



*An Initiative of NSW Clinical
Pharmacologists & Pharmacists
Funded by the NSW Department of Health*

MYCOPHENOLATE MOFETIL

A Position Statement of the NSW Therapeutic Assessment Group Inc.

February 2001

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EXECUTIVE SUMMARY

The following summarises the status regarding various conditions for which mycophenolate mofetil (MMF) has been used. For further detail regarding the pharmacokinetics, adverse reactions and precautions relating to MMF, the TGA approved product information should be consulted.

Approved indications and Section 100 listings

- MMF is approved in Australia for the prophylaxis of solid organ rejection in adults receiving allogeneic organ transplants and in paediatric patients (2 to 18 years) receiving renal transplants. The Section 100 listing at present applies only to renal and cardiac allograft rejection.

Efficacy demonstrated in double-blind trials involving large patient numbers:

- Prevention of renal and cardiac allograft rejection;
- Prevention of liver allograft rejection (now an FDA approved indication);
- Rescue therapy of acute rejection in renal transplant patients.

Efficacy reported in smaller studies:

- Prevention of rejection in lung transplantation;
- Prevention of rejection in pancreas transplantation;
- Prevention of rejection in corneal transplantation;
- Prevention and treatment of GVHD in bone marrow transplantation and stem cell transplantation;
- Other aspects of transplantation, eg treatment of acute rejection in other than renal transplantation, cyclosporin nephrotoxicity, etc (see attached);
- Psoriasis.

Case reports indicate potential:

- Various glomerulonephritides, renal vasculitis and lupus nephritis;
- Various skin conditions (for psoriasis - see above; for other disorders - see attached);
- Uveitis and refractory ocular inflammation;
- Myaesthesia gravis;

- Biliary cirrhosis;
- Autoimmune haemolytic anaemia;
- Obliterative bronchiolitis syndrome;
- Retroperitoneal fibrosis;
- Wegener's granulomatosis;
- Autoimmune hepatitis;
- Other transplantation situations including intestinal transplantation (see attached);
- Control of HIV replication (minimal data).

Uses which are controversial

- Inflammatory bowel disease;
- Rheumatoid arthritis – some studies demonstrated positive results but, following the preliminary results from a substantial study, the manufacturers have not pursued this indication further.

Adverse reactions

The principal adverse reactions that have been associated with MMF combined with cyclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting. Also, evidence exists of a higher frequency of certain infections, such as cytomegalovirus (CMV), tuberculosis and atypical mycobacterial infection. Uncommon but serious life-threatening infections such as meningitis have been reported. As with other immunosuppressants, risk of malignancy is a consideration with MMF and long-term data, particularly *vs* azathioprine, are yet to be accumulated.

Conclusion

MMF is beginning to replace azathioprine in a number of transplantation settings, eg in renal, cardiac, liver and pancreas transplantation. Overall treatment costs have been reported to be lower for MMF compared to azathioprine in the first year after renal transplantation. Cost-benefit data in other situations is yet to become available. Use of MMF in some non-transplant disorders shows promise but careful consideration needs to be taken regarding the agent's adverse reactions profile, including potential for malignancy. A potentially important decrease in MMF absorption following concomitant administration of ferrous sulphate tablets has recently been reported.

MYCOPHENOLATE MOFETIL

For the basic preparation of this position statement on mycophenolate mofetil (MMF), a number of reviews and other documents in particular have been used^{1 2 3 4 5 6 7}.

Mechanism of action

Mycophenolic acid, the active metabolite of MMF mofetil, is a potent immunosuppressant. It is a selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a key enzyme in the *de novo* pathway for purine synthesis. Mycophenolic acid has a higher binding affinity for IMPDH type II, the predominant isoform found in proliferating lymphocytes, than for IMPDH type I, which is used by non-replicating cells⁶. The inhibition of IMPDH type II by mycophenolic acid causes depletion of guanosine nucleotides, inhibiting DNA synthesis, arresting replicating lymphocytes in S phase. Because T and B lymphocytes are dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilise salvage pathways, mycophenolic acid has more potent cytostatic effects on lymphocytes than on other cells. Depletion of guanosine nucleotides leads to the inhibition of glycosylation of adhesion molecules on lymphocytes, a process also considered an action of mycophenolate mofetil.

Further details concerning the mechanism of action of MMF may be found in the review by Allison and Eugui (2000)¹ and Bardsley-Elliot et al. (1999)⁶.

Pharmacokinetics

Mycophenolate mofetil is well absorbed orally with a mean bioavailability of 94%, and is rapidly hydrolysed in the liver to mycophenolic acid. This metabolite is conjugated to form the pharmacologically inactive mycophenolic acid glucuronide (MPAG). Peak mycophenolic acid levels occur approximately one hour post dose, with a secondary peak occurring 6 to 8 hours later, due to enterohepatic recirculation of MPAG and its hydrolysis back to mycophenolic acid in the gastrointestinal tract. Approximately 87% of the oral dose is excreted as MPAG in the urine. The apparent elimination half-life of mycophenolic acid after a single oral dose of MMF is approximately 18 hours. The area under the curve (AUC) is found

to increase following renal transplantation, stabilising after about a month of therapy. Food reduces the C_{max} but has no effect on the AUC. Single dose studies in chronic renal impairment (creatinine clearance $< 25\text{mL}/\text{min}/1.73\text{m}^2$) showed that the AUC for mycophenolic acid was 28-75% higher than in individuals with no or milder renal impairment. Unlike azathioprine, there is no interaction between MMF and allopurinol.

In renal transplant patients, the dose-interval mycophenolic acid AUC values have been found to vary by more than 10-fold following the same MMF dose. This has been suggested to be consistent with a wide variability in the first-pass clearance of mycophenolic acid in transplant patients. It has been proposed that this variability is caused by differences in first-pass gut and/or liver metabolism and clearance of mycophenolic acid and/or enterohepatic cycling. The presence of UDP-glucuronosyltransferase activity in the gastrointestinal tract supports the hypothesis that intracellular gut metabolism of mycophenolic acid via this enzyme contributes to first-pass metabolism and clearance of mycophenolic acid yielding the primary phenolic glucuronide MPAG followed by transfer into the bloodstream⁸.

A potentially important decrease in MMF absorption has recently been reported following concomitant administration of oral MMF with ferrous sulphate tablets⁹. In a randomised crossover study, administration of two sustained-release ferrous sulphate 525mg tablets (each containing 105mg of elemental iron ion) led to an approximate 90% decrease in mycophenolic acid AUC(0-12) in all subjects (n=7). The dose of MMF administered in this study was 1g.

In a recent study¹⁰ the concentration-time profile of mycophenolic acid following IV administration of MMF 1g twice a day was found to be nearly identical to that following oral MMF 1g twice a day even though the IV and oral MMF were not found to be bioequivalent.

Correlations between pharmacokinetic parameters and efficacy or toxicity

The probability of biopsy-proven graft rejection was found to be significantly correlated with mycophenolic acid AUC ($p < 0.0001$) and maximum plasma mycophenolic acid concentration (C_{max})

($p=0.0008$), but not with MMF dose, according to the results of a randomised double-blind concentration-controlled study of MMF in 156 renal transplant recipients¹¹. As mentioned, plasma mycophenolic acid concentrations tend to increase with time, however, they may decline again during the course of long-term therapy (>2 years).

Correlations between plasma trough levels of mycophenolic acid, organ rejection and MMF toxicity have also been reported¹². In this study, mean plasma trough levels (\pm standard deviation), a) from patients who underwent organ rejection were 1.3 ± 0.9 $\mu\text{g/mL}$ ($n=17$); b) from patients who exhibited MMF toxicity were 3.1 ± 2.8 $\mu\text{g/mL}$ ($n=19$), and c) from those who experienced neither side effects nor rejection were 2.2 ± 1.4 $\mu\text{g/mL}$ ($n=15$).

Effect of cyclosporin and tacrolimus on mycophenolic acid levels

Cyclosporin has been reported to reduce median trough mycophenolic acid concentration by 55% in renal transplant recipients receiving MMF and prednisone¹³. Also, a significant increase in mycophenolic acid trough concentrations after discontinuation of cyclosporin has been reported from a study involving 52 patients¹⁴.

Tacrolimus administration has been reported to result in increases in trough mycophenolic acid plasma levels in renal transplant patients receiving MMF^{15 16 17}.

Use in transplantation

Renal transplantation

Prevention of acute rejection

Prevention of renal allograft rejection is an approved Section 100 indication for MMF. For this reason, details regarding the pivotal studies supporting this indication^{18 19 20} will not be included here but may be found elsewhere^{3 4}.

Longer-term follow-up

The pivotal studies were carried out to three years of post-transplant follow-up for analysis of graft loss and patient death^{21 22 23}. Although the studies were not powered to demonstrate a significant difference for these endpoints, there was a consistent trend towards improved outcomes over three years for patients treated with MMF 2 or

3g/day compared with those receiving azathioprine or placebo.

Another group reviewed data on 66,774 renal transplant recipients from the US renal transplant scientific registry using a Kaplan Meier analysis at four years²⁴. In this analysis, MMF was found to decrease the risk of developing chronic allograft failure. The relative risk was reduced by 27% (risk ratio 0.73, $p<0.001$). This improvement was said to be only partly caused by the decrease in the incidence of acute rejection observed with MMF.

Combination with tacrolimus

A reduction in acute rejection rates has been reported when MMF has been combined with tacrolimus and corticosteroids, compared with double therapy without MMF, or triple therapy with azathioprine, according to the results of several randomised non-blinded studies⁶. These results were statistically significant in studies with large (>200) patient numbers. Patient and graft survival rates, however, did not appear to be affected by addition of MMF to tacrolimus-based therapy regimens. Some of these trials were affected by patient cross-over to alternative therapy because of gastrointestinal intolerance or haematological toxicity attributed to MMF.

African American renal transplant recipients have been found to require stronger immunosuppressive regimens to prevent rejection. The combination of MMF with tacrolimus has been reported to have the potential to improve long-term outcome in African American renal transplant recipients²⁵.

Conversion to MMF or azathioprine after transplantation

In a study in which patients were converted from cyclosporin to either MMF or azathioprine one year after transplantation²⁶, significantly less rejections occurred in the MMF group (4/34) compared to patients transferred to azathioprine (11/30). All patients remained on low-dose corticosteroids.

In a randomised, open-label study involving 48 patients, replacing MMF with azathioprine six months after transplantation in low-risk renal allograft recipients was not found to be associated with altered graft function in the short term²⁷.

Rescue therapy for rejection episodes

MMF has been shown to be useful in “rescue therapy” of acute rejection and to reduce the need for anti-lymphocyte globulin for persistent rejection³. Patients treated with MMF were less likely to

experience a subsequent episode of rejection, graft loss or death than those treated with azathioprine. These findings derive from a number of randomised trials in renal transplant patients involving at least 275 patients treated with MMF^{28 29 30 31 32 33}. Efficacy in chronic rejection has also been demonstrated at a dose of MMF of 2g per day^{34 35}.

In a multicentre, double-blind trial of acute rejection in renal transplant recipients treated primarily with cyclosporin, MMF with intravenous corticosteroids was found to be significantly more effective than azathioprine and corticosteroids²⁸. In this study the number of patients receiving MMF was 113 and the dose of MMF was 3g per day. Patients were followed for three years³⁶. During this time, comparing the results with those for azathioprine, MMF patients were less likely to experience a subsequent rejection episode, graft loss or death. Renal function was similar in both treatment groups. The incidence of malignancy was 14.2% in the MMF treatment group and 10.2% in the azathioprine group. No additional lymphomas occurred between one and three years.

In a meta-analysis of three trials³⁷, no difference in graft or patient survival and in mean serum creatinine levels were found for MMF (3g per day), tacrolimus or high-dose IV corticosteroids for acute rejection. However, in this meta-analysis, tacrolimus treatment was found to result in significantly lower rates of recurrent rejection (4-11%) and decreased use of anti-lymphocyte therapy (0-2%) for recurrent rejection episodes compared to MMF (25% and 10% respectively, $p < 0.05$) or to high-dose corticosteroids. Also, patients treated with tacrolimus were said to have had significantly fewer serious adverse events and lower incidence of CMV disease compared with MMF and to high-dose corticosteroids. None of the studies in this meta-analysis were blinded.

MMF treatment has been found useful in patients who have failed tacrolimus therapy for primary immunosuppression³⁴.

Cyclosporin-sparing effect and treatment of cyclosporin-related nephrotoxicity

In an attempt to avoid cyclosporin-related long-term effects (in particular impairment of renal function and increased cardiovascular risk factors), studies have been performed in which patients have been converted to either MMF or azathioprine after a period on cyclosporin.

In the study already mentioned in which patients were converted from cyclosporin to either MMF (n

= 34) or azathioprine (n = 30) one year after transplantation²⁶, a decrease in serum creatinine was found for both MMF and azathioprine. All patients remained on low-dose corticosteroids. In patients converted to MMF, significantly less rejections occurred (4/34) compared to patients transferred to azathioprine (11/30).

However, in another report involving 46 stable transplant patients³⁸, rate of late mild acute cellular rejection episodes subsequent to the conversion from cyclosporin to MMF monotherapy (10.9%) was considered by the authors to be substantial. These authors did not use a fixed dosing regimen but used 12-hour trough levels of mycophenolic acid within 2-6 ug/mL. They acknowledged that underdosing of MMF could have contributed to under-immunosuppression. These authors concluded that the ethical issue remained unresolved whether or not 90% of the patients can be maintained on a nephrotoxicity-free drug regimen for the disadvantage of 10% of patients that may be at risk of late mild acute rejection episodes. They also added that conversion to MMF monotherapy in patients with unstable graft function and beginning chronic allograft dysfunction respectively did not appear to be of substantial benefit.

Patients with cyclosporin nephrotoxicity A reduction in serum creatinine was observed in all patients with cyclosporin nephrotoxicity (n = 17) following conversion from a cyclosporin-prednisone regimen to MMF-prednisone³⁹. No episodes of acute rejection were noted following the change during the study period (20 ± 8 months). Serum lipids and blood pressure also decreased significantly.

Improvement in renal function without increase in the incidence of acute rejection has been found in a number of other studies following the addition of MMF and concomitant reduction or elimination of cyclosporin³. However, the overall long-term effects of reduction or discontinuation of cyclosporin and MMF monotherapy or MMF/corticosteroid therapy in patients with cyclosporin-related nephrotoxicity have not been clearly established.

It should be noted that, when discussing renal effects of cyclosporin, it is important to differentiate the effects of cyclosporin on the tubules from the rare instances of secondary renal damage from haemolytic uraemic syndrome. In the latter situation, cessation of cyclosporin therapy would be mandatory.

Heart transplantation

Prevention of acute rejection

Prevention of cardiac allograft rejection is also an established Section 100 listing for MMF. Again, details regarding the relevant pivotal studies can be found elsewhere^{3,4}.

In summary³, the addition of MMF 1.5g twice a day (n=323) to cyclosporin-based immunosuppression resulted in a survival advantage for MMF compared with azathioprine (n=327)⁴⁰ which extended to three years with reduced graft loss due to rejection, a lower rate of new or progressive transplant coronary atherosclerotic disease and a 36% reduction in patient mortality⁴¹.

On qualitative assessment, a beneficial numerical trend in intracardiac ultrasound end-points with less autopsy-proven significant disease, lower rates of heart failure and atrial arrhythmias has been reported.³

MMF decreased the incidence of early acute rejection after heart transplantation without affecting the lymphocyte subpopulation when compared with azathioprine, according to a review of the clinical and laboratory records of 31 patients who had undergone heart transplantation⁴².

Conversion from MMF to azathioprine

Conversion from MMF to azathioprine, even late after transplantation, can be associated with allograft rejection, according to an open-label study involving 43 stable heart transplant patients treated with MMF⁴³. In this study, treated allograft rejection occurred in 10 of 20 patients converted to azathioprine compared to only 1 of 23 patients remaining on MMF (p = 0.02).

Rescue therapy for rejection

MMF has been found to be an effective rescue therapy in the management of acute or recurrent rejection in heart allograft recipients, according to the results of several small studies^{44 45 46 47}. In these studies 95 patients received MMF. The substitution of MMF for azathioprine was concluded to be associated with a higher likelihood of resolution of the rejection episode and a significantly lower rate of recurrent rejection episodes³.

Liver transplantation

Prevention of rejection

MMF has now been approved by the TGA for “the prophylaxis of solid organ rejection in adults receiving allogeneic organ transplants”. However, the Section 100 listing at present applies only to renal and cardiac allograft rejection. MMF is approved by the US FDA for “the prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants”⁴⁸.

Dual or triple therapy regimens involving tacrolimus or cyclosporin in combination with a corticosteroid with or without azathioprine have, in recent years, been amongst the standard prophylactic regimens in liver transplantation.

A number of studies have now reported on the use of MMF, in combination with tacrolimus- or cyclosporin-based immunosuppressive regimens, comparing its effects with those of azathioprine.

Incidence of acute rejection was found to be reduced in patients receiving MMF in combination with cyclosporin and corticosteroids, compared with those receiving azathioprine with cyclosporin and corticosteroids, according to the preliminary results of one randomised, double-blind study involving over 500 liver transplant patients⁴⁹.

In another study involving 57 patients, when MMF or azathioprine were used in a quadruple regimen including cyclosporin, methylprednisolone and lymphocyte antibodies, less frequent acute rejection episodes occurred in the MMF group: 6/28 (21.4%) vs 13/29 (44.8%) in the azathioprine group (p=0.06)⁵⁰.

Several previous studies have also reported on the use of MMF as additional therapy to tacrolimus and a corticosteroid (dual) regimens.

In one small study⁵¹, the addition of MMF to tacrolimus and corticosteroids resulted in improved patient and graft survival, although a large percentage of patients required discontinuation of MMF due to the development of rejection and/or adverse events.

In the first large randomised, controlled trial evaluating the use of MMF in liver transplantation⁵², the addition of MMF to tacrolimus-based immunosuppression did not improve patient or graft survival although there was a trend towards decreased rejection and nephrotoxicity.

Early corticosteroid withdrawal was reported to be successfully accomplished using a combination of MMF with either cyclosporin (n=36) or tacrolimus (n=35), according to the results of one randomised nonblind study in liver transplant patients⁵³.

Rescue therapy for treatment-resistant rejection episodes

A number of authors have reported encouraging results with respect to rescue therapy for treatment-resistant rejection episodes^{54 55 56 57}.

Of 19 of these patients followed for four years⁵⁸, MMF therapy resulted in complete histologic resolution in 12 patients, partial resolution in two patients and a worsening of rejection in three patients (two patients had no histologic follow-up). Of the six patients who had their cyclosporin discontinued once MMF was started, four patients had complete resolution of rejection.

In one study⁵⁴, 21 of 23 patients responded to MMF following acute rejection while receiving cyclosporin/prednisone/azathioprine maintenance for immunosuppression and had failed high dose corticosteroids and muromonab CD3 for rejection treatment. These patients were converted from azathioprine to MMF with concomitant cyclosporin and corticosteroids. As mentioned, other authors have also reported promising results^{55 56 57}.

Cyclosporin-related nephrotoxicity

Improved renal function has been noted in patients with cyclosporin-related nephrotoxicity, following use of MMF, according to reports in a small number of patients^{59 60 61}.

Partial or total conversion from cyclosporin to MMF in nine stable liver transplant patients with renal function impairment has been reported to be followed by renal function improvement and better control of arterial hypertension without biochemical evidence of graft damage⁵⁹. In this study the dose of MMF was 2g per day, with azathioprine being discontinued when applicable and the cyclosporin dose being slowly reduced until discontinuation or worsening of liver function tests.

In another study, renal function improvement has been reported following conversion to MMF monotherapy 2 g per day in five liver transplant patients with cyclosporin-induced nephrotoxicity⁶⁰. One episode of acute rejection occurred which was successfully treated with intravenous corticosteroids.

MMF substitution of calcineurin inhibitors including cyclosporin (n=19) led to improvement of acute as well as chronic renal dysfunction in most cases, according to the results of a prospective non-randomised study⁶¹.

In this study in 22 liver graft recipients with renal dysfunction and stable graft function between 3 weeks and 12 years after transplantation, calcineurin inhibitors were substituted by MMF at a final dose of 1.5-3g per day. MMF was withdrawn in four patients because of major side effects. Six months after study entry, renal function had improved in 17 of the 22 study patients. One patient developed transient liver dysfunction and a second required retransplantation for progressive cholestasis but without signs of rejection.

Lung transplantation

Significantly fewer episodes of acute rejection occurred with MMF compared to azathioprine, in several small, non-randomised studies in lung transplantation^{62 63}. Although, in these studies, several other end-points did not reach statistical significance, most likely due to small numbers of patients in the trials, MMF treatment was associated with more effective maintenance of lung function compared with azathioprine, as demonstrated by a lower prevalence of obliterative bronchiolitis. Positive results have been noted regarding the use of MMF for the treatment of acute rejection according to one report in eight patients⁶⁴.

Pancreas transplantation

MMF is replacing azathioprine as part of the standard immunosuppressive regimen following pancreas transplantation⁶⁵, a number of studies having supported its use.

In one recent randomised, multicentre, prospective trial involving 150 simultaneous kidney-pancreas transplantation (SPK) patients⁶⁶, trends for most efficacy parameters favoured MMF over azathioprine, and time to renal allograft rejection or treatment failure was statistically significantly longer for MMF.

MMF treatment was found to significantly decrease the incidence of acute rejection compared with azathioprine-treated historical controls in SPK recipients, according to the results of another study⁶⁷ involving 36 patients. A prospective, randomised, single-centre study was conducted by

these authors in which patients received either tacrolimus and MMF (n = 18) or cyclosporin and MMF (n = 18). The incidence of biopsy-proven acute rejection was 11% in both the tacrolimus–MMF and cyclosporin-MMF groups with only two patients in each group experiencing a rejection episode.

This rejection rate was found to be significantly decreased from that of the cyclosporin-azathioprine historical group (77% p<0.01). There were no significant differences in infection rates, including cytomegalovirus, or in metabolic control, hypertension and cholesterol levels.

In another retrospective analysis involving 27 pancreas transplantation patients⁶⁸, acute rejection occurred in 76% of patients in the azathioprine group compared with 53% in the MMF group. There were no significant differences in cytomegalovirus infection. Severe fungal infections were noted in two patients treated with MMF. Malignancy occurred in one patient (pancreas graft lymphoma) on MMF.

A matched-pair analysis using the database of the International Pancreas Transplant Registry was performed to compare outcomes in MMF versus azathioprine recipients⁶⁹. Between July 1, 1995 and June 30, 1997, both MMF and tacrolimus were given to 120 pancreas transplant recipients. Induction therapy was with MMF, tacrolimus, prednisone and antithymocyte globulin or OKT3. Until oral intake was resumed, recipients initially received intravenous azathioprine. From the analysis it was reported that, for SPK recipients, one-year pancreas graft survival rates were 86% with MMF versus 79% with azathioprine (p=NS), kidney graft survival rates were 96% with MMF versus 86% with azathioprine (p=NS). The incidence of first rejection episodes at one year was significantly lower for MMF recipients (15% with MMF versus 43% with azathioprine, p = 0.0003). For recipients of solitary pancreas transplants (PTA and PAK), no difference in graft survival rates between MMF and azathioprine was found. The conversion rate from MMF to azathioprine at one year was 14% for SPK recipients, 26% for PAK, and 39% for PTA (p < 0.007). The most common reason for conversion was gastrointestinal toxicity, in particular for nonuraemic (PTA) or posturaemic (PAK) recipients. The rates of post-transplant infection and lymphoproliferative disease were low for recipients on MMF and tacrolimus.

A number of other small studies have demonstrated a trend towards improved outcomes for pancreas and kidney/pancreas (SPK) grafts with MMF replacing azathioprine administration^{70 71 72}. Most of these studies were retrospective using

historical controls where treatment variables (e.g. Sandimmune vs Neoral administration, bladder vs enteric-drainage of the pancreatic graft, OKT3 vs ATGAM induction) changed over time.

Corneal transplantation

MMF and cyclosporin were found to be comparable for prevention of corneal rejection in high-risk patients in one study involving 41 patients⁷³.

Intestinal transplantation

Some preliminary reports discuss promise for MMF in intestinal transplantation^{74 75}.

Graft-versus host disease (GVHD)

A number of studies have reported efficacy for MMF in the prevention and treatment of GVHD in bone marrow transplantation/stem cell transplantation.

In a pilot study of adult patients undergoing HLA-mismatched bone marrow transplantation (n=8) or peripheral blood stem cell transplantation (n=5), the combination of MMF, cyclosporin, methotrexate and prednisolone as prophylaxis for GVHD was reported to be safe and to result in a low rate of acute GVHD⁷⁶. Three of the 13 patients died prior to day 100 post-transplantation. MMF was reported to be well tolerated with no evidence of severe adverse events.

In one small retrospective analysis, MMF with tacrolimus was reported to be useful for treatment of GVHD in 26 patients resistant to other therapies⁷⁷. In this analysis, salvage therapy with MMF and tacrolimus produced a 46% objective response, however, long-term survival data were not presented. Complete resolution of chronic GVHD and partial improvement responses were reported to have been achieved in 2 and 10 patients, respectively. Of the remaining patients, 3 and 9 patients had stable or progressive disease, and 2 patients were unevaluable due to early death from infectious causes. This regimen was generally tolerated well with primarily gastrointestinal disturbances. Since initial experience with this regimen was positive, a controlled clinical trial is underway.

Other studies have also reported promising results using MMF in these conditions^{78 79 80 81 82 83}.

Non-transplant disorders

The mechanisms of action of MMF suggest that it may also be useful in immunologically driven inflammatory disorders. Preliminary reports suggest that this may be the case; in some cases however, controlled studies are needed to establish efficacy.

Rheumatoid arthritis

MMF has been reported to be potentially effective and fairly well tolerated in rheumatoid arthritis, according to the results of several published studies⁸⁴. Improvement was said to be seen in many patients who had been refractory to several disease-modifying anti-rheumatic drugs. MMF was shown to reduce titres of rheumatoid factor, immunoglobulin levels and the total number of T-cells (CD62⁺) in peripheral blood.

1g twice a day was found to be as effective as 2g twice a day, the lower dose having fewer gastrointestinal side effects, according to the results of one study which was randomised, placebo-controlled, double-blind and involved 153 patients⁸⁵. Marked efficacy was reported to have been seen by week 4, with a peak effect around weeks 8 to 12, which was sustained to week 36.

However, following the preliminary results of a substantial study, the manufacturers have not pursued this indication.

Myaesthesia gravis

The successful treatment of two patients with myaesthesia gravis with MMF has been reported⁸⁶⁸⁷.

Skin conditions

Early open and placebo-controlled studies reported that mycophenolic acid was effective in patients with moderate-to-severe **psoriasis**, including those with severe refractory disease or intolerance to conventional therapy^{88 89 90}. However, clinical trials were halted in 1977 due to concerns regarding the toxicity of the drug (eg, immunosuppressant effects, carcinogenic potential, gastrointestinal effects). Nevertheless a number of authors have continued to attest to the efficacy of mycophenolic acid in psoriasis although a balance with respect to potential toxicity remains an issue^{91 92 93 94 95 96 97}⁹⁸.

Topical mycophenolic acid (1%) was not found to be effective in psoriasis, even under occlusion,

according to the results of a randomised, placebo-controlled trial in seven patients⁹⁹.

Dyshidrotic eczema has been treated successfully with MMF¹⁰⁰. Also value in **bullous pemphigus** has been reported^{101 102 103}, as has potential efficacy in **pemphigus vulgaris**¹⁰⁴. Three cases of relapsing **idiopathic nodular panniculitis** (Pfeifer–Weber–Christian disease) have been reported to have been successfully treated with MMF¹⁰⁵. A combination of MMF and cyclosporin was used successfully in recalcitrant **pyoderma gangrenosum**^{106 107}.

Successful treatment of 12 patients with atopic dermatitis has been reported^{108 109}. Nevertheless, it has been suggested that MMF be used with caution in patients with atopic dermatitis following a report of staphylococcal septicaemia and endocarditis requiring a mitral valve repair in one patient¹¹⁰.

Dermatomyositis

MMF has been found to be effective in four patients with classic skin manifestations and histologic evidence of **dermatomyositis** (mean duration of treatment of 13 months)¹¹¹.

Renal disease

Primary glomerulonephritis Response to MMF with reductions in proteinuria and stabilisation of renal function were demonstrated in eight cases of resistant or relapsing nephrotic syndrome associated with various glomerulonephritides¹¹². In a subsequent report from the same authors after longer follow-up¹¹³, three of the MMF responders were reported to have relapsed after withdrawal of MMF. Additional experience of four patients who did not tolerate MMF and two with recurrent minimal change disease who failed to respond to MMF was also reported.

Idiopathic membranous nephropathy resistant to conventional immunosuppressive therapy has been treated with MMF and, of 16 patients, one had complete remission of the nephrotic syndrome, three had a partial remission; MMF was stopped in four, two for lack of effect and one for intolerance¹¹⁴.

Single case reports have claimed responses to MMF in tubulointerstitial nephritis with uveitis previously refractory to corticosteroids, azathioprine and cyclosporin and in retroperitoneal fibrosis presenting with anuria⁵.

Vasculitis Ten of eleven patients with anti-neutrophil cytoplasm autoantibodies-associated renal vasculitis remained in remission at 12 months, following introduction of MMF 2g per day in place of cyclophosphamide, in one prospective single limb trial¹¹⁵. All patients tolerated MMF and no severe adverse effects were noted.

Salvage of renal function in a case of recurrent immune-complex crescentic glomerulonephritis in an allograft with features of an ANCA-associated systemic vasculitis followed addition of MMF to prednisolone and cyclosporin¹¹⁶.

Clinical remission was achieved within four weeks of MMF treatment and sustained for 11-15 months in a series of three patients with relapsing Takayasu's arteritis, previously treated with corticosteroids in two, or corticosteroids, methotrexate and cyclophosphamide in one¹¹⁷.

Lupus nephritis The authors of one recent small study¹¹⁸ found that MMF was well tolerated and has possible efficacy in controlling major renal manifestations of systemic lupus erythematosus. Twelve patients with relapsing or resistant nephritis previously treated with cyclophosphamide and one patient who refused cyclophosphamide as initial therapy for diffuse proliferative nephritis, but accepted MMF, were included. During combined MMF/prednisone therapy, serum creatinine values remained normal or declined from elevated values and proteinuria significantly decreased. Decreased serum complement component C3 and elevated anti-double-stranded DNA antibody levels at baseline improved in some, but not all, patients. Adverse events included herpes simplex stomatitis associated with severe leucopenia (n = 1), asymptomatic leucopenia (n = 2), nausea/ diarrhoea (n = 2), thinning of scalp hair (n = 1), pancreatitis (n = 1), and pneumonia without leucopenia (n = 1). Recurrence of the pancreatitis led to discontinuation of MMF in this patient; all other adverse events resolved with dose reduction.

One reviewer⁵ reported on a number of studies, including the above, concerning the use of MMF in lupus nephritis refractory to standard immunosuppressive protocols. These studies involved 31 patients. In this review it was concluded that the results were generally positive and allowed reductions in corticosteroid dosing. Severe adverse effects were said to occur in approximately one quarter of the patients and led to withdrawal of MMF in four. It was noted, however, that there were some difficulties in drawing conclusions from these studies. Experience with MMF for other indications, including remission induction or long-term remission maintenance, was said in this review not to have

been reported. Numerous questions including the optimal dose and duration of therapy for MMF in lupus nephritis remain to be addressed in controlled clinical trials.

Ocular Inflammation

On the basis of prior reports, it has been suggested that a controlled clinical trial to assess MMF as a first-line immunosuppressive agent in uveitis or as second- or third-line therapy in refractory ocular inflammation is needed¹¹⁹.

MMF was found to be safe and effective in three patients, one patient with ocular cicatricial pemphigoid, another switched to MMF following high-risk keratoplasty due to cyclosporin allergy, and in combination with cyclosporin therapy in a patient following high-risk keratoplasty in whom cyclosporin alone was insufficient to prevent allograft rejection¹²⁰.

A second pilot study also suggested that MMF may be useful for controlling other types of ocular inflammation with minimal side effects¹²¹. MMF 1g twice daily was administered with corticosteroids, as an additional agent with cyclosporin, or instead of cyclosporin or azathioprine. Ten of eleven patients with uncontrolled ocular inflammation showed a favourable response, leading to improvement of symptoms and the ability to reduce the dose of prednisone.

Biliary cirrhosis

MMF may be an appropriate immunosuppressive drug for use in the long-term treatment of patients with primary biliary sclerosis, including asymptomatic patients^{122 123}. In one report¹²³, two patients, whose response to long-term treatment with ursodeoxycholic acid had been inadequate, were treated with a combination of MMF 2 g per day and ursodeoxycholic acid for 12 months. In both patients this regimen was associated with no clinically significant adverse events, a decrease in elevated serum alkaline phosphatase levels to values close to the upper limit of normal, and an almost complete disappearance of the chronic inflammatory cell infiltrate that had been present in pre-combination treatment liver biopsies.

HIV infection

MMF may contribute to the control of HIV replication by both virological and immunological mechanisms, according to the authors of one study

in 16 patients¹²⁴. In this study, with MMF therapy, there were significant decreases in the mean number of dividing CD4+ T cells. It has been noted, however, in an accompanying editorial, that clinical benefit needs to be appropriately demonstrated¹²⁵.

Autoimmune haemolytic anaemia

The use of MMF for treatment of autoimmune haemolytic anaemia has been described¹²⁶.

Inflammatory bowel disease (IBD)

The use of MMF in refractory inflammatory bowel disease was proposed¹²⁷ and several studies have since appeared in the literature. In Crohn's disease it has been reported that the manufacturers have terminated the international randomised, double-blind trial.

It has also been noted that the possible benefits of the drug in inflammatory bowel disease need to be weighed against its major side effects on the gastrointestinal tract and other potential problems¹.

Crohn's disease As mentioned, termination of the international, controlled trial of MMF in active refractory Crohn's disease has been reported to have been suspended by the manufacturers¹²⁸. The reasons given related to "registration of new innovative medicines" and "slow recruitment into the trial". These authors noted that findings in several preliminary reports, and particularly a recently published unblinded, single-centre comparative trial, have suggested that MMF would be a useful alternative to azathioprine, acting faster and being at least as well tolerated. They note however, that at least two uncontrolled studies had failed to confirm this proposal.

The results from the single-centre comparative trial above have also been reported to be flawed, on the basis of the retrospective nature of the study and problems with differences between the groups compared¹²⁹.

Ulcerative colitis Azathioprine appeared more effective and "safer" than MMF in patients with chronic active ulcerative colitis, according to the authors of one open-label study¹³⁰. In this trial, 24 patients with active ulcerative colitis were randomly assigned to the MMF (20 mg/kg)/prednisolone or azathioprine (2 mg/kg)/prednisolone group. The authors of this study considered that MMF might be an alternative treatment for patients with contraindications to azathioprine. However they noted that, to further evaluate the effects of MMF

in active ulcerative colitis, a placebo-controlled double-blinded study appears warranted.

Other disorders

There have been case reports of some success using MMF in a number of other disorders including obliterative bronchiolitis syndrome¹³¹, retroperitoneal fibrosis¹³², Wegener's granulomatosis¹³³ and autoimmune hepatitis¹³⁴. MMF has also been reported from the results of animal studies to potentiate the antiherpetic activities of a number of antiviral agents^{135 136 137 138}.

Adverse Reactions

The adverse event profile associated with the use of immunosuppressive drugs is often difficult to establish due to the presence of underlying disease and the concurrent use of many other medications. The principal adverse reactions associated with the administration of MMF in combination with cyclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections, such as tuberculosis, cytomegalovirus (CMV) and atypical mycobacterial infection. Gastrointestinal symptoms are the most frequent adverse reaction, usually managed in clinical practice either by dose reduction or by splitting the total dose into three or four doses per day. Uncommon but serious life-threatening infections such as meningitis and infectious endocarditis have been reported.

As with other patients receiving immunosuppressive regimens involving combinations of drugs, patients receiving MMF as part of an immunosuppressive regimen are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. Within three years post-transplant, lymphoproliferative disease or lymphoma developed in patients receiving MMF in immunosuppressive regimens in 0.6% of patients receiving 2g daily in the controlled studies of prevention of renal rejection compared to placebo (0%) and azathioprine groups (0.6%). The incidence of malignancies among the 1,483 patients enrolled in controlled trials for the prevention of renal allograft rejection was low, and similar to the incidence reported in the literature for renal allograft recipients. There was a slight increase in the incidence of lymphoproliferative disease in the MMF treatment groups compared to the placebo and azathioprine groups. This aspect of treatment should be monitored as time progresses in order to further define risks in patients treated with MMF

and to compare these risks with those of other therapies.

The ANZDATA registry of dialysis and transplant patients continues to monitor long-term mortality as well as development of malignancies.

For further details concerning the adverse reactions profile for MMF, the TGA Approved Product Information should be consulted.

Economic considerations

Prevention of rejection in renal transplantation

MMF has been found to be associated with lower overall treatment costs compared to azathioprine as part of an immunosuppressive regimen in the first year after renal transplantation^{139 140}. A three year Markov model has also indicated that MMF is a more cost-effective option than azathioprine, but few details are available⁶. The significantly lower cost of rejection treatment and associated hospitalisations was the key economic factor in reducing the overall cost of treatment with MMF compared with azathioprine, offsetting the higher drug acquisition cost. A lower incidence of graft loss and subsequent dialysis associated with MMF treatment also contributed to the reduced financial impact of this regimen. Also, an eight-fold reduction in rejection-related costs and hospitalisation led to cost savings with MMF compared with azathioprine in the first six months after transplantation in a single-centre Swiss study (n=80)¹⁴¹.

Less certain, however, are the long-term clinical and economic benefits. An economic analysis based on a ten-year projection of graft survival in patients receiving MMF suggested that the acquisition cost of the drug may limit its cost effectiveness for long-term treatment in all patients¹⁴². Nevertheless, the drug may be economically favourable in selected high-risk patients over the long term¹⁴³.

Treatment of rejection in renal transplantation

For the treatment of rejection MMF may also be cost effective, according to one cost-benefit analysis. In this decision-analysis model, MMF proved to be considerably more cost effective than muromonab CD3 (\$US13 730 vs \$US29 060; 1996 values) per graft surviving with the efficacy end-point of graft survival at 90 days after treatment (data obtained from clinical studies of both drugs in Japan)¹⁴⁴.

Other indications

Cost-benefit data regarding MMF has been most extensively studied in renal transplantation as above. Data is yet to become available for other situations.

IV Formulation

An IV formulation of MMF has recently been released. CellCept IV must be diluted with 5% glucose intravenous infusion prior to use. A two-step dilution is required to prepare the infusion solution to the recommended concentration. CellCept IV is physically incompatible with the following infusion solutions: 0.9% normal saline, Ringer's and lactated Ringer's solutions. The prescribing information also states that the intravenous solution should not be mixed or administered concurrently via the same catheter with other intravenous drugs or infusion admixtures.

Refer manufacturer's details regarding reconstitution. It will be noted that the dilution involves a large volume of solution.

Prices

Cellcept price to hospitals in Australia:

250mg 300 capsules: \$534.30 plus GST
500mg 150 tablets: \$534.30 plus GST
500mg powder for infusion, 4 vials: \$105.30 plus GST

Conclusion

MMF is beginning to replace azathioprine in a number of transplantation settings, eg in renal, cardiac, liver and pancreas transplantation. Overall treatment costs have been reported to be lower for MMF in the first year after renal transplantation. Use in some non-transplant disorders also shows promise but careful consideration needs to be taken regarding the agent's adverse reaction profile, including potential for malignancy.

Acknowledgements

NSW TAG acknowledges the assistance of those who reviewed this document: Dr Paul Trevillian (John Hunter Hospital), Dr Josette Eris (Royal Prince Alfred Hospital), Dr David Kingston (Roche Products Pty Ltd).

REFERENCES

- ¹ Allison AC and Eugui EM. Review: Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology* 2000; 47: 85-118.
- ² Becker BN. Mycophenolate mofetil. *Transplant. Proc.* 1999; 31: 2777-2778.
- ³ Mele TS and Halloran PF. The use of mycophenolate mofetil in transplant recipients. *Immunopharmacology* 2000; 47: 215-245.
- ⁴ CellCept[®] TGA Approved Product Information 31st January 2001.
- ⁵ Jayne D. Non-transplant uses of mycophenolate mofetil. *Curr. Opin. Nephrol. Hypert.* 1999; 8: 563-567.
- ⁶ Bardsley-Elliott A, Noble S, Foster RH. Mycophenolate mofetil: A review of its use in the management of solid organ transplantation. *BioDrugs* 1999; 12: 363-410.
- ⁷ NSW TAG Position Statement: Mycophenolate mofetil October 1996.
- ⁸ Shaw LM, Kaplan B, DeNofrio D, et al. Pharmacokinetics and concentration-control investigations of mycophenolic acid in adults after transplantation. *Therapeut. Drug Monitor.* 2000; 22: 14-19.
- ⁹ Morii M, Ueno K, Ogawa A, et al. Impairment of mycophenolate mofetil absorption by iron ion. *Clin. Pharmacol. Ther.* 2000; 68: 613-616.
- ¹⁰ Pescovitz MD, et al. Intravenous mycophenolate mofetil: safety, tolerability and pharmacokinetics. *Clin. Transplant.* 2000; 14: 179-188.
- ¹¹ Hale MD, Nicholls AJ, Bullingham RES, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. *Clin. Pharmacol. Ther.* 1998; 64: 672-683.
- ¹² Mourrad M, Chaib-Eddour F, Malaise J, et al. Analytical and clinical evaluation of the EMIT mycophenolic acid immunoassay in kidney transplantation. *Transplant. Proc.* 2000; 32: 404-406.
- ¹³ Smak Gregoor PJ, van Gelder T, Hesse CJ, et al. Mycophenolic acid plasma concentrations in kidney allograft recipients with or without cyclosporin: a cross-sectional study. *Nephrol. Dial. Transplant.* 1999; 14: 706-708.
- ¹⁴ Smak Gregoor PJ, et al. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* 1999; 68: 1603-1606.
- ¹⁵ Zucker K, Rosen A, Tsaroucha A, et al. Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous *in vitro* findings. *Transpl. Immunol.* 1997; 5: 225-232.
- ¹⁶ Zucker K, Rosen A, Nichols A, et al. A definitive effect of administration of tacrolimus on the pharmacokinetics of mycophenolate mofetil in renal transplant recipients [abstract no. 1051]. 18th Annual Scientific Meeting of the American Society of Transplantation; 1999 May 15-19; Chicago.
- ¹⁷ Hubner GI, Eismann R, Sziegoleit W. Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther. Drug Monit.* 1999; 21: 536-539.
- ¹⁸ European Mycophenolate Mofetil Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporine and corticosteroids for prevention of acute rejection. *Lancet* 1995; 345: 1321-1325.
- ¹⁹ US Renal Transplant Mycophenolate Mofetil Study Group, Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. *Transplantation* 1995; 60: 225-232.

-
- ²⁰ Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 1996; 61: 1029-1037.
- ²¹ Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group, Mathew TH. A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation. Results at three years. *Transplantation* 1998; 65: 1450-1454.
- ²² European Mycophenolate Mofetil Cooperative Study Group. Mycophenolate mofetil in renal transplantation: 3-year results from the placebo-controlled trial. *Transplantation* 1999; 68: 391-396.
- ²³ US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil in cadaveric renal transplantation. *Am. J. Kidney Dis.* 1999; 34: 296-303.
- ²⁴ Ojo AO, et al. Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. *Transplantation* 2000; 69: 2405-2409.
- ²⁵ Weber M, et al. Optimization of immunosuppression in high risk renal transplant recipients - mycophenolate mofetil and tacrolimus in combination reduce early rejection episodes and eliminate the need for induction therapy in African American patients. < <http://www.ast.org/abstracts/asts1293.htm> >, accessed 15 August 2000.
- ²⁶ Smak Gregoor PJ, et al. Randomized study on the conversion of treatment with cyclosporin to azathioprine or mycophenolate mofetil followed by dose reduction. *Transplantation* 2000; 70: 143-148.
- ²⁷ Wuthrich RP, et al. Randomized trial of conversion from mycophenolate mofetil to azathioprine 6 months after renal allograft transplantation. *Nephrol., Dialysis, Transplant.* 2000; 15: 1228-1231.
- ²⁸ Mycophenolate Mofetil Acute Renal Rejection Study Group. Mycophenolate mofetil for the treatment of a first acute renal allograft rejection. *Transplantation* 1998; 65: 235-241.
- ²⁹ Sollinger HW, et al. RS-61443 (mycophenolate mofetil) . A multicenter study for refractory kidney transplant rejection. 1992; *Ann. Surg.* 216: 513- 519.
- ³⁰ Sollinger HW, et al. RS-61443 - a phase I clinical trial and pilot rescue study. *Transplantation* 1992;. 53: 428-432.
- ³¹ The Mycophenolate Mofetil Renal Refractory Rejection Study Group. Mycophenolate mofetil for the treatment of refractory, acute, cellular renal transplant rejection. *Transplantation* 1996; 61: 722-729.
- ³² The Mycophenolate Mofetil Renal Refractory Rejection Study Group. Rescue therapy with mycophenolate mofetil. *Clin. Transplant.* 1996; 10: 131-135.
- ³³ Carl S, et al. Combining FK506 and mycophenolate mofetil for the treatment of acute corticosteroid-resistant rejection following kidney transplantation: a new therapeutic concept. *Transplant. Proc.* 1998; 30: 1236-1237.
- ³⁴ Morris-Stiff G. and Jurewicz WA. Single center experience with mycophenolate mofetil for refractory rejection in cadaveric renal transplantation. *Transplant. Int.* 1998; 11: 204-207.
- ³⁵ Di Maria L, et al. Mycophenolate mofetil (MMF) in the treatment of chronic renal rejection. *Clin. Nephrol.* 2000; 53: 33-34.
- ³⁶ Mycophenolate Mofetil Acute Renal Rejection Study Group, Pescovitz MD. Mycophenolate mofetil for the treatment of renal transplant rejection: 3 year follow-up. *Am. Soc. Transplant. Phys. Ann. Mtg.* 1999; 18: 929 (Abstract) .

-
- ³⁷ The Refractory Rejection Meta-analysis Study Group, Woodle ES, et al. Meta-analysis of FK506 and mycophenolate mofetil refractory rejection trials in renal transplantation. *Transplant. Proc.* 1998; 30: 1297–1298.
- ³⁸ Keunecke C, et al. Mycophenolate mofetil monotherapy: An example of a safe nephrotoxicity/atherogenicity-free immunosuppressive maintenance regimen in a selected group of kidney-transplanted patients. *Transplant. Proc.* 2000; 32 (Suppl 1A): 6S-8S.
- ³⁹ Houde I, Isenring P, Boucher D, et al. Mycophenolate mofetil, an alternative to cyclosporine A for long-term immunosuppression in kidney transplantation? *Transplantation* 2000; 70: 1251-1253.
- ⁴⁰ Kobashigawa J, et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. *Transplantation* . 1998; 66: 507–515.
- ⁴¹ Eisen H, Bourge R, Costanzo, G. Three-year allograft vasculopathy results of the multicenter heart transplant mycophenolate mofetil randomized trial. *Transplantation* 1999; 67: S268 (Abstract).
- ⁴² Mathieu P, et al. Effect of mycophenolate mofetil in heart transplantation. *Can. J. Surg.* 2000; 43: 202-206.
- ⁴³ Taylor DO, et al. Increased incidence of allograft rejection in stable heart transplant recipients after late conversion from mycophenolate mofetil to azathioprine. *Clin. Transplant.* 1999; 13: 296-299.
- ⁴⁴ Taylor DO, et al. Mycophenolate mofetil (RS-61443): Preclinical, clinical, and three-year experience in heart transplantation. *J. Heart Lung Transplant.* 1994; 13: 571–582.
- ⁴⁵ Ensley RD, et al. The use of mycophenolate mofetil (RS-61443) in human heart transplant recipients. *Transplantation* 1993; 56: 75–82.
- ⁴⁶ Kirklin JK, et al. Treatment of recurrent heart rejection with mycophenolate mofetil (RS–61443): initial clinical experience. *J. Heart Lung Transplant.* 1994; 13: 444–450.
- ⁴⁷ Kobashigawa JA, et al. Initial results of RS-61443 for refractory cardiac rejection. *J. Am. Coll. Cardiol.* 1992; 19: 203A, (Abstract).
- ⁴⁸ FDA internet site: < <http://www.fda.gov/cder/>>, accessed 15 August 2000.
- ⁴⁹ Wiesner R. Personal communication - cited in Mele TS and Halloran PF. The use of mycophenolate mofetil in transplant recipients. *Immunopharmacology* 2000; 47: 215-245.
- ⁵⁰ Sterneck M, et al. Mycophenolate mofetil for prevention of liver allograft rejection: initial results of a controlled clinical trial. *Annal. Transplant.* 2000; 5: 43-46.
- ⁵¹ Klupp J, et al. Mycophenolate mofetil in combination with tacrolimus versus Neoral after liver transplantation. *Transplant. Proc.* 1999; 31: 1113–1114.
- ⁵² Jain AB, et al. A prospective randomized trial of tacrolimus and prednisone versus tacrolimus, prednisone, and mycophenolate mofetil in primary adult liver transplant recipients: an interim report. *Transplantation* 1998; 66: 1395–1398.
- ⁵³ Stegall MD, Wachs ME, Everson G, et al. Prednisone withdrawal 14 days after liver transplantation with mycophenolate: a prospective trial of cyclosporine and tacrolimus. *Transplantation* 1997; 64: 1755-1760.
- ⁵⁴ Klintmalm GB, et al. RS-61443 for treatment-resistant human liver rejection. *Transplant. Proc.* 1993; 25: 697.
- ⁵⁵ Gavlik A. Mycophenolate mofetil rescue therapy in liver transplant recipients: An extended follow-up. *Transplant. Proc.* 1997; 29: 2971–2972.

-
- ⁵⁶ Gavlik A, et al. Mycophenolate mofetil rescue therapy in liver transplant recipients. *Transplant. Proc.* 1997; 29: 549–552.
- ⁵⁷ Platz KP, Mueller AR, Neuhaus R, et al. FK506 and mycophenolate mofetil rescue for acute steroid-resistant and chronic rejection after liver transplantation. *Transplant. Proc.* 1997; 29: 2872–2874.
- ⁵⁸ Hebert MF, et al. Four-year follow-up of mycophenolate mofetil for graft rescue in liver allograft recipients. *Transplantation* 1999; 67: 707–712.
- ⁵⁹ Herrero JI, et al. Conversion from cyclosporine A to mycophenolate mofetil in liver transplant recipients with renal function impairment. Liver Unit and Department of Surgery. Clinica Universitaria. Pamplona, Spain. <http://www.a-s-t.org/abstracts98/193.htm> >, accessed 15 August 2000.
- ⁶⁰ Papatheodoridis GV, et al. Mycophenolate mofetil monotherapy in stable liver transplant patients with cyclosporine-induced renal impairment: a preliminary report. *Transplantation* 1999; 68: 155–157.
- ⁶¹ Barkmann A, et al. Improvement of acute and chronic renal dysfunction in liver transplant patients after substitution of calcineurin inhibitors by mycophenolate mofetil. *Transplantation* 2000; 69: 1886-1890.
- ⁶² Ross DJ, et al. Mycophenolate mofetil versus azathioprine immunosuppressive regimens after lung transplantation: Preliminary experience. *J. Heart Lung Transplant.* 1998; 17: 768-774.
- ⁶³ Zuckermann A, et al. Comparison between mycophenolate mofetil- and azathioprine-based immunosuppression in clinical lung transplantation. *J. Heart Lung Transplant.* 1999; 18: 432-440.
- ⁶⁴ Lill J, et al. Therapy of rejection following lung transplantation with mycophenolate mofetil. *Eur. Resp. J.* 1998; Suppl 28: 341-342.
- ⁶⁵ Stratta RJ. Immunosuppression in pancreas transplantation: Progress, problems and perspective. *Transplant Immunol.* 1998; 6: 69-77.
- ⁶⁶ Merion RM, et al. Randomized, prospective trial of mycophenolate mofetil versus azathioprine for prevention of acute renal allograft rejection after simultaneous kidney-pancreas transplantation. *Transplantation* 2000; 70: 105-111.
- ⁶⁷ Stegall MD, et al. Mycophenolate mofetil decreases rejection in simultaneous pancreas-kidney transplantation when combined with tacrolimus or cyclosporine. *Transplantation* 1997; 64: 1695-1700.
- ⁶⁸ Rigotti P, et al. Mycophenolate mofetil (MMF) versus azathioprine (AZA) in pancreas transplantation: A single-center experience. *Clin. Nephrol.* 2000; 53: 52-54.
- ⁶⁹ Gruessner RW, Sutherland DE, Drangstveit MB, et al. Mycophenolate mofetil in pancreas transplantation. *Transplantation* 1998; 66: 318-323.
- ⁷⁰ Odorico JS, et al. A study comparing mycophenolate mofetil to azathioprine in simultaneous pancreas-kidney transplantation. *Transplantation* 1998; 66: 1751-1759.
- ⁷¹ Merion RM, et al. Randomized multicenter open label comparative trial of mycophenolate mofetil versus azathioprine in simultaneous kidney-pancreas transplantation. *Transplantation* 1998; 66: S22 (abstract).
- ⁷² Bruce DS, et al. Tacrolimus/mycophenolate provides superior immunosuppression relative to Neoral/mycophenolate in synchronous pancreas-kidney transplantation. *Transplant. Proc.* 1998; 30: 1538-1540.
- ⁷³ Reis A, Reinhard T, Voiculescu A, et al. Mycophenolate mofetil versus cyclosporin A in high risk keratoplasty patients: a prospectively randomised clinical trial. *Br. J. Ophthalmol.* 1999; 83: 1268-1271.

-
- ⁷⁴ Gruessner RW and Sharp HL. Living-related intestinal transplantation: first report of a standardized surgical technique. *Transplantation* 1997; 64: 1605-1607.
- ⁷⁵ Jamieson NV. Adult small intestinal transplantation in Europe. *Acta Gastro-Enterol. Belg.* 1999; 62: 239-243.
- ⁷⁶ Basara N, et al. Mycophenolate mofetil for the prophylaxis of acute GVHD in HLA-mismatched bone marrow transplant patients. *Clin. Transplant.* 2000; 14: 121-126.
- ⁷⁷ Mookerjee B, Altomonte V, Vogelsang G. Salvage therapy for refractory chronic graft-versus-host disease with mycophenolate mofetil and tacrolimus. *Bone Marrow Transplantation* 1999; 24: 517-20.
- ⁷⁸ Busca A, et al. Mycophenolate mofetil (MMF) as therapy for refractory chronic GVHD (cGVHD) in children receiving bone marrow transplantation. *Bone Marrow Transplant.* 2000; 25: 1067-1071.
- ⁷⁹ Grundmann-Kollmann M, et al. Chronic sclerodermic graft-versus-host disease refractory to immunosuppressive treatment responds to UVA phototherapy. *J. Am. Acad. Dermatol.* 2000; 42 (1 Pt 1): 134-136.
- ⁸⁰ Basara N, et al. Efficacy and safety of mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant recipient. *Transplant. Proc.* 1998; 30: 4087-9.
- ⁸¹ Basara N, et al. Mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant patients. *Bone Marrow Transplant.* 1998; 22: 61-5.
- ⁸² Kiehl MG, et al. Mycophenolate mofetil for the prophylaxis of acute GVHD in HLA-mismatched bone marrow transplant patients. *Clin. Transplant.* 2000 14: 121-126.
- ⁸³ Kiehl MG, et al. New strategies in GVHD prophylaxis. *Bone Marrow Transplant.* 2000; 25 (Suppl 2): S16-S19.
- ⁸⁴ Goldblum R. Therapy of rheumatoid arthritis with mycophenolate mofetil. *Clin. Exp. Rheumatol. R.* 1993; 11Suppl.: S117-119.
- ⁸⁵ Schiff MH and Leishman B. CellCept (mycophenolate mofetil-MMF) a new treatment for RA: A 12-week, double-blind, randomized, placebo-controlled withdrawal trial. *Arthr. Rheum.* 1998; 41 Suppl. 9: S364.
- ⁸⁶ Hauser RA, Malek AR, Rosen R. Successful treatment of a patient with severe refractory myasthenia gravis using mycophenolate mofetil. 1998; *Neurology*: 912-913.
- ⁸⁷ Meriggioli MN and Rowin J. Treatment of myasthenia gravis with mycophenolate mofetil: A case report. *Muscle & Nerve* 2000; 23: 1287-1289.
- ⁸⁸ Linn Jones E, Epinette WW, Hackney VC, et al. Treatment of psoriasis with oral mycophenolic acid. *J. Invest. Dermatol.* 1975; 65: 537-542.
- ⁸⁹ Lynch WS, Roenigk HH. Mycophenolic acid for psoriasis. *Arch. Dermatol.* 1977; 113: 1203-1208.
- ⁹⁰ Epinette WW, et al. Mycophenolic acid for psoriasis. A review of pharmacology, long-term efficacy, and safety. *J. Amer. Acad. of Dermatol.* 1987; 17: 962-971.
- ⁹¹ Geilen CC, et al. Successful treatment of erythrodermic psoriasis with mycophenolate mofetil. *Br. J. Dermatol.* 1998; 138: 1101-1102.
- ⁹² Haufs MG, et al. Psoriasis vulgaris treated successfully with mycophenolate mofetil. *Br. J. Dermatol.* 1998; 138: 179-181.
- ⁹³ Grundmann-Kollmann M, et al. Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J. Amer. Acad. Dermatol.* 2000; 42: 835-837.

-
- ⁹⁴ Tong DW and Walder BK. Widespread plaque psoriasis responsive to mycophenolate mofetil. *Aust. J. Dermatol.* 1999; 40: 135-7.
- ⁹⁵ Gomez EC, et al. Efficacy of mycophenolic acid for the treatment of psoriasis. *J. Amer. Acad. of Dermatol.* 1979; 1: 531-7.
- ⁹⁶ Spatz S, et al. Mycophenolic acid in psoriasis. *Br. J. Dermatol.* 1978; 98: 429-35.
- ⁹⁷ Marinari R, et al. Mycophenolic acid in the treatment of psoriasis: long-term administration. *Arch. Dermatol.* 1977; 113: 930-2.
- ⁹⁸ Kirby B and Yates VM. Mycophenolate mofetil for psoriasis [letter; comment]. *Br. J. Dermatol.* 1998; 139: 357.
- ⁹⁹ Geilen CC and Mrowietz U. Lack of efficacy of topical mycophenolic acid in psoriasis vulgaris. *J. Am. Acad. Dermatol.* 2000; 42: 837-840.
- ¹⁰⁰ Pickenacker A, Luger TA, Schwarz T. Dyshidrotic eczema treated with mycophenolate mofetil. 1998; *Arch. Dermatol.* 134: 378–379.
- ¹⁰¹ Grundmann-Kollman M, et al. Mycophenolate mofetil: a new therapeutic option in the treatment of blistering autoimmune diseases. *J. Am. Acad. Dermatol.* 1999; 40: 957–960.
- ¹⁰² Bohm M, et al. Bullous pemphigoid treated with mycophenolate mofetil. *Lancet* 1997; 349: 541.
- ¹⁰³ Nousari HC, Griffin WA and Anhalt GJ. Successful therapy for bullous pemphigoid with mycophenolate mofetil. *J. Am. Acad. Dermatol.* 1998; 39: 497–498.
- ¹⁰⁴ Enk AH and Knop J. Mycophenolate mofetil is effective in the treatment of pemphigus vulgaris. *Arch. Dermatol.* 1999; 135: 54–56.
- ¹⁰⁵ Enk AH and Knop J. Treatment of relapsing idiopathic nodular panniculitis (Pfeiffer-Weber-Christian disease) with mycophenolate mofetil. *J. Am. Acad. Dermatol.* 1998; 39: 508-509.
- ¹⁰⁶ Hohenleutner U, et al. Mycophenolate mofetil and cyclosporin treatment for recalcitrant pyoderma gangrenosum. *Lancet* 1997; 350: 1748.
- ¹⁰⁷ Nousari HC, et al. The effectiveness of mycophenolate mofetil in refractory pyoderma gangrenosum. *Arch. Dermatol.* 1998; 134: 1509–1511.
- ¹⁰⁸ Neuber K, et al. Treatment of atopic eczema with oral mycophenolate mofetil. *Br. J. Dermatol.* 2000; 143: 385-391.
- ¹⁰⁹ Grundmann-Kollmann M, et al. Successful treatment of severe refractory atopic dermatitis with mycophenolate mofetil. *Br. J. Dermatol.* 1999; 141: 175-176.
- ¹¹⁰ Satchell AC and Barnetson R St C. Staphylococcal septicaemia complicating treatment of atopic dermatitis with mycophenolate. *Br. J. Dermatol.* 2000; 143: 198-203.
- ¹¹¹ Gelber AC, Nousari HC, Wigley FM. Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: A series of 4 cases. *J. Rheumatol.* 2000; 27: 1542-1545.
- ¹¹² Briggs WA, Choi MJ, Scheel PJ. Successful mycophenolate mofetil treatment of glomerular disease. *Am. J. Kidney Dis.* 1998; 31: 213-217.
- ¹¹³ Briggs WA, Choi MJ, Scheel PJ. Follow-up on mycophenolate treatment of glomerular disease. *Am. J. Kidney Dis.* 1998; 32: 898-899.

-
- ¹¹⁴ Zimmerman RF, et al. Mycophenolate mofetil (MMF) treatment of idiopathic membranous nephropathy. *J. Am. Soc. Nephrol.* 1998; 9: 103A.
- ¹¹⁵ Nowack R, Birck R, van der Woude FW. Mycophenolate mofetil is effective for maintenance therapy of systemic vasculitis. *J. Am. Soc. Nephrol.* (in press) - cited in Jayne D. Non-transplant uses of mycophenolate mofetil. *Curr. Op. Nephrol. Hypert.* 1999; 8: 563-567.
- ¹¹⁶ Adams PL, Iskander SS, Rohr MS. Biopsy-proven resolution of immune complex-mediated crescentic glomerulonephritis with mycophenolate mofetil therapy in an allograft. *Am J. Kidney Dis.* 1999; 33: 552-554.
- ¹¹⁷ Daina E, Schieppali A, Remuzzi G. Mycophenolate mofetil for the treatment of Takayasu arteritis: Report of three cases. *Ann. Intern. Med.* 1999; 130: 422-426.
- ¹¹⁸ Dooley MA, Cosio FG, Nachman PH, et al. Mycophenolate mofetil therapy in lupus nephritis: clinical observations. *J. Am. Soc. Nephrol.* 1999; 10: 833-839.
- ¹¹⁹ Kilmartin DJ and Dick AD. Mycophenolate mofetil therapy. *Ophthalmology* 1999; 106: 1645.
- ¹²⁰ Reis A, et al. Mycophenolate mofetil in ocular immunological disorders. A survey of the literature with 3 case reports. *Klin. Monatsbl. Augen-heilkd.* 1998; 213: 257-261.
- ¹²¹ Larkin G and Lightman S. Mycophenolate mofetil. A useful immunosuppressive in inflammatory eye disease. *Ophthalmology* 1999; 106: 370-374.
- ¹²² Altschuler EL. Mycophenolate for primary biliary cirrhosis - convergent thinking. *Eur. J. Gastroenterol. & Hepatol.* 2000; 12: 587.
- ¹²³ Jones EA, et al. Combination therapy with mycophenolate mofetil and ursodeoxycholic acid for primary biliary cirrhosis. *Eur. J. Gastroenterol. Hepatol.* 1999; 11: 1165-1169.
- ¹²⁴ Chapuis AG, et al. Effects of mycophenolic acid on human immunodeficiency virus infection *in vitro* and *in vivo*. *Nature Medicine* 2000; 6: 762-768.
- ¹²⁵ Finzi D, et al. Taking aim at HIV replication. *Nature Medicine* 2000; 6: 735-736.
- ¹²⁶ Zimmer-Molsberger B, Knauf W, Thiel E. Mycophenolate mofetil for severe autoimmune haemolytic anaemia. *Lancet* 1997; 350: 1003-1004.
- ¹²⁷ Nehme OS, Overley CA, O'Brien JJ. The role of mycophenolate mofetil in the management of refractory inflammatory bowel disease (IBD). *Gastroenterology* 1998; 114 (4 Pt. 2): A1049.
- ¹²⁸ Rampton DS, et al. Mycophenolate mofetil in Crohn's disease. *Lancet* 2000; 356:163-164.
- ¹²⁹ Atherton JC. Mycophenolate mofetil for Crohn's disease. *Gut* 2000; 46: 740-741.
- ¹³⁰ Orth T, et al. Mycophenolate mofetil versus azathioprine in patients with chronic active ulcerative colitis: A 12-month pilot study. *Am. J. Gastroenterol.* 2000; 95: 1201-1207.
- ¹³¹ Whyte RI, Rossi SJ, Mulligan MS, et al. Mycophenolate mofetil for obliterative bronchiolitis syndrome after lung transplantation. *Ann. Thorac. Surg.* 1997; 64: 945-948.
- ¹³² Grotz W, von Zedtwitz I, Andre M, et al. Treatment of retroperitoneal fibrosis by mycophenolate mofetil and corticosteroids. *Lancet* 1998; 352: 1195.
- ¹³³ Nowack R, Gobel U, Klooker P, et al. Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. *J. Am. Soc. Nephrol.* 1999; 10: 1965-1971.

-
- ¹³⁴ Richardson PD, James PD, Ryder SD. Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. *J. Hepatol.* 2000; 33: 371-375.
- ¹³⁵ Neyts J and De Clercq E. The immunosuppressive agent mycophenolate mofetil markedly potentiates the activity of lobucavir [1R(1alpha, 2beta,3alpha)]-9-[2,3-bis (hydroxymethyl) cyclobutyl] guanine against different herpes viruses. *Transplantation* 1999; 67: 760-764.
- ¹³⁶ Neyts J and De Clercq E. Mycophenolate mofetil strongly potentiates the anti-herpesvirus activity of acyclovir. *Antiviral Research* 1998; 40: 53-56.
- ¹³⁷ Neyts J, Andrei G, De Clercq E. The antiherpesvirus activity of H2G [(R)-9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine] is markedly enhanced by the novel immunosuppressive agent mycophenolate mofetil. *Antimicrob. Agents & Chemother.* 1998; 42: 3285-3289.
- ¹³⁸ Neyts J, Andrei G, De Clercq E. The novel immunosuppressive agent mycophenolate mofetil markedly potentiates the antiherpesvirus activities of acyclovir, ganciclovir, and penciclovir in vitro and in vivo. *Antimicrob. Agents & Chemother.* 1998; 42: 216-222.
- ¹³⁹ Khosla UM, et al. One-year, single-center cost analysis of mycophenolate mofetil versus azathioprine following cadaveric renal transplantation. *Transplant. Proc.* 1999; 31: 274-275.
- ¹⁴⁰ Sullivan SD, Garrison LP, Best JH. The cost effectiveness of mycophenolate mofetil in the first year after primary cadaveric transplant. *J. Am. Soc. Nephrol.* 1997; 8: 1592-1598.
- ¹⁴¹ Wuthrich RP, et al. Reduced kidney transplant rejection rate and pharmacoeconomic advantage of mycophenolate mofetil. *Nephrol., Dialysis, Transplant.* 1999; 14: 394-399.
- ¹⁴² Schnitzler MA, et al. Ten-year cost effectiveness of alternative immunosuppression regimens in cadaveric renal transplantation. *Transplant. Proc.* 1999; 31(3B Suppl):19S-21S.
- ¹⁴³ Deierhoi MH, Gupta S, Hudson SL. Cost considerations and the use of mycophenolate mofetil in renal transplantation [abstract]. *Transplantation* 1998; 66: S5.
- ¹⁴⁴ Sakamaki H, et al. Cost-effectiveness analysis of mycophenolate mofetil treatment for intractable acute rejection in renal transplantation recipients [abstract]. *Value in Health* 1999; 2: 204.