Sequential maintenance therapy with cyclosporin A and mycophenolate mofetil for sustained remission of childhood steroid-resistant nephrotic syndrome

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Abstract

Background. There is currently no established standard for maintenance therapy of steroid-resistant nephrotic syndrome (SRNS). We report the long-term clinical course, medication, pharmacokinetic data, and renal function of 23 children with primary, non-familial SRNS with focal segmental glomerulosclerosis (FSGS).

Methods. To achieve initial remission, patients were treated with high-dose intravenous (i.v.) methylprednisolone and oral cyclosporin A (CsA). Maintenance therapy included transient alternate day oral prednisolone, CsA and angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers. In 18 patients, mycophenolate mofetil (MMF) (adjusted to achieve blood mycophenolic acid trough concentrations > 2 μg/mL) was sequentially added, and 16 patients were converted to MMF monotherapy.

Results. During a mean follow-up time of 7.0 years (1.7–16.5 years; cumulative observation time 161 patient-years), sustained remission could be achieved in all patients. Five of 23 patients (21%) experienced 10 relapses; all responded to relapse therapy. Maintenance therapy could be permanently discontinued in seven patients (30%). After conversion from CsA to MMF, renal function improved significantly; the eGFR at last follow-up was 137 (range 106–198) mL/min × 1.73 m². The mean number of antihypertensive drugs decreased from 1.86 per patient after initial remission to 0.57 on MMF monotherapy (P < 0.002).

Conclusions. The data of this uncontrolled retrospective study indicate that in children with SRNS/FSGS achieving initial remission, a sequential steroid-free therapy consisting of a combination of CsA and MMF followed by MMF alone (with the addition of ACE inhibitors and angiotensin receptor blockers), can provide sustained long-term remission, preservation of renal function and better control of blood pressure.

Keywords: children; focal segmental glomerulosclerosis; mycophenolate mofetil; nephrotic syndrome; steroid resistance

Introduction

Childhood idiopathic steroid-resistant nephrotic syndrome (SRNS) poses a therapeutic challenge. Patients are at risk for severe complications such as infections [1], thrombosis [2] persistent oedema, progression to end-stage renal disease and recurrence of FSGS after transplantation [3–5]. There is consensus among paediatric nephrologists for initial aggressive treatment to achieve remission [6]. However, the response of proteinuria and the nephrotic syndrome (NS) to pharmacological therapy seems highly variable [7], and there is currently no evidence-based guideline for treatment of SRNS in childhood, both for achieving initial remission and for maintenance therapy, resulting in a high variability in the treatment of FSGS [8].

Treatment with cyclosporin A (CsA) is effective in inducing remission [9, 10], but long-term treatment is accompanied by time- and dose-dependent nephrotoxicity [11]. There is lack of information regarding the efficacy and safety of available pharmacological options during long-term follow-up to maintain remission. It is largely unknown to what degree medications can be tapered or discontinued with a low risk for relapses during long-term treatment of SRNS.

Mycophenolate mofetil (MMF), the pro-drug of mycophenolic acid (MPA), has proven efficacy and tolerability in renal allograft recipients and may be a promising therapeutic option without nephrotoxicity. Previous published experience with MMF in childhood SRNS/FSGS is limited to observations of only a few patients [12–15]. Moreover, MMF has not been evaluated in a systematic fashion either for initial or maintenance therapy of SRNS.

We have previously shown that children with idiopathic primary SRNS respond favourably to induction treatment with intravenous methylprednisolone (MP) given in combination with oral prednisone (PRED) and CsA, with a total initial remission rate of 77% (40 of 52 SRNS patients with idiopathic FSGS) [16]. We have further modified this regimen at our centre by adding MMF in a sequential therapeutic protocol to maintain remission of SRNS and to prevent nephrotoxicity.
We here report the long-term clinical course, medication, pharmacokinetic data and renal function of 23 patients with primary SRNS treated with this protocol after initial response to therapy.

Materials and methods

Between 1993 and 2008, 32 Caucasian children and adolescents were treated at the Charité University Hospital Berlin who were diagnosed as non-syndromal, non-familial, primary SRNS with FSGS proven by renal biopsy and had no evidence for mutations in the WT1, NPHS1, NPHS2 or NPHS3 gene (Figure 1). Thirty of these patients were part of the Berlin/Hannover cohort described previously and all had undergone the same initial treatment protocol (Figure 2) to achieve remission [16]. In this study, we have included 23 of these patients who experienced initial remission of the SRNS and were followed up at our centre. Diagnostic definitions of NS and ‘steroid resistance’ were used according to the International Study of Kidney Disease in Children [17]. Thus, nephrotic syndrome was defined as oedema, hypoalbuminaemia (< 28 g/L) associated with proteinuria >60 mg/kg/24 h; failure of therapy to achieve remission after at least 4 weeks of daily 60 mg/m² PRED treatment was defined as (primary) steroid resistance.

Remission was considered ‘complete’ if creatinine remained normal and protein excretion decreased to normal values (proteinuria/creatinine < 0.2 g/g). Remission was considered ‘partial’ if serum creatinine and albumin remained normal and protein excretion decreased (<1 g/g creatinine).

In the 23 children with SRNS described in the present study, the mean age at onset of nephrotic syndrome was 8.2 years (0.5–11).

Remission was considered ‘partial’ if serum creatinine and albumin remained normal and protein excretion decreased (<1 g/g creatinine).

The mean time to initial remission was 3.7 months. The mean follow-up time was 7.0 years (1.7–16.5 years) and the cumulative observation time was 161 patient-years.

Treatment

At onset of nephrotic syndrome, all patients were treated initially with PRED at a dose of 60 mg/m² daily in three divided doses for 4 weeks (maximum 80 mg/day). After diagnosis of steroid resistance and biopsy (confirming FSGS), induction therapy consisted of: high-dose methylprednisolone (i.v. MP), 500–750 mg/day/m² for 3 days, followed by a combined therapy regime of oral PRED, tapered >6 months from 30 mg/m²/day (4 weeks) to 30 mg/m²/48 h (8 weeks), 20 mg/m²/48 h (4 weeks) and 10 mg/m²/48 h (8 weeks); if no decrease in proteinuria occurred, CsA was started 3–4 days after the MP pulses at a dose of 5 mg/kg/day and later modified to achieve a blood trough level between 80 and 120 ng/mL; if remission was achieved, the CsA dose was lowered to trough levels of >60 ng/mL during follow-up (Figure 2).

In addition, anti-hypertensive and anti-proteinuric therapy with angiotensin-converting enzyme (ACE) inhibitors and in some cases, AT-II antagonists were given to most patients (Table 1).

Mycophenolate mofetil (MMF) was added to this therapeutic regime in a systematic fashion starting in July 2000 to prevent CsA-induced nephrotoxicity. At this time, some patients were in complete remission after discontinuation of CsA monotherapy (No. 2, 6, 15 and 17) and experienced no further relapses without immunosuppressive therapy. MMF was part of the medication in the remaining 19 patients and 16 of these could be converted to MMF monotherapy, whereas 2 patients at the time of this writing were on low CsA/MMF combination therapy (No. 1 and 4). One patient (No. 14) was started on low CsA/MMF therapy at the time of this writing; due to the short duration of treatment, this patient was not included in the analysis of MMF effects, which was thus confined to 18 of the 23 patients.

MMF was started with a dose of 600 mg/m² bovine serum albumin (BSA) twice daily followed by a reduction of CsA by 25–30% and further stepwise reduction to 50% of the initial dose (under control of MMF and CsA trough levels). The MMF dose was adjusted to achieve blood MPA trough levels). The MMF dose was adjusted to achieve blood MPA concentration between 2 and 4.5 µg/mL using CEDIA® MPA Immunoassay (provided by Thermo Fisher Microgenics Corporation).

In all patients with complete remission on CsA, it was attempted to wean CsA and to maintain remission with MMF monotherapy. After a mean period of 12 months of combined treatment with MMF/low-dose CsA, MMF monotherapy was started. Children were treated with MMF over a mean period of 3.6 years (range 0.8–10 years), amounting to a total follow-up time of 65 patient-years of MMF-therapy.

Relapse therapy

Relapses were treated with i.v. MP (500–750 mg/day/m² for 3 days), followed by combined therapy consisting of oral PRED, tapered >3–6 months and CsA. Patient No. 7 had multiple relapses and required intensive therapy including plasma exchange.

Side effects

Side effects of MMF therapy were recorded routinely and included white and red blood cell count, alanine aminotransferase, aspartate aminotransferase and other reported signs and symptoms.
Renal function

Renal function [estimated glomerular filtration rate (eGFR)] was calculated according to the formula published by Schwartz et al. [18].

Kinetic profiles of MPA

In 15 patients, we performed a three-point MPA kinetic profile during monotherapy of MMF (measured at 0, 0.5 and 2 h). The AUC was calculated as follows: [19].

\[
AUC = MPA = 7.75 + (6.49 \times C0) + (0.76 \times C0.5) + (2.43 \times C2)
\]

Statistical analyses

Results were expressed as median, mean, ranges and percentages. Statistical analyses were done with Microsoft Excel and SPSS ver. 18 software. Correlations of variables were estimated by Pearson’s correlation coefficient. Differences in medication and glomerular filtration rate (GFR) before and after MMF treatment were estimated by the Wilcoxon test. A P-value < 0.05 was considered significant.

Results

Clinical course and medication

At start of the study, all patients were in remission of the SRNS [22 complete, 1 incomplete (0.3–0.6 g) albumin/g creatinine with normal serum albumin, Patient No. 1]. All patients except Patient 22 had been brought into remission with the standard initial treatment protocol as described; this patient was initially unresponsive to CsA/PRED, developed acute renal failure (nephrotic crisis) and required extensive therapy including artificial ventilation, immunoabsorption, rituximab and the addition of MMF before experiencing a complete remission (Figure 3). After termination of immunoabsorption, the patient responded with an immediate increase in proteinuria. Rituximab was given once followed by no absorption, the patient responded with an immediate in-

Relapses

Two patients (No. 9 and 21) had one relapse during MMF/low-dose CsA (Figure 3). One patient (No. 4) had two relapses: first during CsA therapy and then without immunosuppressive therapy. One patient (No. 5) had two relapses without immunosuppressive therapy. All of these patients (No. 4, 5, 9 and 21) responded to therapy within 4 weeks. One patient (No. 7) had four relapses: three relapses during CsA therapy and one during therapy with MMF/low-dose CsA. Therapy in this case consisted of (relapse #1) i.v. MP (3 ×), plasmaphaeresis (6 ×), high-dose CsA (remission after 3 months); (relapse #2) i.v. MP (3 ×), high-dose CsA/PRED/MMF (remission after 3 months). The patient has been maintained in long-term remission on MMF monotherapy.

Pharmacokinetics: MPA-AUC

After a median range from 3.9 months on monotherapy with MMF, pharmacokinetic profiles were performed during stable remission of SRNS (Table 1). The mean dosage of MMF was 1026 (range 510–1435) mg/day given in two divided doses. The mean MPA-AUC was 70 (range 39–113) μg/h/mL (Figure 5). There was a significant linear correlation of MMF dosage with AUC (r = 0.609; P = 0.016).

Anti-hypertensive drugs

The mean number of anti-hypertensive drugs was 1.86 (0–5) per patient at the time of initial remission and 1.43 per patient at the time before conversion to MMF (n = 18); at last visit on MMF therapy, it was 0.57 per patient; this difference was statistically significant (P < 0.002). Only one patient (No. 20) had more anti-hypertensive drugs after conversion to MMF than before (4 versus 3), probably due to a progressive metabolic syndrome (Table 1).

Renal function

The eGFR during follow-up is shown in Figure 6. Nephrotoxicity was suspected in a total of eight patients who had increasing serum creatinine levels and was confirmed in all cases (patient number 4, 5, 8, 12, 13, 15, 18 and 19) by renal biopsy. Findings consisted of focal segmental lesions with varying degree of interstitial fibrosis, isometric tubular vacuolization and hyaline arteriolarpathy.

After conversion from CsA to MMF (Table 1), GFR increased significantly (Figure 7) with a rise in eGFR from 107 to 140 mL/min × 1.73 m² after 12 months (n = 16; P = 0.001).

The eGFR at last follow-up was 137 (range 106–198) mL/min × 1.73 m². No patient developed a decrease in eGFR < 90 mL/min × 1.73 m².

Side effects

Most patients had minor side effects from steroids, but three patients suffered from striae (Patients 1, 3 and 22), and Patient 20 had persisting metabolic syndrome during and after steroid treatment. No patient suffered from cataracts, diabetes, severe systemic infectious complications or thrombotic events.

Side effects of MMF therapy were confined to the time of combination therapy with low-dose CsA. Anaemia was found in two patients (No. 10 and 21) and required erythropoietin injections; abdominal pain and nausea were sometimes observed at the beginning of MMF administration but resolved spontaneously. Neither leukopenia nor diarrhoea or the development of lymphoma was noted. No severe side effects were observed during MMF monotherapy.
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<th>Time to initial remission (months)</th>
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<th>AUC (µg·h/mL)</th>
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*aResults from 23 patients with SRNS and remission after initial protocol-therapy. F, female; M, male; CP, cyclophosphamide; LP, lipid aphereses; RIT, rituximab; p, partial; c, complete response; ARB, angiotensin receptor blocker; CAA, calcium antagonist; BBL, beta-blocker; DIU, diuretic; ARF, acute renal failure.
Immunosuppressive treatment in combination with anti-proteinuric and anti-hypertensive drugs has improved patient and renal survival of SRNS during the last decades. However, due to the lack of large-scale controlled clinical trials, treatment has often been performed in an empirical and individualized fashion. In addition, the evaluation of
response to therapy has been confounded by several major factors such as patient heterogeneity (idiopathic versus genetic forms), clinical heterogeneity (primary versus secondary SRNS), histological heterogeneity [Minimal Change Nephrotic Syndrome (MCNS) versus FSGS or other glomerular diseases] and differences in the selection and dosing of drugs [20–22].

Treatment with CsA has evolved as a first line option to achieve partial or complete remission in patients with SRNS [6]. We could previously demonstrate a high rate of complete remission in patients with SRNS to treatment with MP and CsA [16]. However, nephrotoxicity is a severe side effect of long-term CsA treatment necessitating discontinuation of CsA with a high risk for relapse or other therapeutic options. MMF, a non-nephrotoxic immunosuppressive drug with inhibitory effects on T and B lymphocytes, cell-surface markers and cytokine gene expression [23, 24] has confirmed a beneficial effect in a variety of glomerular diseases. In a pilot study, we found that conversion from CsA to MMF therapy resulted in improved renal function without major side effects and long-term remission in six of seven patients [25]. These data and other early case studies indicated that MMF could indeed be a valuable option for clinical use in patients with SRNS/FSGS [26, 27]. During the last 10 years, we have therefore included MMF in a sequential therapeutic protocol in all patients with SRNS achieving initial remission.

This protocol maintained remission in all patients. During a follow-up time of 7.0 years, 5 of 23 patients (21%) experienced a total of 10 relapses and all responded to therapy.
There were only two relapses during 65 patient-years of follow-up in patients treated with MMF therapy \( (n = 18) \), which occurred during combination therapy with CsA; no relapse was observed during MMF monotherapy. At the end of our study, all patients \( (n = 23) \) are in remission, either with a combination of CsA and MMF \( (n = 2; 9\%) \) or MMF alone \( (n = 13; 57\%) \); one patient is currently on CsA monotherapy undergoing conversion to combination therapy. Therapy could be permanently discontinued in seven patients \( (30\%) \). Moreover, normal GFR could be maintained in all patients (Figure 6) and the number of drugs required for control of hypertension decreased significantly. Nine patients needed no anti-hypertensive medication during MMF therapy. MMF was tolerated well and diarrhoea, a common side effect observed in patients with MMF therapy after renal transplantation especially in the first 3 months \[28\], was not observed.

We used MMF to maintain remission after achieving initial remission with MP/CsA therapy. Patient No. 22 was the only exception from this protocol. This case demonstrates the well-known difficulties in achieving initial remission in some cases of SRNS (Figure 3) necessitating rescue therapy with a variety of empirical therapeutic modalities. This patient may have experienced a benefit of rituximab therapy, although proteinuria increased in spite of a depletion of CD 19+ cells; persistent remission could be achieved by additional MMF therapy.

The efficacy of MMF monotherapy in achieving initial remission is currently unknown since controlled studies have not been performed. However, in a case series of nine patients with steroid-resistant FSGS receiving MMF after not achieving initial remission with other therapies, only a reduction in proteinuria without a single case of complete remission was reported \[12\]. Similarly, only a reduction of proteinuria without complete remission was observed after a 6-month course of MMF in a series of 18 patients with SRNS/FSGS \[13\]. Likewise, only one of five patients with SRNS achieved complete remission in a study employing MMF as monotherapy in children with various forms of the NS \[14\]. These studies do not suggest high remission rates with first-line use of MMF to achieve initial remission in SRNS/FSGS. In contrast, a study from China described 24 children with primary SRNS (associated with a variety of glomerular diseases) treated with MMF after not responding to standard PRED treatment for 8 weeks; the majority \( (n = 15) \) were in complete remission after 4 months. However, this study included only three FSGS patients \[15\].

These discrepant results likely reflect differences in patient selection. Unfortunately, controlled studies are lacking both for MCNS and FSGS patients \[8\]. Variations in response to MMF could be due to several other factors, including different times of conversion (as discussed), in the aggressiveness of initial therapy, cumulative effects of combination therapies and in drug dosing. In our study, MMF therapy was guided by MPA trough levels (MPA-C0). We aimed at an MPA-C0 of \( >2 \mu g/mL \), which could be achieved with a dose of 1000–1200 mg/m2 BSA. In patients with MMF monotherapy, we performed therapeutic drug monitoring by three-point AUC kinetic profiles \( >2h \).

At a highly variable mean dose ranging from 510 to 1435 mg/m2/day, the mean MPA-AUC was 70 (range 39–113) \( \mu g \cdot h/mL \), and there was a significant linear correlation of MMF dosage with AUC. These preliminary data permit only limited conclusions; however, since we observed not a single relapse with an AUC of 60–80 \( \mu g \cdot h/mL \), this AUC range seems suitable for maintaining remission on MMF monotherapy. These results are in line with several other studies investigating pharmacokinetic monitoring of MMF therapy in MCNS patients. Thus, patients with the lowest MPA trough levels had the most relapses suggesting cut-off levels of MPA-C0 in the range of 2.0–2.5 \( \mu g/mL \). This confirms other observations suggesting a cut-off level of 2.0 \( \mu g/mL \).
Importantly, MMF clearance with oral dosing in children with the nephrotic syndrome and normal renal function is significantly influenced by body weight and serum albumin levels [31]. Therefore, variations in body weight and serum albumin levels during relapse could have a significant impact on drug exposure and efficacy of MMF with a fixed dose regimen. On the other hand, these factors should result in less variability during stable remission, conceptually favouring initiation of MMF therapy at this time.

The uncontrolled nature of our study is a major limitation, which is shared by virtually all other studies of therapeutic experience in pediatric SRNS. Thus, it cannot be ruled out that long-term observations, in part, could reflect the natural course of the disease in selected patients; however, available long-term studies have shown a time-dependent decrease in renal survival in patients with SRNS with FSGS [20]. Although spontaneous remission in SRNS/FSGS seem to be rare [32], improvement of proteinuria by other factors such as concomitant treatment with ACE inhibitors and angiotensin receptor blockers, dual effects of RAS blockade on blood pressure and podocyte function should be considered [33]. It cannot be ruled out that sustained remission could have been achieved with CsA treatment alone, as illustrated by several of our patients; however, the switch to MMF resulted in an improved GFR, an important benefit for the patient. Finally, the time to initial remission varied considerably between patients, and it could be argued that patients with a rapid response might have been treated differently to achieve sustained remission; hence, earlier tapering or discontinuation of therapy might be possible and should be investigated in future studies.

Only patients with primary SRNS and FSGS on renal biopsy were included in the study. FSGS histological subtypes of most patients included in this study were analysed in our previous report but had no measurable influence on outcome [16]. Although we ruled out syndromic forms of NS on clinical grounds and known hereditary forms of the NS by genetic analysis and family history, the potential of disease heterogeneity remains a further limitation of the study.

Conflict of Interest Statement. None declared.

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Received for publication: 10.12.10; Accepted in revised form: 25.8.11