Mycophenolate Mofetil Treatment in Childhood Steroid-Sensitive Nephrotic Syndrome: Single Center Experience

Çocukluk Çağı Steroid Duyarlı Nefrotik Sendromda Mikofenolat Mofetil Tedavisi: Tek Merkez Deneyimi

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ABSTRACT

Objective: We aimed to investigate the efficacy of mycophenolate mofetil (MMF) for maintaining remission and reduce the number of relapses in childhood steroid-sensitive nephrotic syndrome. The effects of MMF on growth and blood pressure parameters were also evaluated.

Material and Methods: This retrospective, single-center observational study included patients with steroid-sensitive nephrotic syndrome who were treated using MMF between 2009 and 2019 in the Department of Pediatric Nephrology in our hospital.

Results: Ten patients had steroid-dependent nephrotic syndrome; six patients frequently had relapsing nephrotic syndrome in this study. The mean duration of the disease was 93.3±25.0 months and the mean duration of the MMF onset was 33.9±16.7 months after diagnosis. Ten patients showed a 50% or greater reduction in the relapse rate and the prednisolone treatment was discontinued in eight patients for six months or more. Compared to the previous year, before the start of the MMF treatment, there was a 52.7% reduction in the relapse rate and a 36.6% reduction in the cumulative annual dose of steroid after 12 months of MMF treatment. The height z score and the median office systolic blood pressure standard deviation scores of the patients improved after MMF treatment (respectively $p = 0.003$, $p = 0.01$).

Conclusion: The findings suggest that MMF may lead to decreased relapse rates and cumulative steroid dose, which has a positive effect on growth and blood pressure parameters in steroid-sensitive nephrotic syndrome.

Key Words: Blood pressure, Childhood, Growth, Mycophenolate mofetil

ÖZ

Amaç: Mikofenolat mofetilin çocukluk çağı steroide duyarlı nefrotik sendromda remisyonu sürdürme ve relaps sayısını azaltmadaki etkinliğinin belirlemesi amaçlandı. Ayrıca MMF'in büyüme ve kan basıncı üzerindeki etkileri değerlendirildi.

Gereç ve Yöntemler: Bu retrospektif, tek merkezli gözlemsel çalışma, 2009-2019 yılları arasında hastanemiz çocuk nefroloji kliniğinde MMF ile tedavi edilen steroide duyarlı nefrotik sendromlu hastaları içermektedir.

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Bulgular: Çalışmamızdaki 10 hasta steroide bağımlı nefrotik sendrom, 6 hasta sık relaps nefrotik sendromdu. Ortalama hastalık süresi 93.3±25.0 ay ve tanıdan sonra ortalama MMF başlangıç süresi 33.9±16.7 aydı. On hastanın nüks oranında %50 veya daha fazla azalma görüldü ve prednizolon tedavisi 8 hastada 6 ay veya daha uzun süre kesildi. Bir önceki yıla kıyasla, 12 aylık MMF tedavisinden sonra nüks oranında %52.7 ve yıllık kümülatif steroid dozunda %36.6 azalma oldu. Mikofenolat mofetil tedavisi sonrası hastaların boy z skoru ve ortanca ofis sistolik kan basıncı standart sapma skorları iyileşti (sırasıyla p = 0.003, p = 0.01).

Sonuç: Mikofenolat mofetil, steroid duyarlı nefrotik sendromda nüks oranlarını, kümülatif steroid dozunu azaltarak büyüme ve kan basıncı ölçümleri üzerine olumlu etkilere neden olur.

Anahtar Sözcükler: Kan basıncı, Çocukluk çağı, Büyüme, Mikofenolat mofetil

INTRODUCTION

Idiopathic nephrotic syndrome (NS) is the most common chronic glomerular disease in children between 1.5 and 10 years of age (1,2). Approximately 80-90% of these children respond to oral steroids, and in these cases, it is called steroid-sensitive NS (SSNS). Approximately 60% of children with SSNS develop frequently relapsing NS (FRNS) or steroid-dependent NS (SDNS). However, 40–75% of all SSNS cases require long-term steroids and/or other immunosuppressive agents, such as cyclophosphamide, calcineurin inhibitors and mycophenolate mofetil (MMF), to maintain remission and prevent frequent relapses (2-4).

MMF is a prodrug of mycophenolic acid and classified as a reversible inhibitor of inosine monophosphate dehydrogenase. Mycophenolate is used in combination with other immunosuppressant drugs, such as cyclosporine and corticosteroids, to prevent organ rejection after hepatic, renal and cardiac transplants. In addition to the above uses, MMF has also been studied for the treatment of nephrotic syndrome, nephritis and other complications of autoimmune diseases. MMF has been evolving gradually as a new therapeutic agent for pediatric idiopathic NS, especially as a steroid-sparing agent for the prevention of relapses (5,6).

In this study, we aimed to investigate the efficacy of MMF for maintaining remission and reducing the number of relapses in childhood SSNS. Furthermore, the effects of MMF on growth and blood pressure (BP) parameters were evaluated.

MATERIALS and METHODS

This retrospective, single-center observational study included 16 patients with SSNS who were treated with MMF between 2009 and 2019 in the Department of Pediatric Nephrology. The inclusion criteria in this study were as follows: Patients who were 1–18 years of age at the start of the MMF treatment and they had a minimum follow-up time of 12 months after the start of the MMF treatment.

Patient medical records, including clinical and demographic characteristic like age, gender, weight, height, and BMI, physical examination findings, including BP at presentation and each follow-up visit, and laboratory findings, such as serum creatinine, albumin, urinalysis, urinary protein creatinine ratio and 24-h protein excretion, were retrospectively reviewed.

Standard height, weight, and BMI scores were based on Turkish children's growth curves. BMI was calculated as kg/height (m^2). Blood pressures of patients were measured in the out patient setting after a resting period for at least 10 minutes. Mean standard deviation scores (SDS) of three consecutive systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements by the auscultatory method were calculated (7).

Standard definitions were used for NS, remission and relapse (3). A frequent relapse was defined as two or more relapses within six months of the initial response or four or more relapses in any 12-month period. Steroid dependence was defined as two consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy (1-4).

The MMF treatment was started after steroid remission was achieved and it was administered to the patients in two divided doses, with an average dose of 1000–1200 mg/m^2/day. All of the patients received cyclosporine or cyclosporine and cyclophosphamide as other immunosuppressive therapy for at least six months before being treated with the MMF. The frequency of relapse and duration of remission before and after MMF treatment were compared.

This study was approved by the Clinical Research Ethics Committee of Ankara Kecioren Training and Research Hospital (1963 / 11.09.2019).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normality of the distribution of the study variables. Parametric variables were shown as mean±SD, and nonparametric variables were shown as median and IRQ. Categorical variables were presented as numbers and percentages. Student's t-test was used to compare parametric variables and the Mann-Whitney U test was used to compare nonparametric variables. The χ^2test or Fisher's exact test was used to compare categorical variables. The level of statistical significance was set at $p < 0.05$.

RESULT

Sixteen patients who received MMF for FRNS and SDNS were included in this study. The mean follow-up duration was 7.7±2.1 years. All of the patients received cyclosporine or cyclosporine and cyclophosphamide as other immunosuppressive therapy for at least six months before the MMF treatment. Five of the patients were treated using cyclosporine and cyclophosphamide, and 11 of the patients were treated using cyclosporine alone.

The mean age of the patients was 164.8±24.1 months, and the mean age of diagnosis was 70.8±34.1 months. The female to male ratio was 0.8. The mean duration of the disease was 93.3±25.0 months, and the mean duration of the MMF onset was 33.9±16.7 months after diagnosis. The mean dosage of MMF used was 1046.8±78.4 mg/m^2/day. Ten of the patients had SDNS; six patients had FRNS. The renal biopsies were consistent with minimal change disease in nine patients, focal segmental glomerulosclerosis in six patients, and mesangial proliferation in one patient.

The MMF treatment was started after steroid remission was achieved. The number of relapses after the MMF treatment decreased from 3.6/year to 1.7/year, which was significantly lower (p = 0.000). Ten of the patients showed a 50% or greater reduction in the relapse rate and the prednisolone treatment was discontinued in eight patients for six months or more. None of the patients had diarrhea, hematological abnormalities or impaired renal function.

Compared to the previous year, before the start of the MMF treatment, there was a 52.7% reduction in the relapse rate and a 36.6% reduction in the cumulative annual dose of steroid after 12 months of MMF treatment. Relapse numbers of the SSNS patients before and after MMF treatment are given in Figure 1. The mean cumulative steroid dose was 232.5±27.3 mg/kg/year for 0-12 months before MMF and the mean cumulative steroid dose 0-12 months post MMF decreased to147.1±94.3 mg/kg/year (p = 0.004).

The median BMI z-score decreased from 0.8 (IQR;-1.3 - 2.4) at the time MMF was initiated to 0.5 (IQR;-1.4 - 2.9) at the last follow-up visit (p = 0.25). However, no significant difference was detected. The median height z-score at the time of MMF initiation was –0.8 (IQR; -3.2-0.9) and the median height z-score at the last follow-up visit was –0.7 (IQR; -2.4-1.3). The height z score in patients improved significantly after the MMF treatment (p = 0.003).

The median office SBP SDS at the time of MMF initiation was 0.5 (IQR; -0.8-2.3) and the median office SBP SDS at the last follow-up visit was -0.2 (IQR; -0.8-1.7) (p = 0.01). The median office DBP SDS at the time of MMF initiation was 0.3 (IQR; -0.3-2.3) and the median office DBP SDS at the last follow-up visit was 0.2 (IQR; -1-1.8) (p = 0.08). Office SBP SDS of the patients before MMF was significantly higher than after MMF. Office DBP SDS of patients before MMF did not differ significantly after MMF. Clinical and laboratory characteristics of patients before and after MMF treatment are given in Table I.

DISCUSSION

The present study aimed to investigate the effects of MMF on disease outcome, blood pressure levels and growth parameters in pediatric SSNS patients. MMF acts by inhibiting de novo purine synthesis by inhibiting the mofetil inosine monophosphate dehydrogenase enzyme. In particular, it inhibits T and B lymphocyte proliferation. These functions may be accountable for the amelioration of inflammation and/or the structural remodeling characteristics of the glomerular disease (6,8,9).

Steroid dependent NS and FRNS are clinical conditions with high morbidity due to the toxicity of the long-lasting steroid therapy with high doses of prednisone, as well as to the length of the disease (2,3). Over the past decade, there have been many studies on the benefits of MMF treatment in SDNS and FRNS. In most of the studies, the MMF was shown to result in a significant reduction in the frequency of relapses, as well as the cumulative dose of the steroid required, irrespective of the previous alternative drugs used (5,10,11). MMF also contributes to renal function by reducing the cyclosporine and/or steroid-induced effects. Previous studies have shown efficacy and protection for 12 months or more (5,11-13). Our study suggests that although the MMF was useful for preventing relapses and

Table I: Clinical and laboratory characteristics of patients before and after MMF treatment.

	Before MMF treatment (n=16)	After MMF treatment (n=16)	p
BMI z-score, median (IQR)	0.8 (IQR; -1.3 - 2.4)	0.5 (IQR; -1.4 - 2.9)	0.25
Height z-score, median (IQR)	–0.8 (IQR; -3.2 - 0.9)	–0.7 (IQR; -2.4 - 1.3)	0.003
Office SBP SDS, median (IQR)	0.5 (IQR; -0.8 - 2.3)	-0.2 (IQR; -0.8 - 1.7)	0.01
Office DBP SDS, median (IQR)	0.3 (IQR; -0.3 - 2.3)	0.2 (IQR; -1 - 1.8)	0.08
CSD, mg/kg/year, mean ± SD	232.5±27.3	147.1±94.3	0.004
Serum glucose level, mg/dL, mean ± SD	97.2±18.9	98.1±17.5	0.86

BMI: *body mass index,* ***SBP:*** *systolic blood pressure,* ***DPB:*** *diastolic blood pressure,* ***CSD:*** *cumulative steroid dose*

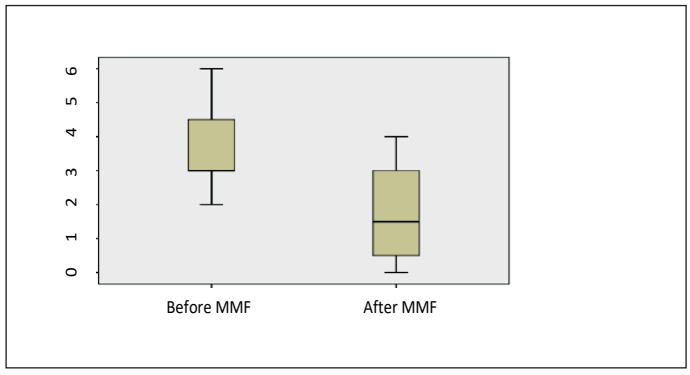

Figure 1: Relapse numbers of the SSNS patients before and after MMF treatment.

sparing steroids, it had no disruptive effect on the disease. The number of relapses after the MMF treatment decreased from 3.6/year to 1.7/year (p = 0.000) in our study. When compared to the previous year, before the start of the MMF therapy, there was a 52.7% reduction in the relapse rate and a 36.6% reduction in the cumulative annual dose of steroid after 12 months of MMF treatment. Ten of the patients showed a 50% or greater reduction in the relapse rate, and the prednisolone treatment was discontinued in eight patients for six months or more. In all of the studies, the MMF showed the ability to decrease the relapse rate and the cumulative prednisone dose (5,8,14,15). Consistent with the literature, our study showed similar positive effects regarding steroid sparing.

It should be noted that there is considerable non-uniformity in both the MMF dosage and duration and in the other drugs used both before the MMF and with the MMF. The MMF dosage was calculated based on the body weight and the body surface area, and it varied from 600 mg/m^2/day to 1200 mg/m^2/day and from 25 mg/kg to 40 mg/kg, respectively. The mean dosage of MMF used was 1046.8±78.4 mg/m^2/day in our study. In addition, there seems to be a wide variation in the therapy duration, from three months to seven years. The previous studies have not shown any significant variations in the outcomes regarding the efficacy and side effects based on the MMF dosage administered per day (5,9,16,17). However, the studies involving MMF for longer durations provide an indication that the MMF is more efficacious for maintaining remission if the therapy duration is increased from several months to several years. Some studies have concluded that administering MMF for more than 12 months is more efficacious than administering it for six months. Moreover, the treatment continuation beyond 12 months resulted in sustained steroid-sparing and reduced the need for alternative treatments while maintaining low relapse rates (14,17,18). The mean duration of the MMF onset was 33.9±16.7 months after diagnosis. This study included the use of MMF for more than 12 months for the benefit of maintaining remission.

The principal toxicities of MMF are gastrointestinal and hematological and they include leukopenia, diarrhea, and vomiting. MMF has an efficacy similar to that of cyclosporine, but with fewer side effects, especially no risk of nephrotoxicity and no adverse cosmetic events. Digestive trouble, infectious events, anemia, lymphopenia and thrombocytopenia have been reported in several studies, but they were always mild and transient (4,18-20). None of the patients in our study required an MMF withdrawal due to unacceptable side effects.

There are few studies on the effects of other immunosuppressants on growth in children. In the present study, the height z score in 75% of the patients improved following MMF treatment, and the median height z score at the last follow-up visit was higher than at the time of initiation of MMF treatment (p = 0.003). MMF had a similarly positive effect on BMI in the SSNS patients in this study, but no significant difference was detected (p = 0.25).The median office SBP SDS of patients before the MMF treatment was significantly higher after MMF. The median office SBP SDS of patients improved after the MMF treatment (p = 0.01). These effects may arise from the decrease in cumulative steroid dose after MMF treatment. Although our patient group was relatively few, to our knowledge, this is the first study in the literature evaluating the effects of MMF on growth and blood pressure parameters in children with SSNS.

In conclusion, long-term treatment with MMF has been shown to reduce the relapse rates in patients with SSNS. MMF causes decreased cumulative steroid dose, which had a positive effect on growth, blood pressure parameters in SSNS. MMF seems to have a positive efficacy and side effect profile as a steroid protective agent in maintaining the remission in childhood SSNS. Although there appears to be general agreement on the efficacy of MMF in preventing relapses in NS, there is still no consensus on the optimal dosage and duration of MMF treatment. These data support the efficacy and safety of MMF treatment for longer than 12 months. The limitations of the present study are its retrospective design and the low number of cases.

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