Published in final edited form as:

Transpl Infect Dis. 2009 August ; 11(4): 290–297. doi:10.1111/j.1399-3062.2009.00407.x.

Mycophenolate mofetil: effects on cellular immune subsets, infectious complications, and antimicrobial activity

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Abstract

Mycophenolate mofetil (MMF) is one of the most frequently used immunosuppressive drugs in solid organ transplant recipients. MMF is an inhibitor of inosine-5'-monophosphate, and is able to preferentially inhibit B-cell and T-cell function. The immunosuppressive abilities of MMF have made it one of the most successful anti-rejection drugs in transplant patients, but patients also appear to have increased susceptibility to infections, specifically cytomegalovirus and BK virus. Despite its association with an increased risk of infection, MMF has also exhibited antimicrobial activity against pathogens including hepatitis C, *Pneumocystis jirovecii*, and human immunodeficiency virus. A thorough understanding of the functions of MMF on the immune system and interaction with infectious pathogens could be helpful in implementing preventative strategies against opportunistic infections in transplant patients.

Keywords

mycophenolate mofetil; solid organ transplant; cytomegalovirus; BK virus

Mycophenolate mofetil (MMF) is a morpholinoethyl ester and a prodrug of mycophenolic acid (MPA), a potent inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH) (1). First approved by the US Food & Drug Administration for use in renal transplantation in 1995, MMF has now been used for over 10 years as an immunosuppressive agent in solid organ transplant recipients (2). According to the Scientific Registry of Transplant Recipients, currently 86% of renal transplant recipients receive MMF as part of their immunosuppressive regimen, most frequently in combinations with prednisone (Pr) and tacrolimus (Tac) (3). MMF is unique among transplant medications in its ability to inhibit both T-lymphocyte and B-lymphocyte activity. Its anti-B-lymphocytic activity has been targeted for the treatment of rheumatologic disease, and already has proven efficacy against lupus nephritis (4,5). However, the broad immunosuppressive abilities that make MMF an efficacious drug for transplant and autoimmune diseases might also enhance the risk of infectious complications (6).

Mechanism of action

The development of MMF as an immunosuppressive agent stemmed from observations in patients with 2 genetic illnesses. Children with an absence of adenosine deaminase, an enzyme responsible for the *de novo* production of guanosine monophosphate, had a combined immunodeficiency involving deficiencies in both T and B lymphocytes (7). However, children born with Lesch–Nyhan syndrome, a deficiency of hypoxanthine-guanine phosphoribosyl transferase, and thus the salvage production of guanosine monophosphate, suffered from neurologic abnormalities and gout, but had normal immune function (8). These 2 observations led scientists to look for an inhibitor specific for *de novo* guanosine monophosphate synthesis. MPA, a fermentation product of *Penicillium brevicompactum* and related fungi, is an inhibitor of IMPDH, and preferentially inhibits *de novo* guanosine synthesis. Depletion of *de novo* guanosine causes a lack of deoxyguanosine triphosphate, suppressing DNA synthesis and proliferation of T and B lymphocytes (9). An advantage of MPA is its preferential inhibition of the type II isoform of IMPDH. The type II isoform is expressed almost exclusively in activated T and B lymphocytes, while the type I isoform is expressed in most other cells. Therefore, the activity of MPA is specifically targeted toward T and B lymphocytes (10,11). MMF is the ester prodrug of MPA, and was found to increase oral bioavailability of the drug (12). Most studies have looked at the function and effects specifically of MPA on immune cells. However, because MMF is metabolized *in vivo* to MPA, no difference in immune activity is expected. MMF has now become one of the most frequent medications given to patients post transplant, and has proved extremely efficacious in preventing graft rejection.

Activity against T lymphocytes

MPA inhibits T-lymphocyte proliferation by decreasing *de novo* guanosine production and ultimately DNA synthesis in T lymphocytes. MPA has also been shown to increase apoptosis in human T lymphocytes, specifically in activated T lymphocytes (9). This was demonstrated by Nakamura et al. (13) when peripheral blood T lymphocytes stimulated with staphylococcal enterotoxin B and treated with MPA, showed a marked increase in apoptosis. Their findings suggested that MMF can induce apoptosis in antigen-activated T lymphocytes (13). Cohn et al. (14) also found that MPA increased apoptosis of activated T cells, specifically MOLT-4 cells, a human T-lymphocyte cell line derived from a patient with acute lymphoblastic leukemia.

Studies have also examined the effects of MPA on cytotoxic T cells, mostly in an effort to understand the effectiveness of MPA in preventing transplant rejection. Eugui et al. (15) showed that MPA exhibited a dose-dependent decrease in cytotoxic T-cell activity in mice.

Activity against B lymphocytes

As with T lymphocytes, MPA inhibits B lymphocytes via inhibition of IMPDH, and thus DNA synthesis in B lymphocytes. In addition, *in vitro* studies have shown that MPA inhibits the proliferation of human B lymphocytes and immunoglobulin (Ig) production in response to *Staphylococcus* protein A-sepharose (10). Jonsson and Carlsten (16) demonstrated that when a B-cell hybridoma was exposed to MPA, a decrease in IgG production occurred, as well as a decrease in cytokine levels and decreased proliferation of the cells.

In animal studies, MPA was first shown to inhibit antibody formation in rats immunized with sheep red blood cells (15). Subsequent studies found that MPA inhibited antibody production in response to influenza virus hemagglutinin in mice (9). Kimball et al. (17) found that when mice treated with equine-derived polyclonal antithymocyte immunoglobulin (ATGAM) received MMF, they had a significant decrease in the production of anti-ATGAM antibodies.

More recent literature suggests a reduction in pathogen specific Ig production in patients receiving MMF. Zmonarski et al. (18) studied 33 renal transplant patients who were found to have clinical cytomegalovirus (CMV) disease while on immunosuppression with 1 of 3 regimens: azathioprine (Aza) + cyclosporine (CyA) + Pr, or MMF + CyA + Pr, or Tac + MMF. The authors found no difference in CMV IgG levels between the patients on different regimens, but there was a decrease in CMV IgM production in the patients receiving MMF (18).

Other immunosuppressive activity

MPA has also been shown *in vivo* to inhibit the capacity of dendritic cells to efficiently present antigens to T lymphocytes (19). MPA reduces the recruitment of monocytes into sites of graft rejection and inflammation, and also increases apoptosis of monocytes (9). Studies also have found that MPA directly influences the function of endothelial cells, specifically disrupting leukocyte adhesion. In addition, the recruitment of lymphocytes and monocytes into inflammatory tissues is decreased by MPA (9).

Infectious complications associated with MMF

Infection in the post-transplantation period is a major cause of patient morbidity and is the most frequent cause of death of patients in the early post-transplant period (20). While the suppressive activity of MPA on multiple immune cell types results in decreased rates of transplant rejection, which is beneficial, it also dampens the normal immune response to infectious agents, which is detrimental. Pourfarziani et al. (21) performed a retrospective cohort study of patient and graft survival and causes of post-transplant admissions in renal transplant recipients who received either Aza or MMF as part of their immunosuppressive regimen. Their results showed that patient and graft survival rates were higher in patients who received MMF rather than Aza, and that rates of re-hospitalization for rejection were lower in MMF recipients. However, the rate of re-hospitalization for infection was significantly higher in patients who received MMF (50% versus 37%; $P = 0.002$), though neither the sites of infection nor the specific pathogens involved were described. The authors also found a small increase in mortality and intensive care unit admissions in the MMF cohort (21).

Another study demonstrated that late introduction of MMF, >1 year post transplant, resulted in increased rates of infection. Thirty patients receiving a regimen of prednisolone, CyA, and Aza post transplant were switched from Aza to MMF. The rate of infection increased significantly in patients after they were switched to MMF, with a preconversion rate of 26.7% and a post-conversion rate of 66.6% ($P < 0.0005$). Most post-conversion infections were upper respiratory tract infections (*Haemophilus influenzae* or *Staphylococcus aureus* in most cases, with 1 episode of *Moraxella catarrhalis*), followed by urinary tract infections (mostly *Escherichia coli* or *Klebsiella* species), 1 case of septic arthritis with *Streptococcus pneumoniae*, and 1 case of *S. pneumoniae* septicemia. All infections except 1 occurred >1 month after the patient was switched to MMF. The rate of recurrent infection also increased significantly post conversion to MMF, with a rate of 6.6% before conversion to MMF and 43.3% post conversion ($P < 0.0005$). The authors suggest that a possible contributing factor was decreased renal function post transplant, essentially increasing serum levels of MMF with standard doses (6).

CMV

The infectious complication most frequently associated with MMF is CMV disease. During the initial trials of MMF in transplant patients, MMF was associated with an increased rate of CMV disease. The US Renal Transplant Mycophenolate Mofetil Study Group, in a comparison of patients treated with MMF versus Aza, found a dose-dependent increase in tissue invasive

CMV disease with MMF versus Aza (10.8% at 3 g/day and 9.1% at 2 g/day versus 6.1% with Aza), but no statistical analysis was presented (22).

Moreso et al. (23) also found a dose-dependent increased rate of CMV disease in patients receiving MMF. In their study, patients who received high-dose Pr with Cya and MMF at 3 g/day had a very high incidence of CMV disease. But if either the Pr or Cya dose was decreased, or if the MMF dose was decreased to 2 g/day, the incidence of CMV disease decreased (23). However, use of ganciclovir prophylaxis in these study populations was not disclosed. In 2004, Wang et al. (24) reviewed randomized clinical trials in which patients received either Aza or MMF as part of their regimen. They looked at a total of 20 trials with 6870 patients who had undergone renal transplantation. They found a statistically significant increase in CMV disease in patients receiving 3 g/day of MMF versus Aza. While there was also an increase in CMV disease in patients receiving 2 g/day of MMF, the difference was not statistically significant (24). However, several other studies have also demonstrated an increased rate of CMV disease in patients on MMF at the recommended dose of 2 g/day (25–28). Jorge et al. (2) retrospectively examined the outcomes of the 280 renal transplants performed over a 10-year period. While MMF was successful in reducing early acute rejection and prolonging graft survival, there was a significantly higher rate of CMV disease in patients receiving MMF at the standard dose of 2 g/day versus Aza (2). A caveat in evaluating these studies is that in all 3, the use of ganciclovir prophylaxis was not noted. In both the Moreso and the Wang studies (23,24), MMF was associated with a statistically significant increase in leukopenia, especially at the higher dose of 3 g/day. Hence, it remains unclear whether the increase in CMV disease was secondary to increased leukopenia, or due to a direct action of MMF itself.

A recent study by the RESITRA network of the Spanish study group of infection in transplantation, which reported on the development of CMV disease after renal transplantation, did not list MMF among the risk factors (29). This study had the advantage of being very large (1470 renal transplant patients) and prospective. CMV disease occurred in 6.7% of patients, and after univariate and multivariate analyses, the factors independently associated with a statistically significant increase in CMV disease included donor age >60, Cya use, and chronic graft dysfunction. However, it is important to note that an analysis of the effect of MMF on CMV risk would have been difficult to ascertain, because a majority of the study patients (83.7%) received MMF as part of their post-transplant immunosuppressive regimen. Along the same lines, it is also noteworthy that use of sirolimus was associated with a decreased incidence of CMV disease, and that there was a statistically significant decrease in the use of MMF in patients who were taking sirolimus. Therefore, although the RESITRA study is important for advancing our knowledge of risk factors for CMV disease, it does not directly address the question of CMV disease as it pertains to MMF use.

Zmonarski et al. (18) found that patients with CMV disease who were receiving MMF had decreased levels of serum anti-CMV IgM compared with patients who were receiving Aza. In this study, 75 patients who underwent renal transplantation were monitored for the presence of CMV pp65 antigen. If the patient became pp65-positive 1–5 months post transplant, they were enrolled in the study. Serum CMV IgG and IgM levels were measured at the time of transplantation, 1–5 months after transplantation, and at the time of diagnosis of CMV disease. While no difference was found in CMV IgG levels in patients receiving regimens containing MMF versus Aza, there were statistically significant lower levels of IgM in the patients receiving regimens with MMF. Zmonarski et al. (18) suggest that decreased CMV IgM may have important clinical significance, as it may correlate with more severe CMV disease. Unfortunately the study was very small, with a total enrollment of 33 patients. A retrospective study by Hardwick et al. (30) specifically examined CMV IgG levels in renal transplant recipients who received either Aza or MMF and developed CMV disease. They reviewed serum CMV IgG antibody levels as determined by enzyme immunoassay (drawn approximately 1

month after transplantation), and found no difference between the level of CMV IgG in patients on MMF versus Aza (30). As in the Zmonarski study (18), the authors did not find a decrease in CMV IgG in patients receiving MMF, but they did not examine CMV IgM levels. The underlying vulnerability of patients on MMF to CMV disease has yet to be thoroughly understood, but these studies raise the possibility that CMV IgM levels may correlate with the risk of CMV disease in patients receiving MMF.

Although CMV disease may occur more often in those patients who are on MMF, MMF-treated patients tend to have better outcomes with CMV. This is believed to be due to a synergistic effect of MMF on ganciclovir (31). In a study by Giral et al. (32), patients with CMV disease receiving MMF had less CMV disease-associated graft loss than patients receiving Aza. Hence, although the incidence of CMV disease may be higher in patients with MMF, once ganciclovir is started, patient outcomes tend to improve. Future studies may consider investigating at what point to start ganciclovir therapy in patients receiving MMF and whether preemptive or prophylactic ganciclovir may be safer in this more vulnerable population.

BKV

BKV infection has emerged as an especially important infection in the transplant recipient. BK virus nephropathy (BKVN) has been associated with allograft dysfunction and graft failure in 1–8% of renal transplant recipients, with a loss of the allograft occurring in half the cases (33–35).

BKV viremia has been associated with the use of higher dose immunosuppressive regimens (36). Several studies have shown that regimens that include MMF with Tac increase the incidence of BKV viremia. Mengel et al. (37) examined 1276 renal biopsies from 638 renal transplant patients and found that of the patients with BKVN, 6 of the 7 were on highly immunosuppressive regimens that included Tac and/or MMF. Shi et al. (38) studied 7 cases of BKVN in 80 renal transplant recipients and found that a significantly higher number of patients who developed BKVN had been on Tac and MMF. Upon histological examination, all of the patients who had severe BKVN had been receiving Tac and MMF. In addition, all graft failures occurred in patients on MMF and Tac (38). Finally, Barton et al. (39) found that MMF use was an independent risk factor for development of BK viruria in non-renal solid organ transplant recipients. In 34 non-renal solid organ transplant (lung, liver, heart, heart-lung) patients with chronic renal dysfunction, 5 had BKV viruria, all of whom were receiving MMF (5 of 19 [26%] versus 0 of 15 who were not; $P = 0.03$) (39).

While agents such as cidofovir and leflunomide have been investigated as possible therapies for BKVN, at this time the standard treatment is reduction in or removal of immunosuppression, which again emphasizes the essential role that immunosuppressive drugs play in the development of BKVN (40).

Other infections associated with MMF

MMF use has also been associated with increased susceptibility to varicella disease. Lauzurica et al. (40) published 4 case reports of disseminated varicella among 275 renal transplant recipients. The authors noted that, before the initiation of MMF, they had never seen a case of varicella in their transplant recipients. However, other studies have not found a significant association (41).

Meier-Kriesche et al. (27) found a statistically significant increase in fungal infections in their geriatric renal transplant population receiving MMF versus Aza, but the specific organisms and sites of infection were not reported.

Possible antimicrobial activity of MMF

Interestingly, while MMF is associated with an increased risk of infection, published reports suggest that it may have antimicrobial effects against certain pathogens (Table 1) (42–52). The first published reports of the antimicrobial properties of mycophenolate were published in the 1960s when *in vitro* studies showed inhibition of vaccinia virus, herpes simplex virus, Coxsackie virus, and influenza virus by MMF (53,54). Since that time, studies have identified other infections inhibited by MMF.

In vitro studies with dengue virus showed that MPA completely inhibited infection of human cells by the virus (42,43). In patients with chronic hepatitis C virus (HCV) disease, MMF was shown to be a potent *in vitro* inhibitor of HCV replication. Interestingly, the inhibition was independent of cell proliferation and guanosine depletion, so the true mechanism of action is unknown (44). However, a prospective randomized trial of MMF in liver transplants with HCV showed no impact on patient survival, graft survival, rejection, or rate of HCV recurrence. The authors suggest that while MMF has *in vitro* activity against HCV, the overall immunosuppressive properties of the drug may dominate *in vivo* (45). MMF was also found to have some activity against hepatitis B virus *in vitro* (46), but has not been found to be effective *in vivo* (47).

MMF has been shown to have a possible protective effect against *Pneumocystis jirovecii* pneumonia (PCP) (48,49). This has raised the question of the necessity of PCP prophylaxis in patients on MMF. Isolated reports suggest MMF may also have activity against Coxsackie virus (50), West Nile virus (51), and yellow fever virus (52). At this point, MMF is not a standard therapy for any of these infections.

Finally, MMF has demonstrated activity against human immunodeficiency virus (HIV) both *in vivo* and *in vitro* (55–61). Its role against HIV is somewhat controversial. MPA is consistently shown to increase the activity of other antiretrovirals, but it is unclear if MPA alone has effective activity against the virus (62,63). MPA is known to be active against HIV especially in combination with abacavir (64,65). The mechanism of anti-HIV activity is believed to be secondary to guanosine triphosphate depletion, with the inhibition of reverse transcriptase, and also through a reduction in gp120 expression in transformed cells (66). Several studies suggested that MPA may have a role in the treatment of multidrug-resistant HIV infection; however, clinical trials have failed to show a significant benefit from the addition of MMF to anti-retroviral regimens. Sankatsing et al. (55) found that MMF did not significantly increase either the plasma HIV-1 RNA decay rate or the decay rate of latently infected cells when it was added to a triple class antiretroviral regimen in treatment-naïve patients.

Conclusion

As the use of MMF increases in transplant recipients and in autoimmune diseases, it has become more important to fully understand its impact on infectious complications. Further studies are needed to investigate how the effects of MMF on immune cells predispose patients to specific infections. Such information may make it possible to anticipate the infections, and help determine the choice and length of prophylactic antimicrobials in transplant recipients receiving MMF.

In addition, the possible antimicrobial activities of MMF could be utilized in sparing patients from unnecessary prophylaxis, or in guiding the use of MMF in specific populations. For instance, if further studies are able to fully decipher the relationship between MMF and PCP, an argument could be made for modifying PCP prophylaxis in patients receiving MMF. In doing such, patients could be spared the possible hematopoietic side effects of trime-thoprim-

sulfamethoxazole. Given the *in vivo* activity of MMF against HIV, future studies could investigate the possible benefits of using MMF in HIV-positive transplant patients.

A better understanding of the activity of MMF against these infections could benefit future transplant recipients and improve the overall outcomes of patients in the post-transplant period.

Acknowledgments

This work was supported by grants from National Institutes of Health Grants R01AI045459 and R01AI035370 to L.P.

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Table1

The effects of mycophenolate mofetil (MMF) on select infections

Pathogen	Related studies Author (year), reference	Findings	Proposed mechanism of action
Dengue virus (DV)	Diamond et al. (2002), (42)	<i>In vitro</i> , MPA blocked DV infection of hepatoma cell lines by 99%	MPA prevents the synthesis and accumulation of DV RNA
	Takhampunya et al. (2006), (43)	<i>In vitro</i> , MPA resulted in a fivefold increase in defective DV RNA production in monkey kidney cells	MPA depletes intracellular GTP pool, inhibiting DV RNA production and viral replication
Hepatitis C virus (HCV)	Henry et al. (2006), (44)	<i>In vitro</i> HCV-replication model with a luciferase reporter gene; MPA inhibited HCV replication to 75%; Inhibition was independent of guanosine production	Unknown, but appears to be independent of guanosine depletion
	Jain et al. (2002), (45)	Randomized clinical trial of patients with HCV undergoing liver transplant; received either TAC plus prednisone, or TAC plus prednisone plus MMF; MMF had no impact on patients survival, graft survival, rejection, or rate of HCV recurrence	MMF either has no anti-HCV activity, or its immunosuppressive properties overwhelm its antiviral effect in the clinical setting
Hepatitis B virus (HBV)	Wu et al. (2003), (46)	<i>In vitro</i> , 2.2.15 cells were treated with different concentrations of MPA. MPA decreased expression of HBsAg, HBeAg, and HBV DNA in a dose-dependent manner	MPA suppresses expression of HBsAg and HBeAg as well as replication of HBV DNA
	Ben Ari et al. (2001), (47)	Prospective study of 4 liver allograft recipients with recurrent HBV infection resistant to lamivudine received MMF, in addition to decreased doses of corticosteroid and cyclosporine. After 8 weeks of therapy, serum ALT increased in 2 patients, remained stable in 1 patient, and decreased in 1. Serum HBV DNA levels increased in 3 patients, and decreased in 1	MMF at the dosage used is not effective at suppressing HBV replication
<i>Pneumocystis jirovecii</i>	Oz et al. (1997), (48)	Virus-free Sprague–Dawley rats were treated with TAC, sirolimus, dexamethasone, and/or MMF. Increased rates of PCP seen in rats which received TAC, sirolimus, or dexamethasone, but none of the rats treated with MMF or MMF plus dexamethasone had PCP	Unclear mechanism by which MMF appears to have antimicrobial action against <i>Pneumocystis</i>
	Husain et al. (2002), (49)	Combined data from 4 clinical trials where patients received MMF. None of the patients receiving MMF developed PCP (0/1068) while 10 of the patients not receiving MMF developed PCP (1.8%)	Unclear mechanism by which MMF exerts protection against PCP
Coxsackie virus B3 (CVB3)	Padalko et al. (2003), (50)	C3H-mice were infected with CBV3 and received twice daily MMF for 7 days. Mice who received MMF had significant reduction in the development of CBV-induced myocarditis (dose dependent)	Unclear, but not believed to be due to inhibition of viral replication since the titers of infectious virus and viral RNA were increased in mice treated with MMF
West Nile virus (WNV)	Morrey et al. (2002), (51)	MA-104 cells infected with New York WNV; assays used to measure inhibition of virus showed MPA to be one of the most potent antivirals; it was even more active against a Ugandan strain of WNV	Unclear antiviral activity <i>in vitro</i> against WNV
Yellow fever virus (YFV)	Neyts et al. (1996), (52)	Used the attenuated vaccine strain 17D of YFV to evaluate inhibitory effect in infected Vero cells. MPA was a strong inhibitor of YFV, but had little or no effect on Bunya virus Punta Toro or HSV	MPA has anti-YFV activity, but it is not merely cytotoxic, given the lack of activity against Bunya virus Punta Toro and HSV

GTP, guanosine triphosphate; TAC, tacrolimus; MPA, mycophenolic acid; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B virus early antigen; ALT, alanine aminotransferase; PCP, *Pneumocystis jirovecii* pneumonia; TAC, tacrolimus; HSV, herpes simplex virus.