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Treatment of Steroid and Cyclophosphamide-Resistant Nephrotic Syndrome with Mycophenolate Mofetil and High Dose Dexamethasone (DEX)

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Abstract

Background: Clinicians often face with therapeutic challenges during the treatment of children with steroid-resistant nephrotic syndrome (SRNS). The management of SRNS is primarily aimed at decreasing proteinuria and inducing remission. Mycophenolate mofetil (MMF) in combination with steroids is known to have some efficacy in the management of SRNS. The aim of this study is to evaluate the outcome of MMF/DEX therapy regimen.

Material and methods: We reported a prospectively longitudinal clinical series of patients with SRNS, all of whom have been treated with Mycophenolate mofetil and oral dexamethasone (DEX). We enrolled 29 children who were previously treated with steroid and cyclophosphamide at Ege University, Children's Hospital. Treatment with MMF/DEX was administered for up to 52 weeks. These children were followed for a period of 2 years. Complete remission was defined as negative or trace proteinuria on urinalysis with a serum albumin level of >2.5 g/dl. On the other hand, partial remission was defined as a serum albumin level of >2.5 g/dl, but developing persistent proteinuria at non-nephrotic levels.

Results: Following the course of MMF/DEX, 68.9% (20/29) of children achieved a complete remission and 33.4% (1/29) remained at partial remission. After 24 months of follow- up, 55.1% (16/29) of children on MMF/DEX reached a complete remission and 13.7% (4/29) remained at partial remission.

Conclusion: MMF/DEX can be an effective and safe maintenance therapy among children with SRNS.

Keywords: Nephrotic syndrome; Children; Mycophenolate mofetil; Dexamethasone; Steroid resistance

Introduction

The nephrotic syndrome is caused by renal diseases that increase the permeability across the glomerular filtration barrier. It is characterized by four clinical features. Nephrotic range proteinuria and hypoalbuminemia are used diagnostically. Edema and hyperlipidemia may not be observed in all patients. Resistance to steroid therapy is defined by the absence of remission after one month of daily prednisone therapy at a dose of 2 mg/kg per day. Almost 80% of children with nephrotic syndrome respond to steroids. Approximately 20% are unresponsive to a standard regimen of oral corticosteroids [1]. The underlying renal histology in these patients is usually focal segmental glomerulosclerosis (FSGS) [2].

Various treatment regimens have been used in patients with steroid-resistant nephrotic syndrome, such as a treatment with calcineurin inhibitors, cyclophosphamide and high-dose intravenous corticosteroids [3]. Several protocols have been used in these patients and variable results have been obtained [4]. The optimal therapy of patients with steroid-resistant nephrotic syndrome is controversial [5]. Many agents have been assessed, including methylprednisolone, cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors, and rituximab, but not in randomized trials [6,7].

MMF is an immunosuppressant drug. MMF is the inhibitor of inosine monophosphate dehydrogenase, an enzyme required for purine synthesis pathway. MMF strongly inhibits both T- and B-lymphocyte proliferation. MMF may reduce urine protein excretion in steroid-resistant patients. It may have a better side effect profile compared to the other agents [8,9]. We reported our experience with 29 patients with idiopathic steroid-resistant nephrotic syndrome, who were treated with Mycophenolate mofetil and oral dexamethasone. Nowadays, a number of therapeutic options are available. We used MMF/DEX therapy regimen as a third-line treatment of children with steroid-resistant NS.

Patients and Methods

We prospectively studied all patients aged 1-11 years, with initial steroid and cyclophosphamide-resistant nephrotic syndrome who presented to the Pediatric Nephrology Services of our hospital. We enrolled 29 children treated with Mycophenolate mofetil and oral dexamethasone and followed-up at Ege University, Children's Hospital between September 2011 and May 2014. Children with idiopathic nephrotic syndrome who were previously treated steroid and cyclophosphamide were included in the study. Inclusion criteria were: (1) being aged 1 to 11 years without hypertension, gross hematuria, or extra renal symptoms and normal complement levels (2) having idiopathic nephrotic syndrome, (3) no response to a standard regimen

of oral corticosteroids (4) no response to oral cyclophosphamide, (5) eGFR >60 mL/min per 1.73 m^2, and (5) either minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) on renal histopathology. Exclusion criteria were: congenital nephrotic syndrome, secondary causes of nephrotic syndrome (known etiology; e.g., lupus erythematosus, immunoglobulin A nephropathy, amyloidosis; known chronic infection, such as tuberculosis, HIV, hepatitis B or C; and known malignancy). Patients who had received a previous therapy with steroid and cyclophosphamide were treated within 30 days of enrollment.

Nephrotic syndrome was defined by the presence of hypoalbuminemia (<2.5 g/dl), proteinuria (>40 mg/m^2/h or protein/creatinine ratio >2 g/g), with or without edema [10]. We initiated the practical application of steroid therapy when the diagnosis of idiopathic NS was established. We started the treatment with 2 mg/kg (maximum dose of 60 mg/day) of prednisolone daily for 4 weeks followed by alternate-day prednisone of 2 mg/kg (maximum dose of 60 mg/day), and then continued with a dose of 1.5 mg/kg alternate-day for 4 months with tapering off the dose. Patients were considered to be SRNS when they did not respond to the treatment with 2 mg/kg prednisolone for 4 weeks daily [11]. It is our practice to perform renal biopsy in all patients with nephrotic syndrome with initial steroid resistance. Within our practical application, we administered an oral cyclophosphamide treatment to the patients unresponsive to steroid therapy. We gave 3 mg/kg/day dose of cyclophosphamide for 10 weeks. Afterwards, we started MMF/DEX therapy regimen.

Complete remission was defined as negative or trace proteinuria <4 mg/m^2/h (by the dipstick method or a urinary protein/creatinine ratio of ≤ 0.20 mg/mg) on urinalysis for 3 consecutive days and a serum albumin level of >2.5 g/dl. Partial remission was defined as a serum albumin level of >2.5 g/dl, but developing persistent proteinuria at non-nephrotic levels (<40 mg/m^2/h). The state of remission included both complete remission and partial remission. Steroid resistant was described as failing to achieve remission following 4-week prednisone 2 mg/kg/day. Relapse of nephrotic syndrome was defined as increased proteinuria and a serum albumin level of ≤ 2.5 g/dl. The parents were instructed to test the urine protein regularly. Blood levels of urea, creatinine, albumin, cholesterol, and 24-h urine protein, weight and height were recorded every 3 months. EGFR was estimated at baseline and then every 3 months by using the modified Schwartz formula [12].

We administered MMF/DEX therapy regimen, dosage of MMF (25-36 mg/kg per day, maximum 2 g/d), was given in two equal daily doses, and DEX (0.9 mg/kg per dose, maximum 40 mg) was given on two consecutive days at the start of weeks 1-8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 34, 38, 42, 46, and 50. MMF and DEX dose adjustments were made in 30% decrements for pre-specified toxicities. Treatment with MMF/DEX was given for up to 52 weeks. We followed by 3-month intervals or whenever necessary. Laboratory studies included the total serum cholesterol, serum triglycerides, renal function, blood count, serum total protein and albumin, and 24-h proteinuria.

FSGS was defined as segmental hyalinosis and sclerosis of one or more glomeruli on light microscopy, and immunofluorescence demonstrating segmental deposition of IgM and C3 in capillary loops [13]. Renal tissue was classified into histologic subgroups as previously described [14].

Written informed consent was obtained from each parent of the children. They were also informed on the side effects of the medication. The study was approved by the Institutional Review Board of our institute.

Statistical Analysis

Results were presented as the mean ± standard deviation. Categorical variables were analyzed using Chi- square test. To test the association among the variables, we used the paired samples T test. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 29 patients were included in this study. There were 23 male (76%) and 6 (20%) female patients. The mean age at the time of the diagnosis of NS was 4.79 ± 3.79 years (age range, 1 to 11 years). The mean duration of the disease before initiation of MMF/DEX administration was 6.24 years (range: 3-12.0 years). All patients underwent biopsy soon after the diagnosis of SRNS. Of these, 22 had focal segmental glomerular sclerosis (73.3%) and 7 had minimal change nephropathy (26.7%). All patients were treated with steroid (2 mg/kg/day for 4 weeks, at a maximum dose of 60 mg/day) and cyclophosphamide (3 mg/kg/day for 10 weeks) medications previous to the study period. The demographic characteristics at the time of the first admission are shown in Table 1.

Age at onset of the disease (years)	4.79 ± 3.79
Age at the beginning of MMF/DEX therapy (years)	9.93 ± 4.26
Duration of the disease (years)	6.24 ± 4.18
Gender	
Male n (%)	23 (76%)
Female n (%)	6 (20%)
Weight (kg)	38.2 ± 23.1
Height (cm)	135.3 ± 25.4
Histology, n (%)	
Minimal Change Nephropathy	7 (26.7%)
FSGS	22 (73.3%)
FSGS: focal segmental glomerulosclerosis, Data on age at onset, duration of the disease and age at the beginning of MMF/DEX therapy are presented as the mean ± standard deviation (SD), those on gender and renal histology are given as the number (n), with the percentage in parenthesis	

Table 1: Baseline characteristics of the patients.

There were no significant differences found in the average proteinuria, eGFR, serum albumin, total serum cholesterol, serum triglycerides and renal function levels of these patients at the beginning and at the end of the treatment, or over a year after the treatment. No serious side-effects were observed. Side effects were usually moderate; thus, all patients tolerated the MMF/DEX therapy regimen (Table 2).

	Before MMF/DEX treatment	After MMF/DEX treatment	p value
24-h urinary protein levels (mg/m^2/h)	151.6 ± 185.8	28.07 ± 61.33	0.02
Serum albumin (mg/l)	1.98 ± 0.9	3.45 ± 1.18	0.55
Cholesterol (mg/dl)	297.4 ± 94.6	216 ± 59.8	0.3
eGFR (ml/min/1.73 m^2)	202.6 ± 114.7	173.3 ± 94.6	0.21

Table 2: Patients' Baseline Characteristics According to Outcome at 12 Months after the Course of MMF/DEX.

After the course of MMF/DEX, 68.9% (20/29) of children achieved a complete remission and 3.4% (1/29) remained at partial remission. After 24 months of follow-up, 55.1% (16/29) of children on MMF/DEX achieved a complete remission and 13.7% (4/29) remained at partial remission. The annualized relapse rate for patients with a treatment course of MMF/DEX was 2.4 relapse/years at the end of the therapy. After a follow up of two years, relapse rate was found 1.4 relapse/years (Table 3).

Remission	12 months	24 months
Complete remission n (%)	20 (68.9%)	16
Partial remission n (%)	(55.1%)	
Median duration (month) complete remission (range)	1 (3.4%)	4 (13.7%)
Relapse	8.3 (6-12)	18.2 (13-24)
Rate of relapse/years, median (range)	2.4 (0-5)	1.4 (0-3)

Table 3: Responses to MMF/DEX therapy.

A total of 20 children had a complete remission on MMF therapy. Fourteen (63.6%) of 22 children with FSGS had a complete remission on MMF/DEX therapy and six (85.7%) of 7 children with MCN also achieved a complete remission on MMF therapy.

Discussion

Persistent heavy proteinuria is a risk factor for progression of glomerular disease to chronic renal failure. However, it is unclear whether therapy is aimed at reducing proteinuria in patients with steroid resistant nephrotic syndrome. Nevertheless, remission of proteinuria significantly reduces morbidity in these patients. Several therapeutic strategies have been applied in steroid-resistant nephrotic syndrome.

Several studies have reported that MMF is effective in steroid-dependent nephrotic syndrome (SDNS) [15,16]. In this study, we evaluated the therapeutic effects of MMF/DEX therapy regimen in children with steroid and cyclophosphamide-resistant nephrotic syndrome. We administered the MMF/DEX therapy regimen recommended by Gibson et al. [17]. In our study, 29 patients were followed for two years. We followed these patients for one year during the MMF/DEX treatment and one year after the treatment. Our study reveals a high rate of cumulative sustained remission among pediatric patients with idiopathic SRNS treated with MMF/DEX therapy. 20 of 29 (68.9%) children responded completely at the end of the MMF/DEX treatment. During 24 months of follow-up after the MMF/DEX treatment, 16 of 29 (55.1%) children had a completely remission. One study reported that six of seven patients had a complete remission and one had a partial remission with the MMF treatment. MMF was administered to all patients together with prednisolone [18]. Mello et al. [19] studied 52 patients with idiopathic nephrotic syndrome (INS) who were both steroid and cyclophosphamide-resistant. They administered only MMF. They found that the rate of a complete remission was 23% and partial remission was 35.5% in patients who received the MMF treatment.

In a study conducted by Gargah et al. [20], six patients with SRNS were treated with MMF combined with oral prednisolone at a dose of 1 mg/kg/day. Only 1 patient with MCD achieved a complete remission. Li et al. [21] studied 24 children with steroid-resistant idiopathic nephrotic syndrome. MMF was initiated at a dose of 25-30 mg/kg daily for 6-12 months. After 6 months, 15 patients (62.5%) exhibited a complete remission.

Mendizabal et al. [22] reported that in five patients with SRINS whose renal histopathological pattern was FSGS, only one achieved a complete remission and one reached a partial remission. A prospective trial of NIH compared cyclosporine with low-dose alternate-day prednisone to a combination of oral pulse dexamethasone and mycophenolate mofetil [23]. Partial or complete remission was achieved in 22 of 66 patients in the mycophenolate/dexamethasone group and 33 of 72 cyclosporine-treated patients at 12 months.

Hogg et al. [24] reported a clinical trial of CsA versus mycophenolate mofetil (MMF) and dexamethasone (DEX) in patients with FSGS was published. They showed that 39 patients (54.2%) in the CsA group and 26 patients (39.4%) in the MMF/DEX group achieved a complete or partial remission after 6 months of therapy.

Here we report that 29 children with SRNS were treated with the combination of MMF and dexamethasone. This report is the largest single-center experience in SRNS children treated with MMF/DEX. Results showed that 20 patients (68.9%) had a complete remission, and one (3.4%) had a partial remission. This study had a higher rate of complete remission in SRNS children treated with MMF than other studies carried out. However, this may be related to the onset of the treatment in our study. In the present study, we initiated this regimen as a third-line therapy when we did not receive a response from cyclophosphamide.

In conclusion, this study confirms the efficacy of MMF/DEX therapy regimen in patients with steroid and cyclophosphamide-resistant nephrotic syndrome and found that mycophenolate had a few side effects on children. Mycophenolate showed a decreased relapse rate each year. We recommend that cyclophosphamide treatment should be started at first, if no response is obtained at the end of 10 weeks of this treatment, then MMF/DEX therapy regimen should be administered as a third line treatment regimen to children with SRNS,

as we have demonstrated that this regimen has a high rate of remission and a low rate of relapse.

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