Transpl Int (2000) 13 [Suppl 1]: S333–S335

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Mycophenolic acid trough levels after kidney transplantation in a cyclosporine-free protocol

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Abstract Twenty-seven stable kidney transplant recipients treated with cyclosporine and prednisone were converted to mycophenolate mofetil (MMF) and prednisone 1 year after transplantation. After conversion the patients were treated with a standard daily dose of 1 g MMF b.i.d. and 10 mg prednisone for 4 months. Thereafter, two MMF dose reductions were performed with a 4-month interval. Mycophenolic acid (MPA) trough levels were measured at regular intervals. A relation was found between MPA trough levels and MMF dose. The median MPA trough level for patients treated with 1 g MMF b.i.d. was 4.3 μg/ml (0.95–15.5) and 3.0 μg/ml (0.73–7.8) for patients treated with 750 mg b.i.d. ($P = 0.0002$). The MPA trough levels further decreased from 3.0 to 2.3 μg/ml (0.6–6.63) in patients treated with 500 mg MMF b.i.d. ($P = 0.01$). Dose reduction of MMF from 1 g to 750 mg b.i.d. could be performed without acute rejections. A further dose reduction to 500 mg b.i.d. elicited 3 rejections. Patients experiencing an acute rejection had a median MPA trough level of 2.3 μg/ml (1.26–3.38) compared to 3.8 μg/ml (1.48–6.52) in patients without an acute rejection ($P = 0.25$). We conclude that there is a significant relation between MPA trough levels and MMF dose. MPA trough levels were not predictive of rejection in the present study.

Key words Mycophenolate mofetil · Mycophenolic acid · Therapeutic drug monitoring · Kidney transplantation

Introduction

At present the combination of cyclosporine (CsA), mycophenolate mofetil (MMF) and prednisone is the standard immunosuppressive drug regimen after kidney transplantation in most centres. The recommended dose for MMF is 1 g b.i.d., while therapeutic drug monitoring is not advised by the manufacturer. However, others have stressed the importance of therapeutic drug monitoring [1]. Moreover, these recommendations are based on the use of MMF in combination therapy with CsA and prednisone from the time of transplantation. Whether such a strategy also holds true in patients not treated with CsA can only be speculated. We demonstrated a significant difference in mycophenolic acid (MPA) trough levels between patients treated with or without CsA in combination with MMF and prednisone, resulting in almost twice as high MPA trough levels in patients discontinuing CsA [2, 3]. Therefore, it is reasonable to assume that higher MPA trough levels might reflect an increased area under the curve (AUC), i.e. immunosuppression. Considering this, lowering the MMF dose might be possible without an increased risk for the occurrence of an acute rejection. This paper describes the results of dose reduction and MPA trough levels in renal transplant patients treated with MMF and prednisone.

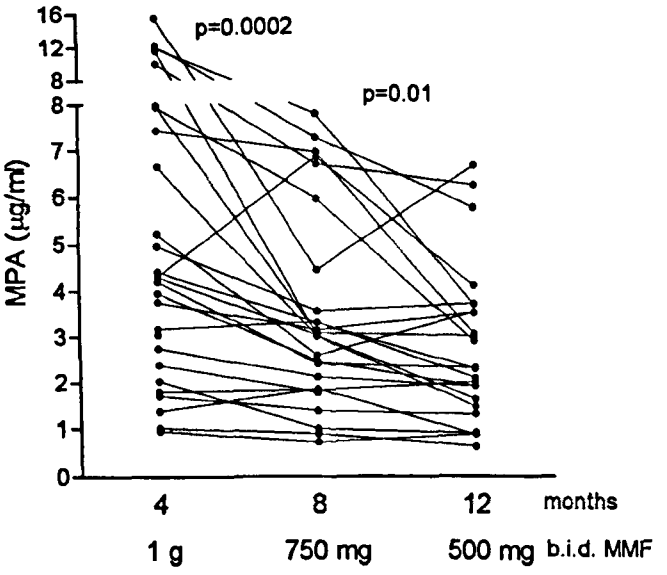

Fig.1 Relation between fasted 12-h mycophenolic acid (*MPA*) trough levels and mycophenolate mofetil (*MMF*) dose

Patients and methods

We performed a prospective study including a cohort of 27 stable kidney transplant recipients, who were transplanted between September 1995 and January 1997 and treated with CsA and prednisone for 1 year. Hereafter, these patients were converted to MMF with a standard daily dose of 1 g b.i.d., without altering the prednisone dose (10 mg). Four and 8 months after this conversion a dose reduction of MMF was performed, resulting in a daily dose of 750 and 500 mg b.i.d., respectively. The end of follow up for analysis was 1 year after conversion. Fasted MPA 12-h trough levels were measured at outpatient visits. For MPA measurements, an immunoassay was used (EMIT-mycophenolic acid assay, which was kindly provided by Dade Behring, San Jose, Calif., USA). For this assay, we participate in the quality assessment scheme from Dr. Holt, St. George's Hospital, London [4]. Four 12-h AUCs (AUC_{0-12}) were performed; two patients treated with 1 g and two patients with 500 mg MMF b.i.d. Clinical and laboratory examinations were routinely performed during outpatient visits. MPA trough levels at the maximum time of duration, just before dose reduction, were used for comparison (4, 8 and 12 months after conversion). In the event of an acute rejection, the closest prerejection MPA trough level was used and compared to two MPA trough levels from patients converted at approximately the same time, with similar MMF dose as control. Results are given as medians with range or means with standard deviation, unless stated otherwise. Paired and unpaired comparisons of numerical data were performed using Wilcoxon's signed ranks and Mann-Whitney tests, respectively. A P value < 0.05 was considered significant.

Results

A significant relation was found between MPA trough levels and MMF dose when comparing all individual MPA levels at 4, 8 ($P = 0.0002$) and 12 months ($P = 0.01$) after conversion (Fig. 1). The 12-h AUCs for four patients are shown in Fig. 2. The mean AUC_{0-12} was 98.2 ± 38.0 vs 58.2 ± 8.4 µg.h/ml for 1 g vs 500 mg MMF b.i.d., respectively. No relation between the AUC and MPA trough levels was present in the limited number of patients studied. Acute rejection occurred in three patients after the second dose reduction. There was no significant difference between the median MPA trough levels in the three patients experiencing an acute rejection; 2.3 µg/ml (1.26–3.38) compared to the controls 3.8 µg/ml (1.48–6.52; $P = 0.25$). Patients with high MPA trough levels (> 3.5 µg/ml) had no signs of rejection.

There was no deleterious effect on renal function after the first MMF dose reduction, when comparing serum creatinines at 4 months (112.5 µmol/l) vs 8 months (112.1 µmol/l) after conversion ($P = 0.52$). However, the serum creatinine at 12 months after conversion had

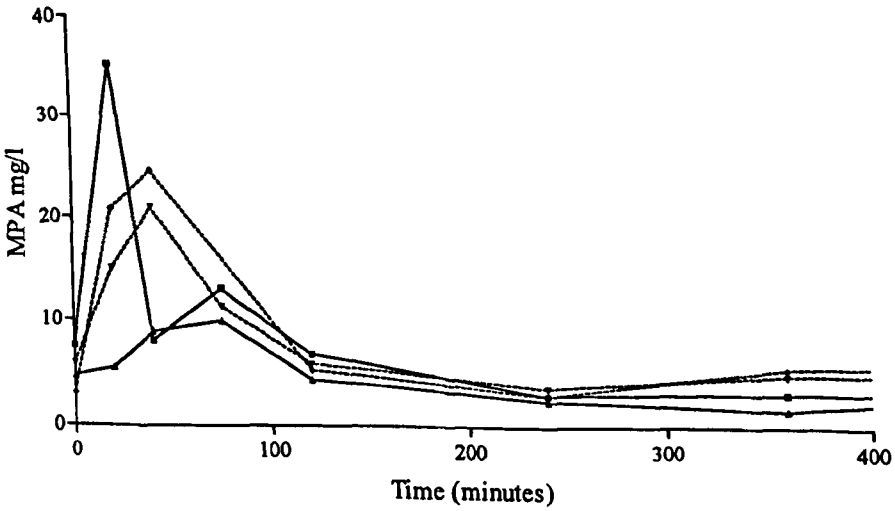

Fig.2 First 6 h of 12-h area under the curve of two patients treated with 1 g MMF b.i.d. (*dashed lines*) and two patients treated with 500 mg MMF b.i.d. (*solid lines*)

increased significantly compared to 8 months from 112.1 to 123.4 μmol/l ($P = 0.0164$). This increase was attributable to three patients: two patients had a recurrence of their original kidney disease and one patient had chronic rejection. If the analysis was censored for these patients, the serum creatinine was 112.1 μmol/l at 8 months and 113.4 μmol/l at 12 months ($P = 0.08$). If the analysis was censored for the three patients with acute rejection, the serum creatinine was 111.1 μmol/l at 8 months and 119.4 μmol/l at 12 months ($P = 0.05$).

Discussion

The dilemma facing the clinician in the management of the renal transplant recipient is finding the lowest possible immunosuppressive regimen without endangering the graft. We describe the results of a subanalysis, focusing on the possibility of MMF dose reduction and the relation with MPA trough levels. MMF dose reduction from 1 g to 750 mg b.i.d. was uneventful, whereas a further dose reduction of MMF to 500 mg b.i.d. was accompanied by three acute rejections in 27 patients. A decrease in renal function was found for the last 4 months of follow up, which was attributable to chronic rejection ($n = 1$) and recurrence of the original kidney disease ($n = 2$). When the goal of maintenance immunosuppression is to achieve zero acute rejections, a policy of reducing the dose of MMF to 750 mg b.i.d. seems to be safe. With regard to therapeutic drug monitoring, a significant relation between MMF dose and MPA trough level was found for individual patients. However, no clear relation could be demonstrated in the patients with rejection when comparing median MPA trough levels to controls as defined in the methods section. It must, however, be stressed that only a small number of rejections occurred. Moreover, AUC could be a better index for impending rejection than trough level. Indeed, although only a limited number of AUCs were performed, a difference between patients treated with either 1 g or 500 mg MMF b.i.d. seems to exist especially in the first 6 h of the total 12-h AUC.

Acknowledgements This study was supported by grant C95.1472 from the Dutch Kidney Foundation.

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