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Cytomegalovirus Infection and Abdominal Pain with Mycophenolate Mofetil

Is There a Link?

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Abstract

Mycophenolate mofetil (MMF) is an immunosuppressive agent that exerts relatively selective antiproliferative effects on T and B lymphocytes. Efficacy has been demonstrated in large-scale randomised studies, but the use of MMF is complicated by gastrointestinal upset and is associated with an increased incidence of tissue-invasive cytomegalovirus (CMV) disease.

The gastrointestinal tract is a well recognised site for invasive CMV disease, and it has therefore been hypothesised that the abdominal pain commonly seen with MMF is related to CMV infection. This has only been tested in a single small uncontrolled study, where abdominal pain was associated with the presence of CMV on endoscopic biopsy. In contrast, the toxicity profile in 85 patients with psoriasis who had received relatively high dosages of mycophenolic acid, the active moiety of MMF, for up to 13 years showed that the incidence of gastrointestinal upset fell dramatically over time.

We can find little evidence that CMV disease explains the gastrointestinal adverse event profile associated with MMF, and instead support the contention that high local concentrations of MMF have a direct toxic effect on cells of the small intestine. We do not recommend any changes to current policy on CMV prophylaxis in patients receiving MMF, although we recognise that some severe gastrointestinal adverse effects may be CMV-associated. The use of trough plasma concentration monitoring, divided doses and a gradually increasing dosage schedule may be of value in limiting toxicity.

1. Mycophenolate Mofetil (MMF)

1.1 Pharmacology

Mycophenolate mofetil (MMF) is an immunosuppressive agent introduced into clinical practice in 1995 for the prevention and treatment of allograft rejection. More recently, it has also been used for the treatment of autoimmune disease. MMF is a prodrug that is rapidly hydrolysed by esterases to the active compound mycophenolic acid (MPA) [fig. 1]. MPA was initially isolated from a Penicillium culture at the end of the 19th century,[1] and studied at the beginning of the 1970s for the treatment of refractory psoriasis and cancer.[2] MPA is a potent, noncompetitive, reversible inhibitor of eukaryotic inosine monophosphate dehydrogenase

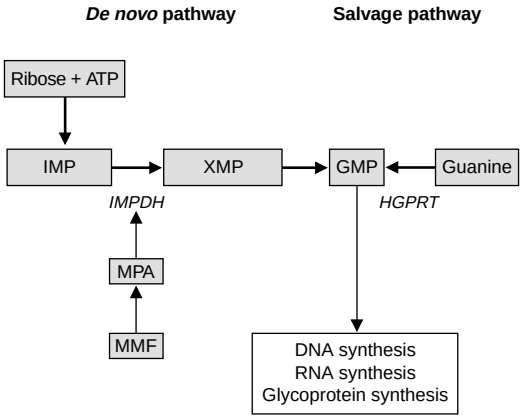

Fig. 1. Inhibitory action of mycophenolate mofetil (MMF) and its relationship to the *de novo* and salvage metabolic pathways of purine nucleotide biosynthesis. After absorption, MMF is converted to mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase (IMPDH). This blocks *de novo* purine nucleotide synthesis and depletes the cell of guanosine 5′-monophosphate (GMP). Lymphocytes are highly dependent upon this pathway and are therefore very sensitive to MMF. Most other cells can also use the salvage pathway, which recycles sugars and other products to guanine and GMP, and are therefore relatively resistant to MMF. **ATP** = adenosine 5′-triphosphate; **HGPRT** = hypoxanthine-guanosine phosphoribosyl transferase; **IMP** = inosine 5′-monophosphate; **XMP** = xanthosine 5′-monophosphate.

(IMPDH). This inhibition blocks the *de novo* pathway of purine nucleotide synthesis and depletes the cell of guanine nucleotides. Lymphocytes depend primarily on *de novo* purine nucleotide synthesis, as compared with neutrophils which may also use a salvage pathway, and MMF therefore exerts a degree of specificity towards T and B cells. In addition to effects on lymphocyte proliferation and antigen-specific antibody responses, MMF may exert additional immunosuppressive actions via inhibition of the glycosylation of intercellular adhesion molecules.[3]

1.2 Indications

MMF is currently licensed for the prophylaxis of acute renal or cardiac transplant rejection in combination with calcineurin inhibitors (cyclosporin and tacrolimus) and corticosteroids. MMF has been evaluated as prophylaxis against acute renal allograft rejection in 3 large, randomised, double-blind trials at dosages of 2 or 3 g/day. The European Mycophenolate Mofetil Co-operative Study Group[4] was a placebo-controlled trial, whereas the US Renal Transplant Mycophenolate Mofetil Study Group[5] and the Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group[6] compared MMF with azathioprine. Patients who received MMF had significant reductions in rates of treatment failure in each study and required fewer courses of bolus corticosteroid therapy for acute rejection. MMF has been studied, albeit in smaller patient groups, as prophylaxis against acute rejection in liver, cardiac and pancreas transplantation.[7] MMF also seems to be an effective agent in rescue therapy for refractory rejection in renal,[8] liver[9] and cardiac[10] allografts, and may play a role (beyond the advantage conferred by the reduction in the incidence of acute rejection) in the prevention of chronic allograft dysfunction.[11] Other uses of MMF have included Crohn's disease, inflammatory eye disease, lupus nephritis and vasculitis, although clinical experience in most of these nontransplant settings remains limited.[12] This review will focus on evidence derived primarily from studies in renal transplantation, the area in which the largest body of experience with MMF can be found.

1.3 Adverse Effects

The principal adverse effects of MMF are gastrointestinal, haematological (anaemia, leucopenia and thrombocytopenia) and opportunistic infection (most commonly herpes simplex and cytomegalovirus).[13] The multicentre study in the US[5] reported that 3 patients receiving MMF had developed lymphoproliferative disease compared with none in the azathioprine group. In the Tricontinental study,[6] the numbers for the MMF and azathioprine groups were 4 and 1, respectively. It remains to be determined whether these reports represent a true increase in the incidence of cancer. The 3-year follow-up reports on toxicity from the 3 renal transplant studies do not demonstrate any additional toxic effects.[14] The adverse events data from the

Table I. Adverse events for mycophenolate mofetil 2 and 3 g/day in combination with cyclosporin in the renal allograft rejection prophylaxis trials. Values are the percentage of patients experiencing the events

Adverse event	European study[4]			US[5] and Tricontinental[6] studies[a]		
	placebo (n = 166)	MMF 2 g/day (n = 165)	MMF 3 g/day (n = 160)	azathioprine (n = 326)	MMF 2 g/day (n = 336)	MMF 3 g/day (n = 330)
Gastrointestinal						
Abdominal pain	10.8	11.5	11.3	23.0	26.0	31.0
Nausea	2.4	4.2	6.3	20.0	14.0	20.0
Vomiting	1.2	2.4	3.8	6.0	12.0	16.0
Diarrhoea	12.7	12.7	15.6	12.7	12.7	15.6
Haematological						
Anaemia	1.8	4.2	6.8	10.0	15.0	9.0
Leucopenia	4.2	10.9	13.8	30.0	19.0	35.0
Thrombocytopenia	4.8	4.2	3.1	12.0	9.0	5.0
Infections						
Systemic	NR	NR	NR	15.0	15.0	19.0
Opportunistic						
CMV viraemia	13.3	15.8	15.0	13.6	13.2	12.2
CMV tissue invasion	2.4	3.0	6.9	6.1	8.0	10.9
herpes simplex	6.0	14.5	11.3	19.0	17.2	20.0
herpes zoster	1.8	6.7	5.0	5.6	5.9	7.3
Pneumocystis pneumonia	2.4	0.0	0.0	1.6	0.0	0.0

a Weighted means.

CMV = cytomegalovirus; **MMF** = mycophenolate mofetil; **NR** = data not reported.

European, Tricontinental and US studies are summarised in table I.

1.4 Strategies for Reduction of Adverse Effects

The role of therapeutic drug monitoring in MMF therapy remains uncertain. Full pharmacokinetic profiles are cumbersome and expensive. A limited sampling procedure can be used to predict the area under the concentration-time curve (AUC),[15] but initial studies have not demonstrated a relationship between the plasma AUC of MPA and MMF toxicity.[16,17] A small pilot study of 15 patients indicated that trough MPA concentrations may predict the occurrence of adverse effects,[18] although a larger subsequent study failed to confirm this finding and instead suggested that the most important predictor of adverse events was MMF dosage.[17] The absorption of MPA is reduced and delayed by food[19] and, although the manufacturer recommends that MMF be taken on an empty stomach, the administration of the drug with food may reduce peak MPA concentrations and the incidence of gastrointestinal upset.[20] By the same token, MMF has also been given in 3 or 4 divided daily doses with food to improve compliance.[20]

An increase in MPA trough concentrations and AUCs in patients who received tacrolimus as compared with patients who received cyclosporin has been reported,[21] and this is probably a consequence of tacrolimus-mediated inhibition of MPA glucuronidation.[22] Clinical data from the US FK506/MMF Dose-Ranging Kidney Transplant Study Group indicated that the combination of tacrolimus plus MMF 1 or 2 g/day had a similar adverse event profile to that of tacrolimus plus azathioprine, with the exception of an increased frequency of diarrhoea (44.1% with 1g and 63.8% with 2g *vs* 40.7% with azathioprine) and paraesthesiae in both groups who received MMF.[23] The efficacy of an MMF 1 g/tacrolimus combination in

preventing episodes of acute rejection in this study was no different to that of tacrolimus plus azathioprine,[23] and the high frequency of diarrhoea with MMF 2g/tacrolimus clearly represents a major barrier to tolerability.

The European tacrolimus/MMF data revealed that the combination of tacrolimus with MMF 1 g/day and corticosteroids was associated with a far lower acute rejection rate than that seen with tacrolimus plus corticosteroids alone (13.8 *vs* 32.8%),[24] although it should be noted that the rejection rate in the group that did not receive MMF was higher than that previously reported for this combination.[25] This may be a reflection of the fact that there was no lower limit set for the tacrolimus target concentrations in the European study, which may be of particular importance as no azathioprine was used. By a similar token, these data do not allow the important comparison between tacrolimus plus MMF 1 g/day and tacrolimus plus azathioprine to be made. A 1.5 g/day regimen may represent an acceptable therapeutic compromise, although this is unproven.

In combination with cyclosporin, the incidence of many MMF-associated adverse events, including gastrointestinal upset and opportunistic infection, can be reduced by avoiding the 3 g/day regimen (table I). The interaction between these 2 agents is complex in that the combination of MMF with cyclosporin is associated with lower trough MPA concentrations than those seen with identical MMF doses used alone,[26] despite the fact that cyclosporin *in vitro* inhibits the activity of the enzyme uridine diphospho-glucuronyl transferase, which converts MPA to an inactive glucuronide metabolite.[22]

2. Cytomegalovirus (CMV) Infection in Transplant Recipients

2.1 Incidence and Significance

Cytomegalovirus (CMV) infection remains a significant cause of morbidity and mortality after transplantation, with the incidence of symptomatic infection in kidney, liver, heart and heart-lung transplant recipients reported as 8, 29, 25 and 39%, respectively.[27] In contrast with the self-limiting mononucleosis-like syndrome associated with CMV infection in an immunocompetent host, the solid organ transplant recipient presenting with CMV infection frequently displays tissue-invasive disease, particularly of the lung, liver, gastrointestinal tract and eye. CMV infection itself may modulate the immune system, resulting in a higher net state of immunosuppression and an increased risk of bacterial and fungal infections.[28,29] A role for CMV has also been proposed in the pathogenesis of chronic renal allograft rejection,[30] transplant renal artery stenosis,[31] accelerated atherogenesis in cardiac allografts[32] and bronchiolitis obliterans in lung allografts.[33]

2.2 Strategies for Prevention

Primary CMV infection is mainly transmitted to transplant recipients by the donor organ, and to a lesser extent by blood products, whereas secondary infection occurs when endogenous virus is reactivated in a CMV-seropositive individual. The risk of infection is closely related to the intensity of immunosuppression, particularly the use of antilymphocyte antibody therapy.[34-35] A lack of cellular and humoral immunity, as defined by the absence of anti-CMV antibodies, places the recipient in a high risk category for symptomatic primary CMV infection upon receiving a CMV-seropositive donor organ, and a number of prophylactic strategies for such high risk 'D^+/R^-' pairings and for individuals receiving antibody induction therapy have been proposed. These have been reviewed elsewhere,[36] but include passive immunoprophylaxis with CMV hyperimmune globulin, antiviral therapy with aciclovir, ganciclovir or valaciclovir, and a pre-emptive approach where antiviral agents are administered to individuals developing serological evidence of CMV infection but before symptoms develop.

3. CMV and Abdominal Pain with MMF-Based Immunosuppression

3.1 Data from the Large Randomised Trials

The occurrence of gastrointestinal adverse effects and CMV infection (both in terms of CMV viraemia and tissue-invasive disease) has been clearly documented for all 3 large-scale trials of MMF for prophylaxis against acute renal allograft rejection. In the European study,[4] the incidence of total gastrointestinal adverse events was 45.5 and 52.5% for the MMF 2 and 3 g/day groups, respectively, compared with 41.6% in the placebo arm, whereas the incidence of abdominal pain was 11.5 and 11.3% for the MMF 2 and 3 g/day groups versus 10.8% with placebo. The incidence of CMV viraemia was similar in all 3 groups (which had been balanced for donor and recipient CMV seropositivity), although there was a higher percentage of tissue-invasive CMV disease with MMF 3 g/day. In the Tricontinental trial,[6] abdominal pain was noted in 26% of patients receiving MMF 2 g/day and 31% of patients receiving MMF 3 g/day compared with 23% of patients receiving azathioprine. The incidences of CMV viraemia and CMV tissue-invasive disease, respectively, were 12 and 6% with azathioprine, 12 and 7% with MMF 2 g/day and 11 and 11% with MMF 3 g/day, results in accordance with those of the European study. In the US study,[5] gastrointestinal adverse effects were again more frequent with MMF 2 and 3 g/day than with azathioprine. There were no differences between the groups in the incidence of CMV viraemia, but CMV tissue invasion was more common in both groups that received MMF (10.8% with 3 g/day and 9.1% with 2 g/day *vs* 6.1% with azathioprine).

3.2 Is MMF a Risk Factor for CMV Infection?

Although data from all these 3 studies suggest an increase in CMV tissue-invasive disease with MMF compared with placebo or azathioprine, the relatively small numbers of patients developing CMV in all groups precluded any meaningful statistical analysis. This issue has therefore been specifically addressed in 3 case-control studies.[37-39]

There was no evidence that MMF was an independent risk factor for CMV infection as defined by immunoglobulin G seroconversion.[37,38] However, the frequency of CMV disease, defined as CMV infection plus evidence of viral syndrome (fever for at least 48 hours with 1 or more of malaise, arthralgia, leucopenia or thrombocytopenia) or CMV organ involvement, was significantly higher in patients who received MMF 2 g/day than in patients who received azathioprine (58 *vs* 18%, $p < 0.05$) in one study,[39] and in patients who received MMF (most receiving 2 g/day) compared with placebo (67 *vs* 30%, $p < 0.05$) in a second study.[38] Although the weaknesses of such case-control designs should be recognised, these findings are in accordance with the trends reported in the multicentre trials and we believe they are likely to represent real differences.

However, although there will be reporting and analytical differences between the 3 large randomised trials, it is noteworthy that the incidence of tissue-invasive CMV in the azathioprine arms of the US and Tricontinental studies is similar to that in the MMF 3 g/day arm of the European study (table I). Furthermore, data from a small nonblind study suggest that the incidence of CMV tissue invasion is greatly reduced by using a combination of MMF 3 g/day with low dosage cyclosporin,[40] consistent with the possibility that the high incidence of CMV infection observed with MMF is not a specific consequence of this agent but rather results from an increase in total immunosuppressive exposure. The trial data, however, do not indicate that the use of MMF is accompanied by an increase in bacterial or fungal infections, mitigating against the suggestion that it is a general attenuation of the immune response that is primarily responsible for the increased incidence of CMV disease.

It has therefore been suggested that MMF induces specific changes in the primary response to CMV infections, which leads more frequently to symptomatic disease. However, the effect of MMF upon natural killer cells and upon activated viral-

specific cytotoxic T lymphocytes, known to be important in recovery from primary CMV infection, is not known.[38]

3.3 Abdominal Pain with MMF Therapy – Is CMV the Culprit?

The gastrointestinal tract is a well-recognised site for invasive CMV disease,[41] and the possibility of an aetiological link between the increased incidences of both CMV disease and gastrointestinal adverse events which is seen with MMF therapy was first raised by the authors of the Tricontinental study.[6] These data could not, however, exclude the alternative hypothesis, namely that the increased diagnosis of CMV invasion was attributable to more frequent endoscopic investigation in these patients.

Kaplan et al.[42] therefore sought to determine the prevalence of active CMV in the upper gastrointestinal tracts of renal transplant patients who received MMF and who presented with persistent abdominal pain during the first 6 months after transplantation. Given that the incidence of abdominal pain with MMF therapy may be as high as 30%,[6] the demonstration of such a causal relationship might have important implications with respect to strategies for prophylaxis against CMV infection in patients who receive MMF. All 62 renal allograft recipients receiving MMF in a single centre were evaluated in this study, and the 10 patients who presented with persistent mid-epigastric pain during the first 6 months underwent oesophagogastroduodenoscopy with biopsy. Of the 10 patients, 9 showed gastric or duodenal ulceration, and biopsy specimens on these 9 patients showed both inclusion bodies and positive staining for p52 delayed early DNA-binding protein, diagnostic of CMV disease. On logistic regression analysis, the D^+/R^- pairing, but not the use of MMF dosages greater than 2 g/day, emerged as a statistically significant independent risk factor for the development of abdominal pain. The conclusion was that CMV was likely to play a role in much of the abdominal pain seen in patients receiving MMF therapy.

However, this study is open to criticism. The numbers involved were small and, more importantly, the study was entirely uncontrolled. The absence of endoscopic studies on either patients who received MMF without symptoms of mid-epigastric pain, or on patients receiving other forms of immunosuppression, prevents any firm conclusion with respect to causality. Furthermore, as the investigators stated, no investigations were performed during the study to determine the extent of systemic activation of CMV in these patients.

The long term use of MPA in psoriasis has allowed a revealing systemic toxicity profile to be drawn from 85 patients who had received the drug for up to 13 years.[43] In patients who had received about 3 g/day of MPA, 75% initially had gastrointestinal symptoms, including cramping, diarrhoea and nausea. Over several years of therapy, the frequency of these symptoms dropped to between 11 and 27%. Although it remains possible that many of these cases were caused by self-limiting CMV disease, the overall burden of immunosuppression in these patients was less than in the typical transplant recipient, and these data mitigate against a causal role for CMV in the typical gastrointestinal toxicity profile associated with MMF.

The implication instead is that noninfective mechanisms, such as local irritation and interference with the rapidly dividing cells of the gastrointestinal tract,[44] are the more important contributors. In a rodent model it has been shown that MPA does not inhibit proliferation of small intestinal epithelial cells under conditions in which this agent did inhibit proliferation of lymphocytes in lymph nodes and the spleen.[45] This is likely to reflect the fact that MPA has significantly greater activity on IMPDH type 2, expressed in lymphocytes, than on IMPDH type 1, the constitutive isoform expressed in other cell types. However, MPA may be present at particularly high concentrations in the gut after oral administration,[46] and it is known that high dosages of MMF can inhibit the proliferation of basal epithelial cells of the small intestine in mice,[47] thus providing a potential local mechanism of toxicity. Furthermore, an association has been demon-

strated, albeit in a single patient, between MMF and villous atrophy, which had completely regressed 6 months after withdrawal of the drug.[46] Recent data also reveal the potential of an acyl glucuronide metabolite of MPA to induce the release of the proinflammatory cytokines interleukin-6 and tumour necrosis factor-α from human mononuclear leucocytes,[48] and although not yet studied in intestinal epithelial cells, this may represent a significant pathway for the generation of local adverse effects.

4. Conclusions

CMV is undoubtedly associated with severe gastrointestinal adverse events. Although the incidence of CMV enteropathy is likely to be increased in patients receiving MMF, such events are likely to account for a minor proportion of the gastrointestinal toxicity related to the use of this drug, which instead is most probably consequent upon local antiproliferative and proinflammatory effects. While encouraging a high degree of vigilance for early evidence of CMV infection, we would not recommend extending the current strategy adopted by most units for CMV prophylaxis in those at greatest risk, namely D^+/R^- patients and those receiving antibody induction therapy, to include all individuals receiving MMF.

The incidence of adverse events with MMF therapy has been demonstrated, albeit in a small group, to be associated with high trough concentrations of the drug,[18] and it may be that alteration in the administration regimen to reduce these trough concentrations to below 4 mg/L may limit toxicity. Experience (largely anecdotal) also suggests that adverse effects may be reduced if MMF is given in divided doses (usually 4 times, rather than twice, daily) and with food. This strategy, together with the use of a gradually increasing dosage schedule, should be explored further.

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