Conversion study from mycophenolate mofetil to azathioprine in stable renal allograft recipients

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Three large randomised controlled clinical studies have shown that mycophenolate mofetil (MMF) in combination with cyclosporine (CsA) and steroids is superior to azathioprine (AZA) or placebo in preventing acute cellular rejection in the first year after renal transplantation.1-3 Our previous study also confirmed that MMF was very effective in reducing the incidence of acute rejection by 55% in the first 6 months when compared with AZA in triple therapy.4 In tacrolimus (TAC)-based regimen, MMF is also more effective in preventing acute rejection than AZA.5 However 3-year graft survival is similar in both MMF-and AZA-treated patients.6 7 The objective of this study is to examine the effect of switching MMF to AZA in stable renal allograft recipients within one year after transplantation.

Patients and Methods:

From July 1997 to January 2001, 65 renal transplant patients (M:F = 43 : 22, mean age 40.9 ± 12.4 years) receiving MMF for at least three months were recruited for this retrospective study at Princess Margaret Hospital. 36 of 65 patients (55%) continued MMF treatment throughout the 3 years study period. The remaining 29 patients (45%) were switched from MMF to AZA, aiming at 1-1.5 mg/kg/d. AZA dose was adjusted according to side effect. Concerning other immunosuppressive agents used in MMF group, 28 patients received CsA-prednisolone (Ps) and 8 patients received TAC-Ps immunosuppression. They were comparable with that of AZA group, which consisted of 23 patients on CsA-Ps and 6 patients on TAC-Ps regimen. During every follow-up visit, clinical and biochemical parameters were checked. In the protocol, first-line treatment for biopsy-proven acute rejection was 500mg intravenous methylprednisolone for 3 consecutive days. Steroid-resistant rejection was to be treated with OKT3 or converted to TAC. The pre- and postconversion serum creatinine and 24-hour proteinuria were compared using two-tailed t test.

Results

There was no significant difference between the demographic data of MMF and AZA groups. The mean MMF dose was 1.4 ± 0.4 g/dl and 1.3 ± 0.3 g/dl respectively (P>.05). At 7.7 ± 3.8 months after transplantation, 29 patients were converted from MMF to AZA with mean AZA dose 51.3 ± 9 mg/dl. Before conversion, there were 5 acute rejection episodes (13.9%) in MMF group and 4 (13.8%) in AZA group (P>.05). After switching to AZA, there was no acute rejection at one year in MMF group and 4(13.8%) in AZA group (P<.05). They occurred at 2, 5, 6 and 8 months. 3 years after conversion, there was no acute rejection in MMF group and total 6 (20.7%) in AZA group (P<.01). The remaining 2 episodes were documented at 30 months. Biopsy-proven chronic allograft nephropathy occurred in 2 AZA-treated patients but none in MMF (P<.05).

In MMF group, the serum creatinine on day of conversion (baseline), 1 year and 3 years after conversion were 132.7 ± 36.8μmol/l, 115.5 ± 33.5μmol/l and 119.7 ± 28.4μmol/l . Whereas in AZA group, the corresponding serum creatinine were 144.2 ± 51.2μmol/l, 132.9 ± 48.6 μmol/l and 139.7 ± 39.4μmol/l (P = 0.35, P = 0.19 and P = 0.14). Concerning 24-hour proteinuria, there was no significant difference between MMF and AZA groups at baseline, 1-year and 3-year after substituted by AZA (0.22 ± 0.22 g/d vs 0.2 ± 0.18 g/d, P = 0.37; 0.19 ± 0.27 g/d vs 0.27 ± 0.62 g/d, P = 0.58 g/d; 0.15 ± 0.14g/d vs 0.24 ± 0.27g/d, P = 0.84 respectively).

Discussion:

The benefit of reduction of acute rejection by MMF as compared to AZA in CsA- and TAC-based is clearly shown in various studies.1-5 However, 1-year and 3-year patient and graft survival are similar. Is it safe to switch from MMF to AZA within one year after transplantation. Our data clearly demonstrated that the early conversion from MMF to AZA was associated with increased incidence of acute rejection 2 to 30 months later. Long-term use of MMF is associated with a reduction in the incidence and risk of late rejection.8 The serum creatinine and 24-hour proteinuria in AZA group was higher than MMF group although not reaching statistical significance up to 3-year follow-up. It is probably due to the small sample size and relative short duration of follow-up. In view of the potential risk of acute rejection after switching from MMF to AZA and the probable trend of creeping up serum creatinine, it is advisable to continue MMF, unless severe adverse event or infection occurs. 2 patients had chronic allograft nephropathy (CAN) in AZA group. Multiple factors, both alloantigen-dependent and alloantigen-independent, appear to contribute to the pathogenesis of CAN.9-10 MMF inhibits lymphocyte proliferation, adhesion molecule glycosylation, and smooth muscle proliferation. Some studies revealed that MMF was effective to retard the
progression of CAN.\textsuperscript{11,12} Hence, MMF has additional benefit in the maintenance immunosuppression. In conclusion, this retrospective study provides some evidence that in patients with stable renal function, early substitution of MMF by AZA may result in increased risk of acute rejection and CAN. Larger prospective study with longer duration of follow-up is necessary to assess the long-term graft and patient survival.

References