CASE REPORT

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Conversion from Mycophenolate Mofetil to Enteric-coated Mycophenolate Sodium (*myfortic*®) in Patients with Gastrointestinal Side Effects: Case Studies

Anita Boswell and *Magdi Shehata*

Kidney Transplant Unit, Nottingham University Hospitals, City Campus, Nottingham, UK

1. Case Study 1

A 45-year-old mother with end-stage renal failure (ESRF) secondary to glomerulonephritis and receiving haemodialysis therapy underwent a kidney transplant from a deceased donor in May 1990. Her maintenance immunosuppressive regimen comprised of cyclosporine 200 mg twice a day and prednisolone 10 mg once a day (table I), and at the time of transplantation it was noted that she had a high level of cytotoxic antibodies. Before transplantation the patient was also known to have ulcerative colitis.

In August 2000, deteriorating kidney function was observed. The estimated glomerular filtration rate (GFR) was 35 mls/min compared with a previous value of 47 mls/min. There was no proteinuria. A renal biopsy was planned, but the patient failed to attend. In the absence of biopsy results, it was assumed that the patient was suffering from cyclosporine-related nephropathy, and she was converted from cyclosporine to mycophenolate mofetil (MMF) 1000 mg twice a day and her steroid dose remained unchanged (table I). In March 2003, she was admitted to hospital with weight loss (4 kg in total), diarrhoea and dehydration, and a subsequent colonoscopy confirmed a flare-up of her ulcerative colitis, which was treated with steriod-based enemas. In May 2003, she experienced up to four episodes a day of diarrhoea, possibly related to ulcerative colitis, losing weight as a consequence and becoming lethargic. She also became increasingly anxious about leaving the house because of the diarrhoea. In August, she was again admitted to hospital with dehydration, and the MMF dose was reduced to 500 mg three times a day. Four months later, she was again admitted to hospital for dehydration and weight loss, and the MMF dosage was reduced to 500 mg twice a day (table I). By February 2005, the diarrhoea had subsided, but her kidney function continued to deteriorate with an estimated GFR of 30 mls/min and it was felt that she would benefit from an increased dose of MMF. The patient was, however, reluctant to increase the dose of MMF in view of the previous diarrhoea. Instead, she was converted to enteric-coated mycophenolate sodium (EC-MPS, *myfortic*®) 360 mg twice a day. Four months later, in June, the EC-MPS dose was increased to 540 mg twice a day, but one month later the evening dose was reduced to 360 mg because of loose motions (table I). This new regimen has provided a slight improvement in kidney function (estimated GFR 37 ml/min), together with a resolution of diarrhoea and relief from the patient's anxiety concerning her diarrhoea.

2. Case Study 2

The patient was a 56-year-old woman who was on continuous ambulatory peritoneal dialysis for ESRF as a result of type 1 diabetic nephropathy.

Table I. Time course of immunosuppressive drugs for case study 1

Date	Drug	Dose	Reason for change
May 1990 (transplant)	Cyclosporine	200 mg b.i.d.	
	Prednisolone	10 mg/day	
August 2000	MMF	1000 mg b.i.d.	Deteriorating kidney function
	Prednisolone	10 mg/day	
August 2003	MMF	500 mg t.i.d.	Hospitalisation for GI adverse events
	Prednisolone	10 mg/day	
December 2003	MMF	500 mg b.i.d.	Hospitalisation
	Prednisolone	10 mg/day	
February 2005	EC-MPS	360 mg b.i.d.	Deteriorating kidney function
	Prednisolone	10 mg/day	
June 2005	EC-MPS	540 mg b.i.d.	
	Prednisolone	10 mg/day	
July 2005	EC-MPS	540 mg am/360 pm	Loose motions
	Prednisolone	10 mg b.i.d.	

b.i.d. = Twice a day; **EC-MPS** = enteric-coated mycophenolate sodium; **MMF** = mycophenolate mofetil; **t.i.d.** = three times a day.

She received a deceased-donor kidney transplant in March 1995, with initial immunosuppression consisting of cyclosporine, prednisolone and azathioprine (table II). On day 8 post-transplant, she experienced mild-to-moderate rejection, which was treated with four doses of methylprednisolone. Follow-up biopsy showed some infarcted tissue, and she was discharged home on cyclosporine and prednisolone only, with stable but elevated serum creatinine with an estimated GFR of 25 mls/min.

In 2001, it was noted that her kidney function had gradually deteriorated further, with an estimated GFR of 18 mls/min. A further biopsy was

Table II. Time course of immunosuppressive drugs for case study 2

Date	Drug	Dose	Reason for change
March 1995 (transplant)	Cyclosporine	350 mg b.i.d.	
	Prednisolone	20 mg o.d.	
	Azathioprine	300 mg o.d.	
Day 8	Cyclosporine	350 mg b.i.d.	Graft rejection
	Methylprednisolone	500 mg i.v.	
	Azathioprine	300 mg o.d.	
Day 12	Cyclosporine	350 mg b.i.d.	
	Prednisolone	20 mg o.d.	
	Azathioprine	300 mg o.d.	
April 1995	Cyclosporine	300 mg b.i.d.	
	Prednisolone	10 mg o.d.	
2001	MMF	1000 mg b.i.d.	Deteriorating kidney function
	Prednisolone	10 mg o.d.	
December 2001	MMF	500 mg t.i.d.	Skin rash; GI adverse events
	Prednisolone	10 mg o.d.	
July 2004	MMF	500 mg b.i.d.	GI adverse events
	Prednisolone	10 mg o.d.	
June 2005	EC-MPS	360 mg b.i.d.	GI adverse events
	Prednisolone	10 mg o.d.	
July 2005	EC-MPS	540 mg b.i.d.	Improvement in adverse events and kidney function
	Prednisolone	10 mg o.d.	

b.i.d. = Twice a day; **EC-MPS** = enteric-coated mycophenolate sodium; **MMF** = mycophenolate mofetil; **o.d.** = once a day; **t.i.d.** = three times a day.

performed that indicated cyclosporine-related nephrotoxicity, and the patient was converted from cyclosporine to MMF 2000 mg/day. She developed a skin rash (a diagnosis of Stevens–Johnson rash was excluded), so the MMF dose was reduced to 500 mg three times a day (table II). In July 2004, after a course of antibiotics for a foot infection, she developed diarrhoea, which was initially attributed to the antibiotic therapy. However, it did not resolve after discontinuation of the antibiotics, and it was assumed to be MMF related. At this time, stool samples and colonoscopy showed normal results. As the diarrhoea continued, the patient found it necessary to wear incontinence pads, and she became increasingly anxious about leaving the house. The MMF dose was reduced further to 500 mg twice a day, but occasional bouts of diarrhoea persisted. The patient was asked to complete a Gastrointestinal Symptom Rating Scale (GSRS) questionnaire, and was found to have a total score of 54. In June 2005, she was converted from MMF to EC-MPS 360 mg twice a day (table II) in an attempt to relieve the diarrhoea. Her symptoms improved, the diarrhoea resolved and she again felt happy to leave the house. Her GSRS score also improved considerably after conversion to EC-MPS, to a total score of 15.

The improvement in her gastrointestinal symptoms continued, and an improvement in her estimated GFR (22 mls/min) was also seen. In July 2005, the EC-MPS dose was increased further to 540 mg twice a day (table II) and a further improvement in her estimated GFR was seen (27 mls/min).

3. Case Study 3

The final case was a 39-year-old man with ESRF of unknown cause, who received continuous ambulatory peritoneal dialysis before a kidney transplant from a deceased donor in September 1999. Before transplantation, he was working full time. After transplantation, he initially received cyclosporine, prednisolone and azathioprine (table III). In January 2003, however, kidney function deteriorated to an estimated GFR of 25 mls/min and as he was reluctant to undergo a biopsy. He was converted from azathioprine to MMF 1000 mg twice a day in March 2003 and cyclosporine was withdrawn (table III). However, one month later, he developed diarrhoea, with five to six episodes a day. The MMF dose was reduced from 1000 mg twice a day to 500 mg three times a day, but the diarrhoea continued. The patient was reluctant to reduce the MMF dose further, and all investigations undertaken to determine the cause of the diarrhoea were normal. The symptoms continued and were not relieved with loperamide. Finally, in May 2003, the MMF dose was further reduced to 360 mg twice a day (table III). With the

Table III. Time course of immunosuppressive drugs for case study 3

Date	Drug	Dose	Reason for change
September 1999 (transplant)	Cyclosporine	200 mg b.i.d.	
	Prednisolone	5 mg o.d.	
	Azathioprine	100 mg o.d.	
March 2003	MMF	1000 mg b.i.d.	Deteriorating kidney function
	Prednisolone	5 mg o.d.	
April 2003	MMF	500 mg t.i.d.	Gastrointestinal adverse events
	Prednisolone	5 mg o.d.	
May 2003	MMF	500 mg b.i.d.	Gastrointestinal adverse events
	Prednisolone	5 mg o.d.	
May 2005	EC-MPS	360 mg b.i.d.	Gastrointestinal adverse events
	Prednisolone	5 mg o.d.	
June 2005	EC-MPS	540 mg b.i.d.	Improvement in diarrhoea
	Prednisolone	5 mg o.d.	

b.i.d. = Twice a day; **EC-MPS** = enteric-coated mycophenolate sodium; **MMF** = mycophenolate mofetil; **o.d.** = once a day; **t.i.d.** = three times a day.

reduced MMF dose, the symptoms improved slightly, but the patient was worried about the lower dose of medication. At this stage, the patient completed the GSRS questionnaire, and was found to have a GSRS score of 53. In May 2005, the patient was converted from MMF 500 mg twice a day to EC-MPS 360 mg twice a day (table III). His diarrhoea improved and the EC-MPS dose was increased to 540 mg twice a day. Conversion from MMF to EC-MPS improved the patient's symptom burden as measured by GSRS, with a GSRS score of 12 after conversion.

4. Discussion

MMF has offered an important advance in rejection prophylaxis, but gastrointestinal complications are frequent[1,2] and can be problematical. MMF-related gastrointestinal complications may be alleviated by dose splitting,[1] but may persist and require MMF dose reduction or discontinuation,[1] with an increased risk of lowered patient compliance. The case studies presented here highlight the impact that MMF-related gastrointestinal complaints can have on patients' lives, as recently demonstrated in a study confirming that gastrointestinal complications significantly reduce health-related quality of life.[3]

These cases demonstrate that a switch from MMF to EC-MPS can be achieved safely with no increased risk of rejection. All patients tolerated EC-MPS, with an improvement in gastrointestinal symptoms and an increase in the EC-MPS dose, with a resulting improvement in the mycophenolic acid dose. All the patients recorded an early improvement in their subjective assessment of their symptoms, with decreased anxiety about incontinence, and returned to a more normal life. These case reports are compatible with those of a trial in which 177 MMF-treated maintenance renal transplant patients experiencing gastrointestinal complaints were converted to EC-MPS: conversion led to a significant improvement in the gastrointestinal symptom burden, psychological well-being and health-related quality of life.[3] These findings suggest that EC-MPS can provide an effective alternative mycophenolic acid therapy in patients who suffer MMF-related gastrointestinal side effects.

References

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Correspondence and offprints: *Anita Boswell*, Kidney Transplant Unit, Nottingham University Hospitals, City Campus, Hucknall Road, Nottingham NG5 1PB, UK.
Tel: +44 115 969 1169 (ext. 45023);
fax: +44 115 962 7678;
e-mail: anita.boswell@nuh.nhs.uk