CLINICAL REVIEW

Mycophenolate mofetil: A unique immunosuppressive agent

KERRI A. HOOD AND DAWN G. ZAREMBSKI

Abstract: The mechanism of action, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of mycophenolate mofetil are reviewed.

Mycophenolate mofetil is used to prevent or treat allograft rejection after solid-organ transplantation. A prodrug, mycophenolate mofetil is rapidly hydrolyzed to mycophenolic acid after oral administration. Mycophenolic acid inhibits de novo purine synthesis, resulting in antiproliferative effects on T and B lymphocytes. The absolute bioavailability of mycophenolic acid is 94% for oral administration; the maximum plasma concentration occurs after two hours. Mycophenolic acid undergoes hepatic glucuronidation to an inactive salt that is renally excreted. Clinical trials of mycophenolate mofetil in renal transplant patients suggest that the drug is effective for the prevention of acute rejection and as rescue therapy. Clinical data on mycophenolate mofetil therapy in liver transplant patients are too limited to permit conclusions. Clinical trials of the drug for primary immunosuppression in heart transplant patients have not been conducted, but studies of this agent as rescue therapy suggest efficacy. Mycophenolic acid has proved useful for long-term management of psoriasis. The most common adverse effects of mycophenolate mofetil are gastrointestinal. Nephrotoxicity and overt hepatotoxicity have not been reported, but the drug may be linked to bone marrow suppression and certain malignancies. Mycophenolate mofetil is available as a 250-mg capsule for oral use. The recommended initial dosage is 1 g twice daily.

Mycophenolate mofetil appears to be a useful addition to the armamentarium of immunosuppressive drugs, particularly for kidney transplant patients, but more study is needed to clarify its role.

Index terms: Dosage; Immunosuppressive agents; Mechanism of action; Mycophenolate mofetil; Pharmacokinetics; Toxicity

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Mycophenolate mofetil (formerly RS-61443) is the morpholinoethyl ester of mycophenolic acid, which was originally isolated in 1896 from a penicillium culture. Mycophenolic acid was eventually found to have antineoplastic, antibacterial, antifungal, and antiviral properties[1-10] and, still later, immunosuppressive properties.[11-14] Mycophenolate mofetil was developed to improve the bioavailability of the parent compound.[15] After beneficial effects were observed in animals, Sollinger et al.[16] conducted the first human trials in kidney transplant recipients. FDA has since approved the marketing of mycophenolate mofetil for the prevention of rejection in patients with allogeneic renal transplants. Mycophenolate mofetil is also being studied as rescue therapy in organ transplant patients with documented rejection despite standard immunosuppressive therapy.[10,17-21]

This article reviews the mechanism of action, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of mycophenolate mofetil.

Mechanism of action

There are two major pathways for purine biosynthesis. In the de novo pathway, which operates in T and B lymphocytes, 5-phosphoribosyl-1-pyrophosphate (PRPP) is converted to inosine monophosphate, which is further modified to guanosine monophosphate (GMP) by the rate-limiting enzyme inosine monophos-

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phate dehydrogenase (IMPDH). Guanosine triphosphate (GTP) is then produced and becomes involved in DNA synthesis. Mycophenolic acid is a potent, selective, reversible, noncompetitive inhibitor of IMPDH.[22-24] When this enzyme is inhibited, depletion of intercellular guanosine nucleotide pools occurs, leaving adenosine triphosphate pools unaffected. Reduction of GTP production slows the transfer of saccharide moieties to glycoproteins that are expressed on some adhesion molecules that recruit monocytes and lymphocytes to sites of inflammation and graft rejection. GMP may be synthesized in cells other than lymphocytes via a salvage pathway involving PRPP and guanine, which are converted to GMP via hypoxanthine-guanine phosphoribosyltransferase.

Mycophenolic acid also inhibits proliferation of T and B lymphocytes and suppresses humoral immune responses by B lymphocytes. Mycophenolic acid does not inhibit cytokine (interleukin-1 and interleukin-2) production in humans.

Pharmacokinetics

Absorption. Mycophenolate mofetil is rapidly absorbed after oral administration; there is quick presystemic conversion to mycophenolic acid (the active metabolite).[25] Mycophenolic acid undergoes further metabolism to mycophenolic acid glucuronide (MPAG), which is pharmacologically inactive.[26] After oral administration, mycophenolate mofetil cannot be measured in plasma. Mycophenolate mofetil is extensively absorbed in healthy volunteers; mean relative bioavailability of mycophenolic acid is 94% for oral administration.[25] Maximum plasma concentration (C_{max}) occurs roughly two hours after oral administration. Plasma mycophenolic acid concentrations are <2.5 µg/mL within 12 hours after oral administration.[27] Secondary peaks in plasma levels have been observed as mycophenolic acid undergoes enterohepatic circulation.[15] The extent to which mycophenolic acid undergoes enterohepatic recirculation has not been determined in humans.

In renal transplant patients receiving 100–3500 mg of mycophenolate mofetil per day, serum concentrations and area under the plasma concentration–time curve (AUC) increased proportionally with the dose.[16] Plasma mycophenolic acid concentrations and AUC early in the posttransplant period were approximately 50% lower than in stable renal transplant patients. Maximum plasma mycophenolic acid concentrations and AUC increased substantially between posttransplant days 1 and 20 in patients receiving mycophenolate mofetil 1750 mg twice daily (C_{max}, <2 µg/mL on day 1 and >15 µg/mL on day 20).

Steady-state serum concentrations are typically achieved by day 7, but interpatient variability has been observed.[27]

Most pharmacokinetic analyses of mycophenolate mofetil have been conducted in renal transplant patients. Pharmacokinetic values may vary in recipients of other solid organs.

Food lowers the C_{max} of mycophenolic acid; however, the AUC is not affected.[25]

Distribution. Mycophenolic acid binds to plasma albumin in a concentration-dependent manner, with the plasma concentration of unbound mycophenolic acid increasing as the dose increases.[28] Increasing total plasma mycophenolic acid concentrations are associated with increases in the fraction of free mycophenolic acid. Binding of mycophenolic acid is not altered despite the presence of supratherapeutic concentrations of cyclosporine, prednisone, tacrolimus, warfarin, digoxin, or phenytoin. However, high plasma concentrations of MPAG, which may occur early after renal transplantation, do increase the free fraction of mycophenolic acid. Furosemide in high concentrations produces minimal increases in free plasma mycophenolic acid. High doses of aspirin that produce salicylate concentrations of >250 mg/L may displace mycophenolic acid from serum albumin. In addition, a reduction in the serum albumin concentration from 41.4 g/L to 20.7 g/L is associated with a 2.2-fold increase in the free fraction of mycophenolic acid. Inhibition of IMPDH increases in proportion with increasing concentrations of unbound mycophenolic acid. Increases in serum albumin concentrations in vitro increase the mycophenolic acid concentration needed for 50% inhibition of IMPDH.[29]

Binding of mycophenolic acid to α_1-acid glycoprotein is insignificant.[30] Mycophenolic acid is minimally bound to plasma lipoproteins in a concentration-independent manner. Mycophenolic acid and MPAG are found almost exclusively in plasma; little is distributed into cells. Plasma, not whole blood, should be used for analyzing mycophenolic acid concentrations.

Metabolism. After oral administration, mycophenolate mofetil undergoes hydrolysis to mycophenolic acid. An inactive phenolic glucuronide and three additional inactive metabolites, *N*-(2-carboxymethyl)-morpholine, *N*-(2-hydroxyethyl)-morpholine, and the *N*-oxide of *N*-(2-hydroxyethyl)-morpholine, are subsequently formed.[26] Alcoholic cirrhosis does not appear to appreciably alter the hepatic metabolism of mycophenolic acid to MPAG.[25]

Excretion. Mycophenolic acid is primarily eliminated by the kidneys; >90% of a dose is excreted in the urine as MPAG.[9] MPAG is excreted via glomerular filtration and tubular secretion.[25] Alterations in plasma mycophenolic acid and MPAG concentrations have been observed in patients with renal insufficiency. In a single-dose study, the mean mycophenolic acid plasma AUC increased almost twofold in patients with severe renal impairment.[25] MPAG AUC increased threefold to sixfold. C_{max} was reduced by approximately one third in the same group. Hemodialysis did not appear to significantly alter plasma mycophenolic acid or MPAG con-

centrations. A minimal amount of mycophenolate mofetil was eliminated in the feces.

Efficacy in renal transplantation

Prevention of acute rejection. Forty-nine renal allograft patients were randomly assigned to receive one of eight mycophenolate mofetil dosage regimens (100–3500 mg/day).[16] Additional immunosuppressive therapy consisted of Minnesota antilymphocyte globulin, cyclosporine (initiated once the serum creatinine concentration was <3 mg/dL), and prednisone. One patient died on postoperative day 1 after an acute myocardial infarction and was replaced. Five other patients did not complete the trial (four patients for reasons not presumed to be associated with mycophenolate mofetil therapy). Mycophenolate mofetil was discontinued in a single patient with hemorrhagic gastritis believed to be related to the drug. Mycophenolate mofetil appeared to be otherwise well tolerated. Bone marrow suppression, hepatotoxicity, and nephrotoxicity were not observed. There were fewer severe rejection episodes in patients receiving the higher dosages of mycophenolate mofetil (>2 g/day). In addition, rejection in patients receiving the higher dosages was less severe and easier to reverse.

Next, 43 of the 49 patients were enrolled in a long-term follow-up trial (14–26.5 months).[31] Patient and graft survival at 18 months were 100% and 95%, respectively. No patients were withdrawn from the trial. Five patients had adverse effects requiring a reduction in their mycophenolate mofetil dosage. Four episodes of acute rejection were observed in four patients more than four months after surgery. Rejection episodes were successfully reversed in one patient with bolus doses of corticosteroids and in one patient with muromonab-CD3 therapy. In the remaining two patients, acute rejection was managed by increasing the mycophenolate mofetil dosage to 3 g/day.

In another randomized, placebo-controlled, double-blind trial, Sollinger and the U.S. Renal Transplant Mycophenolate Mofetil Study Group[32] assessed the ability of mycophenolate mofetil to prevent acute rejection in 449 patients with cadaveric renal transplants. The patients received mycophenolate mofetil 2 g/day (n = 167) or 3 g/day (n = 166) or azathioprine 1–2 mg/kg/day (n = 166) for the first six months after transplantation. Additional immunosuppressive therapy included antithymocyte globulin, cyclosporine, and prednisone. Four patients (two assigned to a mycophenolate mofetil group and two to the azathioprine group) did not receive study medication and were excluded from the analysis. Primary study endpoints were biopsy-proven rejection, treatment failure (described as graft loss), and withdrawal from the study for any reason despite a lack of biopsy-proven rejection. Rejection and treatment failure occurred in 79 members (47.6%) of the azathioprine group, 52 members (31.1%) of the mycophenolate mofetil 2-g/day group, and 52 members (31.1%) of the mycophenolate mofetil 3-g/day group (p = 0.0015 for azathioprine versus mycophenolate mofetil 2 g/day and p = 0.0021 for azathioprine versus mycophenolate mofetil 3 g/day). The percentage of patients with rejection managed by applying clinical judgment (without biopsy confirmation or a ruling of "presumptive rejection") did not differ significantly among the treatment groups (azathioprine, 6%; mycophenolate mofetil 2 g/day, 4.8%; and mycophenolate mofetil 3 g/day, 5.4%). Kaplan-Meier estimates of graft loss were 8.6%, 1.8%, and 6.7% for the azathioprine, mycophenolate mofetil 2-g/day, and mycophenolate mofetil 3-g/day groups. Graft loss was mostly secondary to rejection.

Adverse effects and opportunistic infections were documented in all three treatment groups. Anemia, hypertension, and diarrhea were the adverse effects most frequently reported for mycophenolate mofetil. Diarrhea and other gastrointestinal complications, including esophagitis, gastritis, and gastrointestinal hemorrhage, occurred more frequently in the mycophenolate mofetil groups than in the azathioprine group. In addition, a higher frequency of adverse effects was reported in the mycophenolate mofetil 3-g/day group than in the 2-g/day group. Opportunistic infections occurred in all three treatment groups, with cytomegalovirus (CMV) being the most frequently reported pathogen. A higher frequency of tissue-invasive CMV infection was observed in mycophenolate mofetil recipients (6.1%, 9.1%, and 10.8% in the azathioprine, mycophenolate mofetil 2-g, and mycophenolate mofetil 3-g groups, respectively). Two azathioprine recipients developed *Pneumocystis carinii* pneumonia (PCP); this illness was not observed in the mycophenolate mofetil groups. Three patients given mycophenolate mofetil 3 g/day developed aspergillus or mucor infections. Similar infections were not observed in either the 2-g group or the azathioprine group. No hepatotoxicity was reported, and neutropenia and thrombocytopenia occurred infrequently.

The European Mycophenolate Mofetil Cooperative Study, a randomized, double-blind, placebo-controlled trial, also evaluated the efficacy of mycophenolate mofetil in patients with first or second cadaveric renal transplants.[33] The patients received placebo (n = 166) or mycophenolate mofetil 2 g/day (n = 165) or 3 g/day (n = 160). Additional immunosuppressive therapy included cyclosporine and prednisone. Antibody induction therapy was not used, and azathioprine therapy was not allowed during the trial. Primary endpoints were similar to those in the U.S. trial. Control patients had a significantly higher rate of biopsy-proven rejection, presumed rejection, or treatment failure than patients in either of the mycophenolate mofetil groups (p < 0.001).

A significant difference between the placebo group and the mycophenolate mofetil groups was observed

during the first six months in the frequency of biopsy-proven rejection or treatment failure ($p < 0.001$). Corticosteroids or antilymphocyte agents or both were given for rejection within the first six months after transplantation to 172 patients (86 [50%], 47 [27.3%], and 39 [22.7%] members of the placebo, mycophenolate mofetil 2-g/day, and mycophenolate mofetil 3-g/day groups, respectively). Forty-two patients (17 [41%] in the placebo group, 11 [26%] in the 2-g/day group, and 14 [33%] in the 3-g/day group) suffered graft loss or died within the first six months. Rejection was the primary cause of graft loss. Fourteen of the 15 deaths were unrelated to mycophenolate mofetil therapy. One death, secondary to hemorrhagic pancreatitis, may have been.

Overall, 151 patients withdrew prematurely from the trial because of adverse effects or unsatisfactory responses (placebo group, 34.9%; 2-g group, 22.4%; and 3-g group, 35%). Adverse effects necessitating discontinuation of study medication were observed to a greater extent in patients receiving mycophenolate mofetil therapy. Study medication was discontinued in the placebo group more commonly as a result of an unsatisfactory response.

Gastrointestinal adverse effects were more frequently noted in the mycophenolate mofetil groups, including serious events such as large-bowel perforation. Hematologic toxicity, including leukopenia and anemia, was more frequent in patients given mycophenolate mofetil.

Tissue-invasive CMV infection was more frequent in patients receiving mycophenolate mofetil 3 g/day than in the other groups. However, a similar rate of CMV viremia was seen in all study groups. Other viral infections occurred more frequently in the mycophenolate mofetil groups than in the placebo group. Four placebo recipients developed PCP, and one developed a fungal infection. These opportunistic infections were not observed in the mycophenolate mofetil groups.

Rescue therapy. After observing the efficacy of mycophenolate mofetil as maintenance therapy for renal transplant recipients, Sollinger and colleagues[17] proceeded with a multicenter pilot study of this agent for the treatment of acute allograft rejection. Seventy-five patients with biopsy-proven rejection who failed to respond to muromonab-CD3 or antilymphocyte globulin were enrolled in this open-label study. The patients received mycophenolate mofetil 2 or 3 g/day; the therapy was begun within 48 hours after biopsy. The sample consisted of patients with transplants from living relatives ($n = 11$) or living unrelated persons ($n = 3$) and patients with primary cadaveric transplants ($n = 50$) or secondary cadaveric transplants ($n = 11$). Renal function improved or stabilized in 52 (69%) of the 75 patients. Success was reported for 79% of patients with serum creatinine concentrations of <4.0 mg/dL, compared with 52% of those with creatinine concentrations of >4.0 mg/dL. Therapy was discontinued in 19 patients because of treatment failure and in 11 additional patients because of complications; the drug discontinuation in 4 of these 11 patients was directly attributed to adverse effects of mycophenolate mofetil (pancreatitis, CMV-associated colitis, hemorrhagic gastritis, and other gastrointestinal problems).

Summary. The two large cooperative trials showed that mycophenolate mofetil is an acceptable alternative to azathioprine for primary immunosuppression in the first six months after kidney transplantation. Mycophenolate mofetil's usefulness beyond the first year remains to be demonstrated. Since the European researchers did not give their control group azathioprine, discretion should be used in interpreting these results.

Mycophenolate mofetil has not been extensively studied as rescue therapy in renal transplant recipients. The studies that have been conducted suggest that mycophenolate mofetil offers an alternative when traditional therapies have failed. The timing of treatment and the degree of renal impairment appear to be keys in using this drug as rescue therapy.

Efficacy in liver transplantation

There is limited information to date on the use of mycophenolate mofetil in liver transplant recipients. A handful of case reports describing the use of mycophenolate mofetil for maintaining immunosuppression exist. Freise et al.[34] described the use of mycophenolate mofetil and prednisone in four liver transplant patients. All the patients had previously been maintained on cyclosporine and prednisone and had developed cyclosporine-induced complications. Therapy had been continued for more than one year in all patients without evidence of rejection.

Klintman et al.[18] used mycophenolate mofetil to treat 23 liver transplant patients receiving cyclosporine, prednisone, and azathioprine for maintenance immunosuppression and persistent acute rejection. Enrollees had biopsy-verified rejection despite receiving high-dose corticosteroids and muromonab-CD3. Mycophenolate mofetil therapy (dosage not stated) was begun 4–44 weeks after liver transplantation; the follow-up period was 5–11 months. Twenty-one patients (91%) responded, with 14 showing resolution of rejection and 7 demonstrating improvement. Sixteen of the patients continue to receive mycophenolate mofetil therapy. Four patients had underlying, biopsy-proven chronic rejection; maintenance immunosuppressive therapy in these patients was the same as in the 23 patients at the start of the study. All four patients had also received high-dose corticosteroids or muromonab-CD3 or both for acute rejection episodes. Chronic rejection was not improved by mycophenolate mofetil therapy.

In summary, data on mycophenolate mofetil in liver transplant patients remain limited. To better understand the potential impact in liver transplant patients, large, randomized, double-blind trials are needed.

Efficacy in heart transplantation

Clinical trials of mycophenolate mofetil for primary immunosuppression in heart recipients have not been conducted. However, the drug has been evaluated as rescue therapy for drug-resistant rejection in heart transplant patients. Ensley et al.[19] studied the drug's efficacy in dosages ranging from 500 mg to 3 g/day (assigned nonrandomly) in 30 patients with mild acute rejection (International Society of Heart and Lung Transplantation [ISHLT] grade 1b or 2) given more than 28 days after surgery. The patients had had an average of 2.4 rejection episodes before enrollment. The researchers used the Utah Transplantation Affiliated Hospitals Cardiac Transplantation Program (UCTP) rejection grading system; UCTP grade 3 rejection is equivalent to an ISHLT grade of 1b or 2. Concomitant immunosuppressive therapy (prednisone and cyclosporine) was not altered during the eight-week study period.

Complete resolution of acute rejection (ISHLT grade, 0) occurred in 20 (66%) of the patients within four weeks. The mean ISHLT rejection score upon completion of the trial was significantly reduced (1.8 at eight weeks versus 3.0 at baseline, $p < 0.001$). Corticosteroid dosages and cyclosporine levels were unchanged during the study period. Mycophenolate mofetil was discontinued in eight patients—in four as a result of continued mild rejection and in four because of progression to moderate rejection (ISHLT grade 3A or 3B). Higher dosages were associated with a nonsignificant reduction in the occurrence of progression to moderate rejection (2 [33%] of 6 patients receiving 500 mg/day versus 2 [8%] of 24 patients receiving 1 g/day or more). Mycophenolate mofetil therapy was continued as long-term prophylaxis in the 20 responders for an average of 430 days. During long-term follow-up, the rate of reported moderate rejection was 0.24 episode per patient-year. The therapy was well tolerated, with discontinuation necessary in only one patient (because of gastrointestinal complaints). Hepatotoxicity and nephrotoxicity were not observed during the initial eight-week trial period. The rate of major infectious complications was 0.2 episode per patient-year during the long-term follow-up.

In a similar trial, Kirklin et al.[20] evaluated mycophenolate mofetil for the management of 17 heart transplant patients with persistent ($n = 5$), refractory ($n = 1$), or recurrent ($n = 11$) rejection. The drug was administered at 3 g/day for two months. In seven patients the dosage was increased to 3.5 g/day five days after the start of therapy. The patients were also permitted to enroll in a long-term follow-up study. The frequency of rejection for the group as a whole was reduced from 0.67 episode per month for the six-month period immediately before therapy to 0.27 episode per month for the six-month period after therapy began ($p < 0.0001$). A reduction in the frequency of rejection episodes occurred regardless of the amount of time after transplantation. However, a greater reduction in the frequency of rejection was observed less than six months after surgery (1.18 and 0.35 episodes per month before and after mycophenolate mofetil therapy, respectively, $p = 0.0002$) than more than six months after surgery (0.33 and 0.18 episode per month before and after therapy, $p = 0.4$). (The frequency of rejection is typically greatest in the early posttransplant period and declines with time.)

Two patients died after the start of therapy. One patient, in whom mycophenolate mofetil therapy was begun six days after retransplantation, died of CMV sepsis 68 days later. The second patient had multiple-organ-system failure before starting mycophenolate mofetil therapy and died of pulmonary dysfunction 72 days later.

The therapy was continued after the initial two-month study period in 14 of the 17 patients. One patient discontinued mycophenolate mofetil therapy after complaining of severe gastrointestinal adverse effects. An additional eight patients had gastrointestinal symptoms that resolved after a temporary reduction in the dosage. Adverse effects potentially attributable to mycophenolate mofetil therapy were not seen in seven patients. Clinically significant alterations in hepatic and renal function were not observed. In addition, bone marrow suppression was not observed. Infection rates were unchanged before and after the start of therapy.

Kobashigawa et al.[21] reported on 15 cardiac transplant patients treated with mycophenolate mofetil for persistent or refractory rejection. Azathioprine was discontinued upon the diagnosis of rejection, and mycophenolate mofetil therapy was begun at 2–3 g/day. All nine patients with moderate rejection improved, as shown by repeat biopsy (mean time to repeat biopsy, 16 days). Complete resolution of rejection was apparent in six of these nine patients an average of 39 days after the start of mycophenolate mofetil therapy. All six patients with documented mild rejection demonstrated improvement on repeat biopsy conducted after an average of 19 days of therapy. Resolution was complete in five of these six patients after an average of 47 days following the initiation of mycophenolate mofetil therapy. Adverse effects were not reported.

Taylor et al.[10] monitored 33 of the patients enrolled in the trials discussed above to assess mycophenolate mofetil as chronic maintenance therapy. The patients had had an average of 2.8 episodes of acute rejection each before mycophenolate mofetil therapy began. Mean time from transplantation was 295 days, while follow-up averaged 23.7 months (range, 2–37.4 months). Sixteen patients were withdrawn from therapy: four because of rejection, four because of adverse drug reactions, and eight for reasons unrelated to the study medication. Thus, 17 patients received myco-

phenolate mofetil therapy for an average of 33 months. Thirty-seven episodes of rejection were documented during the study period (28 episodes of mild rejection [ISHLT grade 1B or 2] and 9 episodes of moderate rejection [grade 3A or 3B]). Nineteen of the 28 episodes of mild rejection were initially managed by increasing the mycophenolate mofetil dose (average increase, 818 mg). Resolution of rejection was noted on repeat biopsy at day 13 in 13 of these 19 rejection episodes. Additional immunosuppressive therapy was not altered during these episodes. Five patients continued to have persistent rejection, which was resolved by high-dose oral corticosteroids. One patient progressed to moderate rejection, with resolution occurring after i.v. corticosteroids were given. Thus, increasing the mycophenolate mofetil dosage was successful in treating 13 (68%) of 19 episodes of mild rejection. All nine episodes of moderate rejection necessitated brief courses of i.v. corticosteroids; resolution of rejection was seen at first biopsy in six patients. Three of the nine patients were switched to azathioprine—two at the initial diagnosis of rejection and one after documented persistent rejection. Rejection occurred an average of 240 days after the initiation of mycophenolate mofetil therapy. The mean corticosteroid dosage was reduced from 15.5 mg/day at the time of enrollment to 6.8 mg/day at the time of rejection. Gastrointestinal complaints were the most frequently reported adverse effects during the 782 patient-months of mycophenolate mofetil therapy. Transient leukopenia occurred in 15% of the patients.

Mycophenolate mofetil is effective in the management of cardiac transplant recipients with biopsy-proven rejection despite triple-drug immunosuppressive therapy. For these individuals, mycophenolate mofetil replaces azathioprine in the immunosuppressive armamentarium. Institution of mycophenolate mofetil therapy may be considered in the management of biopsy-proven rejection as an alternative to traditional therapy. Randomized trials comparing mycophenolate mofetil with azathioprine for primary immunosuppression are needed. Data from ongoing clinical trials are needed before mycophenolate mofetil can be recommended in primary immunosuppressive regimens immediately after cardiac transplantation.

Other uses

Mycophenolic acid, the active metabolite of mycophenolate mofetil, has been used in the treatment of several immune-mediated diseases. Since the early 1970s, mycophenolic acid has been studied for the management of psoriasis.[35-38] Initial reports were limited by small sample sizes and short treatment periods. Epinette et al.[35] reported on the compassionate use of mycophenolic acid in 85 patients for periods up to 13 years. Mycophenolic acid dosages throughout the study averaged 2–3 g/day. Gastrointestinal complaints, which occurred in 72% of the patients during the first year of therapy, were the primary adverse events noted. The frequency of gastrointestinal complaints decreased to <27% by year 4. A flu-like syndrome occurred in 4–38% of the patients per year. Six patients developed malignant neoplasms. Dose-limiting leukopenia was observed in several patients.

Marinari et al.[36] reported on the use of oral mycophenolic acid in the management of 35 psoriasis patients for an average of 89 weeks. Mycophenolic acid dosages ranged from 2.4 to 7.2 g/day. Treatment was associated with a good or excellent response in all but two patients. Dose-related gastrointestinal complications were the most frequently reported adverse effects. In addition, two cases of herpes zoster and nine cases of herpes simplex were noted. A flu-like syndrome lasting 7–10 days and involving low-grade fever, malaise, myalgia, and nonproductive cough was observed in 17 patients. The flu-like syndrome occurred in the winter at least six months into the mycophenolic acid therapy. A reduction in hemoglobin concentration of 1–2 g/dL was noted in 13 patients, mild leukopenia (white blood cell count, 3900/mm^3) was observed in 1 patient, and mild thrombocytopenia (platelet count, 110,000/mm^3 and 120,000/mm^3) was reported in two patients.

The antitumor efficacy of mycophenolic acid has been evaluated in patients with a wide range of malignancies.[7-9] Beneficial effects of mycophenolic acid were minimal. Mycophenolic acid is currently not indicated in the management of neoplastic disorders.

Improvement in rheumatoid arthritis has been observed after the administration of mycophenolic acid to patients resistant to conventional therapy (including corticosteroids, gold salts, and methotrexate).[39] The role of mycophenolate mofetil in the management of rheumatoid arthritis and other immunologic disorders remains to be defined.

Drug interactions

Pharmacokinetic interactions. No clinically significant pharmacokinetic interactions were observed between mycophenolate mofetil and single doses of ganciclovir, trimethoprim–sulfamethoxazole, and oral contraceptives.[25] Significant alterations in cyclosporine pharmacokinetics were not observed after the administration of mycophenolate mofetil 3 g/day. Interactions between mycophenolate mofetil and agents not commonly used in the solid-organ-transplant population have not been well documented.

MPAG undergoes renal tubular secretion. Animal data indicate that plasma mycophenolic acid and MPAG concentrations may be increased by the concomitant administration of probenecid.[25] Although this has not yet been studied in humans, probenecid and other agents that undergo renal tubular secretion may alter serum MPAG concentrations. MPAG plasma concentrations were increased after the administration of acyclovir.[25] Competition for renal secretion may

exist between acyclovir and MPAG.[25] The impact of ganciclovir on renal tubular secretion of MPAG remains to be determined.

Administration of cholestyramine has been associated with a 40% reduction in the AUC of mycophenolic acid as a result of alterations in the enterohepatic recirculation of MPAG.[25] Concomitant administration of mycophenolate mofetil and cholestyramine is not recommended.[25] Other agents that alter enterohepatic recirculation should also be avoided. Reduced absorption of mycophenolate mofetil has been noted with magnesium- and aluminum hydroxide-containing antacids.[16] If such antacids and mycophenolate mofetil are both indicated, the agents should not be administered simultaneously.

Pharmacodynamic interactions. The addition of agents with myelosuppressive properties to mycophenolate mofetil therapy, as commonly occurs after transplantation, might increase the risk of bone marrow suppression in transplant patients. Vigilant monitoring of these individuals for evidence of bone marrow suppression is warranted. The combined use of ganciclovir and mycophenolate mofetil may result in a synergism that increases the risk of leukopenia.[17] The combined use of azathioprine and mycophenolate mofetil may produce synergistic and potentially toxic immunosuppression.

Adverse effects

Data on the adverse effects of mycophenolate mofetil are available from large, randomized, multicenter trials (Table 1). In general, mycophenolate mofetil is well tolerated. Adverse effects are primarily gastrointestinal. There have been no reports of nephrotoxicity. Overt hepatotoxicity has not been reported; however, transient elevations in liver enzymes have been noted in a few patients.[16] One hundred thirteen (12.4%) of the 910 patients enrolled in all published trials have required discontinuation of mycophenolate mofetil therapy for reasons directly attributed to the agent, including gastrointestinal complaints, cholestasis, hemorrhagic gastrointestinal complications, pancreatitis, and leukopenia.[10,16-21,32-34]

Gastrointestinal effects. Gastrointestinal effects are typically mild and may resolve after dosage adjustments, such as a reduced total daily dose or a change to three-times-daily therapy. Mild gastrointestinal effects include nausea, vomiting, diarrhea, constipation, and dyspepsia. Occasional severe complications, including cholecystitis, hemorrhagic gastritis, large-bowel perforation, and pancreatitis, have been observed.[17,33] In addition, there have been a few reports of mild ileus.[23] One death was related to intestinal obstruction.[40]

Bone marrow suppression. Initial reports questioned the association between mycophenolate mofetil therapy and myelosuppression, given the concomitant administration of additional agents with myelosuppressive properties.[27] Reports of leukopenia, thrombocytopenia, and anemia in psoriatic patients receiving mycophenolic acid as the sole immunosuppressive agent make an association between mycophenolate mofetil and bone marrow suppression likely.[35-38] In addition, in the European Mycophenolate Mofetil Cooperative Study,[33] an increased frequency of leukope-

Table 1.
Adverse Effects of Mycophenolate Mofetil in Renal Transplant Patients[25,32,33]

Adverse Effect	Frequency (%)			
	Placebo	Mycophenolate Mofetil		Azathioprine 1–2 mg/kg/day or 100–150 mg/day
		2 g/day	3 g/day	
Gastrointestinal				
Diarrhea	12.7	31.0	36.1	20.9
Abdominal pain	10.8	24.7	27.6	23.0
Dyspepsia	5.4	17.6	13.6	13.8
Nausea	2.4	19.9	23.6	24.5
Vomiting	1.2	12.5	13.6	9.2
Opportunistic infections				
CMV[a] (viremia)	13.3	13.4	12.4	13.8
CMV (tissue-invasive disease)	2.4	8.3	11.5	6.1
Herpes simplex	6.0	16.7	20.0	19.0
Herpes zoster	1.8	6.0	7.6	5.8
Candida species	7.8	0.6	0.6	0.3
Pneumocystis carinii	2.4	0.3	0.0	1.2
Aspergillus and *Mucor* species	0.6	0.3	0.9	0.3
Myelosuppression				
Leukopenia	4.2	23.2	34.5	24.8
Anemia	1.8	25.6	25.8	23.6
Thrombocytopenia	4.8	10.1	8.2	13.2

[a]CMV = cytomegalovirus.

nia was observed in the mycophenolate mofetil groups compared with patients receiving placebo. The percentage of patients receiving concomitant antilymphocyte agents was not significantly greater in the mycophenolate mofetil group during the study period.

Myelosuppression associated with mycophenolate mofetil therapy includes anemia, leukopenia, and thrombocytopenia.[10,16-21,32-34] Neutropenia, while rarely reported, does occur and may be related to concomitant administration of ganciclovir.[17] The frequency of myelosuppression in the two large randomized renal transplant studies ranged from 7% to 35%, with anemia and leukopenia being the most frequently reported manifestations.[32,33] Pancytopenia and agranulocytosis were rarely reported. Myelosuppression was frequent 30–180 days after transplantation. In most cases, myelosuppressive effects improved approximately one week after mycophenolate mofetil therapy was stopped. Similar rates of myelosuppression were observed with azathioprine.

Malignancies. Immunosuppressed patients are at increased risk for lymphomas and certain other malignancies. Nonmelanoma skin cancer has occurred in patients taking mycophenolate mofetil; it does not appear to be related to the dosage.[32,33] Lymphomas and lymphoproliferative disorders have occurred more commonly in mycophenolate mofetil-treated groups than in groups receiving placebo or azathioprine, but the overall frequency was <2%.[32,33]

Long-term follow-up of mycophenolate mofetil therapy in transplant recipients remains limited. In one study, though, 6 (7%) of 85 psoriasis patients developed malignancies during long-term (up to 13 years) mycophenolic acid administration.[35] The management of these psoriasis patients involved mycophenolic acid as the sole immunosuppressive agent. A greater incidence of malignancies may be observed with long-term administration of mycophenolate mofetil in transplant patients receiving additional immunosuppressive therapy.

Infections. Patients receiving immunosuppressive therapy are at greater risk for infectious complications. Opportunistic infections observed with mycophenolate mofetil therapy are similar to those observed with azathioprine.[32] CMV infection, including both tissue-invasive disease and viremia, is the most commonly observed opportunistic infection, having occurred in 186 (20.4%) of the 910 patients studied thus far.[10,16-21,32-34] Additional opportunistic infections noted during mycophenolate mofetil therapy include herpes simplex (14%), herpes zoster (5%), and candidal infections (1.9%). PCP and other fungal complications are rarely observed. The risk of infection may be related to the mycophenolate mofetil dosage. The combined data from the two large U.S. and European studies show that herpes simplex and tissue-invasive CMV occurred more commonly at 3 g/day than 2 g/day.[32,33] In addition, heightened risk of CMV infection has been observed in patients with increases in 12-hour mycophenolic acid AUCs.[41] In the U.S. and European trials, a definitive increase in additional opportunistic infections (herpes zoster and candida) was not observed in the mycophenolate mofetil 3-g/day groups.[32,33] An increased risk of infection has been observed in patients receiving mycophenolate mofetil concomitantly with muromonab-CD3.[42]

Contraindications and precautions

Mycophenolate mofetil is contraindicated in individuals with documented hypersensitivity to the drug and to mycophenolic acid. Animal studies do not indicate an impact of mycophenolic acid on spermatogenesis; however, failure of implantation in females was observed.[5] Because teratogenic effects have been seen in animals, women of childbearing potential should take measures to prevent conception while receiving mycophenolate mofetil.[25] Animal data also indicate that mycophenolate mofetil may be excreted in breast milk.[25] Women receiving mycophenolate mofetil should be instructed of potential harm to nursing infants. Not enough is known about mycophenolate mofetil's effects in pediatric patients for it to be recommended for pediatric use.

Monitoring

Patients receiving mycophenolate mofetil should be monitored for signs and symptoms consistent with rejection of the transplanted organ, for the development of infection or malignancy, and for the common adverse effects. Patients with gastrointestinal reactions should be instructed to take their medication with food. Alternatively, mycophenolate mofetil may be administered three times daily. In some cases the dosage may have to be reduced.

Mycophenolate mofetil is associated with a 23.2–34.5% frequency of leukopenia.[32,33] The risk of leukopenia may be increased during concomitant administration of ganciclovir and other myelosuppressive agents. Additional bone marrow-suppressive effects may occur. Complete blood counts should be done periodically.

Alterations in plasma albumin concentrations have been associated with increased concentrations of unbound mycophenolic acid. The immunosuppressive activity of mycophenolate mofetil is directly related to the concentration of unbound mycophenolic acid, with inhibition of IMPDH activity increasing as the free fraction of mycophenolic acid increases. Albumin concentrations should be routinely assessed in transplant patients receiving mycophenolate mofetil as immunosuppressive therapy.

Dosage and administration

Mycophenolate mofetil (Cellcept, Roche Laboratories) is available as a 250-mg capsule for oral use. The manufacturer recommends an initial dosage of 1 g twice daily.[25] The average daily wholesale cost of myco-

phenolate mofetil 1 g twice daily is approximately $15.[43] Mycophenolate mofetil therapy should be used in conjunction with cyclosporine and prednisone.[25] Clinical trials have demonstrated efficacy of mycophenolate mofetil in dosages up to 3 g/day.[32,33] However, high dosages have not demonstrated greater efficacy, and they increase the risk of adverse effects. Such doses should be avoided in patients with severe renal dysfunction (glomerular filtration rates of <25 mL/min).[32,33] Specific recommendations about mycophenolate mofetil dosages in patients with moderate or severe renal dysfunction are currently lacking. Notwithstanding reductions in maximum plasma mycophenolic acid levels, the AUC remains unchanged with concomitant ingestion of food.[25] To alleviate gastrointestinal adverse effects, mycophenolate mofetil may be administered with food in affected patients. Should neutropenia develop, mycophenolate mofetil therapy should be interrupted or the dosage adjusted accordingly.

Formulary considerations

Mycophenolate mofetil currently has FDA-approved labeling for use in the prophylaxis of rejection in allogeneic renal transplant patients. This drug provides an alternative to azathioprine for primary immunosuppression and may be used as rescue therapy. From current clinical data, it is unclear whether mycophenolate mofetil will supplant azathioprine in primary immunosuppressive regimens. Further clinical studies and pharmacoeconomic analyses are warranted, given the substantial cost of mycophenolate mofetil. However, centers experienced in solid-organ transplantation should have mycophenolate mofetil on the formulary. Institutions may wish to establish guidelines for the use of mycophenolate mofetil, with special attention given to targeted patient groups.

Conclusion

Mycophenolate mofetil has shown efficacy in the prevention of acute rejection after renal transplantation and is a promising rescue agent in kidney and heart transplant patients with acute rejection resistant to alternative therapy. More study is needed to assess the impact on long-term graft survival.

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