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Single centre experience with mycophenolate mofetil for refractory rejection in cadaveric renal transplantation

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Abstract Ten patients with refractory rejection following renal transplantation were treated with mycophenolate mofetil (MMF) in an attempt to salvage the allografts. All cases of rejection were biopsy-proven. Seven of the patients had initially been on tacrolimus-based triple therapy and three were on cyclosporin-based regimens. Those on cyclosporin had been unsuccessfully converted to tacrolimus prior to receiving MMF. All patients had received at least one course of methylprednisolone pulse therapy and three had been given OKT3 prior to MMF. MMF was prescribed at a dose of 2000 mg per day in two divided doses and was given in addition to tacrolimus and prednisolone. Eight of the ten patients showed evidence of reversal of rejection, as indicated by improvement in renal function following commencement on MMF, whilst two patients experienced ongoing rejection and underwent graft nephrectomy. One of the patients successfully treated has since had his MMF discontinued due to gastrointestinal intolerance. We conclude that MMF is effective in salvaging renal allografts with resistant rejection and that it has an acceptable side-effect profile.

Key words Mycophenolate mofetil, renal transplantation, rejection · Renal transplantation, rejection, mycophenolate mofetil · Rejection, renal transplantation, mycophenolate mofetil

Introduction

Mycophenolate mofetil (MMF) is a semi-synthetic, new immunosuppressive agent that is a morpholinoethyl ester derivative of mycophenolic acid (MPA) [1]. Following oral administration and absorption, MMF is hydrolysed to MPA, a potent inhibitor of de novo guanine synthesis. The anti-proliferative activity of MMF appears to be highly specific for lymphocytes which depend on de novo synthesis of purine, whereas other cell types may utilise a secondary salvage pathway that is unaffected by MMF.

MMF acts via non-competitive inhibition of the enzyme inosine monophosphate dehyrdogenase (IMPDH), which is crucial in de novo guanine nucleotide synthesis. Several in vitro studies have shown that this prevents the proliferative responses of both B and T cells, and also inhibits the generation of cytotoxic T cells and the production of antibody by B cells [2, 3]. In addition, Allison and colleagues have shown that MMF also blocks the transfer of sugar residues to glycoprotein ligands on activated lymphocytes and adhesion molecules on target cells [1]. They propose that MMF could inhibit the recruitment of macrophages and lymphocytes into areas of rejection, thus preventing further allograft damage. MMF could therefore be useful not only in the prophylaxis of rejection but also in the treatment of ongoing rejection.

The results of a multi-centre trial from the United States reports encouraging early results supporting the role of MMF in the treatment of refractory rejection [7]. We report our experience over the past 7 months in

Table 1 Incidence and treatment of rejection episodes prior to commencing mycophenolate mofetil (*Tx* transplantation, *MP* methylprednisolone, *CyA* cyclosporin A, *Tacro* tracrolimus, *MMF* mycophenolate mofetil, *BR* borderline rejection, *CR* cellular rejection (grades I–III), *VR* vascular rejection)

No.	Time to first rejection (days)	Episodes rejection	Rejection grade	Primary therapy	Treatment prior to MMF	Time Tx to MMF (days)
1	7	3	BR, CR I, CR I	Tacro	4500 mg MP	23
2	17	3	CR I, CR I, BR	Tacro	4500 mg MP OKT3	38
3	9	2	CR II, CR I	Tacro	2500 mg MP	19
4	9	1	VR	CyA	1500 mg MP CyA to Tacro	18
5	9	4	BR, BR, BR, BR	CyA	3000 mg MP CyA to Tacro	25
6	4	2	CR III, CR II	Tacro	2500 mg MP	11
7	10	3	CR I, CR II, CR II	Tacro	4000 mg MP	31
8	4	2	CR II, CR II	Tacro	2000 mg MP	23
9	11	4	BR, CR I, CR I, CR I	CyA	3000 mg MP CyA to Tacro OKT3	34
10	82	5	B, CR II, CR II, B, CR I	Tacro	7000 mg MP	192

ten renal transplant recipients at the Cardiff Renal Transplant Unit.

Materials and methods

During the 7-month period from August 1996 to February 1997, ten cadaveric renal transplant recipients were commenced on MMF (Cellcept, Roche) for refractory rejection. Refractory rejection was defined as continued deterioration in renal function despite pulse therapy with high-dose intravenous methylprednisolone (500 mg for 3 days). The group consisted of six males and four females with a mean age of 48.5 years (range 28–68 years).

Nine patients had received a first kidney transplant whilst one patient was on his third renal allograft. Two patients had greater than 50% panel-reactive cytotoxic antibodies (PRA), and the remainder had a PRA less than 30% at the time of transplantation. One of these patients underwent OKT3 induction. The median HLA mismatch was two with a maximum of one DR mismatch.

Seven patients were started on tacrolimus-based triple therapy and three on cyclosporin-based triple therapy. The administered dose of tacrolimus (Prograf, Fujisawa) was 0.2 mg/kg per day and that of cyclosporin (Neoral, Sandoz) was 8 mg/kg per day. In addition all patients received azathioprine, 1.5 mg/kg per day and prednisolone, 0.3 mg/kg per day. The target levels for tacrolimus were 5–15 ng/ml; those for cyclosporin were 150–200 ng/ml. For all patients, drug levels were kept within these therapeutic ranges throughout their postoperative course and no patient was exposed to a period of under-immunosuppression. The three patients initially on cyclosporin were converted to tacrolimus at 13, 17 and 45 days post-transplantation, and at 5, 8 and 6 days, respectively, prior to the introduction of MMF.

Nine patients were commenced on MMF within 24 h of completing steroid pulse therapy because of continued deterioration in renal function, and one patient who developed rejection whilst receiving OKT3 treatment was commenced on MMF on the 8th (final) day of OKT3 therapy. Mycophenolate therapy was commenced by means of a simple switch with the introduction of 2000 mg of MMF in two divided doses instead of the azathioprine.

Results

The pre-conversion data of the ten patients are summarised in Table 1. All patients had biopsy-proven, acute cellular rejection, and changes of vascular rejection were evident in one case. The median time to onset of the first episode of rejection was 9 days (range 4–82 days) post-transplantation and the median number of rejection episodes requiring treatment prior to conversion was three (range one to five episodes).

All patients with refractory rejection received methylprednisolone pulse therapy, median dose 3000 mg (range 1500–7000 mg). Two patients also received treatment with OKT3 at a dose regimen of 5 mg for 2 days and 2.5 mg for 8 days. The median time from transplantation to conversion to MMF was 23 days (range 11–192 days).

Seven of the patients are currently still on MMF. One patient with vascular rejection experienced continued rejection that was not responsive to manipulation of her immunosuppressive therapy and eventually required a graft nephrectomy. A second patient who underwent OKT3 induction developed haemolytic uraemic syndrome and then developed a cytomegalovirus (CMV) infection. She experienced five episodes of rejection pre-conversion to MMF and two further episodes after conversion. In addition, she experienced gas-

Table 2 Patient outcome following conversion to mycophenolate mofetil (*CMV* cytomegalovirus, *UTI* urinary tract infection, *PI* peritoneal infection, *BR* borderline rejection, *CR* cellular rejection (grades I–III), *VR* vascular rejection)

No.	Creatinine at conversion (μmol/l)	Current creatinine (μmol/l)	Fall in creatinine (μmol/l)	Follow-up (days)	Complications
1	693	135	558	229	BR Coliform UTI
2	254	202	–	–	Diarrhoea MMF stopped
3	222	222	149	73	
4[a]	611	–	–	–	Oral *Candida* Coliform PI VR
5	683	148	535	136	–
6	971	137	834	140	Oral *Candida* BR + CMV
7	213	147	66	83	
8	140	122	22	77	Coliform UTI
9	333	278	55	56	CR I + CMV
10[a]	169	–	–	–	Diarrhoea

[a] Graft nephrectomy

trointestinal intolerance necessitating division of the MMF into four equal doses. In view of the poor results, she discontinued her immunosuppression and underwent graft nephrectomy.

Three other patients have experienced further biopsy-proven rejection episodes, two of which were associated with CMV infection. Both patients with CMV/rejection responded to a combination of intravenous ganciclovir therapy and methylprednisolone pulse (500 mg for 3 days) and the rejection resolved in each case. A third patient with rejection unrelated to CMV responded to pulse methylprednisolone therapy.

The results of conversion to MMF are summarised in Table 2. The median follow-up time post-conversion for patients still on MMF is 138 days (range 56–229 days). The median creatinine at the time of conversion was 333 μmol/l (range 140–971 μmol/l) and the median current creatinine for patients responding to MMF is 147 μmol/l (range 122–632 μmol/l). A fall in creatinine levels was observed in eight of the ten patients and the median reduction for this group was 70 μmol/l (range 22–834 μmol/l).

Two patients suffered recurrent urinary tract infection with coliform organisms, there were two episodes of oropharyngeal *Candida* infection and one peritoneal fluid infection. All infections responded to appropriate anti-microbial therapy. One patient who had severe diarrhoea has discontinued therapy.

Discussion

Morris et al. demonstrated that MMF could reverse established cardiac allograft rejection [4] whilst Platz and co-workers, in a canine model, showed that MMF in combination with cyclosporin and prednisolone was effective in prolonging renal allograft survival [5]. These studies led to the evaluation of MMF in the clinical setting.

Early phase 1 clinical trials of MMF performed at the University of Wisconsin, Madison, and the University of Alabama, Birmingham, demonstrated the safety and tolerability of MMF in patients undergoing cadaveric renal transplantation [6]. There was a statistically significant correlation with an inverse relationship between number of rejection episodes and dose of MMF and between requirements for prednisolone/OKT3 and MMF dosage.

A multicentre study examining the role of MMF in refractory rejection was established to compare MMF (with cyclosporin and maintenance corticosteroid) to pulse intravenous prednisolone (in addition to triple therapy) in the treatment of refractory rejection. The design was a randomized, open-label study and patients received 1500 mg of MMF twice daily. The latest update of this study [7], reporting results of 150 patients, noted a 45% reduction in graft loss and patient death at 6 months. In addition, there was a halving of the incidence of biopsy-proven, acute rejection episodes over the subsequent 6 months, and when rejection did occur, it did so later in the MMF-treated group. The incidence of CMV infection was noted to be greater in the MMF group whilst *Candida* was more commonly seen in the steroid-treated group. There were four cases of malignancy including two lymphoproliferative disorders and one lymphoma in the MMF group and one case of lymphoma in the steroid-treated group.

Our study has confirmed the role of MMF as rescue therapy in resistant renal allograft rejection. Eight of

the ten patients treated with MMF at a dose of 1000 mg twice daily showed evidence of reversal of rejection, as indicated by improvement in renal function following commencement on MMF. There were four opportunistic infections in our series consisting of two CMV infections that precipitated rejection episodes and two cases of oropharyngeal *Candida*. These figures are similar to historical controls receiving anti-lymphocyte preparations at our institute. No patient in this cohort has developed a malignancy.

At the time of commencement of MMF, all patients were receiving tacrolimus-based triple therapy. The results achieved in this series, despite a 50% reduction in dose compared with the American multicentre series, may have been due to an augmentation of MMF pharmacokinetics by tacrolimus [8]. Zucker et al. showed that significantly higher MPA concentrations are obtained in patients receiving tacrolimus than in individuals on cyclosporin-based therapy (Sandimmun or Neoral).

In conclusion, this small experience confirms the results of the American multi-centre study of MMF in refractory rejection by showing that MMF is successful in reversing severe, ongoing renal allograft rejection.

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