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Mycophenolate Mofetil as a Rescue Therapy in Frequently Relapsing/Steroid-Dependent Nephrotic Syndrome in Children; Ability to Maintain Remission

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Introduction. Nephrologists usually encounter therapeutic challenges and dilemmas when treating steroid-dependent nephrotic syndrome (SDNS) and frequently relapsing nephrotic syndrome (FRNS). Due to the serious side effects of long-term administration of corticosteroids, physicians administer steroid adjuvants to maintain remission and to limit the cumulative dosage of corticosteroids. Among these adjuvants, it is postulated that mycophenolate mofetil (MMF) is an impressive option owing to its fewer side effects, acceptable tolerance, and high effectiveness.

Methods. This comparative study was performed on a group of SD/FRNS patients who were on MMF therapy for an average duration of 2.75 years and on regular follow-up at the Department of Nephrology of Imam Reza Hospital, Kermanshah, Iran.

Results. A total of 32 patients with a male to female ratio of 1.2:1 were enrolled. The mean duration of follow-up prior to and following the initiation of MMF therapy was 2.63 and 2.75 years, respectively. The results obtained from the comparative analysis of the recurrence rate and the dose of corticosteroids used prior to and following the initiation of MMF therapy revealed that this therapy significantly lowered the recurrence rate ($P < .05$) and the corticosteroid dose ($P < .05$). Hence MMF is a well-tolerated and effective agent in decreasing the recurrence rate (64.52%) and the cumulative dosage of corticosteroid (43.88%) in complicated nephrotic syndrome patients.

Conclusion. There were no significant differences between the patients treated with MMF as the first steroid-sparing agent and those treated with MMF as the second or third agents.

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INTRODUCTION

Although most patients with idiopathic nephrotic syndrome (INS) respond well to steroids, frequent and long-term use of them, especially in patients with corticosteroid dependence and frequent relapses, can lead to serious side effects.[1,2] Use of non-steroidal drugs such as cyclosporine, cyclophosphamide, and levamisole in addition to reducing side effects and the cumulative dosage of corticosteroids has been shown to be effective in reducing the disease recurrence. However, adverse effects of these drugs such as nephrotoxicity in cyclosporine and gonadic toxicity in cyclophosphamide may limit their use.[1,3,4]

Mycophenolate mofetil (MMF) is a mycophenolic acid (MPA) prodrug that is hydrolyzed to

mycophenolic acid (MPA) after ingestion. In fact, MPA is a selective, potent, and active metabolite of MMF, which reversibly inhibits the enzyme required for the synthesis of purines (i.e., inosine monophosphate dehydrogenase).[5,6] Accordingly, MMF strongly inhibits B cell and T cell proliferation by inhibition of de novo purines production [3,5] which plays an essential role in the pathogenesis of idiopathic nephrotic syndrome in children.[1,5] Mycophenolate mofetil has been used for the treatment of lupus nephritis, membranous glomerulonephritis , IgA nephropathy and for prevention of allograft rejection.[5,6,7] Since 2000, the effectiveness of MMF in patients with corticosteroid-dependent nephrotic syndrome and frequently relapsing nephrotic syndrome has been demonstrated.

Mycophenolate mofetil is currently considered as an adjunct drug with low adverse effects in the treatment of complicated nephrotic syndrome.[7] Since there are limited studies on MMF therapy in Asian patients and due to the varied efficacy of MMF among different races,[6,8] we aimed to present the results of our clinical experience in treating patients with nephrotic syndrome who received MMF and corticosteroid to determine the effectiveness of MMF in lowering recurrence rate and steroid dosage among Iranian children.

MATERIAL AND METHODS

Methods

In this comparative study, we aimed to evaluate the effectiveness of MMF in controlling the recurrence of INS in children with steroid-dependent or frequently relapsing nephrotic syndrome. The statistical population comprised of all children with steroid-dependent or frequently relapsing INS who were 1 to 12 years old at the onset of the disease, referred to the pediatric nephrology clinic of Imam Reza Hospital in Kermanshah, Iran, during 2006 to 2018, and received MMF treatment for a required duration. Inclusion criteria included INS patients with a disease onset age of 1 to 12 years and at least 6 months elapsed since the initiation of MMF therapy. Exclusion criteria were less than 6 months of follow-up and treatment discontinuation due to MMF adverse effects. After obtaining informed consent and explaining the research objectives, 32 INS patients were enrolled according to the inclusion and exclusion criteria. Required data was extracted from the patients' medical records and files.

Th participants were categorized into two groups of 22 and 10 patients. The first group (n = 22) received MMF as the second or third choice when other steroid-sparing agents such as levamisole, cyclophosphamide, and cyclosporine failed to control recurrences. However, as of 2016, MMF is our first choice in the control of relapses in SD/FRNS patients (second group, n = 10).

All the patients consumed 60 mg/m^2/d oral prednisolone for four weeks and then 40 mg/m^2/d every other day for four weeks. The prednisolone dose gradually decreased over 3 to 6 months. In steroid-dependent or frequently relapsing INS patients, MMF was administered at a dosage of 600 mg/m^2 every 12 hours. Relapses were treated by increasing the corticosteroid dose by 60 mg/m^2/d until urine protein was negative for three consecutive days, and then corticosteroid dose was changed to the previous dose or slightly higher every other day. If the disease did not recur with a gradual decrease in the dose of corticosteroid, MMF dose was tapered. Necessary information to evaluate the effect of MMF in maintaining remission, including patient's sex, age at the onset of the disease, age at the initiation of MMF treatment, type of nephrotic syndrome, type of complementary drugs, priority of treatment with MMF, occurrence of recurrence after cessation of MMF treatment, follow-up period, duration of follow-up after discontinuation of MMF treatment, time of first recurrence after recovery, number of recurrences before and after MMF, and corticosteroid dosage (mg/kg/month), at least 6 months after the onset of MMF, was recorded through interviews with patients and based on patient files. We also evaluated complete blood count (CBC), liver enzymes, urea, and creatinine every three months to detect and control hematological complications, and the presence of gastrointestinal complication was assessed by taking the patients' history.

As the entire project and analyses pursued a therapeutic intention, no patient was deprived from receiving their standard treatment in accordance with the executive protocol of the research project, and it was specified that in case of any severe side effects, MMF was discontinued and the patient was excluded. The facilitators also ensured that all the patient information would be kept confidential. This study was funded by Kermanshah University

of Medical Sciences (97894) and approved by the Ethics Committee of the university (code of ethics: IR.KUMS.REC.1397.938). Lastly, the study has been registered on the Iranian Registry of Clinical Trials (IRCT20130812014333N113).

Data Analysis Method

To describe the frequency distribution of gender, type of complementary drug, type of patient treatment priority, and probable recurrence, descriptive statistics (i.e., frequency and percentage) were used. To express the mean age, the average recurrence rate, drug dose, and follow-up period, descriptive statistics, including minimum and maximum, median and mode, mean and standard deviation, were employed.

To evaluate the normal distribution of the data related to follow-up duration, recurrence rate, and the dosage of corticosteroid used before and after the initiation of MMF therapy in the two groups with different MMF therapeutic priorities, the Kolmogorov-Smirnov test was utilized. In addition, to confirm the hypothesis of normal data distribution, paired *t*-test was run. Otherwise, Mann–Whitney U test as a nonparametric test was preferred to be applied. As the current research is of a comparative type, to evaluate the differences between the two groups in terms of mean recurrence intervals, medication dosages, and follow-up periods before and after the initiation of MMF therapy, paired-samples *t*-test was applied, to examine the difference in the effectiveness of the MMF therapy between the two treatment study groups, the non-parametric Mann-Whitney U test was used. All the analyses were performed using SPSS, version 20. A *P* value of less than .05 was considered statistically significant.

RESULTS

Overall, 32 INS patients including 18 (56.3%) boys and 14 (43.8%) girls with the mean age of 9.50 ± 4.19 years (age range: 4 to 22 years) were enrolled. The mean age at the onset of disease was 5.12 ± 3.75 years (onset age range: 2 to 16 years). The patients were followed up and evaluated to examine the effectiveness of MMF therapy on relapse rate, corticosteroid dosage, and time of the first relapse after recovery. The mean duration of follow-up was 1.96 years (median follow-up time of one year and a follow-up range of 0.5 to 13 years, Table 1).

Before initiating MMF therapy, the mean follow-up duration for these patients was 2.63 ± 3.23 years with a median follow-up duration of 1 year and a range of 1 to 13 years. Furthermore, prior to MMF therapy, recurrence rate was reported to be 0 to 6

Table 1. Baseline Characteristics and Clinical Records of Patients Treated with MMF

Factor	Levels	Number (%) (n = 32)	
Sex of the Patient	Boy	18 (56.3)	
	Girl	14 (43.8)	
Type of Nephrotic Syndrome	Frequent Recurrence	28 (87.5)	
	Corton Dependent	4 (12.5)	
Type of Complementary Drug Used by the Patients	Levamisol	16 (50)	
	Cyclosporine	4 (12.5)	
	Cyclophosphamide	2 (6.25)	
	Mycophenolate Mofetil	10 (31.25)	
Priority of Treatment with MMF	Primary Treatment	10 (31.25)	
	Subsequent Treatments	22 (68.75)	
Occurrence of Recurrence After Cessation of Treatment with MMF	Recurrence	12 (37.4)	
	No Recurrence	20 (62.6)	
	Number	**M ± Std**	**Min to Max**
Current Age of Patients	32	9.5 ± 419	4 to 22
Age of Onset of the Disease		5.12 ± 3.75	2 to 16
Age of Onset of MMF Treatment		7.75 ± 4.33	3 to 17
Study Follow-up Time		1.96 ± 3.33	0.5 to 13
Duration of Follow-up Study After Discontinuation of MMF Treatment		1.00 ± 1.9	0 to 8
Time of First Recurrence After Recovery		0.51 ± 0.9	0 to 4

Abbreviations: M, mean; Std., standard deviation; Min, minimum; Max, maximum; MMF, mycophenolatemuftil.

times per year with an average rate of 2.19, and the average dose of corticosteroid used was 46.25 ± 5.96 mg/kg/month with a range of 30 to 60 mg/kg/month. Regarding drug supplementation history, 16 (50.0%) patients used levamisole, 4 (12.5%) used cyclosporine, and 2 (6.25%) patients used cyclophosphamide. Further, 10 (31.25%) patients consumed MMF as their initial adjuvant, and for the remaining 22 patients, MMF was administered as their second-line adjuvant (Table 1).

After the initiation of MMF therapy, the patients were followed up for an average duration of 2.75 years with a median follow-up duration of 2 years and a range of 1 to 10 years. The mean age at the initiation of MMF therapy was 7.75 ± 4.33 years with a range of 3 to 17 years.

During the follow-up period, the average recurrence rate was 0.62 times per year (range: 0 to 2 times per year), and the average dose of corticosteroid was reduced by 25.62 ± 6.32 mg / kg/month with a range of 10 to 40 mg/kg/month (Tables 1 and 2). After the discontinuation of MMF treatment, average duration of follow-up was 1 year (1 ± 1.90), with the range of 0 to 8 years. During this period, the recurrence rate observed in the patients increased slightly (0 to 3 recurrences). However, the average recurrence rate decreased by about 0.53 times. During this period, 20 (62.6%) patients showed no recurrence and 12 (37.4%) patients reported 1 to 3 recurrences. After the discontinuation of MMF therapy, the mean time to the first recurrence was 0.51 ± 0.9 years, with a range of 0 to 4 years. Also, no adverse side effects for MMF therapy were reported for any of the cases (Table 1).

Comparison of average follow-up duration prior to and following MMF therapy did not show a statistically significant difference ($P > .05$). In evaluating the effect of MMF therapy on recurrence rate and the dose of corticosteroid, the results from comparing the recurrence rate and the dose of corticosteroid used before and after the initiation of MMF therapy showed this treatment significantly lowered the recurrence rate by about 64.52% ($P < .05$) and decreased the cumulative dose of corticosteroid by about 43.88% ($P < .05$, Table 2; Figures 1 and 2).

Table 2. Results of Comparing the Average Time of Follow-up, Number of Relapses and Dosage of Corticosteroids (Before and After Treatment with MMF)

Factors	Time Points (n = 32) M ± Std. (Min to Max)		Diff	Paired T-Test	*P*
	Before MMF	After MMF			
Follow-up Period by Year	2.63 ± 3.23 (1 to 13)	2.75 ± 1.93 (1 to 10)	0.125	-0.22	> .05
Number of Recurrences	2.19 ± 1.73 (0 to 6)	0.62 ± 0.79 (0 to 2)	1.56	6.36*	< .0001
Dosage of Corticosteroids (mg/kg/month)	46.25 ± 5.96 (30 to 60)	25.62 ± 6.32 (10 to 40)	20.62	14.95*	< .0001

Values are presented as mean ± standard deviation (minimum to maximum).
A paired samples-T Test was used to compare variables before and after MMF.
*$P < .05$.
Abbreviations: M, mean; Std., standard deviation; Min, minimum; Max, maximum; MMF, mycophenolatemuftil; Diff: mean's differences; Paired-T Test: paired samples t-test ($\alpha = 0.05$).

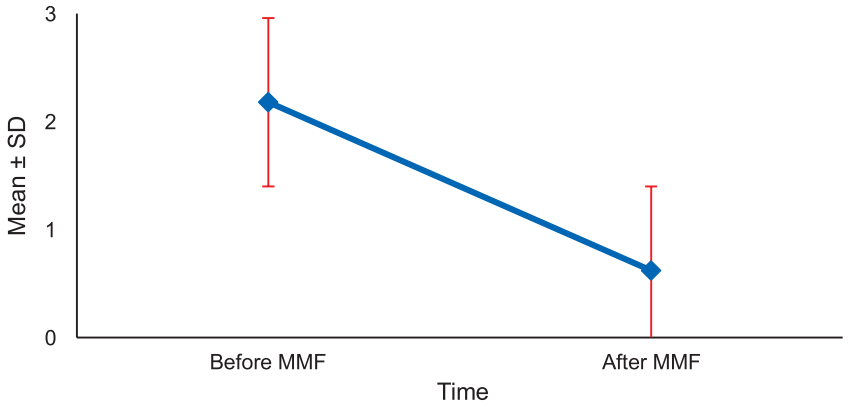

Figure 1. The Average Number of Relapses Before and After Treatment with MMF

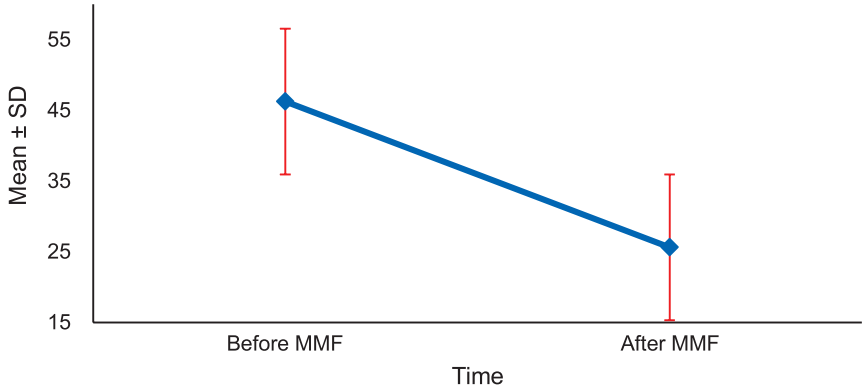

Figure 2. The Mean Value of Steroids Consumed in Patients Before and After Onset of MMF Therapy

According to the results, there was no significant difference in the mean duration of follow-up, recurrence rate, and corticosteroid dose before and after MMF therapy between the second group of patients for whom MMF was prescribed as the first therapeutic medication and the first group receiving it as the subsequent therapeutic medication (all $P_s > .05$, Table 3; Figures 3 and 4).

DISCUSSION

This report is a long-term single-center experience in treating 32 SDNS /FRNS patients. The principal objective of this trial was to determine whether MMF can reduce the disease recurrence rate and cumulative dose of corticosteroid. Mycophenolate mofetil in patients with SD/FR nephrotic syndrome reduced the relapse frequency by 64.52%; we also

Table 3. Results of Comparing the Average Reduction in Each of the Factors: Time of Follow-up, Number of Relapses and Dosage of Corticosteroids (Before and After Treatment with MMF), Based on the Priority of Treatment with MMF

Factors	Priority Treatment for MMF		Diff	*P*
	MMF as First Steroid-sparing Agent (n = 10)	MMF as Subsequent Steroid-sparing Agent (n = 22)		
Follow-up Period Before MMF by Year	3.50 ± 4.09	2.23 ± 2.78	1.27	> .05
Follow-up Period After MMF by Year	2.50 ± 1.43	2.84 ± 2.15	0.36	> .05
Number of Recurrences Before MMF	2.60 ± 1.78	2.00 ± 1.72	0.60	> .05
Number of Recurrences After MMF	0.50 ± 0.85	0.68 ± 0.78	0.18	> .05
MMF Dosage of Corticosteroids Before, mg/kg/month	47.50 ± 4.86	45.68 ± 6.42	1.82	> .05
Dosage of Corticosteroids After MMF, mg/kg/month	27.0 ± 7.53	25.0 ± 5.77	2.0	> .05

Values are presented as mean ± standard deviation.
A independent samples Mann Whitney test was used to compare variables between the two groups.
Abbreviations: M, mean; Std., standard deviation; Min, minimum; Max, maximum; Diff, mean's differences; M-V-U T, independent samples Mann Whitney test (α = 0.05); MMF, mycophenolatemuftil.

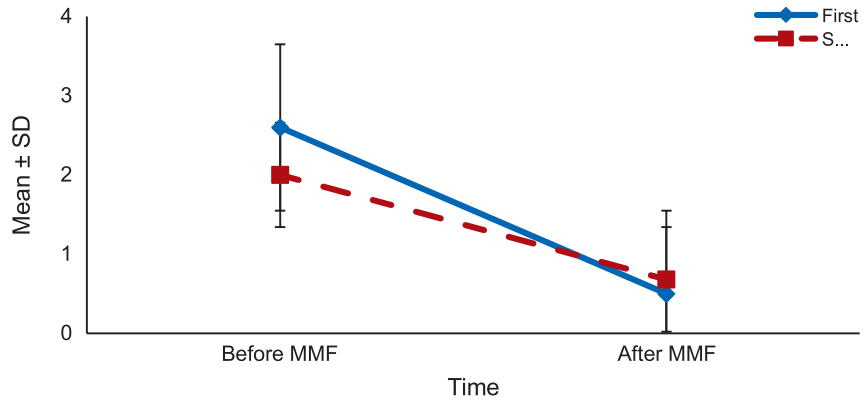

Figure 3. The Mean Number of Relapses in Patients Treated with MMF as the First and Second Supplemental Drug

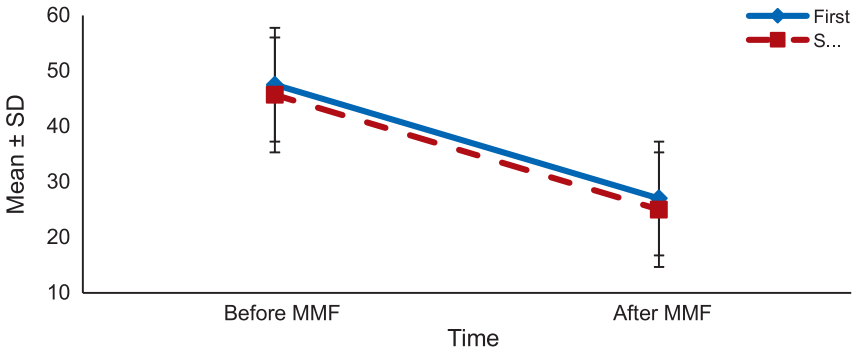

Figure 4. The Average Daily Steroid Dose of MMF-treated Patients as the First and Second Supplemental Drug

revealed the steroid-sparing effect of MMF with 43.88% reduction in steroid dosage.

It was found that MMF is an effective agent in reducing the disease recurrence rate and the cumulative dosage of corticosteroid in complicated nephrotic syndrome patients. Steroid-sensitive nephrotic syndrome (SSNS) is the most common type of nephrotic syndrome in children with a variable clinical course.[4,9] About 60% of patients with SSNS are frequently relapsing (FR) or steroid-dependent (SD). There is controversy over the most effective clinical approach to SD/FRNS, and different drugs have been used with variable results.[4,5,10] Steroids are one of the first drugs have been used in these patients, but dependence on steroids or frequent relapses requires the maintenance of high levels of corticosteroids, which cannot be continued in long term due to their side effects.[1,5,11] This necessitates the use of adjuvants such as levamisole, alkylating agent, and calcineurin inhibitors in these patients to reduce the dose of corticosteroids.[1,6] Meanwhile, long-term use of these steroid-adjuvants can also cause significant side effects. For example, long-term use of calcineurin inhibitors including cyclosporine and tacrolimus in addition to nephrotoxicity can be associated with cosmetic, metabolic, and neurological complications.[1,8,12] Among these drugs, MMF, a lymphocyte proliferation inhibitor, has been shown to have satisfactory results in maintaining remission in these patients in a variety of studies.[1,4,13] Mycophenolate mofetil therapy as a therapeutic option in SD/FRNS patients was first reported in adults, and many studies have revealed that in patients on long-term treatment with cyclosporine, switching to MMF is not only effective in maintaining remission, but also improves glomerular filtration rate.[1,10] Table 4 displays the results of some similar studies on the use of MMF in nephrotic syndrome in children.

The SD/FRNS patients in our research were almost homogeneous coming from a single center, and they were treated with a similar protocol. In addition, all of them had been shown poor therapeutic response to previous medications.

Mycophenolate mofetil therapy duration varies from 2.4 to 42 months in different studies.[5,8,14] Hasan et el. in 2013 used one of the longest MMF therapies in the literature with a duration of 2.1 years for SDNS.[4] Although the effect of MMF therapy duration on the prognosis of patients with SD/FRNS is nebulous, most articles recommend a duration of at least 12 months for this type of therapy.[1,5,4,5,15]

In this study, we followed patients with complicated nephrotic syndrome prior to the initiation of MMF with an average duration of 2.63 years and after the onset of MMF therapy with an average duration of 2.75 years. Thus, although this study is compressive in design, the results are valid thanks to the long-term follow-up.

One strength of the present study was the follow-up of the patients after the discontinuation of MMF for one year (1 ± 1.90), and the follow-up revealed a slight increase in recurrence subsequent to the discontinuation of the drug.

Contrary to our study, in a prospective multicenter study, Yang *et al.* (2019) evaluated the efficacy of MMF after calcineurin inhibitor (CNI) and corticosteroid therapy in two groups of children with SDNS managed with or without MMF. However, the results failed to corroborate the effectiveness of MMF in reducing the relapse rate in SDNS.[15]

Table 4. Some Published Trials on MMF in SD/RF Nephrotic Syndrome in Children

Author	Study Design	Duration, Daily Dosage	Relapse Rates1 & Conclusion	Adverse Effects
Bagga[19] (2003)	Prospective (19 SDNS)	12 months; 20 to 25 mg/kg/d	14 SDNS showed a 50% or greater reduction in relapse rates and failure of MMF therapy was seen in 3 patients	GI discomfort, abdominal pain, hepatitis
Gellermann[21] (2004)	Prospective (7 FRNS)	25.4 months; 1,000 mg/m^2/d	5 of 6 patients with nephrotic syndrome had no recurrence during MMF therapy	Juvenile conglobate acne
Mendizábala[9] (2005)	Prospective (21 SDNS); previous Cyclosporine therapy	8.4months; 828 to 1,772 mg/m2/d	During MMF 1.5 ± 1.7; steroid sparing (n = 15); remission (n = 9); relapse in 7 on withdrawal	GI discomfort, resolved with dose reduction
Hogg[3] (2006)	Prospective (33 FRNS,6 SDNS)	6 months;1,200 mg/m2/d	Pre-MMF 6–8.1; during MMF 0.47–1.1; 75% in remission through 6 months	Varicella, gastritis Leukopenia
Fujinaga[12] (2007)	Prospective (12 SDNS)	11 months; 1,220 mg/m2/d	Pre-MMF 2.7 ± 1.6; during MMF 0.6 ± 0.9 ; cyclosporin & prednisolone sparing	None
Yang[15] (2019)	Prospective, 34 patients with steroid-and cyclosporine -dependent NS, 16 were receive MMF and 18 were randomized to the control group	12-months , 23–33 mg/kg/day, with a maximum dose of 750 mg twice daily	MMF ineffective in influencing rates of remission in SDNS	GI discomfort
Karunamoorthy[18] (2019)	Retrospective, 87 SDNS	12-months, 28.5mg/kg/d	Remission in 83% of patients but 100% relapse after discontinuation of MMF	No significant adverse effects, Except for mild cases of diarrhea, leukopenia, urinary tract infections

Abbreviations: MMF, mycophenolatemuftil; SDNS: steroid-dependent nephrotic syndrome; FRNS, frequently relapsing nephrotic syndrome.

Several studies have been performed in different communities that confirmed the effectiveness of MMF as a suitable adjuvant therapy.[5,9] For instance, Baudouin *et al.* (2011) reported outcome of MMF therapy in 23 SDNS[1], Afzal *et al.* (2007) presented their experience in treating 42 SDNS patients,[5] Banerijee *et al.* (2013) discussed the long-term therapeutic effects of MMF on 46 SDNS patients with no previous response to levamisole and cyclophosphamide,[16] and Hassan *et al.* (2013) in a long-term research examined the effectiveness of MMF as a second-line drug in 73 patients with SDNS.[4] This group of research has identified MMF as an effective second-line agent in the treatment of SDNS. Findings of these studies were consistent with our results.

The research performed by Hogg *et al.* on patients with FRNS[3] and the study conducted by Mendizabal *et al.* on patients with SDNS[9] evaluated the possibility of withdrawing steroids after 2 and 4 months of MMF treatment, which was successful in 75% and 51% of patients, respectively. Ogarek *et al.* suggested MMF as the first immunosuppressive drug in patients with steroid-dependent/frequently relapsing nephrotic syndrome.[17]

Examining the effectiveness of MMF in 87 SDNS, a 2020 retrospective research in India revealed that although MMF was effective in reducing remission in 83% of cases, the disease recurred after halting the MMF therapy in 100% of cases.[18] In our study, the discontinuation of MMF led to relapse in 37.4% of the patients.

In agreement with the above-mentioned studies, our results obtained from comparing the recurrence rate and the corticosteroid dose used prior to and following the utilization of MMF therapy indicated that this type of therapy significantly reduced the recurrence rate ($P < .05$) and the dose of corticosteroid consumed by patients ($P < .05$). Another result in the current study which , rarely mentioned in previous studies was that no *significant* difference observed between the patients treated with MMF as the first steroid-sparing agent and those treated with MMF as the second or third agent. Therefore, subsequent initiation of MMF can be effective in such cases.

In this study, in line with the previous researches, since there is no MMF dosage recommendation

for children with SD/FRNS, the researchers used the dose of 1200 mg/m^2/d similar to the one administered for children undergoing kidney transplant.[1,7,19,20] Administration of MMF, like many other medications, may be associated with hematological (e.g., leukopenia/neutropenia), gastrointestinal (e.g., diarrhea, abdominal pain, and weight loss) dermatological (e.g., verrucae), and neurological (e.g., paresthesia and headache) complications.[20,21] However, in most studies, MMF has been well tolerated and found to be associated with mild side effects such as abdominal pain and spontaneous neutropenia.[1,5,20-22] In this study, we observe no serious side effects leading to MMF discontinuation or shifting to another medication.

CONCLUSION

This study confirmed that MMF is a relatively safe and effective second-line medication for SD/FRNS patients in Iranian pediatric population in decreasing the rate of recurrence and corticosteroid dose, even when patients have previously received other second-line medications.

LIMITATIONS

The retrospective nature of the current research may have led to the underestimation of the adverse effects of MMF. Due to the absence of a cohort study and a control group not receiving MMF, the authors could not compare the results of the control group with patients receiving MMF. Additionally, as biopsies were not performed, it was not possible to compare the histopathological patterns with the effectiveness of MMF.

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CONFLICT OF INTERESTS

The authors declared no conflict of interests.

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