Increased incidence of infections following the late introduction of mycophenolate mofetil in renal transplant recipients

Rajesh Hanvesakul, Chandrashekhar Kubal, Seema Jham, Esha Sarkar, Kevin Eardley, Dwomoa Adu and Paul Cockwell

Department of Nephrology and Renal Transplantation, University Hospital Birmingham, Edgbaston, Birmingham B15 2TH, UK

Abstract

Background. Late introduction of mycophenolate mofetil (MMF) is used in renal transplant patients to allow calcineurin inhibitor (CNI) withdrawal. This change in treatment may alter the immunosuppressive load predisposing patients to infections. To assess this we have analysed infection rates in 30 consecutive patients with chronic allograft nephropathy commenced on MMF for CNI withdrawal.

Methods and results. The study period was from 12 months pre-commencement to 12 months post-commencement. At commencement, patient mean age was 51.2 ± 12.9 years and mean time post-transplant was 3170 ± 2130 days. Estimated glomerular filtration rate (eGFR) at the start of the study period and at conversion was 30.7 ± 12.1 ml/min and 23.1 ± 9.9 ml/min, respectively. The mean dose of MMF post-conversion was 1575 ± 428 mg/day. Estimated GFR had stabilized at 12 months post-conversion to 25.3 ± 12.2 ml/min. There was a significant increase in infections following conversion: pre-conversion, 26.7% (8/30); post-conversion, 66.6% (20/30) ($\chi^2 = 24.5$, $P < 0.0005$). There was an inverse correlation between eGFR at conversion and infection rates post-conversion ($r = -0.379$, $P = 0.039$). There were no hospitalizations for infection pre-conversion and 6 patients (20%) were hospitalized post-conversion, for a total of 285 days (7–107).

Conclusion. There is significant morbidity associated with an increased incidence of infection after late introduction of MMF at standard doses in renal transplant recipients. This risk may be related to GFR at the time of conversion.

Keywords: chronic allograft nephropathy (CAN); CNI withdrawal; infections; mycophenolate mofetil (MMF); renal transplant

Introduction

Chronic allograft nephropathy (CAN) is a major cause of kidney transplant loss [1]. Calcineurin inhibitors (CNI) are implicated in the progression of renal arteriopathy, glomerulopathy and interstitial fibrosis in CAN and their withdrawal in this setting may lead to an improvement in renal function [2–4]. Mycophenolate mofetil (MMF) is commonly introduced to allow the safe withdrawal or minimization of CNI; in addition to providing immunosuppressive cover for CNI withdrawal, MMF also has anti-fibrotic properties that may stabilize renal function [2–7]. However, the pharmacokinetics (PK) of mycophenolic acid (MPA), the active moiety of MMF, are unpredictable in deteriorating renal function and there may be a risk of over-immunosuppression in this setting. To further assess this, we have analysed the incidence of infection in a cohort of patients with low estimated glomerular filtration rate (eGFR) and CAN who have been converted to MMF.

Methods

We identified and included all patients under long-term follow-up in the renal transplant clinic at our centre that had been commenced on MMF for CAN, with complete CNI (ciclosporin or tacrolimus) withdrawal and where the patients were at least 12 months post-transplant at conversion and complete follow-up data were available. All patients were on a triple-regime immunosuppression comprising a CNI, azathioprine and prednisolone at the time of conversion.

At conversion, azathioprine was immediately stopped and MMF was introduced over 1 week to a target dose of 1500–2000 mg/day. The CNI was then withdrawn at a dose of 25% a week from the baseline dose over 4 weeks. Individuals were then maintained on MMF and prednisolone. All individuals were clinically well at the time of conversion with normal white cell counts and differentials. All clinical data for analysis were extracted retrospectively from automated electronic databases, which collate results in real time. Infections were defined by clinical infections...
Table 1. Demographic and immunosuppression details

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at conversion (years)</td>
<td>51.2 ± 12.9</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>22.8</td>
</tr>
<tr>
<td>Ethnicity (Caucasian:IA)</td>
<td>26.4</td>
</tr>
<tr>
<td>Time post-transplant at conversion (days)</td>
<td>3170 ± 2130</td>
</tr>
<tr>
<td>CNI at conversion (ciclosporin:taolimus)</td>
<td>21.9</td>
</tr>
<tr>
<td>Prednisolone dose at conversion (mg/day)</td>
<td>5.8 ± 5.1</td>
</tr>
<tr>
<td>Mean MMF dose post-conversion (mg/day)</td>
<td>1575 ± 428</td>
</tr>
</tbody>
</table>

Data expressed as mean ± standard deviation.
M: male; F: female; IA: Indo-Asian ethnicity; CNI: calcineurin inhibitor; MMF: mycophenolate mofetil; mg: milligrams.

(positive bacterial cultures and/or unequivocal clinical diagnosis) necessitating treatment with anti-microbial agents. Hospitalization episodes were collected from the hospital admission and coding database.

The study period was from 12 months pre-conversion to 12 months post-conversion to match time-dependent changes in estimated glomerular filtration rate (eGFR), infection rates and hospitalizations.

Statistical analysis was performed in SPSS 14. We used the paired t-test, ANOVA and chi-square ($\chi^2$) for comparisons of means and categorical variables respectively. The Mann–Whitney test was used when data were not normally distributed. Correlation analysis was performed to determine the association between eGFR and infection rates. Multivariate regression analysis was used to assess the independent variables associated with infection. A $P$-value of <0.05 was considered significant.

Results

Patients

A total of 30 patients were identified and included in this study. Basic demographic and clinical data are shown in Table 1. The eGFR (by aMDRD) in the study group equated to chronic kidney disease (CKD) stages 3–5, and therefore represented moderate to advanced CKD. In 27 patients, CAN was confirmed by renal biopsies before conversion. Three patients were converted on clinical grounds.

Laboratory parameters

There was a trend towards an improved eGFR (ml/min) after conversion (Figure 1): pre-conversion, 30.7 ± 12.1; at conversion, 23.1 ± 9.9; post-conversion, 25.3 ± 12.2. There was no significant difference in serum albumin (g/l) over the study period: pre-conversion, 41 ± 3.7; at conversion, 39.7 ± 3; post-conversion, 39.2 ± 3.9.

Infections

An increased number of patients sustained infection in the 12 months following the introduction of MMF with CNI withdrawal: pre-conversion, 26.7% (8/30); post-conversion, 66.6% (20/30) ($\chi^2 = 24.5, P < 0.0005$). With the exception of one patient, all infections occurred at least 1 month after MMF introduction and therefore after complete CNI discontinuation. The mean time to first infection after MMF introduction was 6.2 ± 4.0 months. More patients sustained recurrent infections following the introduction of MMF: pre-conversion, 6.6% (2/30); post-conversion, 43.3% (13/30) ($\chi^2 = 70.4, P < 0.0005$). Furthermore, there was a strong inverse correlation between time to first infection post-conversion and number of infections post-conversion (correlation = $-0.58; P = 0.006$), so the earlier the first infection post-conversion, the greater the total number of infections post-conversion.

The number of infections and sites of infections are shown in Figures 2 and 3, respectively. Before conversion
most infections were urinary tract infections. After conversion both urinary tract and respiratory tract infections occurred frequently. Post-conversion infections included fungal pneumonitis, septic arthritis and septicemia. Individuals withdrawn from either ciclosporin or tacrolimus had increased infections within the first 12 months on MMF without CNI.

All urinary tract infections were confirmed by microscopy, culture and sensitivity. Urinary tract infections were commonly as a consequence of either *Escherichia coli* or *Klebsiella* bacteriuria. Respiratory tract infections were diagnosed on clinical grounds and where positive cultures were available showed infections from *Haemophilus influenzae* or *Staphylococcus aureus*, and on one occasion *Moraxella catarrhalis*. Septic arthritis occurred in one patient with a pyogenic knee aspirate positive for *Streptococcus pneumoniae*. Septicaemia occurred in one patient with *S. pneumoniae*-positive blood culture. MMF treatment was terminated in five patients before the end of post-conversion follow-up due to severe or recurrent infections. All patients with infections had CMV PCR tested for primary, recurrent or concurrent CMV infection. No patients who were tested had CMV viraemia pre- or post-conversion. CMV prophylaxis was not used in any of these patients.

**Predisposing factors**

The incidence of post-conversion infections negatively correlated with eGFR at conversion (Figure 4). Further, the number of recurrent infections post-conversion negatively correlated with eGFR at conversion ($r = -0.379; P = 0.039$). There was no significant association between pre-conversion infections and eGFR at conversion. By multivariable analysis with post-conversion infection as the dependent variable, there was an independent association with eGFR ($P = 0.049$), but no association with analysed covariates of age, albumin at conversion or MMF dose post-conversion.

Hospitalizations occurred in six patients (20%) post-conversion, for a total of 285 days (range 7–107). Hospitalization was significantly associated with low eGFR at conversion ($P = 0.043$). All of these episodes were for the management of infection. The reasons for hospitalization comprised pneumonia requiring intravenous antibiotic treatment (two patients), fungal pneumonitis requiring intravenous anti-fungal treatment (one patient), multi-resistant urinary tract infections requiring intravenous antibiotic treatment (three patients), septic arthritis requiring drainage and intravenous antibiotic (one patient) and intensive care admission for profound septicemia (one patient). There was one death as a consequence of bronchopneumonia and respiratory failure.

One episode of acute rejection occurred in one patient 10 months following MMF conversion that was successfully treated with high-dose steroids. CAN was progressive in four patients post-conversion who required dialysis before the end of the follow-up period.

**Discussion**

MMF is a potent immunosuppressive drug [2–5,8,9]. It has an established role in de novo therapy following renal transplantation [10] and as a therapeutic option for CNI withdrawal regimes in CAN [2–4]. The active moiety, MPA, is a highly specific non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase [11]. Through this pathway MPA acts to inhibit both T-cell and B-cell proliferation [11,12].

Consistent with other studies we demonstrate an improvement in the rate of decline in eGFR following the introduction of MMF and CNI withdrawal [2–4]. By matching pre- and post-conversion periods we were able to control for eGFR, infections and hospitalizations over a fixed time period. We found that infection rates and hospitalizations were directly related to eGFR at conversion, and were
independent of the mean daily dose of MMF received by the patient cohort. Furthermore this effect could not be explained by the immunosuppression regime as all individuals were maintained on only two immunosuppressants, i.e. MMF and steroid.

There are no published guidelines on the timing of late introduction of MMF; the GFR range at introduction or the dosing requirement. In studies where there is conversion at a maintained GFR there is no strong evidence of an increased rate of infection [13–16]. Afzali and colleagues also demonstrate that conversion to low-dose MMF (1 g/day) was associated with a minimum incidence of infection in their cohort (5 infective events in 89 patients, with only 1 event requiring cessation of MMF). However, mean GFR at conversion in their patient cohort was higher than that in our study at 37.2 ml/min [17]. In the creeping creatinine study, where mean GFR at the time of conversion was around 30 ml/min and a standard dose of 2 g/day MMF was used, there were increased numbers of infections (22%), serious opportunistic infections (4%) and three deaths from sepsis within a year post-conversion [3]. Douloux and colleagues also report a significant hospitalization rate (29%) post-conversion in their series of MMF conversions for CAN [18].

A key factor in the bioavailability of MPA is renal function [19]. Most studies on MPA PK have primarily focussed on de novo therapy where the eGFR is usually >50 ml/min [12]. Studies in this setting utilizing MPA area under the time-concentration curve (AUC) measurements have shown a significant relationship between high MPA AUC levels and infections [20]. There has been no direct assessment of the clinical implications of the significant increase in MPA levels that occur with fixed drug doses in renal insufficiency [21]; however, a study by Naesens and colleagues in stable renal allograft recipients clearly demonstrates an inverse relationship between GFR (ranging from 25 to 80 ml/min/1.73 m²) and total MPA exposure [22]. Although we have not measured MPA levels in this study, multivariable analysis showed no correlation between infections and post-conversion MMF dose, indicating that patients with lower eGFRs who had increased infections did not receive different doses of MMF doses than the whole cohort. From the data of Naesens et al. [22] this may indicate that patients with lower eGFRs had increased MPA exposure (and therefore infection risk). This inference should be approached with caution, however, as there is large inter- and intra-patient variability of MPA independent of eGFR [23,24] that may have masked a dose effect in a study of this size. Prospective randomized studies incorporating MPA measurements are required to further explore the risks and benefits of MPA use in CAN.

This study shows that CAN patients converted to MMF at standard doses are at a significant risk of recurrent infections and hospitalization. Furthermore, this risk was correlated to eGFR at the time of conversion. These findings are important as patients are increasingly selected for salvage therapy at a low eGFR, where renal impairment may have a direct impact on drug exposure. As a consequence, we have changed our local practice and now convert patients for CAN using a lower dose of MMF of 500 mg twice daily. However, many clinicians continue to convert to doses consistent with those used in de novo studies; this practice now needs careful re-appraisal.

Conflict of interest statement. None declared. We confirm that the results presented in this paper have not been published previously in whole or part, except in abstract format.

References


Received for publication: 7.1.08

Accepted in revised form: 19.6.08