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Adverse Gastrointestinal Effects of Mycophenolate Mofetil

Aetiology, Incidence and Management

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Contents

Abstract

Mycophenolate mofetil (MMF) is a relatively new immunosuppressive drug. It inhibits inosine monophosphate dehydrogenase, a key enzyme in the *de novo* pathway of purine synthesis, and thus causes lymphocyte-selective immunosuppression. Large clinical trials have revealed the efficacy of MMF in the prevention of allograft rejection when administered together with cyclosporin or tacrolimus and corticosteroids.

Although the adverse effect profile of MMF is comparatively benign, gastrointestinal adverse effects are a major concern. These effects are partially explained by the increased immune suppression, by the mode of action and by interactions, particularly with other immunosuppressants. The aetiology of the rarest gastrointestinal adverse effects is still not completely clear. Therapy depends upon the clinical gravity of the adverse effects and is therefore a case of waiting and ob-

serving. An adjustment of dosage of immunosuppressants according to the clinical situation and, particularly in the case of MMF, spreading the total dosage over more than 2 daily doses are often sufficient. Should adverse effects persist for a longer period of time and be of a more serious nature, a comprehensive invasive diagnostic process is necessary, including endoscopy and biopsy and the search for opportunistic infections. In this case, dosage reduction or the complete withdrawal of MMF seems to be unavoidable.

Severe gastrointestinal complications with MMF are rare, but when they do occur they may require extensive diagnosis and treatment. In the future, therapeutic drug monitoring and, where necessary, pharmacological modifications of MMF could lead to a further reduction of adverse effects with an equal or even increased efficacy.

Organ transplantation is a widely used procedure for patients with end-stage organ failure. Acute rejection is still the most frequent cause of graft loss within the first year. With calcineurin inhibitor–based immunosuppression (cyclosporin and tacrolimus), 40 to 60% of renal transplant recipients experience at least 1 episode of acute rejection during the first year.[1] Treatment of acute rejection involves administration of high doses of corticosteroids and/or antilymphocyte preparations,[2] and graft loss is common in patients who do not respond. In recent years, several new immunosuppressive drugs have been tested in large clinical trials and some of them have already been licensed for several indications.

Mycophenolate mofetil (MMF) is one of these new immunosuppressive agents. It prevents the replication of T and B lymphocytes by inhibiting the *de novo* pathway of purine synthesis.[3] By its unique mode of action it improves baseline immunosuppression without adding significant toxicity. The drug has been shown to prevent rejection in several animal transplant models,[4] and even to be capable of reversing ongoing rejection.[5] However, gastrointestinal adverse effects with MMF seem to be a major concern. Most gastrointestinal adverse effects are of an irritative nature, but some gastrointestinal haemorrhages and intestinal perforations have also been reported. This review attempts to summarise the current knowledge of the aetiology, incidence and management of these gastrointestinal adverse effects.

1. Mode of Action and Pharmacology

The aetiology of the gastrointestinal adverse effects of MMF is not absolutely clear. It is a combination of several effects. In order to understand this, knowledge of the mode of action, pharmacology and metabolism is of crucial importance. All of these have been previously reviewed.[6,7] The following paragraphs attempt to summarise the current knowledge for the reader.

MMF is the ester of mycophenolic acid (MPA),[8,9] which is the biologically active component. The main mechanism of action of MPA is the inhibition of inosine monophosphate dehydrogenase (IMPDH), a key enzyme in the *de novo* pathway of purine synthesis,[3] which is required for the proliferation and function of T and B lymphocytes.[10,11] Since T and B lymphocytes rely solely on this pathway for the production of guanosine nucleotides, the proliferation of these cells is specifically inhibited (fig. 1).[14] In addition, further modes of action exist.[5] Two isoforms of IMPDH have been identified with different expressions and sensitivity to MPA.[15,16]

Following oral administration, MMF is rapidly absorbed and hydrolysed to free MPA, the active metabolite. MPA potently, selectively and reversibly inhibits IMPDH. Unlike most other cells, lymphocytes rely on the *de novo* pathway more than the salvage pathway (hypoxanthine-guanine phosphoribosyltransferase) for purine biosynthesis. Enterocytes rely approximately 50% on the *de novo*

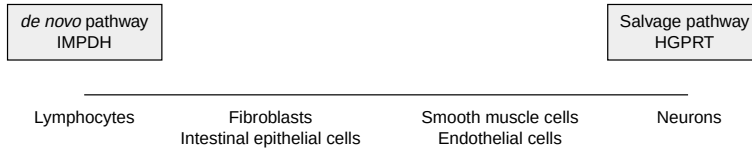

Fig. 1. Classification of different cell types and tissues according to the relative importance of the two pathways for purine synthesis. Inosine monophosphate dehydrogenase (IMPDH) is a key enzyme in the *de novo* pathway of purine synthesis. IMPDH is selectively and reversibly inhibited by mycophenolic acid (MPA). The antiproliferative effect of MPA can be reversed by the addition of guanosine or deoxyguanosine. The major purine salvage pathway is catalysed by hypoxanthine-guanine phosphoribosyltransferase (HGPRT). Lymphocytes rely almost solely on the *de novo* pathway. Neurons and brain cells are almost independent of IMPDH. Most other cell types are somewhere between the two extremes. Enterocytes are approximately 50% dependent on IMPDH. However, these data concern only short term treatment, and information on dependency during long term treatment is not available. However, induction of IMPDH in lymphocytes by long term therapy with mycophenolate mofetil has been shown[12] (reproduced from Allison AC, Eugui EM. Mycophenolate mofetil, a rationally designed immunosuppressive drug. Clin Translpant 1993; 7: 96-112,[13] with permission from Munksgaard International Publishers Ltd., Copenhagen, Denmark).

pathway; however this may change during long term therapy with drugs such as MMF.[12]

After oral administration, MMF is subject to complete first-pass metabolism to MPA. The bioavailability of MMF is excellent (90% is found as MPA). MMF is, under normal conditions, not detectable in plasma. The pharmacokinetics of this drug are complicated by the fact that MPA glucuronide (MPAG), which is the glucuronidated (and pharmacologically inactive) metabolite of MPA, undergoes enterohepatic recirculation, allowing sustained plasma concentrations of the drug. The mean terminal half-life, including enterohepatic recirculation, of MPA is 15.8 hours. Peak plasma concentrations occur 0.6 to 0.7 hours after administration. Recently, 2 other metabolites have been identified in the plasma of patients undergoing immunosuppressive therapy with MMF,[17] 1 of which shows immunosuppressive activity comparable to that of MPA.[18] So far it remains unclear whether these metabolites also contribute to adverse effects. However, in predose trough samples concentrations up to those of MPA are reached.

In renal transplant recipients, the area under the curve (AUC) of MPA is generally proportional to dosage over a range of 100 to 3500 mg/day.[19] Pharmacokinetic parameters of MPA in renal transplant recipients differ between the immediate post-transplantation period and later periods. The AUC and peak plasma concentration (C_{max}) of MPA are approximately 50% lower in the early post-transplant period (<40 days post-transplantation) than in stable renal transplant recipients. This difference is possibly attributable to increased clearance in the early post-transplant period.[20]

Interaction studies with cyclosporin, ganciclovir, aciclovir, cotrimoxazole (trimethoprim-sulfamethoxazole) and an aluminium/magnesium-containing antacid (Maalox™) did not reveal any clinically relevant effects of MMF on these drugs that would have required an adjustment of their dosage. On the other hand, the co-administration of antacids and MMF inhibits the absorption of MMF: C_{max} and AUC (0 to 24 hours) are 38 and 15% lower, respectively. The administration of cholestyramine may reduce plasma concentrations of MPA considerably. The administration of MMF together with food to renal transplant patients decreased C_{max} by approximately 40% but had no effect on AUC, suggesting that the extent of absorption was unaffected.[20]

There is strong evidence that MPA trough concentrations are influenced by both calcineurin inhibitors used in combined immunosuppressive regimens.[21,22] Zucker and co-workers described a dose-dependent inhibition of UDP-glucuronosyltransferase (UDPGT) by cyclosporin and tacrolimus, which led to an increase in MPA concentra-

tion and a reduction in MPAG concentration.[23] In the case of cyclosporin a reciprocal inhibitory effect was found, whereas for tacrolimus the mechanism of the competitive inhibition remained unclear. However, the elevated MPA concentrations in patients receiving tacrolimus compared with those on cyclosporin are not completely explained by the competitive inhibition of UDPGT. Gregoor et al.[24] described an increase in MPA concentrations after cessation of cyclosporin, and suggested that a second mechanism could be responsible for decreasing MPA concentrations in the presence of cyclosporin. Further analysis is necessary to evaluate the mechanism and clinical relevance of these findings, although the effect of cyclosporin on MPA plasma concentrations[25] has recently been further elucidated.[26,27] Co-administration of tacrolimus and MMF does not increase MPA exposure, but coadministration of cyclosporin inhibits the enterohepatic recirculation of MPA, thereby decreasing exposure to MPA. In addition, postoperative development of the albumin level plays a decisive role, particularly for liver transplantation.[28]

Mean AUCs (0 to 12 hours) of MPA and MPAG are generally higher in patients with impaired renal function, but in large clinical trials no apparent relationship was found between these higher AUCs and the incidence of adverse events. This might be different for patients receiving long term treatment, where the clearance may be lower.[20] Recent data revealed that free MPA concentrations and the free fraction of MPA are elevated in many patients with severe renal dysfunction when receiving short term therapy with MMF.[29] This increase in free MPA and the free fraction of MPA appears to be attributable both to the uraemic state *per se* and to competition for albumin binding sites with the renally eliminated metabolite MPAG. Whether patients with severe renal insufficiency may need adjustment of their MMF dosage is so far unclear, although recently published data indicate that a judicious decrease in the MMF dosage may be appropriate in some patients with chronic renal impairment.[29] The increased free MPA concentration may in part explain the favourable effects of MMF, compared with azathioprine, on long term graft survival in patients with delayed graft function.[30]

A new formulation of mycophenolate (mycophenolic acid sodium salt; ERL-080) is currently in phase III clinical trials for the prevention of kidney transplant rejection when administered with cyclosporin microemulsion. There are signs that ERL-080 may be as efficacious as MMF, but without the gastric irritation.[31,32] However, it is still too early to expect conclusive evidence, and further clinical studies in comparison with MMF must verify this hypothesis.

2. Aetiopathogenesis of Gastrointestinal Adverse Effects

The definitive aetiology of the gastrointestinal adverse effects of MMF is unknown. Different factors may explain different effects, and a combination of different and partially divergent mechanisms may lead to a specific gastrointestinal disorder. The following are the most prominent aetiological factors.

2.1 Nonspecific Effects

One main reason for the reported gastrointestinal adverse effects of MMF is quite straightforward. The enhanced immunosuppression caused by the addition of MMF to other immunosuppressive regimens[33-35] increases the general susceptibility to common infectious diseases. MMF is highly lymphocyte-specific. However, it does not facilitate specific immunosuppression. Every additional immunosuppressant increases the risk, not only of specific and opportunistic infections, but also of the common infectious diseases. Some of the reported gastrointestinal adverse effects of MMF are trivial gastrointestinal infections that might not have emerged without MMF or would have remained without clinical manifestations. One should keep in mind that this is not a specific effect of MMF, but an effect of the increased immunosuppression.

There are some indications that MMF particularly increases the susceptibility of the gastrointestinal tract to infectious diseases. Guerard et al.[36] described 2 cases of MMF-associated intestinal microsporidiosis. Both patients exhibited chronic diarrhoea and massive bodyweight loss. Stool analysis revealed microsporidian spores, identified as *Enterocytozoon bieneusi* by polymerase chain reaction. Despite treatment for several weeks, the clinical symptoms and positive stool analysis remained until MMF was discontinued and replaced by azathioprine. The investigators speculated that the lack of interferon-γ resulting from the T helper cell depletion induced by MMF was probably responsible, at least in part, for the onset of microsporidiosis. In the large scale renal studies, MMF was not associated with an increase of opportunistic infections but a search was not made for microsporidia.[33-35]

2.2 Specific Effects in the Gastrointestinal Tract

Single dose acute toxicity in rats is associated with gastrointestinal toxicity, evidenced by excess fluid secretion, mucosal reddening and ulceration in the stomach and small intestine. Dogs given oral doses of MMF 60 mg/kg once daily exhibited gastrointestinal erosion and necrosis. An increased frequency of diarrhoea and soft faeces occurred in dogs given 30 mg/kg/day over a period of 1 year. Moreover, high doses of MMF inhibit the proliferation of basal epithelial cells of the small intestine in mice.[37]

Dependency on the *de novo* pathway of purine synthesis varies widely between cell types. Thus, cell types and tissues can be arranged according to their dependence on the *de novo* and salvage pathways of purine synthesis (fig. 1). Lymphocytes are on one extreme, brain cells the other and most cell types, able to use both pathways, occupy intermediate positions. Enterocytes are approximately 50% dependent on the *de novo* pathway.[13,14] So far it is unclear what happens under long term treatment with IMPDH inhibitors. There are hints that with long term therapy an induction of IMPDH activity may occur, at least in lymphocytes.[12,38] If this is true not only for lymphocytes it may explain the low additional incidence of gastrointestinal adverse events comparing the 6-month and 3-year data from the large trials in renal transplantation (tables I and II).

At first glance it may seem as if a considerable increase in the incidence of a number of adverse events, such as diarrhoea, exists. However, these tables show cumulative data: table I refers to a period of 6 months and table II to a period of 36 months, including all the events of the first 6 months. In fact, for the longer period of time only a few additional events occur. This is particularly the case when one takes into consideration that, for instance, diarrhoea is in no way qualified or quantified, and even 1 case of diarrhoea (e.g. any trivial gastrointestinal infection) would have led to a report.

Thus, most gastrointestinal adverse events seem to occur in the first 6 month postoperative phase, when the MPA plasma concentrations are highest. The direct effect of MMF on enterocytes, resulting in diarrhoea, usually starts very rapidly after MMF treatment is initiated and disappears soon after MMF withdrawal.[39] After administration of [^{14}C]MMF labelled in the MPA moiety, all tissues with the exception of the intestines, stomach and caecum exhibited concentrations of radioactivity well below those in plasma.[3] Thus, MPA is present in a high concentration in the epithelial cells of the gastrointestinal tract. It seems possible that high local concentrations of MPA, not reflecting systemic exposure, may contribute to the gastrointestinal adverse events. In several studies, withdrawal of MMF because of gastrointestinal adverse events was significantly related to the MMF dose, whereas withdrawal for other adverse events was not.[40] Therefore, all adverse effects seem to be related to C_{max}, whereas immunosuppressive activity seems to be related to total exposure (AUC). This relationship offers opportunities for the management of gastrointestinal adverse effects (section 4).[41]

Table I. Gastrointestinal adverse events with mycophenolate mofetil (MMF) in prevention of acute rejection in cadaveric renal transplantation. Data are based on intention-to-treat analysis and are from 3 blinded, randomised, clinical trials[a] at 6 months (US and European trials) or 12 months (Tricontinental trial)

Adverse event	Group			
	placebo	azathioprine	MMF 2 g/day	MMF 3 g/day
European trial[33]				
Number in group	166		165	160
Adverse events [number (%)]				
all gastrointestinal effects[b]	69 (41.6%)		75 (45.5)	84 (52.5)
diarrhoea	21 (12.7)		21 (12.7)	25 (15.6)
abdominal pain	18 (10.8)		19 (11.5)	18 (11.3)
dyspepsia	9 (5.4)		5 (3.0)	8 (5.0)
nausea	4 (2.4)		7 (4.2)	10 (6.3)
gastroenteritis	2 (1.2)		4 (2.4)	7 (4.4)
vomiting	2 (1.2)		4 (2.4)	6 (3.8)
stomach ulcer	3 (1.8)		2 (1.2)	2 (1.3)
duodenal ulcer	1 (0.6)		2 (1.2)	1 (0.6)
gastrointestinal haemorrhage	0		0	2 (1.3)
rectal haemorrhage	0		1 (0.6)	1 (0.6)
duodenal ulcer haemorrhage	0		1 (0.6)	0
haemorrhagic pancreatitis	0		0	1 (0.6)
large intestine perforation	0		2 (1.2)	2 (1.3)
US trial[35]				
Number in group		166	167	166
Adverse events (%)				
diarrhoea		23.8	31.5	37.3
oesophagitis		3.0	5.5	6.6
gastritis		0	6.1	3.6
gastrointestinal haemorrhage		1.2	4.2[c]	4.2
Tricontinental trial[34]				
Number in group		162	171	164
Mild-moderate adverse events (%)				
diarrhoea		17	28	31
abdominal pain		23	26	31
nausea		20	14	20
vomiting		8	12	16
Severe adverse events (number)				
enteric infection		NA	NA	n = 9
colitis		NA	NA	n = 3
hepatitis		NA	NA	n = 5

a MMF was added to cyclosporin and corticosteroids and compared with placebo (European study) or azathioprine (US and Tricontinental studies). In the US study, additional antithymocyte globulin induction therapy was used.[33-35]

b Not all single events are listed in this table.

c Exsanguination from bleeding ulcers.

NA = not applicable (data not given).

An effect of cyclosporin on the enterohepatic recirculation of MPA may exist, although this is still speculative.[22] Cyclosporin, originally developed for use as an antibacterial, might decrease the amount of glucuronidase-producing gut flora leading to a lower deglucuronidation of the MPAG, which is excreted with the bile. This may contribute to a locally high enteric concentration of MPA

and MPAG. Finally, enterohepatic recirculation itself may lead to high enteric MPA concentrations.

Diarrhoea is the most frequent adverse effect observed during treatment with MMF, at least in renal transplant recipients. Its pathogenic mechanisms remain unknown. Because of its great proliferative activity, the intestinal epithelium is particularly susceptible to damage by mitotic inhibitors that interfere with normal cell proliferation. Studies in animals, using doses higher than those used in humans, have demonstrated that high doses of MMF inhibit the proliferation of basal epithelial cells of the small intestine.[13] Nevertheless, such an effect has never been reported in humans. Ducloux et al.[39] suggested villus atrophy as 1 of the mechanisms involved in gastrointestinal adverse effects, or at least in MMF-related severe diarrhoea. They reported on a patient with severe diarrhoea, flatulence and weakness with 5 to 10 stools per day 2 months after the introduction of MMF 2 g/day. A thorough examination found no other pathology than the loss of normal villus structures in histological examination of duodenal tissue. The intestinal crypts were markedly elongated and opened onto a flat absorptive surface. 20 days after the withdrawal of MMF, the diarrhoea stopped. Two months later, the duodenal histology was considered improved and 6 months later was considered normal. MMF-induced diarrhoea usually begins very rapidly after MMF treatment and also disappears soon after MMF withdrawal. In this case, diarrhoea occurred 2 months after MMF treatment and disappeared 20 days after its withdrawal. This particular time frame could suggest a different mechanism. Late-onset MMF-induced severe diarrhoea should probably be investigated for villus atrophy. If villus atrophy is proven, further investigations are not warranted.

There may be other mechanisms for gastrointestinal toxicity and diarrhoea. A patient receiving combination therapy with MMF 500mg twice daily, tacrolimus 2 mg/day and corticosteroids after renal transplantation experienced abdominal pain, diarrhoea and major anorexia.[42] Intestinal biopsy revealed that the villus height was normal and that there was no increase in cells in the lamina propria. The most striking observation was the dramatic increase in the number of apoptotic cells located in the tips and mid regions of the villi, and this observation was confirmed by sensitive histochemical techniques. In contrast, there were no apoptotic cells in the crypts.[42]

Self-amplification may also be involved in gastrointestinal damage caused by MMF, since reduced dietary intake of nutrients because of anorexia may reduce purine availability via the salvage pathway at a time when the *de novo* pathway is inhibited by MPA.[43] Experimental studies on the nutritional and intestinal effects of MMF have shown significant increases in villus width, height and sagittal section area in the jejunum of MMF-treated animals.[44] Those changes were associated with a 32% reduction in the number of villi per microscopic field. In the ileum, villus size and density were unchanged. In contrast to many clinical observations, the stools were mildly inspissated with a 22% decrease in stool water content relative to control animals.[44] MMF did cause an apparent reduction in absorptive capacity in the jejunum, which was compensated by an increased uptake in the ileum. The investigators speculated that these findings may represent a pattern of adaptation, where a decrease in nutrient uptake proximally in the intestine causes an increase in absorptive capacity distally.[44,45] Although they found that the observed effects on absorptive capacity *in vitro* did not appear to affect the overall well-being of the animals, in situations where nutrient absorptive capacities are already reduced, this may be more significant.

2.3 Abdominal Pain, Cytomegalovirus Tissue Invasive Disease and Leucopenia

Abdominal pain occurs frequently in renal transplant recipients receiving MMF therapy. The cause of this abdominal pain has not been fully elucidated, but may involve local irritation, as well as the inhibition of rapidly dividing cells of the gastrointestinal tract. There are observations that cytomegalovirus (CMV) infection may account for

Table II. Gastrointestinal adverse events with mycophenolate mofetil (MMF) in prevention of acute rejection in cadaveric renal transplantation. Data are based on intention-to-treat analysis and are from 3 blinded, randomised, clinical trials[a] at 3 years

Adverse event	Patients with adverse event (%)			
	placebo	azathioprine	MMF 2 g/day	MMF 3 g/day
European trial[33]				
	(n = 166)		(n = 165)	(n = 160)
Diarrhoea	13.9[b]		21.2	26.3
Abdominal pain	11.4[b]		15.8	14.4
Nausea	2.4[b]		6.7	9.4
Vomiting	1.8[b]		4.2	6.3
US trial[35]				
		(n = 164)	(n = 165)	(n = 166)
Diarrhoea		32.9	41.8	47.0
Abdominal pain		29.3	31.5	31.9
Nausea		33.5	34.5	34.9
Vomiting		18.3	20.0	18.1
Adverse events leading to study termination		6.7	3.6	8.4
Tricontinental trial[34]				
		(n = 162)	(n = 171)	(n = 164)
Diarrhoea		19.8	35.1	38.4
Abdominal pain		25.9	29.8	34.1
Nausea		21.6	19.3	24.4
Vomiting		7.4	16.4	19.5

a MMF was added to cyclosporin and corticosteroids and compared with placebo (European study) or azathioprine (US and Tricontinental studies). In the US study, additional antithymocyte globulin induction therapy was used.[33-35]

b 1-year data after the last patient reached 1 year post-transplant, comparator patients stopped taking placebo.

some of the gastrointestinal symptoms.[46] The milieu of inflammation and added immunosuppression is conducive to activation of CMV. Kaplan et al.[46] investigated the prevalence of active CMV in patients exhibiting abdominal pain on maintenance MMF therapy. All patients showing midepigastric pain for longer than 3 days underwent esophagogastroduodenoscopy (EGD) with biopsy. CMV was diagnosed by the presence of inclusion bodies and immunohistochemical studies. Nine out of 10 patients exhibiting persistent midepigastric pain showed evidence of gastrointestinal CMV. However, there has been critisism of this study regarding the numbers involved and the missing control group.[47]

In the large trials on renal transplantation there was an overlapping of leucopenia with – separately reported – CMV disease/infections, in particular in the MMF treatment groups. Tissue-invasive CMV disease seems to be the major concern. The incidence of certain opportunistic infections was higher in the active treatment groups than in the placebo group (specifically CMV tissue-invasive disease, herpes simplex and herpes zoster). There is clearly an effect of the overall immunosuppression on the incidence of CMV infection and on the severity of disease.[48] It is, in this connection, tempting to compare the data from the European study with those of the Tricontinental and US studies.[33-35] It appears that the incidence of CMV tissue-invasive disease in the azathioprine groups in the latter 2 studies is even higher than in the MMF 2 g/day group in the European study, which suggests that this opportunistic infection may be the consequence of the cumulative immunosuppression, rather than the use of MMF *per se*. But such a comparison is, despite the similar structure of the studies, not possible for formal reasons (that is the inclusion and exclusion criteria were not the same and the doses of axathioprine were not the same,

therefore interstudy comparison is not possible). However, there is no indication that MMF, more than any other immunosuppressive drug used in combination, is responsible for CMV infection or disease. MMF, compared with azathioprine, is not an independent risk factor for CMV infection,[49] although there are indications that CMV infection may lead more frequently to CMV disease in patients receiving MMF.[50]

In the case of CMV disease, the overall immunosuppression should, whenever possible, be reduced. There is no strong argument supporting MMF withdrawal. In the large clinical trials, which were blinded, MMF was continued in quite a number of cases without negative consequences. But although CMV itself, as well as ganciclovir, can affect the bone marrow, many support the reduction of MMF, which is also potentially myelotoxic. CMV therapy follows the usual guidelines independent of whether MMF therapy is discontinued.[51] In case of ganciclovir resistance, reduction of immunosuppression may be the crucial step in therapy.[52]

2.4 Renal Insufficiency, Metabolites and Paediatric Recipients

Renal insufficiency increases the mean AUC of MPA and MPAG. In the large clinical trials, no relationship between renal insufficiency and adverse effects was found,[33-35] but this may be different during long term therapy.

As well as MPAG, 2 metabolites of MPA have been identified, 1 of these showing immunosuppressive activity comparable to that of MPA.[18] It is likely that metabolites play a role in the occurrence of adverse effects, particularly those of gastrointestinal origin.[40]

More than in adults, paediatric recipients may experience gastrointestinal adverse effects and benefit from therapeutic drug monitoring.[53-57]

3. Incidence

A number of studies have concluded that the overall safety and tolerability of MMF are acceptable and at least equivalent to those of azathioprine.[35,58,59] Furthermore, a number of definite advantages exist with respect to safety, for example in patients with gout.[60] The most frequent adverse effects of MMF involve the gastrointestinal system. The major gastrointestinal adverse effects are diarrhoea, abdominal pain, nausea and vomiting (table I). There are also reports of gastrointestinal haemorrhages and intestinal perforation, but the total numbers are small.

Studies exploring the safety and pharmacokinetics of MMF at dosages ranging from 100 mg/day to 4 g/day suggested a dose-related decrease in the incidence of rejection at dosages of 2 g/day or higher. Doses higher than 3 g/day were associated with gastrointestinal adverse effects of an irritative nature in a certain number of patients. Steady-state plasma concentrations of MPA were reached by day 7 after administration in patients with refractory rejection.[61]

The real incidence of gastrointestinal as well as of other adverse effects of MMF is unknown. In the large randomised blinded trials, which are the most objective source of information, MMF was always used in combination with at least cyclosporin and corticosteroids. Therefore, these trials provide information on the adverse effects that occur because of the supplementary therapy, and these effects are not necessarily those of MMF alone. The lower incidence of gastrointestinal adverse effects in patients with autoimmune diseases is explained to a large extent by the lower concomitant immunosuppression of these patients (see section 3.2 on autoimmune disorders).[62-64] Studies of monotherapy with MMF are naturally rare and as a rule not randomised or blinded. Therefore, one can only describe the common adverse events that occur during combination therapy.

The first reports on gastrointestinal toxicity originated from Platz et al.[5] In a large animal model using mongrel dogs, they found adverse effects of MMF (at that time called RS-61443) 40 mg/kg/day, principally involving the gastrointestinal tract. Nausea, vomiting, diarrhoea, gastritis and anorexia were the most common symptoms and seemed to be dose-related. This initial report on

Table III. Gastrointestinal adverse events of mycophenolate mofetil (MMF) in renal transplantation. Data are from a randomised clinical trial for the treatment of a first acute renal allograft rejection.[71] Patients received cyclosporin, corticosteroids and azathioprine or MMF. Intention-to-treat analysis at 6 months

Adverse event	Incidence [number (%)]	
	azathioprine (n = 108)	MMF (n = 113)
Gastritis	4 (3.7)	12 (10.6)
Anorexia	12 (11.1)	23 (20.4)
Vomiting	18 (16.7)	27 (23.9)
Dyspepsia	21 (19.4)	29 (25.7)
Nausea	30 (27.8)	40 (35.4)
Diarrhoea	42 (38.9)	57 (50.4)
Abdominal pain	26 (24.1)	47 (41.6)

gastrointestinal toxicity was followed by several others in experimental[65,66] and early clinical[67,68] trials.

3.1 Renal, Liver and Heart Transplantation

More reliable information came from the double-blind randomised trials that led to the registration of MMF.[33-35] The data from these 3 pivotal trials have been reviewed several times.[7,69,70] A pooled efficacy analysis of the 3 trials exists,[59] but unfortunately a pooled safety analysis is not available. Table I summarises the published information after 6 months. The considerable differences in the frequency of events such as diarrhoea, abdominal pain, nausea and vomiting remain unexplained. All of these events were reported more frequently in the US[35] and Tricontinental[34] studies than in the European[33] study. As the concomitant medication and geographical aspects cannot explain these differences, one must assume that a difference exists in the stringency of reporting. This difference is even more pronounced in the 3-year data (table II). The lack of clear definitions of diarrhoea, abdominal pain, etc. also has an effect. One-off events will be recorded, as will severe illnesses that required therapeutic intervention. All of these factors reduce the value of the reported statistics. In fact, one can assume that almost every patient experienced diarrhoea once within the 3-year observation period. The same may be true for other gastrointestinal adverse events of an irritative nature. We have to assume that the incidence given in these trials is a combination of randomness of reporting and severity. As long as clear definitions of the adverse events are missing, these data are informative but are far from being exact and comparable.

Studies on MMF for the treatment of renal rejection revealed the same gastrointestinal adverse effects (table III) but at higher incidences, reflecting the higher exposure to immunosuppressive drugs in those patients.[71] In addition, one must take into consideration that MMF was administered at 3 g/day in these studies. More detailed data are provided by a randomised, double-blind, multicentre, concentration-controlled study of the safety and efficacy of oral MMF for the prevention of acute rejection after kidney transplantation.[40] Adverse events were analysed with regard to their dependence on MPA AUC. A clear relationship between AUC and the incidence of biopsy-proven rejection, and between dose and the incidence of adverse events leading to withdrawal, was found (table IV).

Combination therapy of MMF with tacrolimus will be discussed in section 3.3, although most data have also been obtained from kidney transplant patients. Sufficiently large studies on MMF in liver transplantation that allow a correct assessment of the incidence, i.e. randomised and blinded studies, do not exist. Current publications indicate satisfactory efficacy and compatibility.[72-74] However, fre-

Table IV. Relationship of gastrointestinal adverse events with mycophenolate mofetil (MMF) to the area under the concentration-time curve (AUC) of mycophenolic acid in renal transplantation[40]

Adverse event	Number (%) of patients with event		
	low AUC (n = 51)	intermediate AUC (n = 47)	high AUC (n = 52)
Leading to withdrawal of MMF			
Diarrhoea	0	2 (4.3)	5 (9.6)
Vomiting	0	1 (2.1)	3 (5.8)
Abdominal pain	0	0	4 (7.7)
Probably or possibly related to MMF			
Diarrhoea	4 (7.8)	4 (8.5)	10 (19.2)
Vomiting	1 (2)	3 (6.4)	5 (9.6)
Abdominal pain	3 (5.9)	4 (8.5)	7 (13.5)

quent dosage adjustments seem to be required, especially within the framework of the conversion of calcineurin inhibitors to MMF, because of frequent adverse effects, particularly of a gastrointestinal nature.[75] In combination with tacrolimus (section 3.3), special attention to gastrointestinal adverse effects, particularly diarrhoea, is required.

The adverse effects of MMF in heart transplantation are similar to those observed in studies on renal transplantation (table V).[76-78]

Table V. Gastrointestinal adverse events with mycophenolate mofetil (MMF) in heart transplantation[76]

Adverse event	Number (%) of patients with event	
	azathioprine (n = 289)	MMF (n = 289)
Nausea	157 (54)	156 (54)
Vomiting	82 (28)	98 (34)
Diarrhoea	99 (34)	131 (45)
Oesophagitis	8 (3)	21 (7)
Gastritis	10 (4)	19 (7)

3.2 Autoimmune Disorders

The most common adverse events reported in patients with rheumatoid arthritis were, again, anorexia, nausea, vomiting, diarrhoea, constipation, abdominal pain and dyspepsia.[62] However, all of them were reported infrequently compared with transplant recipients, which may be related to the fact that when used to treat autoimmune disease, MMF is administered with considerably less concomitant immunosuppression. In patients with inflammatory bowel disease, the adverse event profile of MMF is apparently altered,[63,64,79-82] and nongastrointestinal adverse events are reported more frequently than in other trials. This may reflect the investigators being more inclined to interpret gastrointestinal disorders as a sign of the underlying disease rather than as an adverse effect. The most frequently observed events were headache, nausea, meningitis, upper airway infection, vomiting, depression and migraine.

3.3 Combination with Tacrolimus

The combination of MMF with tacrolimus and corticosteroids in renal transplantation has been widely evaluated.[83-87] There are 2 randomised trials. The FK506/MMF Dose-Ranging Kidney Transplant Study Group compared MMF 1 g/day, MMF 2 g/day and azathioprine 1.5 mg/kg/day in combination with tacrolimus (target concentration of 5 to 15 μg/L), corticosteroids and induction therapy (5 to 14 days of antithymocyte globulin or muromonab CD3).[87] They found that there was no apparent difference between the azathioprine and MMF 1g group. However, most patients on MMF 2 g/day had their dosage lowered within the first 3 months, primarily because of gastrointestinal or haematological adverse events.[87] The second major trial was a prospective, randomised, trial of tacrolimus/prednisone versus tacrolimus/prednisone/MMF in renal transplant recipients.[84,85] The combination of tacrolimus, corticosteroids and MMF was associated with a lower incidence of rejection than the combination of tacrolimus and corticosteroids. A major advantage of the combination of tacrolimus and MMF is that tacrolimus pharmacokinetics are not altered by MMF;[88] however, MMF pharmacokinetics are strongly influenced.[23]

3.4 Combination with Sirolimus

Sirolimus in combination with MMF for the prevention of acute graft rejection has been analysed to an even lesser extent.[89] In a randomised trial comparing sirolimus with cyclosporin in combination with corticosteroids and MMF 2 g/day, patient and graft survival and the incidence of biopsy-proven acute rejection at 12 month were comparable between sirolimus and cyclosporin, whereas safety profiles were different. The sirolimus/MMF group showed 38% diarrhoea compared with 11% in the cyclosporin/MMF group. MMF was withdrawn at 6 months.[89] When evaluating these results, it should be taken into consideration that the rate of patients with diarrhoea was considerably lower than described in the earlier prophylactic studies.[33-35] At the same time, the MPA concentrations in the sirolimus group were higher than in the cyclosporin group, so that in this case various effects overlap each other.

3.5 Paediatric Patients

The experience in children is limited.[90,91] Nevertheless it is obvious that MMF will be used increasingly in children in view of their more vigorous immune response. In 1999, 35% of North American paediatric renal transplant recipients received MMF.[92] However, large randomised blinded trials are missing. Single centre studies report controversial data, from no additional efficacy[93,94] to a major advantage.[95] It is likely that elevated free MPA concentrations in children with renal insufficiency[29] are of more importance than in adults, and may partially contribute to the increased incidence of adverse effects.[96] However there is evidence that substitution of MMF for azathioprine leads to an improvement in immunosuppression and renal function in children with ongoing chronic rejection[97] and chronic cyclosporin nephrotoxicity.[98] It is important to realise that the pharmacokinetics of MMF are influenced by the concomitant immunosuppression,[53] and therefore it seems advisable to monitor AUC in paediatric patients on MMF.[54,55] Limited sampling may be sufficient to predict the AUC with sufficient accuracy.[56]

Currently, it is recommended to commence MMF at a dosage of 600 mg/m^2 twice daily. Close monitoring is necessary, especially for small children, to avoid significant nutritional problems which could occur with the use of MMF.[57]

Table VI. Incidences of gastrointestinal adverse events possibly related to mycophenolate mofetil (MMF) therapy

Adverse events	Reported incidence (%) during MMF combination therapy[a,b,c]	Estimated rate (%) of clinically significant gastrointestinal adverse events[d]
Diarrhoea	0 to 50	5 to 10
Abdominal pain	1 to 40	5
Dyspepsia	0 to 25	0
Nausea	2 to 50	5
Gastritis	1 to 10	2
Gastroenteritis	1 to 4	2
Vomiting	1 to 35	<10
Ulcer disease	3	2
Gastrointestinal haemorrhage	1 to 4	3
Large intestine perforation	1	1
Oesophagitis	3 to 7	3
Anorexia	10 to 20	3

a Summary of events reported by several studies.[33-35,40,71,76,99-101] Incidences may be extremely different depending on dosage, indication, time point and transplanted organ.

b MMF always given in combination with cyclosporin and corticosteroids, and in some cases after antithymocyte globulin or rejection therapy (pulse therapy with corticosteroids).

c The lower value represents the lowest reported incidence with the incidence in the comparator group subtracted. The higher value usually represents the incidence with MMF 3 g/day or during enhanced immunosuppression.

d Estimates for adult patients from the reports of different studies, the detailed data from the European study,[32] personal experience and communication with different clinical experts. However this is subjective information and should be treated as such.

3.6 Overview

Table VI attempts to summarise the information from major studies by estimating rates of MMF-attributable gastrointestinal adverse events. The range of reported incidence is enormous, and depends strongly on the interpretation of the information: is the realistic incidence the reported incidence with MMF minus the incidence in the comparator group? How important are the reported effects? Unfortunately, there is no information available on the clinical severity of the reported effects. For example, the term 'diarrhoea' may represent a mild discomfort of 2 or 3 days duration and several stools per day, or a severe disease with bodyweight loss, anorexia and malabsorption of immunosuppressive drugs with watery and bloody stools for several weeks. The data published to date on MMF fail to give this type of information, and further data are indispensable.

Table VI also attempts to give some realistic information on the incidence to be expected of clinically significant gastrointestinal events when using MMF in combination therapy. However, this is subjective information and represents the personal experience of the author as well as a number of clinical experts.

4. Management of Gastrointestinal Adverse Effects

The management of adverse gastrointestinal effects is strongly dependent on their nature and severity. Fortunately, most gastrointestinal effects are of an irritative nature. However, some of the effects that manifest themselves as mild disorders may develop into life-threatening disease. The management of these effects must consider the severity, the possible threat, the available diagnostic and therapeutic procedures with their own risks and hazards, and the cost factor. For practical reasons, we divide the management into 3 sections: mild, moderate and serious gastrointestinal events. However, this categorisation is academic. In clinical practice an event may change rapidly from a mild disorder to a serious life threatening disease. A possible example of this situation: abdominal pain may be categorised as a mild disorder, but abdominal pain under corticosteroids may also be the first clinical symptom of intestinal perforation, a life-threatening complication.

4.1 Mild

Mild gastrointestinal symptoms are frequently self-limiting. They are part of normal life. Symptoms such as occasional vomiting, mild abdominal pain and infrequent diarrhoea are typical examples. If the clinical situation allows observation of these symptoms and does not recommend immediate intervention, the first choice is to do nothing, but to be on the alert. Nausea, constipation and mild abdominal pain often disappear within several days. Symptomatic treatment may be helpful.

If the symptoms persist and remain mild, the concomitant, especially immunosuppressive, medication should be carefully reviewed. Frequently, a reduction of the overall immunosuppressive load is possible and may be the best available treatment. The mechanism of reduction depends on the personal preferences of the physician, and may consist of reducing cyclosporin, corticosteroids or MMF. The possibilities for corticosteroid or cyclosporin reduction or discontinuation, and for immunosuppressive regimens using MMF alone, have been widely reviewed.[7,102-110] In individual cases one should decide according to the clinical situation whether arguments possibly exist for reducing one or the other immunosuppressive drug. For example, signs of nephrotoxicity or hyperlipidaemia could be an indication for the reduction of cyclosporin. An indication for the reduction of MMF could be a time-related connection between introduction of MMF and gastrointestinal symptoms, plus a history of gastrointestinal illnesses (ulcers, bleeding, diverticulum). More than for other combinations, the coadministration of tacrolimus enhances the immunosuppressive and adverse effects of MMF.[21,23] In this case, the clinical need for such a vigorous therapy should be examined closely.

Should an overall reduction of immunosuppression not seem possible, a change in the administration of the total daily dose of MMF to form 2 or 3 divided doses may be sufficient to treat adverse effects.[7,35,78] There is strong evidence that a high MPA trough concentration is associated with an increased risk of adverse effects.[41] Additionally, administration with food may be helpful.[7]

If these measures are not successful, a reduction of the dosage of MMF by 50% will eradicate most mild gastrointestinal problems. If all these measures do not have the necessary effect, the problem can no longer be considered to be only mild.

4.2 Moderate

All moderate gastrointestinal problems, whether considered to be caused by an adverse effect, or an intercurrent disease, or both, must be thoroughly diagnosed. If serious nausea, vomiting, anorexia, abdominal pain and bodyweight loss persist for more than 10 days, an upper tract endoscopy (EGD) with biopsies from oesophagus, stomach and duodenal tissue is mandatory. Standard stool cultures and parasitological examination are necessary and rare complications must be taken into consideration.[36] Again, before a specific treatment is introduced, the available options to reduce the overall immunosuppression should be examined. Drugs that overlap in toxicity (such as, for

example, corticosteroids and MMF in the case of ulcer disease) should be avoided whenever possible before further treatment is commenced. Nausea, vomiting and diarrhoea could be treated symptomatically for a limited period of time. However, treatment for more than 2 weeks without further diagnostic measures is not recommended.

As well as reduction in immunosuppression whenever possible, the treatment of ulcer disease includes proton pump inhibitors and *Helicobacter pylori* eradication where indicated. If no specific treatment is possible or is ineffective, the MMF dosage should be reduced. Whenever possible, reduction is preferable to withdrawal, as rebound rejections may occur.

4.3 Serious

Serious gastrointestinal adverse effects of MMF are rare. However, in the 3 controlled trials on renal transplantation,[33-35] serious gastrointestinal adverse effects occurred only in the treatment groups. Among 658 patients (European and US study only) treated for 6 months, 4 stomach ulcers, 3 duodenal ulcers, 17 gastrointestinal haemorrhages, 4 large intestine perforations and 1 haemorrhagic pancreatitis were seen. These serious events cannot clearly be attributed to MMF itself, but may be related to the introduction of MMF to the immunosuppressive regimens.

In cases of ulcer disease in patients receiving MMF, withdrawal of the drug is recommended. Large intestine perforations and ischaemic colitis may also be related to MMF.[111] Presently, MMF withdrawal and intensive treatment according to general clinical guidelines is necessary. A temporary increase in corticosteroid therapy may help to prevent rebound rejection and to treat relative adrenocortical insufficiency. However, increased corticosteroids possess their own risks of perforations and peritonitis. The exact pathological mechanism of these serious complications remains elusive, and some patients may be more susceptible to these effects than others.

There are limited reports on further gastrointestinal adverse effects of MMF, and these require further analysis and attention.[112]

Table VII summarises the management options proposed in this chapter and suggests some common treatment guidelines. These guidelines are intended to help, but they are not intended as arguments to withhold any diagnostic or therapeutic measures. Every patient needs the full attention of his or her physician in order to obtain the best available therapy.

4.4 Therapeutic Drug Monitoring

Immunosuppressive drugs such as cyclosporin or tacrolimus are initially administered on a mg/kg basis with later dosage adjustment to achieve a target blood concentration. MMF is usually administered at a fixed dose of 2g/day as recommended by the manufacturer. Therapeutic drug monitoring is not generally suggested to optimise its activity or reduce its toxicity, with the exception of adjustments for extremes of body size in adults and children.[113] However this is not generally accepted.[7]

Van Gelder et al.[40] reported a randomised, double-blind, multicentre, concentration-controlled study of the safety and efficacy of oral MMF for the prevention of acute rejection after kidney transplantation. They found that MPA predose (trough) concentration and AUC were significantly related to the incidence of biopsy-proven rejection, whereas the MMF dose was significantly related to the occurrence of adverse events. The results suggest that individualisation of the MMF dose based on the AUC of MPA may have merit. However, the costs and benefits of this strategy has not been compared with the fixed dose strategy currently in use.

More sophisticated models that account for the time course of the risk of rejection may allow even more rational adjustment of MMF dosage or MPA AUC target with time.[114] Langman et al.[115] investigated a combination of pharmacokinetic and pharmacodynamic monitoring. The relationship between MPA concentration in plasma, IMPDH activity in whole blood and nucleotide concentration in lymphocytes was investigated in renal transplant

Table VII. Management of gastrointestinal adverse effects of mycophenolate mofetil (MMF)

Adverse event	Symptoms	Important diagnostic/-therapeutic procedures	Management options
Mild			
Vomiting	Occasional, no bodyweight loss	No specific diagnostic procedures indicated	1. Observation 2. Reduction of immunosuppressive therapy 3. Dose splitting (twice daily to 3 times daily) 4. Administration with food 5. 50% dosage reduction of MMF 6. Symptomatic treatment (nausea, constipation, diarrhoea) for a limited period of time (10 days)
Abdominal pain	Mild, occasional		
Diarrhoea	Occasional (<4 stools/day) no bodyweight loss, less than 10 days		
Nausea	Mild		
Constipation	Occasional		
Gastroenteritis	Short duration, known aetiology		
Moderate			
Serious nausea	Persistent, no response to symptomatic treatment	Review of pharmacotherapy, OGD and colonoscopy with biopsies, stool cultures, parasitological examination	1. Reduction of immunosuppressive therapy 2. Symptomatic pharmacotherapy (nausea, vomiting, diarrhoea) 3. 50% dosage reduction of MMF 4. MMF withdrawal if indicated
Continuous vomiting	No regular food intake, bodyweight loss, inadequate levels of immunosuppression		
Anorexia	Bodyweight loss		
Severe diarrhoea	Continuous, bodyweight loss, persistence >10 days		
Abdominal pain	Moderate to severe pain, persistence		
Serious			
GI haemorrhage	Any kind of GI bleeding	Immediate endoscopy	1. MMF withdrawal 2. Intravenous corticosteroids may be required for rebound rejection 3. Specific treatment of GI complications (endoscopic treatment of bleeding, pharmacotherapy of ulcer disease, surgery, intensive care treatment if indicated)
Perforation	Any gastrointestinal perforation	Immediate surgery	
Ulcer disease	Gastric, duodenal and rectal ulcer, not healing within 10 days of treatment	Endoscopy, biopsies pharmacotherapy	
Anorexia	Severe bodyweight loss, malnutrition	OGD, colonoscopy, biopsy, stool cultures	

OGD = oesophagogastroduodenoscopy; **GI** = gastrointestinal.

recipients who were randomised to receive either MMF or azathioprine in combination with cyclosporin and prednisone. They found an inverse relationship between the MPA concentration and IMPDH activity in whole blood. The peak concentration of MPA achieved 1 hour after administration resulted in an approximately 40% inhibition of IMPDH activity. However, no correlation with MPA AUC was studied. No statistically significant difference between the predose and the 12-hour postdose activity was observed.

Recently, Sanquer et al.[38] reported an analysis of the pharmacological activity of MMF in stable kidney transplant recipients receiving MMF therapy for different periods from 2 months to 3 years. They found that long term treatment with MMF was associated with an induction of IMPDH activity. MPA trough blood concentrations were also altered as described before,[12] but changes were not consistent in any particular direction.

Paediatric patients tend to have a higher incidence of adverse gastrointestinal events. In a comparison of adults and paediatric patients, the incidence of gastrointestinal symptoms was significantly higher in the children (54.5 *vs* 21.6%; $p = 0.02$).[57] Significant bodyweight loss was seen more often in the smaller paediatric patients (bodyweight ≤ 15kg) compared with the larger paediatric patients (60 *vs* 11.7%, $p = 0.05$). The necessity to discontinue MMF was significantly higher in the

paediatric patients, especially in those who weighed less than 15kg.

The available data suggest that therapeutic drug monitoring will enable individualised therapy with MMF, according to the clinical needs of the organ (type of organ transplant, histocompatibility, time after transplantation) and the recipient. It is obvious that large proportions of the reported gastrointestinal effects are preventable.[40]

5. Conclusion

MMF is a valuable new immunosuppressive drug that is highly effective in the prevention of acute allograft rejection and increasingly tested in other indications. MMF offers a relatively benign safety profile, but gastrointestinal adverse effects are a major concern. The mode of action of MMF and its pharmacokinetics partially explain the aetiology of the observed gastrointestinal effects. Published safety data from the initial trials on efficacy are not appropriate for detailed analysis of gastrointestinal adverse events. More accurate data suggest that the gastrointestinal adverse effects are mainly related to C_{max}, whereas the efficacy is related to AUC. This may offer possibilities to retain the efficacy and reduce the adverse effects with different administration regimens.

Most gastrointestinal adverse events are of an irritative nature and are frequently self-limiting. However, some serious events such as intestinal perforations and gastrointestinal haemorrhage are a major concern. A central register of serious adverse events would be helpful in investigating the mechanism and real incidence of these effects. Finally, drug monitoring will help to optimise MMF therapy and to reduce adverse effects.

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