CASE REPORT

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Complete Resolution of Severe Diarrhoea after Conversion from Mycophenolate Mofetil to Enteric-coated Mycophenolate Sodium (*myfortic*®) in a Patient at High Immunological Risk

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1. Case Study

The patient, a 49-year-old man, was diagnosed with end-stage renal failure as a result of chronic glomerulonephritis in 1986. After 5.5 years of haemodialysis, the patient received a first renal allograft in January 1992. Six months later, however, the patient experienced a dextrocerebral haemorrhage with sinistral hemiparesis, and rapid chronic transplant vasculopathy was diagnosed. Haemodialysis was restarted and continued until a second renal transplant was undertaken in February 2002. Concomitant illnesses at the time of transplantation included renal anaemia, hypertension and secondary hyperparathyroidism, which necessitated a parathyroidectomy before transplantation.

The second renal transplant proceeded without complications and postoperative dialysis was not necessary. Details of the transplantation are shown in table I. The patient's hospital stay was uneventful, with no infections or episodes of acute rejection, and he was discharged with stable creatinine values of 150 μmol/l, and details of the serum creatinine levels are shown in figure 1. The initial immunosuppressive regimen comprised cyclosporine microemulsion (CsA-ME; 150 mg twice a day, trough level 130–150 ng/ml), mycophenolate mofetil (MMF; 1000 mg twice a day) and corticosteroids (day 0, 500 mg intravenously; day 1, 250 mg intravenously; day 2, 125 mg intravenously, then 100 mg/day by mouth) with antithymocyte globulin for 7 days (ATG-Fresenius; 5 mg/kg per day). After 3 months, the CsA-ME maintenance dose was reduced to 100 mg twice a day (trough level 80–100 ng/ml). The steroid dose was tapered over the first 3 months post-transplant to a maintenance dose of 5 mg/day. The patient experienced occasional bouts of diarrhoea that did not initially require any treatment. Cytomegalovirus seroconversion (pp65 positive) occurred several times and was successfully treated, initially with ganciclovir and subsequently with valganciclovir. In October 2003, cytomegalovirus-associated colitis was diagnosed by coloscopy and histological analysis. This was treated with intravenous ganciclovir and also required a reduction of the MMF dose from 1000 mg twice a day to 500 mg twice a day. The CsA-ME dose was increased (trough level 150 ng/ml) to ensure adequate immunosuppressant coverage. Serum creatinine was in the range 141–159 μmol/l.

Three months later, the patient complained of a substantial increase in the number of bouts of diarrhoea. Episodes started approximately 2 h after each dose of MMF, and were becoming more frequent over time, reaching 10–15 episodes a day, with approximately 3 kg weight loss in one week.

Table I. Patient and transplant characteristics (second transplant)

Cold ischaemia time	14 hours
Cytomegalovirus serology	
Donor	Positive
Recipient	Negative
Donor:	
Age	48 years
Sex	Female
HLA mismatch	1-2-1

HLA = Human leukocyte antigen.

Bacteriology of stool cultures and histological analysis after coloscopy revealed no pathological findings. In April 2004, the patient was converted from the reduced MMF dose of 500 mg twice a day to enteric-coated mycophenolate sodium (EC-MPS, *myfortic*®) 360 mg twice a day. The diarrhoea improved within one day of conversion, and resolved completely within the next few days. No further episodes of diarrhoea were subsequently reported, allowing an increase in the EC-MPS dose to 720 mg twice a day and a reduction in the CsA-ME dose to achieve a lower trough level (80–100 ng/ml). The patient remains on this regimen, which is well tolerated with no recurrence of diarrhoea or EC-MPS-related adverse events. There has also been no recurrence of cytomegalovirus infection. Serum creatinine levels were stable (141–159 μmol/l) before and after conversion to EC-MPS, and the patient has no signs of chronic transplant vasculopathy.

2. Discussion

The development of immunosuppressive therapies over the past 20 years has led to substantial reductions in the rates of acute rejection. In particular, the introduction of MMF in the mid-1990s was an important contributor to improved outcomes, with studies showing significantly improved patient and graft survival compared with azathioprine in renal transplant recipients.[1,2] The management of gastrointestinal side effects,

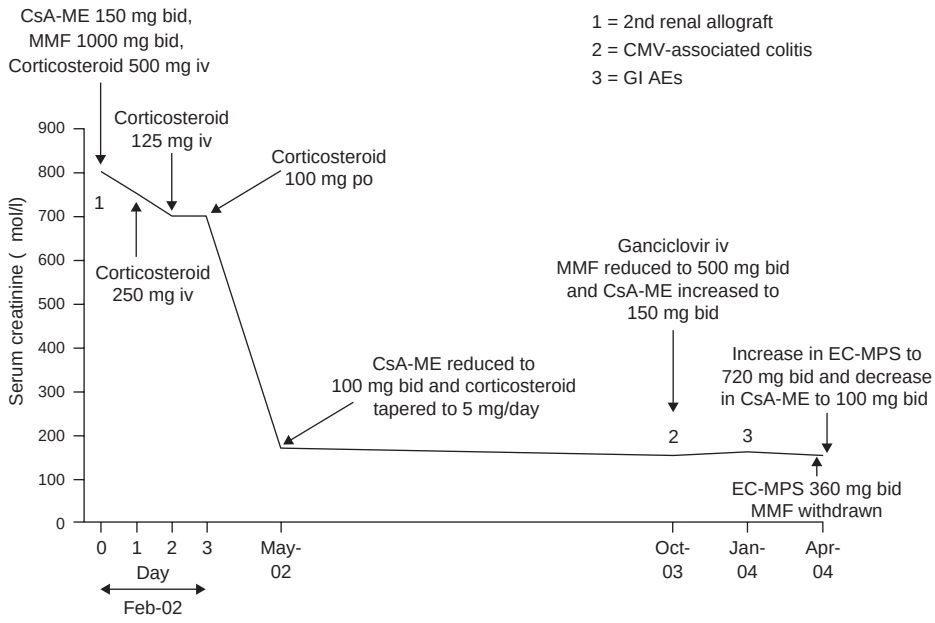

Fig. 1. Serum creatinine levels and medication levels over time. **AE** = Adverse events; **bid** = twice a day; **CMV** = cytomegalovirus; **EC-MPS** = enteric-coated mycophenolate sodium; **GI** = gastrointestinal; **iv** = intravenously; **MMF** = mycophenolate mofetil; **po** = by mouth.

however, remains problematical, and dose changes or dose reductions have been linked to significantly poorer patient outcomes.[3] In a study conducted by Pelletier et al.,[4] 70% of patients required some change to their MMF dose, of which 21% were caused by gastrointestinal side effects. This is consistent with our case study, in which episodes of diarrhoea developed during treatment with MMF, and eventually became intolerable for the patient. The diarrhoea did not resolve after an initial MMF dose reduction, and the immunological risk profile of the patient suggested that further dose reductions were not appropriate. The patient was instead converted to equimolar EC-MPS. Previous studies have shown that conversion from MMF to EC-MPS is safe[5] and that a 1000 mg dose of MMF is equivalent to 720 mg EC-MPS.[6] In our patient, there was complete resolution of the diarrhoea within one week of conversion, and there has been no recurrence of symptoms to date, even when the dose of EC-MPS was increased to the recommended level of 720 mg twice a day. Importantly, this allowed the cyclosporine trough level to return to the initial maintenance target of 80–100 ng/ml, thereby reducing the potential for cyclosporine-related nephropathy.[7]

The objective of a modern immunosuppressive therapy is to achieve a meaningful balance between effectiveness and adverse events. This can be particularly problematical in patients at increased immunological risk, because toxicity is more likely as a result of the necessary intensity of immunosuppression in these individuals. The development of newer formulations of established immunosuppressive agents that offer improved tolerability and safety may allow such problems to be avoided, thus maximizing treatment outcomes and quality of life for the patient. Further studies of EC-MPS, with larger numbers of patients, are now awaited with interest to confirm the excellent gastrointestinal tolerability profile observed in our clinic.

In conclusion, in this patient at high immunological risk of rejection, conversion from MMF to EC-MPS led to the resolution of frequent, severe episodes of diarrhoea, allowing immunosuppressive coverage to be maintained without the use of increased CsA-ME exposure.

References

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