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Effect of adding Mycophenolate mofetil in paediatric renal transplant recipients with chronical cyclosporine nephrotoxicity

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Abstract Cyclosporine (CyA) has made a great impact on 1-year allograft survival, however, after years, renal function deteriorates, possibly due to chronic toxicity. Recently, Mycophenolate mofetil (MMF) was introduced as a non-nephrotoxic immunosuppressant that might be effective in chronical transplant arteriolopathy. We therefore started MMF at a dose of 600 mg/m^2 b.i.d. in 18 pediatric renal transplant recipients (10.8 ± 3.9 (SD) years of age at transplantation, 11/18 with a history of rejections) with biopsy-proven chronic arteriolopathy and other signs of CyA toxicity at a mean follow up time of 6.2 ± 2.7 (range 2.3–11.8) years after transplantation. One month prior to conversion, mean serum creatinine was 171 ± 96 μmol/l, lower than at the time of conversion (188 ± 100 μmol/l, $P = 0.003$, paired t-test). At last follow-up (median 13.7 months, range 5.0 to 25.0 months) after conversion, mean serum creatinine decreased significantly to 127 ± 69 μmol/l ($P = 0{,}0003$, paired t-test). The CyA dosage was reduced from a mean of 150 ± 39 mg/m2 per day to 59 ± 13 mg/m^2 per day in 7 patients, and CyA was discontinued in 11 patients after a median period of nine months (range 1–18 months). After a median period of 21 days, a pharmacokinetic profile was performed in all patients. The mean MMF dose was 1117 ± 319 mg/m^2 per day (range 675–1774 mg/m^2 per day). The mean Mycophenolic acid (MPA) trough concentration was 4.0 ± 2.0 μg/ml, range 1.4–7.9 μg/ml. Mean 12 h MPA AUC was 70.6 ± 28.1 (range 31.9–127) μg × h/ml. Except for one patient with diarrhea associated with a high AUC, and for one patient with a steroid-sensitive rejection episode after 566 days, no other patient experienced side effects or a rejection episode. Prednisolone was left unaltered at 2–4 mg/m^2 per day. We conclude that MMF allows safe reduction of CyA with markedly better graft function, suggesting that chronical CyA-toxicity partially accounts for deteriorating allograft function.

Key words Cyclosporine toxicity · Renal transplantation · Mycophenolate mofetil · Drug monitoring · Pharmaco-kinetic

Introduction

Although the introduction of Cyclosporine (CyA) has vastly improved 1-year allograft survival in children when compared to immunosuppression with Azathioprine and steroids, long term allograft survival may not be improved [27]. The incidence of acute rejection episodes, possibly in association with unsatisfactorily low CyA concentrations in the first year, have been associated with poor long term outcome [11, 32]. There also is a

problem with the narrow therapeutic window of CyA, and, at least partially, chronical deterioration of allograft function is attributable to CyA-toxicity associated with high area under the curve (AUC) [15]. Because of the toxicity and the possibility of long term side effects and/or overimmunosuppression, several authors have reported attempts to discontinue CyA and continue with steroids and Azathioprine (Aza) [14, 31]. These concepts have been associated with a number of immunological problems and are no longer pursued. Recently, Mycophenolate mofetil (MMF) has been introduced as a new powerful immunosuppressant [7] that also might have a beneficial effect on chronical transplant arteriolopathy [33]. Mycophenolate mofetil (MMF), the 2–4-morpholino ethyl ester of mycophenolic acid, is an inhibitor of the inosine monophosphate dehydrogenase, an enzyme in the de novo synthesis of purines [18]. MMF in combination with CyA has been demonstrated to be more powerful than Azathioprine in combination with CyA [30]. Therefore a rationale evolved for replacing Aza with MMF in long term renal transplant recipients with evidence of CyA-toxicity, thus allowing a safer reduction of CyA without an increased risk of rejection. Here, we present our retrospective analysis of 18 patients with chronical arteriolopathy in their long-term renal allograft who all experienced progressive loss of renal function and who all were started on MMF.

Patients and methods

Eighteen pediatric and adolescent renal transplant recipients (9 females, 9 males; 17 cadaveric and one living related donor grafts) with a mean age of 17.2 ± 4.2 SD years at the time of entering the study were diagnosed to have chronical CyA-toxicity confirmed by biopsy after a mean of 6.2 ± 2.7 (range 2.3–11.8) years post renal transplantation. Underlying causes of end stage renal failure were nephronophthisis ($n = 3$), hypoplasia/dysplasia ($n = 7$), obstructive uropathy ($n = 2$), glomerulonephritis ($n = 3$), infantile cystinosis ($n = 1$), xanthogranulomatous pyelonephritis ($n = 1$) and hemolytic uremic syndrome ($n = 1$). At the time of transplantation, the mean age was 10.8 ± 3.9 SD years (range 4.8–16.0). The donor age comprised 21.8 ± 19.1 years (range 5.0–63.0 years). The grafts were performed between October 1984 and February 1995. Mean cold ischemia time was 32 ± 16 h (range 2.5 (life donation) to 60 h), and the median secondary warm ischemia time was 36 ± 8 min (range 28–55 min). Only one patient had a panel reactive antibody screening of 5 %, all the others were negative. All patients had at least one AB compatibility (median 3, range 1–3) and one DR compatibility (median 1, range 1–2). Three grafts showed delayed initial function whereas 15 grafts functioned immediately. Thirteen patients received an immunosuppressive protocol including cyclosporin, Azathioprine and steroids (triple therapy), and five patients had an ATG-induction therapy followed by a triple therapy. Sixteen patients abided the triple therapy, and Azathioprine was weaned off in two patients. Only 7 patients did not undergo a rejection episode, 7/18 patient had one rejection episode, 4/18 showed two or more rejection episodes. Only two rejection episodes occurred in two patients beyond the first year after transplantation, one of those was steroid resistant and was successfully treated with Tacrolimus. Tacrolimus was discontinued in that patient because of diabetes mellitus occurring 6 months after conversion to Tacrolimus, and the patient was successfully reconverted to CyA, Aza and steroids. Four patients became CMV IgG-positive after transplantation, and three rejection episodes were associated with CMV infection. Eleven patients were hepatitis C-positive, 2/11 patients had evidence of chronical aggressive Hepatitis C confirmed by liver biopsy, and 4/11 others had a chronical persistant Hepatitis-C infection.

The patients had repetitive simultaneous Cr-51 EDTA clearances [4] for determination of glomerular filtration rate (GFR) and I-123 hippurate clearances for determination of effective renal plasma flow after renal transplantation with a modification previously described [10].

After conversion, GFR was estimated using a height/creatinine ration (Schwartz formula [28]).

At a mean follow-up time of 6.2 ± 2.7 years (range 2.3–11.8 years) after transplantation, chronical CyA-toxicity was confirmed by a biopsy in each patient. In each case, witnessed informed consent was obtained for the study from the patients, and in case of minors, of their parents. This study has thus been carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. After confirming the diagnosis of CyA-associated chronical toxicity, the patients discontinued Aza in cases of prior application. 24 h later, MMF administration was started at a target dose of 600 mg/m^2 b.i.d. . The Prednisolone dose was left unchanged at 2–4 mg/m^2 per day.

Each patient underwent a full pharmacokinetic MPA profile done at a mean of 21 ± 11 days after conversion (range 10–39). Some patients had only one PK profile, but some had up to four PK profiles. Repetitive EDTA whole blood samples were harvested before and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h after oral intake of MMF with a standard meal consisting of rolls, butter, jam, and fruit tea. They had free access to non-dairy product drinks during the day and had a normal lunch at noon. Mycophenolic acid (MPA) concentrations were measured using a commercially available EMIT assay [23] and in very few early cases with a new HPLC method [2]. There was good agreement between the two methods (unpublished results). The area under the curve was calculated using the trapezoid rule. The mean follow-up time after conversion to MMF was 13.7 months (range 5.0–25.0 months). Statistical comparison was performed by using the Student's paired t-test for normally distributed parameters, and the Mann-Whitney test for not normally distributed parameters.

Results

Patients showed a progressive deterioration of Cr-51 EDTA and I-123 hippurate clearance after renal transplantation (Fig. 1). Despite of the progressive, slow deterioration of allograft function, the patients included in this study showed a rather marked increase of serum creatinine which led to the admission and the renal biopsy. One month prior to conversion, mean serum creatinine was 171 ± 96 μmol/l, significantly lower in comparison to the serum creatinine at time of conversion after renal biopsy (mean serum creatinine was 188 ± 100 μmol/l, $P = 0.003$, paired t-test). Following conversion, at the time of the last follow up, mean serum creatinine was significantly lower at 127 ± 69 μmol/l ($P = 0.0003$, paired t-test). Figure 2 summarizes the

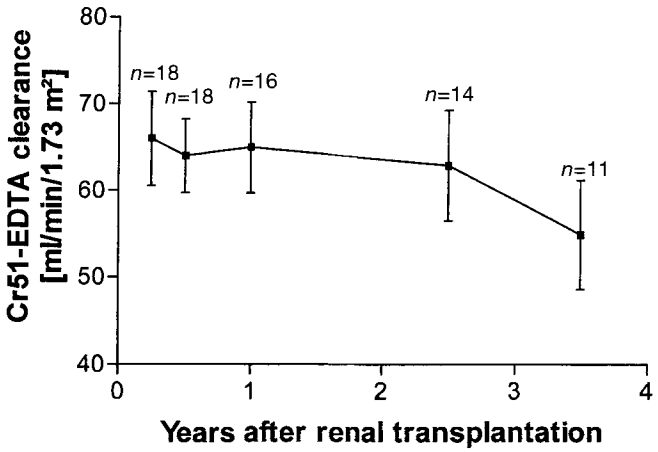

Fig. 1 Mean Cr51-EDTA clearance (as a marker of glomerular filtration rate, GFR) in the pediatric renal transplant recipients ± SEM and deterioration of GFR with time after transplantation

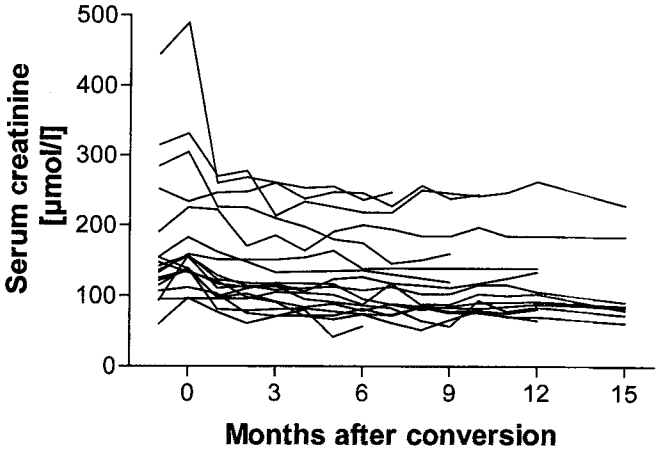

Fig. 3 Serum creatinine in the 18 pediatric renal transplant recipients one months prior to conversion, at conversion and monthly after conversion. There was a significant decrease of serum creainine ($P = 0.003$, paired t-test)

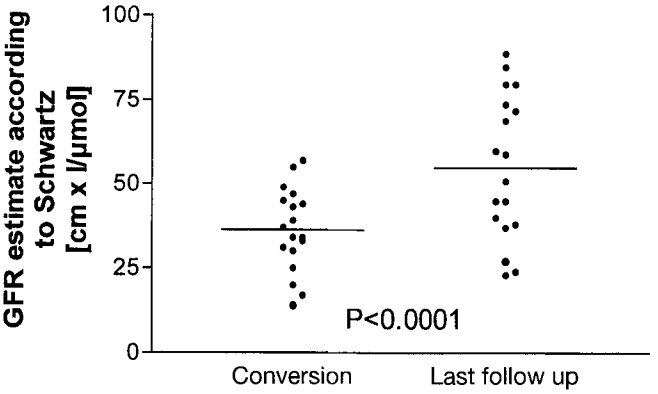

Fig. 2 Improvement of GFR estimated according to the Schwartz formula at the time of conversion to MMF and at last follow up. There was a highly significant increase of GFR ($P < 0.0001$, paired t-test)

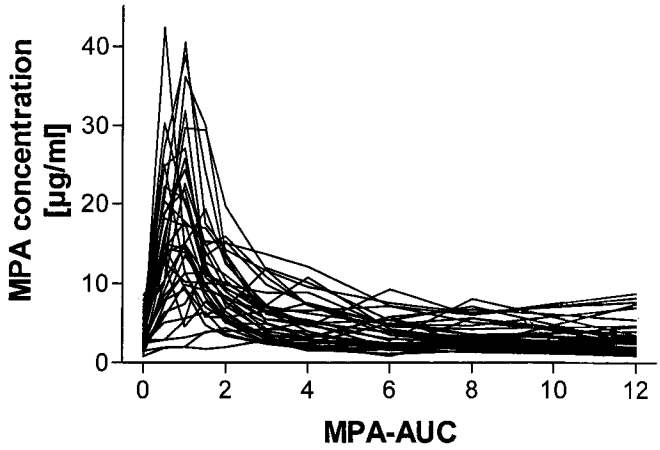

Fig. 4 Pharmacokinetic profiles of mycophenolic acid *(MPA)*, the main metabolite of the prodrug Mycophenolate mofetil. 36 profiles were measured in the 18 patients, showing a characteristic sharp early C_{max} with a median t_{max} of 60 min, and a lower, variable second peak after 4–12 h, representing MPA that originates from enterohepatic recirculation

GFR estimate according to Schwartz in these eighteen patients which increased from 36.3 ± 12.4 ml/min/1.73m² to 55.4 ± 21.7 ml/min/1.73 m², $P < 0.0001$, paired t-test. Figure 3 demonstrates the course of serum creatinine of each individual case. Only one patient experienced a steroid sensitive rejection episode after the conversion to MMF after 566 days in combination with a very low MPA concentration. Serum creatinine was lower in each patient compared to the time of conversion.

After conversion, the CyA dose was gradually decreased, usually in 25 mg steps every two to four weeks. During follow up, the CyA dosage was reduced from a median of 150 ± 39 mg/m² per day to a mean of 59 ± 13 mg/m² per day in 7 patients. CyA trough concentrations in these 7 patients decreased from 130 ± 11 ng/ml to 63 ± 40 ng/ml ($P = 0.0016$, paired t-test). CyA was discontinued in 11 patients after a median of nine months (range 1–18 months). This dose reduction was statistically significant ($P < 0.0001$, paired t-test).

When of the pharmacokinetic profile was performed in all patients, the mean MMF dose was 1117 ± 319 mg/m² per day (range 675–1774 mg/m² per day). The mean MPA trough concentration was 4.0 ± 2.0 µg/ml, range 1.4–7.9 µg/ml. Mean 12 h AUC was 70.6 ± 28.1 µg × h / ml (range 31.9–127 µg × h/ml). Pharmacokinetic profiles of MPA in the time concentration curve are shown in Fig. 4. In the total of 36 profiles obtained from the 18

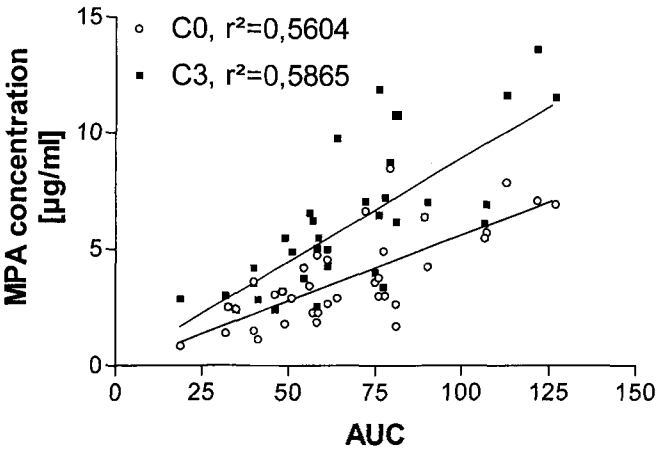

Fig. 5 Correlation of the trough *(C0)* and the 3-hour concentration *(C3)* with the area under the curve *(AUC)* of the MPA profiles, showing a significant positive correlation with the AUC. Because of the variability of the second peak, we prefer to use the three hour MPA concentration, which in our experience should be targeted between 2.5 and 7 ng/ml

patients, the correlation between pre dose trough concentration and AUC was $r^2 = 0.56$. The correlation was best with the 3-h post dose trough concentration (i.e. concentration 3 h after oral intake) at $r^2 = 0.59$. Except for one patient with abdominal pain and diarrhea associated with a high AUC, no other patient had experienced side effects. The number of antihypertensives (median 3, range 1–5, all Metoprolol, plus Ca^{2+} channel antagonists, Dihydralazine, Enalapril or Ramipril, Clonidin, Bunazosin) in all patients remained unchanged over the observation period. However, in two patients, a markedly better control of hypertension was noted. Hemoglobin was not significantly different at time of conversion (11.2 ± 1.6 g/dl) and during the last follow up (11.1 ± 1.6 g/dl, $p = 0.7310$, paired t-test). No patient developed leucopenia below 5.0 Gpt/l or thrombocytopenia below 150 Gpt/l. Also, no patient showed elevation of transaminases above their previous values; and in fact, one of the two patients with chronical, aggressive or persistent Hepatitis C showed significant improvement of liver function. In the latter patient, the ALAT decreased significantly from a median of 2.0 (range 1.3–4.8) µmol/l × s before conversion to a median of 0.56 (range 0.50–0.93) µmol/l × s ($P = 0{,}0002$, Mann-Whitney test) and the plasma choline esterase increased significantly from a median of 108 (range 84–134) to a median of 125 (range 109–156) µmol/l × s ($P = 0.014$, Mann-Whitney test) after conversion.

Discussion

Recent advances and the availability of new immunosuppressive drugs have lead to a continuous improvement of short term allograft survival and reduction of acute rejection episodes. However, there is major concern about long term cyclosporine nephrotoxicity. A number of strategies have been tried to minimize toxicity, such as t.i.d. dosing, for both the classical cyclosporin as well as for the new microemulsion of cyclosporine in pediatric solid organ transplantation [13, 16]. In heart transplant patients, chronical renal failure due to CyA induced nephropathy is a major limitation [19, 25]. Without any doubt, the most unpleasant side effect of CyA is its action to depress renal function [20]. There is a danger of developing structural damage to the kidney which is often difficult to distinguish from sequelae of rejection episodes. Renal biopsy is the only standard tool with which to evaluate these structural alterations. Arteriolar lesions are considered to be the hallmark of cyclosporin toxicity [3, 21] Late alterations consist of fibrous thickening of the small vessels, especially of the arterioles and of the glomerular basement membranes [17, 34], and in the long run stripped interstitial fibrosis [34]. In this study, all patients underwent a renal biopsy and all showed these findings.

While deterioration of graft function in the patients in this study clearly relates to CyA toxicity, as of today there are no convincing protocols to overcome this problem. Conversion to Aza was associated with an increase of the rejection rate [14, 31]. MMF is a new, promising immunosuppressant for the prevention of allograft rejection and was shown to be superior to AZA [12]. Nephrotoxity is also not a prominent feature of MMF [30]. Therefore, it seemed logical to repeat the attempts to change immunosuppression to the non-nephrotoxic immunosuppressant MMF, followed by dose reduction or discontinuation of CyA, as has been done in heart transplant recipients [19, 25].

Apart from the more intense immunosuppressive action compared to that of Aza, MMF has also been associated with a better tolerability in patients with hepatitis [22, 35] showing a possible virostatic effect [1], and has also been claimed to be an antiproliferative agent [6], possibly reducing progression of renal insufficiency. Indeed, there was an improvement of serum creatinine in all our patients and no patient progressed into renal failure. There were 11/18 patients with hepatitis C in the cohort of the patients of this study, and no patient showed deterioration of hepatic function: On the contrary, hepatic function improved in the two patients with chronical aggressive hepatitis C. There is scarce data suggesting a positive effect of MMF on chronical Hepatitis C [26] and EBV infection [1].

As of today, there are only few publications that recommend a dosage for MMF in pediatric renal transplant

recipients. We used a starting dose of MMF of 1200 mg/m^2 per day in two divided doses as suggested by Ettenger et al. [5]. Therapeutic drug monitoring (TDM) is not generally mandatory for treatment of patients with MMF. However, with the uncertainty of the appropriate dose in pediatric patients, TDM was considered for pediatric transplant recipients [29]. In our center, we regularly rely on TDM for monitoring MMF therapy [8], especially after the experience of a very low dose requirement in the combination of MMF with Tacrolimus [9] in pediatric patients. The mean AUC of 70.6 ± 28.1 μg × h/ml achieved with the given dose of approximately 600 mg/m^2 b.i.d. is just slightly higher than the expected pediatric range [34]. The regression line of the MPA AUC versus time after commencement did not differ significantly from zero. However, there was a trend from an average AUC of 70 after 3 weeks to an average AUC of 60 μg × h/ml beyond 100 days (data not shown). Also, the dose normalized AUC dropped slightly from 0.7 to 0.6 μg × h/ml per mg/m^2, but again this did not reach statistical significance. Our data confirm the dosing regimen proposed by Ettenger et al. [5]. Using TDM, there were remarkably few side effects of MMF. The red and white blood cell counts (data for white cell count not shown) were unaffected by MMF treatment in all patients. Diarrhea was only noted in one patient. No other side effects were noted. We conclude that TDM can indeed be helpful for minimizing side effects of MMF in pediatric renal transplant recipients.

Unexpectedly, there was no pronounced effect on hypertension despite a significant dose reduction of CyA and discontinuation of CyA in 11 patients. Possibly, the follow up was too short and the fact that 7/18 patients still were on CyA may accomplish for this finding. It currently remains unclear at what time schedule for reducing CyA one might aim. Cyclosporine was tapered in steps of 25 mg every four weeks. Only in one patient was cyclosporine reduced more quickly as he had a relatively rapid increase of serum creatinine and pronounced histological changes. We recommend to "taper" CyA according to serum creatinine very slowly, just so that serum creatinine stops rising. This paper shows that the introduction of MMF in combination with steroids and very slow reduction of CyA forms a safe and efficient alternative treatment modality for immunosuppression in patients with biopsy proven CyA toxicity, resulting in substantial improvement of allograft function.

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