

Mycophenolate mofetil for treatment of idiopathic nephrotic syndrome – a single center experience (preliminary study)

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ABSTRACT

Introduction: Mycophenolate mofetil (MMF) is used in treatment of idiopathic nephrotic syndrome in children (INS).

Purpose: To evaluate clinical results of MMF treatment in steroid-dependent (SD) and steroid-resistant (SR) nephrotic syndrome.

Materials and methods: A retrospective analysis of 26 patients (19 boys, 7 girls) with SDINS and SRINS treated with MMF during the years 2003–2013 was made. The remission length of INS and number of relapses per year before the introduction of MMF and after 12 months was calculated. An analysis of the side effects was made.

Results: The median age of INS diagnosis was 26.5 months (IQRs 24–36 months). Nineteen of the patients (73%) suffered from SDINS whereas the remaining 7 (27%) had SRINS. Twenty three (88.5%) patients underwent renal biopsy: minimal change disease (MCD) in 69.6% (n=16), focal segmental glomerulosclerosis (FSGS) in 17.4% (n=4), membranoproliferative glomerulonephritis (MPGN) in 8.7% (n=2) and mesangial cell proliferation in one case. The median MMF dosage was 956.0 mg/m²/24h (IQRs 768.1–1059.7

mg/m²/24h). Eleven patients (42.3%) were taking MMF together with cyclosporine A (CsA). In patients suffering from SDINS, there was a trend to lower the recurrence rate during MMF treatment [2.0/year (IQRs 0.25–2.0 per year) vs 2.0/year (IQRs 1.0–2.75 per year), p=0.09]. Remission without proteinuria was significantly longer in patients treated with MMF; remission median was 8.5 month (IQRs 6.25–11.0 month) vs 4.5 month (IQRs 4.0–7.5 month), (p=0.014), similarly the average length of remission without corticosteroids was 6.0 months (IQRs 0.25–8.5 months) vs 3.0 months (IQRs 0.0–7.25) months (p=0.028). In children SRINS, 4/7 children MMF treatment was clinically ineffective. Side effects of the treatment were: leucopenia (n =10), hyperbilirubinemia (n = 3), gastrointestinal disorders (n = 1) and anemia (n = 1).

Conclusion: This study confirmed the efficacy of the treatment with MMF in SDINR in comparison with previously used drugs, with a small number of side effects.

Key words: Idiopathic nephrotic syndrome, mycophenolate mofetil, child, recurrence

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INTRODUCTION

In children, idiopathic nephrotic syndrome (INS) is the most common type of nephrotic syndrome (NS). In almost 10% of cases, it is steroid-resistant [1]. Mycophenolate mofetil (MMF), an immunosuppressive agent currently used in transplantology, can also be used as one of the therapeutic options in steroid dependent (SD), steroid resistant (SR), and frequently relapsing (FR) nephrotic syndrome in children [1-4].

Mycophenolate mofetil is currently regarded as a reasonable alternative in severe cases of INS in children [5]. When compared to other second-line therapies such as alkylating agents, and calcineurin inhibitors, it presents a different and less pronounced spectrum of clinical adverse effects (nephrotoxicity and gonadotoxicity) [6,7]. The effectiveness of MMF in maintaining remission, preventing relapses and limiting side-effects of long-term corticotherapy remains comparable with other therapies mentioned above [1,8-9]

From the biochemical point of view, MMF is metabolized in the liver to mycophenolic acid, an active moiety that is a selective, strong, reversible and non-competitive inosine monophosphate dehydrogenase inhibitor. This enzyme is required in the *de novo* pathway of guanine nucleotide synthesis [2]. As a result, it inhibits the proliferation of B and T lymphocytes, suppresses antibody formation, induces the apoptosis of antigen activated T cells and inhibits mesangial cell proliferation [3].

According to current KDIGO guidelines, MMF can be used as a first-line drug in the treatment of SDINS and frequently relapsing NS in children [5]. Whereas, in the treatment of SRINS MMF is recommended as a second-line drug that can be used after unsuccessful treatment with calcineurin inhibitors [5].

There are several studies, which prove the effectiveness of MMF in steroids, cyclosporine or cyclophosphamide refractory patients with primary glomerulopathies [2,7,9-11].

The aim of study was to assess and evaluate the therapeutic effects and complications of MMF in children with steroid-dependent and steroid-resistant nephrotic syndrome.

This is a single center retrospective case note review. It summarizes ten years experience in treating INS with MMF in our centre, and it evaluates the safety and effectiveness profile of MMF as a steroid-sparing agent.

MATERIALS AND METHODS

An analysis of clinical documentation of children treated between 2003 and 2013 in a tertiary reference pediatric nephrology center was performed. Twenty six (19 boys, 7 girls) children

treated with MMF due to INS were included into our study. Inclusion criteria was INS treated with MMF, with at least a 12-months follow-up.

This was a retrospective study and did not require any local ethics committee permissions. Since MMF is still a soft off-label drug in Poland, parental consent was indispensable.

The KDIGO definitions of nephrotic syndrome were used as follow [5]:

- Remission: urine albumin nil or trace for 3 consecutive days by dipstick or urinary protein/creatinine ratio < 200mg/g
- Relapse: urine dipstick 3+ or more, or urine protein/creatinine ratio \geq 2000mg/g for three consecutive days
- Steroid resistance: failure to achieve remission after 8 weeks of steroid treatment
- Steroid dependence: two relapses during steroid treatment or a relapse within 14 days of caesation of steroid administration.
- Frequent relapses: two or more relapses in 6 months of initial response, or 4 or more within any 12-months

For this retrospective case note review we assume the complete remission as an absence of proteinuria during the maintenance therapy of MMF. Patients who had frequent relapses were included in the steroid-dependent group.

The set of data included into the assessment comprised: kidney pathology, clinical course of the disease, length of remission, number of relapses – before and after MMF administration. We compared the data 12 month before and 12 months on MMF treatment. The initial dose of MMF was set at 1000 mg/m²/24h, but adjusted thereafter by clinical efficacy and appearing complications. The clinical aspect of conversion was reported.

Statistical analysis

The data was presented as medians and interquartile ranges (IQRs) or percentage. In statistical analysis the Wilcoxon signed-rank test was used. Statistical significance was considered as $p < 0.05$.

RESULTS

Median age at the time of diagnosis of INS was 26.5 months (IQRs 24-36 months). The study group was composed of 73% (n=19) steroid-dependent patients aged 24 months (IQRs 24-36), (fifteen boys and four girls), and 7 steroid-resistant (four girls and three boys) aged 48 months (IQRs 22-66); all of the patients were Caucasian. Twenty three patients underwent a renal biopsy. In the SDNS group, a renal biopsy was performed in 16 (84.2%) out of 19 patients, with the results of: minimal change disease (MCD) in fourteen cases (87.5%) and two cases (12.5%) of focal segmental

glomerulosclerosis (FSGS). Histological evaluation of the steroid-resistant group revealed: minimal change disease (n=2), membranoproliferative

glomerulonephritis (MPGN; n=2), focal segmental glomerulosclerosis (n=2) and mesangial cell proliferation (n=1).

Table 1. Drug doses and clinical details of steroid dependent INS patients; abbreviations: INS-idiopathic nephritic syndrome, M-male, F-female, MCD-minimal change disease, FSGS-focal segmental glomerulosclerosis, MMF-mycophenolate mofetil, CsA-cyclosporine A.

Case	Gender	Age onset (year)	Renal biopsy	MMF mg/m ² /24h	Steroids mg/kg/24h	CsA mg/kg/24h
1	M	12	no	1119.6	1.1	0.0
2	M	12	MCD	1040.8	0.6	0.0
3	M	7	no	879.2	0.6	0.0
4	M	15	MCD	911.3	0.0	2.6
5	F	9	no	810.9	0.9	0.0
6	M	18	FSGS	937.5	0.2	0.0
7	M	17	MCD	1028.2	0.3	0.0
8	M	13	FSGS	1199.2	0.6	0.0
9	F	9	MCD	839.7	1.2	2.2
10	M	14	MCD	774.2	0.3	2.5
11	F	19	MCD	671.9	0.5	3.0
12	F	5	MCD	1125.8	0.8	0.0
13	M	14	MCD	1104.4	0.2	1.5
14	M	16	MCD	766.1	0.6	3.5
15	M	12	MCD	1063.6	0.6	0.0
16	M	10	MCD	748.7	0.4	3.4
17	M	11	MCD	1119.6	0.0	0.0
18	M	10	MCD	1151.2	0.7	0.0
19	M	7	MCD	889.9	1.7	0.0

Before the commencement of MMF therapy, SD patients received combined treatment with steroids, chlorambucil, cyclophosphamide and cyclosporine A. Cyclophosphamide therapy was applied on 15 patients, chlorambucil on 3 patients and cyclosporine A on 17 patients. We observed side-effects of cyclosporine A therapy such as: nephrotoxicity (n=9), hypertrichosis (n=15) and gingival hypertrophy (n=11).

Furthermore, we observed the side-effects of long-term steroid therapy in the majority of SD patients (n=12). The most common complications related to steroid administration were: hypertension (n=8), acne (n=7), increase in weight leading to obesity (n=5) and hypercholesterolemia (n=5). In one case, MMF was used as a first-line drug for INS treatment. Ineffectiveness of previous treatment, as well as complications mentioned above were the direct reason for conversion to MMF in the remaining SD patients. The median age of MMF implementation in this group was 12 years (9.5-14.5). MMF was administered in the median dose of 937.5 mg/m²/24h (825.28-1111.96) with steroids in the dose of 0.6 mg/kg/24h (0.29-0.78). Combined treatment protocol (MMF+CsA) was applied in seven steroid-dependent cases and the dose of CsA at the time of the MMF inclusion was

very low (IQRs 0.0-2.57 mg/kg/24h). Doses of the drugs and clinical details are presented in Table 1.

When we compared the initial 12 months of MMF treatment to the twelve month before MMF, in the whole SD group, we observed lower relapses rates and number of relapses per month [1.0/year (0.5-3.0) vs 2.0/year (1.0-2.75), p=0.09 and 0.17/month (0.08-0.23) vs 0.17/month (0.02-0.17), p=0.09 respectively]. The average length of complete remission, 12 months after MMF administration, was significantly longer than before the treatment [8.5 (IQRs 6.25-11.0) vs 4.5 (IQRs 4.0-7.5) months; p=0.014]. The one-year treatment using MMF resulted in a decreased duration of corticosteroid administration, measured by median length of complete remission without steroids [6.0 months (IQRs 0.25-8.5 months) vs 3.0 months (IQRs 0.0-7.25 months), p=0.028]. The mean CsA and steroid doses did not change in the course of MMF therapy. The treatment was discontinued in four SDINS patients due to adverse reactions in two patients, lack of effects in one patient, and complete remission upon finishing the treatment plan in one patient.

In steroid-resistant children cyclophosphamide or cyclosporine A (n=4 and n=6 respectively) was combined with steroids before

MMF inclusion. The side-effects due to cyclosporine A in these patients were as follows: hypertrichosis in 5, nephrotoxicity in 3 and gingival hypertrophy in 2. Hypertension, obesity and hypercholesterolemia were observed as complications of treatment with steroids, in two patients. None of the children could set aside steroid treatment in a remission period within twelve months before MMF.

Therefore, MMF was included to limit the use of steroids, improve the effectiveness of treatment and to minimize the toxicity of the current treatment. The median age of patients at the time of MMF implementation in the SRINS group was 6.0 years (5.0-9.0). The dose of MMF at the time when treatment was started was 695.2 mg/m²/24h (631.6-976.4 mg/m²/24h) with simultaneously given steroids dose of 0.43 mg/kg/24h (0.2-0-0.78 mg/kg/24h). Four patients received treatment according to a protocol combined of MMF and CsA in which cyclosporine A was given in the median dose of 1.98 mg/kg/24h (IQRs 0.0-5.89).

Only two patients were in remission without steroids for eight months of MMF therapy. In one case, no relapses were noticed during the

treatment, but remission was supported by low doses of steroids.

Among the remaining patients in three the therapy was discontinued due to the lack of response to treatment, and in one because of the severe anaemia.

Symptomatic treatment was thereafter applied in patients who did not respond to MMF.

Doses of the drugs and clinical details are presented in table 2.

We observed adverse reaction such as mild leucopenia in 10 (SDINS=7, SRINS=3) of children, hyperbilirubinemia in three - in the two of them dosage reduction was applied, which resulted in the normalization of the bilirubin concentration level.

There were isolated cases of nausea and abdominal pain (n=1), allergic reaction (n=1) and severe anaemia (n=1) mentioned above. Furthermore, a single case of cytomegalovirus infection occurred.

We did not notice alanine aminotransferase (ALAT) level elevation, and trombocytopenia during the study.

Table 2. Drug doses and clinical details of steroid resistant INS patients; abbreviations: INS-idiopathic nephritic syndrome, M-male, F-female, MCD-minimal change disease, FSGS-focal segmental glomerulosclerosis, MPGN-membranoproliferative glomerulonephritis, MCP-mesangial cell proliferation, MMF-mycophenolate mofetil, CsA-cyclosporine A.

Case	Gender	Age onset (year)	Renal biopsy	MMF mg/m ² /24h	Steroids mg/kg/24h	CsA mg/kg/24h
1	F	5	MCD	668.5	0.0	5.8
2	M	5	MPGN	1047.8	0.4	0.0
3	F	12	MPGN	978.3	0.7	0.0
4	F	2	MCP	594.8	1.4	6.2
5	F	7	FSGS	974.5	0.8	0.0
6	M	6	MCD	559.8	0.1	8.3
7	M	11	FSGS	695.2	0.3	2.0

DISCUSSION

For over a decade, MMF was considered as a drug of choice for nephrotic syndrome patients who were non-responsive to prior immunosuppression therapy [1]. Lately, this drug has been postulated to serve as an alternative to cyclosporine A or to cyclophosphamide in steroid-dependent cases [5].

In several reports, authors postulate the benefits of mycophenolate mofetil therapy in reducing relapse rates of INS, as well as its effectiveness in maintaining remissions and minimizing complications [3,10,12]. MMF is also considered safer and less toxic compared to alternative immunosuppression, which makes it an

attractive therapeutic option [13].

Another advantage reported by Baudouin et al. [14] is MMF efficiency as a steroid-sparing agent in pediatric nephrotic syndrome. 24 SDINS children, treated with MMF included in this prospective study, were previously treated with cyclophosphamid or chlorambucil. They received prednisolone at a daily dose of at least 15 mg/m² BSA during the year before inclusion. Previous cyclosporine treatment was exclusion criteria. They observed the cumulative prednisone dose reduction at six months of MMF treatment compared to the baseline (from a median of 459 mg/m²/month to 264 mg/m²/month), as well as 82.6% of included patients were relapse free during six months and 73.9% during 12 months. These observations

allowed the authors to conclude that MMF allows to decreasing prednisone doses in severe SDINS children and when combined with low doses of prednisone it is effective to maintain long-term remission [14].

A similar study was done by Banerjee et al. who showed that a MMF therapy in steroid dependent patient was associated with a good long-term safety profile and caused steroid sparing in severe steroid dependent patients, even leading up to the withdrawal of steroids [13]. This was a prospective study in which 46 pediatric patients with steroid-dependency were included. They observed a reduction in steroid requirements in 70% of patients and steroid cessation in 43% of patients one year after MMF treatment completion.

In our study, we did not observe changes in the steroid doses during MMF therapy, but we noticed that the overall need for steroids reduced significantly as we achieved a longer period during which steroids were not necessary. This should have a favorable impact on lowering the risk of steroid complications.

Other studies showed MMF efficacy in lowering the cyclosporine A doses, inducing remission and reducing relapse rates in SD patients treated with long-term CsA and in CsA resistant INS [10,11,15].

Ostalska-Nowicka et al. [2] also indicated the benefits of MMF in steroid dependent and cyclosporine dependent NS, primary glomerulonephritis and autoimmune glomerulopathies. The study group composed of 85 patients with proteinuric glomerulopathies who showed a variable response to steroids. Thirty three children with idiopathic nephrotic syndrome were included; 29% of them did not respond to MMF therapy. Non responders to MMF were also steroid-resistant. The remained patients with INS achieved a long period of remission during MMF treatment and presented a gradual improvement in kidney function estimated by GFR and decrease of proteinuria. The best results were obtained in the group of lupus nephritis patients, but in the conclusion, the authors confirmed the benefits of MMF inclusion in children with INS. In our study, complete remission was longer during MMF therapy, compared to previous treatment from the mean of 4.94 ± 3.17 month before MMF to 8.2 ± 3.4 month after in SDINS children. In our study, the group of non-responders to MMF mostly consisted of SRINS children (42.8%). We obtained an improvement in kidney function estimated by GFR in SDINS from $101.49 \text{ ml/min/1.73m}^2$ (IQRs 62.97-118.39) to $118.7 \text{ ml/min/1.73m}^2$ (IQRs 105.95-125.52) during MMF treatment. In SRINS patients kidney function (GFR) before treatment was $97.82 \text{ ml/min/1.73m}^2$ (81.0-148.65) and after 12 months of MMF, it was $94.99 \text{ ml/min/1.73m}^2$ (75.49-105.73).

The largest single-center study of the

safety and efficacy of MMF was performed by Hassan et al. It was a retrospective study in which 73 patients with NS, were treated with MMF. This study, like ours, consisted of a variety of patients (steroid resistant, steroid dependent, steroid sensitive and frequent relapsers). Most patients had previously used other second-line therapies. With regard to demography, the majorities were Caucasian and 67% were males, which was comparable to our study where 73% were males, and all the patients were Caucasian. Hassan et al. obtained complete remission in 59% of children with complete withdrawal of previous second-line treatment or only a low-dose steroids treatment. In 49% of children in complete remission, the remission was longer than two years, but 22% of the study group did not demonstrate a positive response to MMF therapy. MMF responders also obtained significant decrease in relapse rate during therapy from the median of 1.5 (IQR 1.2-2.3) per year prior MMF to 0.5 (IQR 0-0.87 per year). In our study seven (26.9%) patients achieved complete remission for one year; five of them were SDINS, and two were SRINS patients. We observed a tendency to lower relapse rate, and remission without proteinuria was significantly longer while steroid administration was shorter and in smaller doses, but these findings were only seen in SDINS group, while in the SRINS group, the treatment was clinically ineffective. Furthermore, our study covered only 12 months of MMF treatment, which is significantly shorter than in the study performed by Hassan et al. where the median length of follow ups was 3.2 years (IQR 1.7-4.7 years) [16].

Our study, as well as other studies showed that MMF is well tolerated and safe, with general mild side effects, and that patients with steroid dependent NS can benefit from this therapy. Common side-effects associated with MMF therapy include viral infections, gastrointestinal dysfunction, fatigue, headache, cough. In the Ostalska-Nowicka et al. study the most common side-effect was frequent infections of the upper respiratory tract which affected 53% of the study group. The next common side effect reported was episodic leucopenia in 24% of subjects [2]. Li et al. reported nausea and vomiting in 12.5%, diarrhea in 8.3% and leukopenia in 12.5% which subsided spontaneously after several weeks [17]. Furthermore, Banerjee et al. noted 9.4% of gastrointestinal symptoms such as abdominal pain, diarrhea, dyspepsia and flatulence [13]. In Hassan et al. study gastrointestinal side effects affected seven children, leucopenia/infections on five and arthralgia two patients. Also three of the children suffered both immunological and gastrointestinal disorders [16]. In contrast, in our study we did not observed any complications from the osteoarticular system. Others like Baudouin et al. and Okada et al. observed several transient gastrointestinal disorders

similar to those seen by the authors above [14,18]. In contrast we did not observe a higher frequency of respiratory tract infections or gastrointestinal disorders. The most common adverse reactions in our patients were: mild leucopenia in 38.5% of patients (n=10), and hyperbilirubinemia which affected on 11.5% of children (n=3). A single case of gastrointestinal disorders, allergic reaction and CMV infection were observed. All the above-mentioned symptoms were transient and mild. One patient discontinued the treatment because of severe anemia. Regardless of the time of treatment, the number of adverse reaction and their severity was low.

However, until now, it is still difficult to determine the benefits of applying mycophenolate mofetil in a steroid refractory patients. Li et al. reported that in SRNS patients under the age of 2 MMF treatment significantly decreased urinary protein excretion [17]. Echeverri et al. retrospectively analyzed 26 patients below the age of 18 with SRNS and showed that MMF therapy results in a decrease of proteinuria, reduction in steroid doses and a decrease in the frequency of relapses [19]. Similar conclusions were made by the Barletta et al. who, likewise, observed the reduction of cyclosporine dosage or even effective discontinuation of steroids and cyclosporine in 35.7% of the patients [20].

Our observation does not seem to confirm this, but the number of SRNS patients was too small to draw definite conclusions. In four out of the 7 SRNS patients, the treatment was discontinued because of a lack of response to MMF. Of the remaining three patients, only one gained substantial benefits from the therapy such as 12-month remission without proteinuria, eight months free of steroids and no relapses, but we cannot exclude the possibility of improvement due to the natural history of the disease.

This study has several limitations. An important limitation was its retrospective character, and a small number of patients involved, which limits the power of analysis. Moreover, the patient group was from a single-center, and the follow-up was short. Further studies with a larger number of patients, unified protocol and longer follow-up are needed to evaluate the MMF effectiveness and safety in children with INS.

CONCLUSIONS

In conclusion, our study confirmed the efficacy of MMF treatment in patients with SDINS. The transfer to MMF resulted in decrease in steroids dose and longer remissions when compared to the prior therapy. The MMF therapy was connected with a small number of clinical side effects. The study gave no support to clinical importance of MMF in the steroid resistant cases.

Conflicts of interest

The authors have declared no conflicts of interest. No funding sources were related with this article

REFERENCES

1. Grenda R. Mykofenolan mofetilu w leczeniu zespołu nerczykowego u dzieci. *Forum Nefrol.* 2013; 6(2):130-4.
2. 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 Dec 31;7(6):1042-8.
3. Nickavar A, Safarzadeh AE, Sotoudeh K, Otukesh H, Hooman N. Mycophenolate mofetil for treatment of idiopathic nephrotic syndrome in children. *Iran J Kidney Dis.* 2012 Sep;6(5):346-9.
4. Kwinta-Rybicka J, Wilkosz K, Wierzchowska-Słowiacka EK, Ogarek I, Moczulska A, Stec Z, Pełkowska A, Sancewicz-Pach K, Pietrzyk JA. Mycophenolate mofetil in treatment of childhood nephrotic syndrome – preliminary report. *Przegl Lek.* 2006;63(3):44-8. (Polish)
5. KDIGO clinical practice guidelines for glomerulonephritis. *Kidney Int.* 2012; 2(S2): 139-274.
6. Gargah TT, Lakhoua MR. Mycophenolate mofetil in treatment of childhood steroid-resistant nephrotic syndrome. *J Nephrol.* 2011 Mar-Apr;24(2):203-7.
7. Hogg RJ, Fitzgibbons L, Bruick J, Bunke M, Ault B, Baqi N, Trachtman H, Swinford R. Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: a report from the Southwest Pediatric Nephrology Study Group. *Clin J Am Soc Nephrol.* 2006 Nov;1(6):1173-8.
8. Dorresteijn EM, Kist-van Holthe JE, Levchenko EN, Nauta J, Hop WC, van der Heijden AJ. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. *Pediatr Nephrol.* 2008 Nov;23(11):2013-20.
9. Klinger M, Durlik M. Zastosowanie MMF w pierwotnych kłębuszkowych zapaleniach nerek. *Nefrol Dial Pol.* 2009;13:67-70.
10. Fujinaga S, Ohtomo Y, Umino D, Takemoto M, Shimizu T, Yamashiro Y, Kaneko K. A prospective study on the use of mycophenolate mofetil in children with cyclosporine-dependent nephrotic syndrome. *Pediatr Nephrol.* 2007 Jan; 22(1):71-6.
11. Fujinaga S, Ohtomo Y, Hirano D, Nishizaki N, Someya T, Ohtsuka Y, Kaneko K, Shimizu T. Mycophenolate mofetil therapy for childhood-onset steroid dependent nephrotic syndrome

- after long-term cyclosporine: extended experience in a single center. *Clin Nephrol.* 2009 Oct;72(4):268-73.
12. Briggs WA, Choi MJ, Scheel PJ Jr. Successful mycophenolate mofetil treatment of glomerular disease. *Am J Kidney Dis.* 1998 Feb;31(2):213-7.
 13. Banerjee S, Pahari A, Sengupta J, Patnaik SK. Outcome of severe steroid-dependent nephrotic syndrome treated with mycophenolate mofetil. *Pediatr Nephrol.* 2013 Jan;28(1):93-7.
 14. Baudouin V, Alberti C, Lapeyraque AL, Bensman A, André JL, Broux F, Cailliez M, Decramer S, Niaudet P, Deschênes G, Jacqz-Aigrain E, Loirat C. Mycophenolate mofetil for steroid-dependent nephrotic syndrome: a phase II Bayesian trial. *Pediatr Nephrol.* 2012 Mar;27(3):389-96
 15. Nikibakhsh AA, Mahmoodzadeh H, Karamyyar M, Hejazi S, Noroozi M, Macooie AA. Treatment of steroid and cyclosporine-resistant idiopathic nephrotic syndrome in children. *Int J Nephrol.* 2011;2011:930965.
 16. Hassan AV, Sinha MD, Waller S. A single-center retrospective study of the safety and efficacy of mycophenolate mofetil in children and adolescents with nephrotic syndrome. *Clin Kidney J.* 2013 Aug;6(4):384-89.
 17. Li Z, Duan C, He J, Wu T, Xun M, Zhang Y, Yin Y. Mycophenolate mofetil therapy for children with steroid-resistant nephrotic syndrome. *Pediatr Nephrol.* 2010 May;25(5):883-8.
 18. Okada M, Sugimoto K, Yagi K, Yanagida H, Tabata N, Takemura T. Mycophenolate mofetil therapy for children with intractable nephrotic syndrome. *Pediatr Int.* 2007 Dec;49(6):933-7.
 19. Echeverri CV, Valencia GA, Higuera LM, Gayubo AK, Rosas LF, Muñoz LC, Sierra J, Zuleta JJ, Ruiz JJ. Immunosuppressive therapy in children with steroid-resistant nephrotic syndrome: single center experience. *J Bras Nefrol.* 2013 Jul-Sep;35(3):200-5.
 20. Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB. Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome. *Pediatr Nephrol.* 2003 Aug;18(8):833-7.