Abstract

The aim of our study was to analyse the efficacy and safety of mycophenolate mofetil (MMF) as part of the complex immunosuppressive therapy in children with different types of primary and secondary glomerulonephritis, who were not eligible for the standard treatment routine suggested by evidence-based guidelines.

Material and methods: The study group comprised 85 children with proteinuric glomerulopathies hospitalized between 2007 and 2010, who were non-responders to immunosuppressive therapy. The dose of MMF was established as 1 g/m²/24 h. Remission was defined as negative proteinuria in three consecutive urinalyses.

Results: The patients were divided into 4 groups: idiopathic nephrotic syndrome (n = 35), primary glomerulonephritis (n = 15), auto-antibody associated glomerulonephritis (n = 20) and lupus nephropathy (LN, n = 15). Ten patients from the first group (29%) and 5 patients each from the second and third group (34% and 25% respectively) did not respond to MMF therapy. On the other hand, all the children diagnosed with LN have reached clinical and biochemical remission.

Conclusions: Alternative rescue MMF therapy should always be taken into consideration in proteinuric patients who are non-responders to steroids, cyclosporine A and cyclophosphamide in whom the initial glomerular filtration rate is higher than 60 ml/min/1.73m². It is recommended that MMF be administered as part of the standard treatment regimen in patients diagnosed with lupus nephropathy. In these groups of patients, the potent benefits of this therapy are higher than expected side-effects.

Key words: mycophenolate mofetil, nephrotic syndrome, outcome, paediatrics.
ma, thrombosis, and metabolic abnormalities such as hypocalcaemia and hypothyroidism, which are the consequence of albumin loss [3]. The most frequent histological form of INS is minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) [4]. Furthermore, in paediatric renal biopsies of INS children, mesangial hypercellularity (MH) can be diagnosed [5]. None of these histological forms are accompanied by immunological deposit formation evaluated by electron microscopy or in immunofluorescence studies. Among different types of secondary glomerulonephritis, systemic lupus erythmatosus (SLE) is judged as the most hazardous cause of secondary glomerulopathy in teenagers [6]. Other causes of secondary glomerulonephritis, for example associated with anti-neutrophil cytoplasmic antibodies dependent vasculitis and bronchial asthma (Churg-Strauss syndrome), are less frequent in children but, similarly, are associated with unfavourable prognosis [7, 8].

The immunosuppressive therapy strategy in INS regularly starts with glucocorticosteroids (GC). Recent reports indicate that more than 90% of paediatric patients with INS respond to this therapy (steroid-sensitive INS) [3]. Unfortunately, steroid-dependent or steroid-resistant NS impels clinicians to introduce cyclophosphamide and/or calcineurin inhibitors [9-11]. This nature of INS remains a challenge for clinicians to achieve successful induction and maintenance of complete remission in nephrotic syndrome.

In SLE dependent nephropathy the therapy procedure follows the clinical course and histological classification of renal biopsies, and is based on the well-experienced complexity of multi-drug immunosuppression [12, 13]. On the other hand, some of the primary as well as secondary glomerulopathies (e.g. Churg-Strauss syndrome) intricate by nephrotic-range proteinuria require parallel GC and optional immunosuppressive therapy (cyclophosphamide and/or azathioprine) determined by validated prognostic criteria (Five Factor Score) [8].

However, considerable toxicity of the above-mentioned procedure and inadequate clinical response to this therapy compelled us to search for more effective and safe treatment.

Mycophenolate mofetil (MMF) is an immunosuppressive agent, which is metabolized in the liver to the active moiety mycophenolic acid. It inhibits inosine monophosphate dehydrogenase, the enzyme that controls the rate of biosynthesis of guanine monophosphate in the de novo pathway of purine synthesis used in the proliferation of B and T lymphocytes, and mesangial cells [14]. According to some preliminary reports, MMF can be used not only in solid-organ transplantation but also as an alternative immunosuppressive therapy, in proteinuric nephropathies [15-17].

In line with the above, the aim of our study was to analyse the efficacy and safety of MMF as part of the complex immunosuppressive therapy in children with different types of primary and secondary glomerulonephritis, who were not eligible for the standard treatment routine suggested by evidence-based guidelines.

Material and methods

Patient population

Patients who were aged 2 to 18 years were eligible for entry into this study when they had evidence of either steroid-resistant NS (SRNS), steroid-dependent NS (SDNS) or frequently relapsing NS (FRNS). Relapse of NS before study entry was defined as proteinuria ≥ 2+ by dipstick for 3 or more consecutive days or recurrence of sufficient clinical features of NS to prompt therapy with daily steroids by the attending physician.

Steroid-resistant NS was defined in patients who failed to respond to a 4 + 4 week course of steroid (prednisolone 60 mg per m²/day for 4 weeks, followed by 40 mg/m² three times a week for 4 weeks in the 6 months before entry). Steroid-dependent NS was defined in patients who had a relapse of NS after a decrease in the dosage of prednisone or within 28 days of stopping prednisone on two or more consecutive occasions in the 12 months before entry. One of these episodes must have been within 3 months before entry). Frequently relapsing NS was defined in patients who responded to prednisone treatment but who had four or more relapses within the 12 months before the screening visit or two or more relapses within the first 6 months after the initial response (if this was in the 6 months before entry).

Patients were allowed to receive a course of cyclophosphamide or chlorambucil in the past but again had to satisfy the entry criteria for steroid dependence and/or FRNS after the course of cytotoxic medication was completed. Female patients of childbearing potential were required to have a negative pregnancy test < 1 week before starting MMF. Such patients had to agree to use two reliable forms of contraception simultaneously before beginning study drug therapy, during therapy, and for 6 weeks after discontinuation of study drug therapy.

Exclusion criteria that were used in the study included the following: absolute neutrophil count < 4 G/l; haematocrit < 0.25; history of significant gastrointestinal disorder; active systemic infection or history of serious infection within 1 month of entry; known infection with HIV or the presence of hepatitis B surface antigen; other major organ system disease or malignancy; administration of live viral vaccine within 6 weeks before study entry; and
current or recent (within 30 days) exposure to any investigational drug.

The study group comprised 85 children with proteinuric glomerulopathies hospitalized between 2007 and 2010, who were non-responders to immunosuppressive therapy. They were admitted to the Department of Paediatric Cardiology and Nephrology, Poznan University of Medical Sciences in Poland. Forty-five boys (aged 12.2 ±6.3 years) and forty girls (aged 11.9 ±7.4 years) underwent a renal biopsy according to the International Study for Kidney Disease in Children recommendations [18, 19]. These indications included steroid-resistant NS (SRNS, n = 11), steroid-dependent NS (SDNS, n = 14), frequently relapsing NS (FRNS, n = 10), primary glomerulonephritis (n = 16), auto-antibody associated glomerulonephritis (AAGN, n = 19) and lupus nephropathy (LN; n = 15). According to WHO definitions, histological evaluation of the study group revealed the following: diffuse mesangial proliferation (DMP, n = 15), focal segmental glomerulosclerosis (FSGS, n = 20), glomerulosclerosis (GS, n = 25), primary mesangial glomerulonephritis (PMG, n = 10) and, finally, lupus nephropathy (n = 15) [20]. Diffuse mesangial proliferation diagnosis was based on the number of cells visible under the electron microscope per mesangial area. INS was classically characterized by the absence of significant deposits in immunofluorescence microscopy, except for FSGS and sclerotic lesions, which were found to bind IgM and C3 antiserum without electron-dense deposits [5]. No IgA nephropathy was diagnosed in the studied population. Detailed information is shown in Table I.

Since MMF is not yet approved for conventional therapy administered in different proteinuric glomerulopathies in Poland [15], we obtained the necessary approval from the Polish Health Department, which authorized MMF use in this group of children. Equally, the study protocol was ratified by the local Ethics Committee of Poznan University of Medical Sciences, and the parents of the study participants gave written, informed consent for the investigation. The study fulfilled the standards recommended by the Helsinki convention.

**Treatment protocol**

The dose of MMF was established as 1 g/m²/24 h in two therapeutic doses given precisely at 7 am and 7 pm. This daily dose was then modified according to the clinical course of proteinuric glomerulopathies. Because there is still no possibility to evaluate plasma concentration of MMF and its metabolites in our department, we carefully studied all the possible clinical side effects, and checked complete blood morphology as well as plasma renal and liver markers to detect any changes necessitating prompt drug withdrawal.

According to Bagga et al., all the patients treated with MMF were additionally given prednisolone 0.5 mg/kg/48 h [21]. Remission was defined as absence of proteinuria (urine albumin nil or trace for three consecutive days by dipstick or boiling test).

**Follow-up and safety assessment**

The more precise patient status was evaluated at the time: zero, 3, 6, 12, 18 and 24 (when applicable) months starting from the beginning of MMF therapy. At each follow-up visit, not only clinical status, but also blood pressure, complete blood morphology including white blood cell count (WBC), serum creatinine, glomerular filtration rate (GFR), electrolytes, lipid profile, bilirubin and liver enzymes (alanine aminotransferase, aspartate aminotransferase), glycaemia and 24-h urinary protein excretion were recorded. Study participants were also monitored for the presence of viral infections (HBV, HCV, EBV and BKV). In addition, in patients diagnosed with LN as well as patients recognized with GN associated with ANCA positive antibodies the serum concentrations of auto-antibodies (anti-ANA, anti-dsDNA, anti-cardiolipin and anti-ANCA) were checked every third month. Each infectious episode was systematically assessed and followed by microbiological tests of blood, sputum or broncho-alveolar lavage and urine analysis (culture). The treatment protocol was arrested in all the patients who developed leucopenia (WBC < 4 G/l). These children were transitionally given only GC and were included back in the treatment protocol when WBC was estimated > 4 G/l in three subsequent blood analyses.

**Statistical analysis**

Data are expressed as mean ± SD unless otherwise stated. A Wilcoxon ranks test was applied to determine whether there was a significant change in relapse rate before and after therapy with MMF. Two variables (proteinuria and GFR) in all the patients were analysed at time zero (at the beginning of the study) as well as at 3, 6, 12, 18 and 24 months of MMF therapy using Spearman’s rank correlation coefficient (Spearman’s rho). Significance was set as p < 0.05; statistical analysis was performed using Statistica 8.0 PL software.

**Results**

Patients were divided into four groups: idiopathic nephrotic syndrome (n = 35), primary glomerulonephritis (n = 15), auto-antibody associated glomerulonephritis (n = 20) and lupus nephropathy (n = 15). Ten patients from the first group (29%) and 5 patients from the second as well as the third group (33.3% and 25% respectively) did not respond to MMF therapy. On the other hand, all the children
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| Clinical indication for MMF treatment | Histology | Age [years] | GFR | Pre-MMF therapy | MMF therapy treatment/remission [months] | % of patients who did not respond to MMF therapy |
|--------------------------------------|-----------|-------------|-----|-----------------|------------------------------------------|-----------------------------------------------|
| Idiopathic nephrotic syndrome FRNS   | FSGS      | 16.3 ±13   | 93 ±11 | PRED, MetPRED, CP, CsA, Tacrolimus, PP | 24 ±2/18 ±6 | ♠ 29 |
| SDNS + CsA DNS DMP                  | 9.9 ±4.4  | 152 ±3     | PRED, CP, CsA | 12 ±3/11 ±4 |                                          |                                              |
| SDNS                                 | GS        | 11.1 ±3.9  | 121 ±4  | PRED, MetPRED, CP, CsA | 12 ±3/6 ±2 ♦ | 33.3 |
| SRNS + CsA toxicity DMP              | 9.2 ±6.7  | 80 ±19     | PRED, MetPRED, CP, CsA, PP | 6 ±3/No remission ♦ |                                          |                                              |
| Primary glomerulonephritis MesGN     | 13.5 ±2.2 | 57 ±21     | PRED, MetPRED, CsA | 12 ±3/6 ±2 ♦ |                                          |                                              |
|                                  | 15.7 ±5.1 | 81 ±15     | PRED, CP, CsA | 18 ±5/12 ±4 |                                          |                                              |
|                                  | 6.5 ±2.0  | 28 ±6      | PRED, MetPRED | 6 ±2/No remission ♦ |                                          |                                              |
| Auto-antibody associated glomerulonephritis Churg-Strauss syndrome | FSGS | 17.1 ±0.9 | 75 ±17 | PRED, MetPRED | 12 ±3/2 ±6 ♦ | 25 |
|                                      | GS        | 14.6 ±2.7 | 97 ±22  | PRED, MetPRED, CsA | 12 ±3/2 ±6 ♦ | 25 |
| Lupus nephropathy                   |           |            |        |                 |                                          |                                              |
| III C/A LN                          | 15.0 ±2.3 | 104 ±32    | PRED, MetPRED, CP, CsA | 12 ±3/9 ±3 | 0♦ | 0♦ |
| IV A LN                             | 13.1 ±4.1 | 92 ±19     | PRED, MetPRED, CP, PP | 12 ±2/10 ±4 | 0♦ | 0♦ |
|                                   | 13.2 ±2.8 | 75 ±15     | PRED, MetPRED, CP, PP | 6 ±3/5 ±2 | 0♦ | 0♦ |

*MMF – mycophenolate mofetil, age/sex – age [years] at the moment of MMF beginning, GFR – glomerular filtration rate [ml/min/1.73 m²], FRNS – frequently relapsing nephrotic syndrome, FSGS – focal segmental glomerulosclerosis, PRED – prednisolone, MetPRED – methylprednisolone, CP – cyclophosphamide, CsA – cyclosporine A, PP – plasmapheresis, FVI – frequent viral infection of upper respiratory tract, SDNS – steroid-dependent nephrotic syndrome, CsA DNS – cyclosporine A dependent nephrotic syndrome, DMP – diffuse mesangial proliferation, leucopenia – a single episode of white blood cell count < 4 G/l, GS – glomerulosclerosis, SRNS – steroid-resistant nephrotic syndrome, ESRD – end-stage renal disease, NS – nephrotic syndrome, MesGN – mesangial glomerulonephritis, patent ANCA – both perinuclear-staining and cytoplasmic-staining antineutrophil cytoplasmic antibodies still present during steroid administration, CsA RNS – cyclosporine A resistant nephrotic syndrome, LN – lupus nephropathy

♠ – remission achieved after 25% MMF dose increase, ♦ – MMF interruption secondary to ESRD or chronic NS, ♣ – chronic WBC < 4 G/l, *p < 0.05
diagnosed with LN reached clinical and biochemical remission ($p < 0.05$ as compared to the former three groups). Non-respondent subjects progressed to ESRD (15 children needed renal replacement therapy) and five patients expressed the next relapse of nephrotic syndrome which needed ciclosporine A therapy to achieve remission. These children were sex and age independent.

Interestingly, 15/25 (60%) children, who were recognized with glomerulosclerosis in renal biopsy evaluation, did not respond to MMF therapy. These children also had a significantly lower GFR as compared to the rest of patients, who achieved remission secondary to MMF administration.

Eighteen patients required a 25% MMF dose increase to obtain remission. They were enrolled from the idiopathic nephrotic syndrome group ($n = 9$), and primary glomerulonephritis ($n = 5$) and auto-antibody associated GN ($n = 4$). Again, LN children did not need MMF dose alteration. The necessity of MMF dose increase was independent of age, sex, initial histology or GFR. It was exclusively related to the clinical course, during which patients who did not respond to the initial MMF dose could be given a higher therapeutic dose.

As regards the previous therapeutic regimens given to our patients prior to MMF commencement, the majority of patients received prednisolone, methylprednisolone, cyclophosphamide and ciclosporine A treatment. Individuals were additionally given tacrolimus and underwent plasmapheresis.

The most common MMF side-effect was frequent viral infection of the upper respiratory tract. That inconvenience affected 53% of children and was independent of MMF dose. The second common side-effect was irregular (episodic) leucopenia. It was diagnosed in 24% of subjects, but first of all referred to LN patients. In a single patient diagnosed with Churg-Strauss syndrome, a constant and chronic leucopenia (over 3 months) was the main side-effect and, consequently, the reason for discontinuation of MMF therapy. That boy, regardless of the beneficial MMF effect on kidney function (GFR improved from 75 ml/min/1.73 m² to 94 ml/min/1.73 m²), was the last subject, besides MMF non-responders, who stopped MMF treatment.

Initially, before commencement of MMF treatment, proteinuria was observed in 65/85 patients (76.5%) (proteinuria exceeded 50 mg/kg/24 h in 44/85 patients (67.7%). During the MMF treatment protocol this sign of kidney failure decreased gradually and finally was absent in the study participants with the exception of 19 children (including 15 patients in whom MMF therapy was arrested). Spearman’s correlation of proteinuria and MMF treatment time was significant ($r = -0.575; p < 0.01$; Figure 1).

On the other hand, twenty children were estimated to have GFR less than 60 ml/min/1.73 m². During the MMF treatment strategy, fifteen of them progressed to ESRD (non-effective rescue therapy; all with glomerulosclerosis), whereas 5 of them showed improvement of kidney function as evidenced by normal GFR and achieved remission with no proteinuria. Again, Spearman’s correlation of GFR and MMF treatment period was significant ($r = 0.293; p < 0.05$; Figure 2).

Discussion

Our challenge to summarize the results of MMF therapy in children with different primary and secondary glomerulonephritides was due to the general opinion that MMF could serve as an alternative drug in the non-responding proteinuric nephropathy treatment regimen [11, 13, 15, 21].

Mycophenolate mofetil is one of the immunosuppressant drugs which have been used to pre-
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vent rejection in organ transplantation. Generally it is used as part of a three-compound regimen of immunosuppressants, including a calcineurin inhibitor (cyclosporine or tacrolimus) and prednisolone. As an immunosuppressant that has drastically decreased the incidence of acute rejection in solid transplant recipients, mycophenolate is increasingly utilized as a steroid-sparing treatment in immune-mediated disorders including immunoglobulin A nephropathy, small vessel vasculitis as well as psoriasis [23, 24].

Its increasing application in LN treatment has demonstrated more frequent complete response and less frequent complications [25] as compared to cyclophosphamide bolus therapy, a regimen with risk of bone marrow suppression, infertility, and malignancy [26]. Further work addressing maintenance therapy showed mycophenolate to be superior to cyclophosphamide, again in terms of response and side-effects [27]. Walsh et al. even proposed that mycophenolate could be considered as a first-line induction therapy for treatment of LN in patients without renal dysfunction [28], suggesting that mycophenolate will be encountered more frequently in medical practice.

In our study, fifteen patients with LN were treated with MMF to induce remission (during the first 6 months of treatment). All of them expressed remission of proteinuria. It cannot be excluded that in some of the patients there was spontaneous remission, although this is not a very common occurrence. All of the children with LN also expressed a diminished number of leucocytes in peripheral blood morphology with negative autoantibodies during immunosuppressive treatment. This inconvenience was, however, episodic.

We have demonstrated that the MMF treatment regimen could also be beneficial in certain cases of steroid and cyclosporine A dependent nephrotic syndrome, primary glomerulonephrites, and autoantibody associated glomerulopathies. We postulate that such a treatment strategy should always be taken into consideration in all patients in whom a standard and recommended treatment protocol fails. Mycophenolate mofetil administration usually generates less frequent and more gentle side-effects. It should be re-considered even in patients with initially low GFR, although the final decision as regards its administration in that group of patients should be evaluated after 3 months to 6 months of treatment. Otherwise, expected benefits could be less than progressive side-effects.

Common adverse drug reactions associated with mycophenolate therapy include diarrhea, nausea, vomiting, infections, leukopenia, and/or anaemia. Mycophenolate mofetil is also believed to be commonly associated with fatigue, headache, and/or cough [29]. Intravenous administration of MMF is sometimes associated with thrombophlebitis and thrombosis. Infrequent adverse effects (0.1-1% of patients) include oesophagitis, gastritis, gastrointestinal tract haemorrhage, and/or invasive cytomegalovirus (CMV) infection [30]. Our studied children have primarily developed frequent viral infections of the upper respiratory tract, which, however were independent from leucopenia. Single leucopenic episodes were observed in 20 patients (including all LN subjects). A single child, diagnosed with Churg-Strauss syndrome, had chronic leucopenia which was augmented independently from MMF dose. This only example of severe leuco- and granulopenia could be related to the basic problem of this patient, but naturally such an observation would need further expanded studies. We did not observe any other side-effects as listed above in the rest of patients, even when they received the 25% higher dose of MMF.

In conclusion, we postulate that alternative rescue MMF therapy should always be taken into consideration in proteinuric patients not responding to steroids, cyclosporine A and cyclophosphamide in whom the initial glomerular filtration rate is higher than 60 ml/min/1.73 m². We recommend that MMF be administered as part of the standard treatment regimen in patients diagnosed with lupus nephropathy. In this group of patients, the potent benefits of this therapy are higher than expected side-effects.

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