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Mycophenolate mofetil added to immunosuppression after liver transplantation – first results

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Abstract Mycophenolate mofetil (MMF) has been used successfully as an immunosuppressive agent after kidney and heart transplantation, but experience with MMF after liver transplantation is still limited. Between August 1995 and January 1996, we treated 20 patients with MMF after orthotopic liver transplantation in an open, prospective study. Five out of eight patients with acute rejection and one patient with early chronic rejection showed a complete response after MMF was added to the immunosuppression. Three patients with chronic rejection did not improve, one died, and two have stable graft function at present. In eight patients who suffered from toxicity, a reduction in the dosage of tacrolimus was attempted with simultaneous MMF therapy. One patient died due to multiple organ failure. Liver function improved completely in one other patient, and partially in three patients after adding MMF. In the remaining three patients, a reduced dosage of tacrolimus or cyclosporin, together with MMF, reduced toxicity, not significantly. In conclusion, MMF appears to be a safe and potentially useful adjuvant immunosuppressive agent for rescue and maintenance therapy.

Key words Mycophenolate, mofetil · Liver transplantation · Immunosuppressive agents

Introduction

All of the currently used immunosuppressive agents have their limitations. Efficacy and safety profiles are likely to gain from new drugs, particularly if their modes of action are different from the ones used thus far. Mycophenolate mofetil (RS-61443, CellCept), after hydrolyzation to mycophenolic acid, inhibits the de novo pathway of purine synthesis in B and T lymphocytes and appears to be an efficacious and safe immunosuppressive agent after kidney and heart transplantation. Experience after liver transplantation is still limited. We present the results of 20 patients who were treated with mycophenolate mofetil (MMF), in addition to tacrolimus or cyclosporin immunosuppression, after orthotopic liver transplantation.

Materials and methods

Between 1 August 1995 and 31 March 1996, 20 patients at the Virchow Clinic Berlin received MMF after liver transplantation. The group consisted of 11 male and 9 female patients, ranging in age from 21 to 65 years (median 45 years). Indications for liver transplantation are shown in Table 1. MMF was started between the 10th postoperative day (POD) and the 56th month after transplantation (median POD 25). The indications for MMF therapy were acute steroid- and/or OKT3-resistant rejection ($n = 8$), early chronic rejection ($n = 4$), and attempted dosage reduction of cyclosporin or tacrolimus ($n = 8$). Patients were treated with 750–1500 mg MMF twice a day for 18–210 days. Complete follow-up information on all patients was obtained through January 1997.

Table 1 Indications for liver transplantation in 20 patients treated with mycophenolate mofetil

Indication	*n*
Primary transplants	
Alcoholic liver disease	5
Cryptogenic cirrhosis	3
Autoimmune cirrhosis	2
Hepatitis B	1
Hepatitis C	2
Primary biliary cirrhosis	1
Hepatocellular carcinoma	1
Budd-Chiari syndrome	1
Congenital liver fibrosis	1
Alagille's syndrome	1
Retransplants	
Ischemic type of bilary lesion	1
Hepatitis C reinfection	1

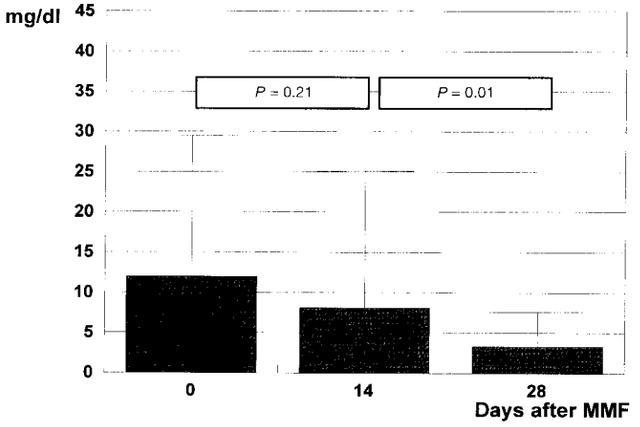

Fig. 1 Bilirubin levels after mycophenolate mofetil (MMF) therapy in eight patients with acute rejection

Results

Acute rejection ($n = 8$)

Eight patients developed acute rejection after orthotopic liver transplantation and were treated with MMF. All received steroids (500 mg prednisolone) for 3 days and four of them OKT3 rescue therapy without immediate response. The median bilirubin level dropped from 12 mg/dl (range 2.0–28.0 md/dl) at the beginning to 8.1 mg/dl (1.0–20.2 mg/dl) after 2 weeks and to 3.3 mg/dl (0.5–4.4 mg/dl) after 4 weeks of MMF therapy ($P = 0.01$; Fig. 1). This treatment was successful in five patients. Because of ongoing rejection, one of three unsuccessful patients received OKT3 10 days after MMF treatment had been started. Two of these three patients had hypoxemic lesions in the liver biopsy due to an accompanying splenic artery steal syndrome, and so an embolization of the splenic artery was carried out. After a mean time of 100 days of MMF treatment, all patients had normalized their bilirubin (0.6–1.3 mg/dl) and transaminase levels (ASAT 11–25 U/l, ALAT 16–36 U/l), and only two patients had elevated cholestasis parameters (GGT 13–83 U/l, AP 63–563 U/l; Table 2).

Three patients who were started on MMF had infections: one woman showed systemic candidiasis and CMV infection and two other patients had asymptomatic urinary tract infections. None of the infections progressed, and only one new wound infection and one new urinary tract infection occurred; these were all managed successfully. In one patient, the dosage of MMF had to be reduced due to gastrointestinal side effects. Leukopenia, with a minimum of 1.9 nl, was registered in another patient. This was reversible after dose reduction to 0.5 g MMF twice a day. No other adverse events were recorded.

Chronic rejection ($n = 4$)

Four patients received MMF because of early signs of chronic rejection after liver transplantation. Therapy started 6 weeks, 3 months, and 1 and 3 years after transplantation. Indications for transplantation were primary biliary cirrhosis, autoimmune cirrhosis, cryptogenic cirrhosis, and hepatocellular carcinoma.

There was complete response in only one case: this patient's bilirubin level dropped from 17.5 mg/dl (POD 42) to 2.0 mg/dl (POD 90) to 0.6 mg/dl (6 months after transplantation); only GGT remained elevated at 149 U/l. A liver biopsy at the start of MMF treatment revealed grade II acute rejection with signs of early chronic rejection and vascular damage.

In another female patient, MMF seemed to have positive effects; however, she eventually died after 10 months from acute meningitis. Her complicated course started with poor initial function, a steroid-responsive episode of acute rejection and biliary strictures. Following endoscopic retrograde cholangiography on POD 107, this patient developed an acute, necrotizing pancreatitis with multiple organ failure. After several laparotomies and over 200 days of intensive care, she recovered and went home. It is almost impossible to assess the benefits and adverse effects of MMF on this patient as it was one of many different drugs given and withheld in the postoperative course. Nevertheless, her bilirubin came down from 21.0 mg/dl to 8.3 mg/dl, despite a highly elevated GGT (392 U/l) and AP (1950 U/l). Unfortunately, acute meningitis, as another infectious complication, was diagnosed 4 weeks after discharge. The patient died despite aggressive therapy. Histology of the transplanted liver showed early chronic rejection with vasculopathy and mild portal bile duct damage.

In two patients with chronic rejection (1 and 4 years after transplantation), liver function remained un-

Table 2 Bilirubin and transaminase values in eight patients with therapy-resistant acute rejection after beginning therapy with mycophenolate mofetil

	Day 0		Day 14		Day 28		*P* (Wilcoxon)
	Median	25 %–75 % Percentile	Median	25 %–75 % Percentile	Median	25 %–75 % Percentile	
Bilirubin (mg/dl)	12	7.25–17.5	8.1	1.475–17.02	3.3	1.2–4.3	0.01
ASAT (U/l)	25	18–70	28	18–50	15	12–21	0.09
ALAT (U/l)	88	37–200	87	35–272	38	35–71	0.03
GGT (U/l)	138	83–234	156	41–266	60	33–197	0.28
AP (U/l)	301	128–595	349	121–668	215	135–461	0.61

changed. Bilirubin was elevated to 1.9 and 2.0 mg/dl; transaminases, GGT, and AP remained high. Yet, liver function is presently stable in both patients and retransplantation has thus far not been indicated during MMF treatment. One of these patients developed an asymptomatic CMV infection; other adverse events have not been found.

Attempted dosage reduction of cyclosporin or tacrolimus

Nephrotoxicity

In two patients, MMF was given when problems with cyclosporin nephrotoxicity were encountered. One patient received a lower dose of cyclosporin 2 years after transplantation; the other was switched to low-dose tacrolimus therapy, together with MMF, 5 years after transplantation. Liver function remained stable, but serum creatinine levels did not change significantly. The levels dropped from 2.0 mg/dl to 1.6 mg/dl, and from 2.8 mg/dl to 2.5 mg/dl, respectively.

Leukopenia

Two years after transplantation, a 49-year-old female developed leukopenia under cyclosporin, azathioprine, and prednisolone immunosuppression. Renal function was reduced (creatinine 2.0 mg/dl) and ascites occurred. After MMF therapy, liver function remained unchanged, and there was no improvement in ascites, leukopenia, or renal function. A liver biopsy did not help to identify the reason for ascites; there was no fibrosis or cellular infiltration.

Hepatotoxicity

Twelve months after liver transplantation for Budd-Chiari syndrome, a 37-year-old male was switched from tacrolimus-based maintenance immunosuppression to cyclosporin and MMF because a liver biopsy showed toxic parenchymal lesions (bilirubin 22.2 mg/dl, ASAT 120 U/l, ALAT 144 U/l, GGT 100 U/l, AP 404 U/l)). Within 4 weeks, liver function had improved: bilirubin dropped to 7.8 mg/dl, ASAT to 34 U/l, ALAT to 58 U/l, GGT to 74 U/l, and AP to 349 U/l.

Clinically suspected rejection or toxicity

A 45-year-old male underwent retransplantation because of chronic rejection and subacute HCV transplant hepatitis. Initial organ function was excellent; bilirubin levels dropped from 38.6 mg/dl preoperatively to 5.7 mg /dl on POD 3 but began rising again the following day. Biopsy showed only mild cholangitis. Immunosuppression was switched from cyclosporin to tacrolimus without any effect. MMF was added on POD 10 and antiviral therapy with ribavirin was started. His bilirubin level dropped from 10.3 to 2.1 mg/dl on day 14. After 4 months, bilirubin is now 1.0 mg/dl and liver enzymes are only slightly elevated (ASAT 19 U/l, ALAT 37 U/l, GGT 72 U/l, AP 292 U/l). There have been no side effects. In this case, it is difficult to differentiate between HCV reinfection and rejection.

Congenital liver fibrosis was the indication for liver transplantation in a 30-year-old male. His postoperative course was complicated because of initial poor function. A first biopsy on POD 9 showed severe parenchymal necrosis without any rejection. Bilirubin levels rose to 26.6 mg/dl. Ascites required a Denver shunt, and hemodialysis was performed because of renal insufficiency. At this point, MMF was added and tacrolimus reduced. Two weeks later, bilirubin was 9.9 mg/dl, and after 2 months liver function was almost normal (bilirubin 2.2 mg/dl, ASAT 14 U/l, ALAT 23 U/l, GGT 142 U/l, AP 396 U/L).

A 53-year-old male underwent liver transplantation for alcoholic cirrhosis. There was initial poor function with high levels of ASAT (3030 U/l) and GLDH (14750 U/l). Induction immunosuppression included low-dose tacrolimus, prednisolone, and ALG for 5 days. The early course was complicated by nephrolog-

ical, neurological, and infectious problems (cholangitis and CMV infection). A biopsy on POD 16 showed severe, prolonged preservation damage. On POD 23, MMF was added to the immunosuppression. The level of bilirubin dropped from 29.3 mg/dl to 15.3 mg/dl after 6 weeks of therapy. No further complications occurred.

A 56-year-old man received a liver transplant for alcoholic liver cirrhosis. Ten days after transplantation, he developed an acute rejection and was treated first with steroids and then with OKT3. While under this treatment, a perforation of a duodenal ulcer occurred. Rejection could be managed, but severe infections (peritonitis, CMV, urine tract infection, systemic candidiasis, and cholangitis) complicated his course. Sepsis and renal, pulmonary, and hepatic insufficiency prompted us to change immunosuppression to low-dose tacrolimus and MMF. When there were no signs of improvement, tacrolimus and MMF were discontinued on POD 67. The patient died 4 months after transplantation of multiple organ failure.

Discussion

All of the currently used immunosuppressive agents have limitations; nephrotoxicity, neurotoxicity, and hepatotoxicity are only a few side effects of these drugs. Immunosuppressive therapy increases susceptibility to viral and other infections. Due to the immunosuppression, there is an elevated risk of developing lymphoma and skin cancers. It has been suggested that a combination of several drugs with different modes of action may lower the side effects and protect the transplanted organ safely.

It was with this concept in mind that MMF was "rationally designed" [2]. This morpholinoethyl ester of mycophenolic acid (MPA) is rapidly hydrolyzed to MPA after oral administration [1]. MPA inhibits inosine-monophosphate-dehydrogenase (IMPDH) in the de novo pathway of purine biosynthesis [4] noncompetitive and reversible. Since lymphocytes rely on de novo purine synthesis, whereas other cells can produce guanosine-monophosphate directly from guanosine (salvage pathway), antiproliferative effects are more potent in lymphocytes. Depletion of Desoxyguanin-5'-triphosphat (dGTP) is principally responsible for the cytostatic effects of MPA, whereas depletion of GTP inhibits the glycosylation of adhesion molecules and the binding of activated lymphocytes to activated endothelial cells [3]. MPA inhibits the proliferation of human arterial smooth muscle cells, so one would expect the risk of proliferative arteriopathy as a manifestation of chronic rejection to be reduced [4, 22, 27]. Another effect of MPA is the suppression of the proliferation of Epstein-Barr virus-transformed B lymphocytes. Because there is a direct correlation between the load of Epstein-Barr virus-infected lymphocytes in the peripheral blood and the risk of posttransplant lymphoproliferative disease (PTLD) [23], MPA should decrease PTLD [1, 2, 4].

This vitro results were proven in several animal models. Morris et al. [16] showed the immunosuppressive effects of MMF in rats after allograft heart transplantation and demonstrated that MMF could halt the progression of advanced rejection. The effectiveness of MMF was also proven in heart allografts in mice and monkeys and in aortic allografts in rats [25]. In combination with cyclosporin and methylprednisolone, MMF seems to be very effective in canine and dog kidney allografts [20, 21]. MMF was able to reverse acute rejection after kidney transplantation in dogs [19], and, in combination with cyclosporin, MMF was found to prolong survival of canine liver allografts [5]. Graft survival in xenotransplantation of cynomolgus monkey hearts to baboons was prolonged with the combination of cyclosporin, prednisone, and MMF instead of azathioprine, steroid pulses, and antithymocyte globulin [15, 18].

The safety of the treatment was first demonstrated in MPA therapy for psoriasis [7]. Eighty-five patients were treated for up to 13 years at a daily dosage of 1.6–4.8 g per day. Common side effects were gastrointestinal symptoms and the development of uncomplicated herpes zoster. Seven malignant neoplasms that arose in six patients were believed to be unrelated to the therapy.

After these very promising preclinical studies, MMF was evaluated in clinical studies after kidney and heart transplantation. It was shown that MMF is an efficacious and safe immunosuppressive for maintenance [6, 8, 10, 12, 24, 28] and rescue [17, 26] therapy.

The data regarding MMF after liver transplantation is quite limited. In a dose escalation study, Hebert et al. [11] reported their experience with MMF for prophylaxis of rejection after liver transplantation. The aim of this study was to evaluate the maximum tolerable dose of MMF in combination with cyclosporin and prednisone. Seven of 17 patients remained rejection-free for 3 months; another seven patients required steroid pulses and three OKT3 therapy. Klintmalm et al. [13] reported on 23 patients with ongoing rejection after steroid and OKT3 therapy. Twenty-one patients responded, 14 with complete resolution of rejection and 7 with partial improvement. Mean bilirubin dropped in 16 patients from 3.9 mg/dl to 2.6 mg/dl in the most recent laboratory data.

In our eight patients with therapy-resistant rejection, the same effects were seen: no patient died or required retransplantation. Overall bilirubin dropped from 12 mg/dl to 3.3 mg/dl after 4 weeks of treatment. After a mean time of 100 days, all patients had normal bilirubin levels and only two showed elevated cholestatic parameters. Changes in bilirubin and ALAT were significant ($P = 0.01$ and $P = 0.03$, respectively). Patients with advanced chronic rejection did not improve with MMF,

but one of our patients with beginning chronic rejection resolved completely within 3 months (bilirubin 17.5 to 0.6 mg/dl). The other three patients did not improve, but retransplantation could be avoided. None of the four patients with chronic rejection reported by Klintmalm et al. [13] improved.

Potentially adverse events appeared in nine patients in the Klintmalm et al. study; the most common ones were gastrointestinal side effects [13]. Hebert et al. [11] also reported this in 10 of 17 patients with a daily MMF dosage of up to 5.0 g. Other side effects included leukopenia, weakness, and rash. Usually all adverse events resolved with dosage reduction. Only one of our patients required dose reduction due to vomiting and diarrhea. Leukopenia was noted in one patient and did not improve after switching from azathioprine to MMF in another.

Hebert et al. [11] reported five opportunistic infections in 17 patients and Klintmalm et al. [13] eight infections in 23 patients. One of our 20 patients died due to a severe meningitis 9 months after transplantation. Seven proven infections (peritonitis, cytomegalovirus, candida, and urinary tract infection) at the beginning of MMF did not progress, and only two other new infections (CMV reinfection, wound infection after laparotomy) occurred. All of them could be managed successfully.

Freise et al. [9] reported on four patients with MMF and prednisolone alone as maintenance therapy. The indication for changing immunosuppression was neurotoxicity after cyclosporin or tacrolimus. At the beginning of MMF therapy, there was an acute rejection in all cases. All rejections resolved and no severe side effects were reported; one patient suffered from nausea and pruritus. In our series in four patients, MMF was added to the immunosuppressive maintenance therapy because of side effects of tacrolimus, cyclosporin, or azathioprine. Nephrotoxicity and hepatotoxicity improved due to a reduction in the cyclosporin or tacrolimus dosage, and no adverse events were noticed. Therefore, MMF might be useful for cyclosporin or tacrolimus dose reduction to prevent severe side effects of IL-2-releasing inhibitors [14].

In addition to the indications reported, MMF was used in several other cases. It was added as an adjuvant agent to the immunosuppressive regimen of patients with poor liver function in order to reduce tacrolimus levels. In one patient with HCV cirrhosis complete response, and in two patients with initial poor function partial improvement, was achieved. In one patient with ongoing peritonitis after ulcer perforation, liver function did not improve, and so MMF was discontinued after 2 weeks of treatment. The patient later died of multiorgan failure.

Despite our limited experience with MMF as immunosuppression after liver transplantation, first results show the efficacy and safety of this drug. MMF was successfully used in rescue therapy. The combination of MMF with cyclosporin or tacrolimus was able to lower the side effects of the IL-2-releasing inhibitors. Adverse events caused by MMF were at an acceptable level and could be managed by dosage reduction. Opportunistic infection did not appear more often than with other immunosuppressive regimens. Randomized trials comparing MMF to other immunosuppressants are needed to confirm our findings and to further evaluate its full potential.

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