2</sup> Its incidence rate in children is 2 to 7 new cases per 100.000;<sup>3</sup> Its prevalence rate is 16 cases per 100.000. NS prognosis correlates with response to steroid therapy. There have been described three categories: steroid-sensitive nephrotic syndrome (SSNS), steroid-dependent nephrotic syndrome (SDNS), and steroid-resistant nephrotic syndrome (SRNS). Approximately 80 to 90% of patients with their first episode will respond to steroids. However, 10 to 15% of children and 5% of adults are considered to be steroid-resistant;<sup>4,5</sup> recent reports indicate that the incidence of SRNS in children is rising and constitutes 23% approximately.<sup>6,7</sup> Other treatments like cyclophosphamide and calcineurin inhibitors have been used to reduce proteinuria, but its toxicities have limited their use.<sup>8</sup>

Mycophenolate mofetil (MMF) has been used in children with SRNS and, although a decrease in relapse rates has been observed after using it, the results have not been consistent in all studies.<sup>9,10</sup> This study aims describing the clinical evolution of children with steroid-resistant nephrotic syndrome treated at the Pablo Tobón Uribe Hospital, and at assessing therapeutic response to MMF as immunosuppressive medication.

## METHODS

A retrospective and descriptive study in which the clinical records of SRNS-diagnosed patients were analyzed. Patients were treated at the Pablo Tobón Uribe Hospital from 2005 to 2011.

NS was defined as the presence of edema, proteinuria higher than 40 mg/m<sup>2</sup>/hour, serum albumin less than 2.5 gr/dl, and hypercholesterolemia.<sup>11</sup> Patients were considered to be steroid resistant when they failed to respond to oral prednisone at a dose of 60 mg/m<sup>2</sup>/day for 4-6 weeks.<sup>12,13</sup> Partial remission was defined when proteinuria continued between 4 mg/m<sup>2</sup>/hour-40 mg/m<sup>2</sup>/hour or between 30-300 mg/dl by multistatic and complete remission when proteinuria levels were below 4 mg/m<sup>2</sup>/hour or > 300 mg/dl by multistatic.<sup>3</sup> Relapse was defined as an increase in the levels of proteinuria, returning to the nephrotic range after

having achieved remission.<sup>2,3</sup> Severe infection was defined as any infection that is severe enough to compromise the patient's life, e.g. bacterial peritonitis, sepsis, and pneumonia.

## SELECTION CRITERIA

The study was made up of all nephrotic children (below 18 years) who were steroid resistant with glomerular filtration rate above 60 ml/min (Schwartz formula) before MMF treatment.

## EXCLUSION CRITERIA

The exclusion criteria included: (1) patients who responded to steroid therapy, (2) patients with Hepatitis B or C, sifilis or VIH positive, (3) family history of NS, (4) patients who were received previously rituximab.

MMF was prescribed at 600-1200 mg/m<sup>2</sup>/day in two divided doses,<sup>13,14</sup> combined with oral prednisolone. Because there is still no possibility to evaluate plasma concentration of MA in our country, we checked side effects like diarrhea and leucopenia. In the patients who developed gastrointestinal side effects, the total daily dose of mycophenolate was decreased 50% for 4 weeks and then increased to the recommended dose and it was withdrawn if gastrointestinal symptoms persisted after 4 weeks. If relapse occurred the dose of prednisolone was increased (up to 60 mg/m<sup>2</sup>/day) in a single daily dose until remission followed by 40 mg/m<sup>2</sup> per dose alternate-day for 4-6 week more.

The patients were classified into two groups. Group 1 (n = 20, 77%) patients were those who had been discontinued cyclophosphamide and/or cyclosporine due to resistance; Group 2 (n = 6, 23%) patients were those who received MMF following initial therapy (prednisone).

Data regarding demographic characteristics, clinical manifestations of the disease, family history, pharmacological treatment, and disease evolution were extracted from the electronic clinical records. The data were recorded in a form previously designed with Microsoft Excel. They were then exported to the program SPSS version 17.0 (SPSS Inc, Chicago, IL, USA) in order to conduct the analyses. Quantitative variables were described through averages or medians with their corresponding standard deviation or percentiles depending on the distribution of the data as evaluated through the Kolmogorov-Smirnov test. When there were very few patients, the variables were described

using minimum and maximum values. Qualitative variables had absolute and relative frequencies. The denominator of the different percentages varies according to the availability of data in the clinical records. For the comparison of the quantitative variables we used the Wilcoxon rank test since the data had no normal distribution.

The ethical review board of the Pablo Tobón Uribe Hospital approved this study. Furthermore, the ethical standards for research on human beings established by Resolution 008430 of 1993 of the Colombian Ministry of Health were followed, and confidentiality was observed regarding the data of patients participating in the study.

## RESULTS

A total of 26 clinical records of patients diagnosed with SRNS were analyzed, 69.2% (n = 18) of them were male and 30.8% (n = 8) female. The age at the moment of diagnosis ranged from 7 months to 16 years, with a median of 25 months (p25: 21.75 months and p75: 39 months). The age at the moment of assessment was 2 to 18 years, with a mean of 10 years (SD 4.98). The evolution time from symptom onset to the last check ranged from 1 to 16 years, with a median of 6 years (p25: 2.54 p75: 11 years) (Table 1).

At the moment of diagnosis, 96.2% of the patients had edema, 50% arterial hypertension, 17.7% acute renal failure and 50% hematuria. All patients underwent kidney biopsy, FSGS was the most frequently histology predominant, it was reported in 57.7% of patients (n = 15), 20% (n = 3/15) who developed chronic renal failure (CRF). Other histological findings are shown in Table 2.

Findings of the renal biopsy and percentage of patients who developed CRF. The second column shows the number and proportion of patients with the respective histopathologic finding. The third column shows the number and percentage of patients who developed CRF within each histological category.

Before MMF treatment all patients received prednisolone 60 mg/m<sup>2</sup>/day for 4-6 weeks followed by 40 mg/m<sup>2</sup> per dose alternate-day for 4-6 week more; 34.6% (n = 9) of them received steroid pulses, 23.1% (n = 6) Cyclophosphamide and 69.2% (n = 18) Cyclosporine.

All patients received MMF; 20 of them were previously receiving Cyclosporine and Cyclophosphamide, but without complete remission. Likewise in 6 patients

**TABLE 1** BASELINE CHARACTERISTICS OF THE STUDY POPULATION

	MCD	FSGS	GM	DMS
N	9	15	1	1
Sex (M:F)	8:1	9:6	0:1	1:0
Mean current age (years) (SD)	10.52 (4.93)	10 (8.34)	13	12
Mean time from diagnosis to begin Micophenolate months (SD)	59.7 (49)	59.5 (48)	60	72
Number (%) of patients with high blood pressure	44.4%	46.6%	100%	100%

GFR: Glomerular filtration rate; MCD: Minimal change disease; FSGS: Focal segmental glomerulosclerosis; GM: Membranous glomerulonephritis; DMS: Diffuse mesangial sclerosis.

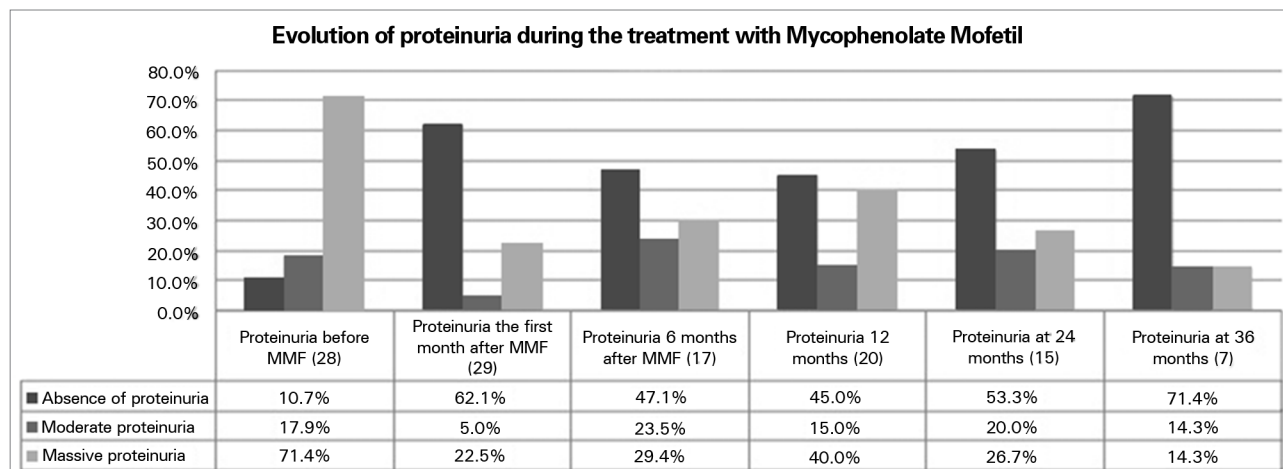
**TABLE 2** RENAL BIOPSY

Findings in the renal biopsy	n (%)	CRF n (%)
FSGS	15 (57.7%)	3 (20%)
Minimal-change disease	9 (34.6%)	0 (0%)
Membranous glomerulonephritis	1 (3.8%)	0 (0%)
Diffuse mesangial sclerosis	1 (3.8%)	0 (0%)

MMF was the first line of immunosuppressive therapy; additionally 88.5% (n = 23) of the patients were administered Enalapril, and 57.7% (n = 15) of them Losartan as additional antiproteinuric medication. On average, MMF was used 5 years after diagnosis (SD ± 3.8 years). The median for treatment duration was 22 months (p25: 10.5 months and p75: 46.5 months).

Before MMF treatment, 73.1% (n = 19) of them had nephrotic range proteinuria, 23.1% (n = 6) had non-nephrotic range proteinuria and 3.8% (n = 1) had no proteinuria, and the last patient was changed to MMF in order to avoid nephrotoxicity for the prolonged use of cyclosporine.<sup>15</sup> One month after treatment initiation, 61.5% (n = 16) achieved remission, while 30.8% (n = 8) of them continued to show no nephrotic range proteinuria and 7.7% (n = 2) nephrotic range proteinuria. The percentage of patients with nephrotic range proteinuria decreased during the treatment with MMF, and more patients achieved remission (Figure 1).

We divided the study population in two groups: Group 1 (n = 20): patients on MMF who received cyclophosphamide and/or cyclosporine previously;

**Figure 1.** Evolution of proteinuria during the treatment with Mycophenolate Mofetil.

and in Group 2 ( $n = 6$ ) patients who did not. One month after beginning MMF, in group 1, 12 patients out of 20 (60%) had complete remission, 6 patients (30%) had partial response and 2 (10%) did not respond. In-group 2 ( $n = 6$ ), 4 patients (66.6%) had complete remission and 2 had (33.3%) partial remission.

The median relapses per year of patients before receiving MMF was 3 (p25: 2.75 - p75: 4). This median became 1 (p25: 1 - p75: 3.25) after using this medication ( $p = 0.08$ ). Furthermore, prior to the start of the MMF treatment, the median of the steroid dose was 1 (p25: 0.5 - p75: 1.62) mg/k/day. After using MMF, this median became 0.07 (p25: 0 - p75: 0.55) mg/k/day ( $p < 0.001$ ), in 8 patients prednisolone was stopped.

Except for three patients who developed chronic renal failure, there was no change in the glomerular filtration rate during the treatment with MMF. The rate started at 158.3 ml/min (SD  $\pm$  65.6) and, after one-year follow-up, it was 151.08 ml/min (SD  $\pm$  53.8).

Regarding the received treatment, 92.3% ( $n = 24$ ) of the patients only required medical treatment (steroid or immunosuppressive therapy), 3.8% ( $n = 1$ ) needed replace renal therapy and 3.8% ( $n = 1$ ) kidney transplantation, in last two patients the MMF was discontinued.

MMF was well tolerated, 11.5% of the patients ( $n = 3$ ) developed diarrhea, and 15.4% severe infections ( $n = 4$ ), in those patients MMF was temporarily suspended. In spite of that, none of these complications were severe enough to require a change of treatment. Six patients after MMF was began required treatment with Rituximab due to the lack of clinical response and persistence of proteinuria. 11.5% (3/26) of the patients developed chronic renal

failure; in these patients the MMF was definitively suspended. No patient died during this treatment.

## DISCUSSION

SRNS patients continue to be a challenge for nephrologists, since they experience many relapses and, in some cases, increased risk for progression to end-stage kidney disease.<sup>11</sup> In recent years, treatment protocols for SRNS have remained mostly unchanged. Some immunosuppressant such as Cyclophosphamide, Cyclosporine, MMF, and Rituximab have been used.<sup>16</sup> However, the most useful therapy having the fewest side effects is yet to be established.<sup>9</sup>

In Colombia, information on the epidemiology, histopathology, and treatment response of SRNS patients is scarce. This stems from the experiences gathered during the last 7 years by the Pediatric Nephrology service of the Pablo Tobón Uribe Hospital with a total of 26 patients with steroid-resistant nephrotic syndrome. The predominant histological characteristic was FSGS; this condition was present in half of the patients, and 20% of them developed CRF, which is also consistent with what was reported in the literature, where this histological subtype is associated with poor response to steroid treatment<sup>17,18</sup> and up to 15-20% of the patients will require RRT 5 years after the onset of the symptoms.<sup>16</sup>

In 1995 MMF was approved by the FDA for use in kidney transplantation. Since then, there is increasingly utilized as a steroid sparing treatment in glomerular immune-mediated disorders,<sup>19,20</sup> including NS.<sup>9,15</sup> MMF has been used in children with SRNS and SDNS, although its efficacy as a steroid-sparing agent<sup>21</sup> and decrease a relapse rates has been observed

after using it, the results have not been consistent in all study.<sup>10</sup> MMF can inhibit mesangial proliferation and decrease the expression of IL-2 and IL-4.<sup>9,22</sup> Its action on glomerular diseases is not very clear, but it is believed that, when it suppresses the proliferation of lymphocytes, it also decreases the production of antibodies and other substances involved in the pathogenesis of NS. Unlike other immunosuppressants, MMF does not alter the metabolism of carbohydrates and lipids; it has no nephrotoxicity side effects and causes no cosmetic alterations.<sup>9,10</sup>

Our results suggest that MMF could induce an improvement in the NS patients, similar to other studies in which MMF was a useful drug for patients with SRNS and SDNS.<sup>21</sup> All patients received MMF, 6 months later, this drug proved to be effective for decreasing proteinuria, relapse rates, the required steroid dosage and not change in the glomerular filtration rate. Moreover, it has an adequate safety profile, since none of the complications observed called for a change of treatment.

Bagga *et al.*,<sup>4</sup> assessed response to mycophenolate in a group of 19 children with SDNS. After 12 months of treatment, the rate of relapse decreased 69.7% (6 to 2 relapses per year) and the required dose of steroids decreased 50% (0.7 to 0.3 mg/kg/day). Unfortunately, the rate of relapse increased to 4.2 per year after discontinuing MMF. In 2003, Montané *et al.*<sup>23</sup> reported their clinical experience with nine SRNS and FSGS patients treated with MMF and angiotensin blockers. After 6 months of treatment, all the patients had resolved the edemas, 3 of them achieved total remission, and 6 partial remission. After 24 months of treatment, their GFR was normal and no significant changes were observed in the prevalence of arterial hypertension. Barletta *et al.*<sup>24</sup> retrospectively analyzed 14 patients with SRNS who had been previously treated with cyclophosphamide and/or cyclosporine. The amount of relapses prior to therapy was  $2.85 \pm 0.4$  compared with  $1.07 (\pm 0.3)$  after 12 months of follow-up ( $p < 0.01$ ). Likewise, 35.7% of the patients were free of steroids and cyclosporine, and the dose of cyclosporine could be reduced for 14.2% of them. Novak *et al.*<sup>25</sup> assessed the response to MMF in 17 children with SDNS who had previously been treated with cyclophosphamide, cyclosporine, or levamisole. the number of relapses decreased from  $0.80 (\pm 0.41)$  to  $0.47 (\pm 0.43)$  relapses per month ( $p < 0.02$ ). Gargah & Lakhoua<sup>26</sup> made a small, single center study in six

patients with SRNS, they used mycophenolate and prednisolone, for 12 weeks, one patient achieved complete remission and other patients had a reduction in proteinuria and increased serum albumin. Li *et al.*,<sup>27</sup> recruited 24 children with SRSN, all patient received prednisone and mycophenolate for 6-12 months, complete remission was achieved in 62.5% of the patients, the author suggests that mycophenolate therapy might be useful in patients with SRSN. De Melo *et al.*<sup>13</sup>, analyze 52 patients with SRNS, the children were divided into two group: group 1 (n = 34): comprised patients who had received cyclosporine before the initiation of mycophenolate therapy and group 2 (n = 18) comprised patients who received only mycophenolate; group 1, complete and partial remission were achieved in 20.6% and 38.6% respectively and group 2 complete and partial remission occurred in 27.8% and 33.3% respectively.

KDIGO guidelines recommend using a calcineurin inhibitor as first-line therapy in children with SRNS, but these drugs are associated with nephrotoxicity, especially in young children<sup>27</sup> in contrast to cyclosporine, MMF does not have any know nephrotoxic side-effects, suggesting that is should be preferred as first option if the is no response to conventional treatments.

Ulinski *et al.*<sup>28</sup> conducted research on the benefits of MMF in reducing nephrotoxicity and controlling the disease in Cyclosporine-treated SDNS patients. They assessed 9 children with SRNS who were being treated with Cyclosporine. Their treatment with MMF started when the GFR became less than 100 ml/min, and had a follow-up of 261 days (85-650). Most patients achieved total remission, the GFR increased significantly ( $76.9 \pm 4.8$  to  $119.9 \pm 5.9$  ml/min/1.73 m<sup>2</sup>), and oral steroids decreased from 0.85 mg/kg/day [0.26-2.94] to 0.29 mg/kg/day [0-1.1] ( $p = 0.026$ ). There were no adverse effects such as diarrhea, hematological alterations or opportunistic infections. Similarly, hypertrichosis and mild gingival hypertrophy disappeared from all children.

This study has some limitations, like retrospective study, only a small number of cases, no unified protocol and no control group; this could explain why six patients required other immunosuppressive medication (rituximab) and three patients during follow-up presented chronic renal failure; however, mycophenolate treatment showed positive results. This suggests that MMF could be useful for treating SRNS with

fewer side effects, it represent a suitable alternative to calcineurin inhibitors especially those patients with renal impairment. A larger randomized controlled trial of this therapy is needed in order to have definitive conclusions regarding relapse rates and side effects after prolonged use.

## REFERENCES

1. Indian Society of Pediatric Nephrology.; Gulati A, Bagga A, Gulati S, Mehta KP, Vijayakumar M. Management of steroid resistant nephrotic syndrome. *Indian Pediatr* 2009;46:35-47. PMID: 19179716
2. Levine SA. Nephrotic Syndrome. In: Brenner BM, Floyd C, editors. *Brenner & Rector's The Kidney*. 7th ed. Philadelphia: WB Saunders; 2003. p.297-313.
3. Geary D, Schaefer F. *Comprehensive Pediatric Nephrology*. 1st ed. Philadelphia: Mosby; 2008. p.1-1098.
4. Bagga A, Hari P, Moudgil A, Jordan SC. Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. *Am J Kidney Dis* 2003;42:1114-20. PMID: 14655181
5. Churg J, Habib R, White RH. Pathology of the nephrotic syndrome in children: a report for the International Study of Kidney Disease in Children. *Lancet* 1970;760:1299-302. PMID: 4193942
6. Srivastava T, Simon SD, Alon US. High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood. *Pediatr Nephrol* 1999;13:13-8. PMID: 10100283
7. Bonilla-Felix M, Parra C, Dajani T, Ferris M, Swinford RD, Portman RJ, et al Changing patterns in the histopathology of idiopathic nephrotic syndrome in children. *Kidney Int* 1999;55:1885-90. PMID: 10231451
8. Tumlin JA, Miller D, Near M, Selvaraj S, Hennigar R, Guasch A. A prospective, open-label trial of sirolimus in the treatment of focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2006;1:109-16.
9. Moudgil A, Bagga A, Jordan SC. Mycophenolate mofetil therapy in frequently relapsing steroid-dependent and steroid-resistant nephrotic syndrome of childhood: current status and future directions. *Pediatr Nephrol* 2005;20:76-81.
10. Ehrich JH, Pape L, Schiffer M. Corticosteroid-resistant nephrotic syndrome with focal and segmental glomerulosclerosis: an update of treatment options for children. *Paediatr Drugs* 2008;10:9-22.
11. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, et al. Management of childhood onset nephrotic syndrome. *Pediatrics* 2009;124:747-57. PMID: 19651590
12. Eknoyan G, Lameire N. Founding KDIGO Co-Chairs. KDIGO Clinical Practice Guideline for Glomerulonephritis KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int Suppl* 2012;2:139-274.
13. de Mello VR, Rodrigues MT, Mastrocinque TH, Martins SP, de Andrade OV, Guidoni EB, et al. Mycophenolate mofetil in children with steroid/cyclophosphamide-resistant nephrotic syndrome. *Pediatr Nephrol* 2010;25:453-60.
14. Ito S, Kamei K, Ogura M, Sato M, Fujimaru T, Ishikawa T, et al. Maintenance therapy with mycophenolate mofetil after rituximab in pediatric patients with steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2011;26:1823-8.
15. Gellermann J, Ehrich JH, Querfeld U. Sequential maintenance therapy with cyclosporin A and mycophenolate mofetil for sustained remission of childhood steroid-resistant nephrotic syndrome. *Nephrol Dial Transplant* 2012;27:1970-8.
16. Haffner D, Fischer DC. Nephrotic syndrome and rituximab: facts and perspectives. *Pediatr Nephrol* 2009;24:1433-8.
17. Banaszak B, Banaszak P. The increasing incidence of initial steroid resistance in childhood nephrotic syndrome. *Pediatr Nephrol* 2012;27:927-32.
18. Nakayama M, Kamei K, Nozu K, Matsuoka K, Nakagawa A, Sako M, et al. Rituximab for refractory focal segmental glomerulosclerosis. *Pediatr Nephrol* 2008;23:481-5.
19. Ostalska-Nowicka D, Malinska A, Silska M, Perek B, Zachwieja J, Nowicki M. Mycophenolate mofetil (MMF) treatment efficacy in children with primary and secondary glomerulonephritis. *Arch Med Sci* 2011;7:1042-8.
20. Wang F, Wang N, Li J. Analysis on the infection among patients with nephrotic syndromes and systemic vasculitis treated with mycophenolate mofetil. *Clin Rheumatol* 2010;29:1073-4.
21. Banerjee S, Pahari A, Sengupta J, Patnaik SK. Outcome of severe steroid-dependent nephrotic syndrome treated with mycophenolate mofetil. *Pediatr Nephrol* 2013;28:93-7.
22. Gbadegesin R, Lavin P, Foreman J, Winn M. Pathogenesis and therapy of focal segmental glomerulosclerosis: an update. *Pediatr Nephrol* 2011;26:1001-15.
23. Montané B, Abitbol C, Chandar J, Strauss J, Zilleruelo G. Novel therapy of focal glomerulosclerosis with mycophenolate and angiotensin blockade. *Pediatr Nephrol* 2003;18:772-7.
24. Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB. Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome. *Pediatr Nephrol* 2003;18:833-7.
25. Novak I, Frank R, Vento S, Vergara M, Gauthier B, Trachtman H. Efficacy of mycophenolate mofetil in pediatric patients with steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2005;20:1265-8.
26. Gargah TT, Lakhous MR. Mycophenolate mofetil in treatment of childhood steroid-resistant nephrotic syndrome. *J Nephrol* 2011;24:203-7.
27. Li Z, Duan C, He J, Wu T, Xun M, Zhang Y, et al. Mycophenolate mofetil therapy for children with steroid-resistant nephrotic syndrome. *Pediatr Nephrol* 2010;25:883-8.
28. Ulinski T, Dubourg L, Saïd MH, Parchoux B, Ranchin B, Cochat P. Switch from cyclosporine A to mycophenolate mofetil in nephrotic children. *Pediatr Nephrol* 2005;20:482-5.