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Preliminary Risk-Benefit Assessment of Mycophenolate Mofetil in Transplant Rejection

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Summary

Mycophenolate mofetil (the morpholinoethyl ester of mycophenolic acid) inhibits *de novo* purine synthesis via the inhibition of inosine monophosphate dehydrogenase. Its selective lymphocyte antiproliferative effects involve both T and B cells, preventing antibody formation. Mycophenolate mofetil has immuno-

suppressive effects alone, but is used most commonly in combination with other immunosuppressants. Mycophenolate mofetil, in combination with cyclosporin and corticosteroids, has been studied in large, randomised clinical trials involving nearly 1500 renal allograft transplant recipients. These trials demonstrated that mycophenolate mofetil is significantly more effective in reducing treatment failure and acute rejection episodes than placebo or azathioprine. Additionally, mycophenolate mofetil may be able to reduce the occurrence of chronic rejection.

Mycophenolate mofetil is relatively well tolerated. The most common adverse effect reported is gastrointestinal intolerance; haematological aberrations have also been noted. The reversible cytostatic action of mycophenolate mofetil allows for dose adjustment or discontinuation, preventing serious toxicity or an overly suppressed immune system. Cytomegalovirus tissue invasive disease and the development of malignancies are concerns that merit evaluation in long term follow-up studies.

Mycophenolate mofetil does not cause the adverse effects typically associated with other commercially available immunosuppressant medications such as nephrotoxicity, hepatotoxicity, hypertension, nervous system disturbances, electrolyte abnormalities, skin disorders, hyperglycaemia, hyperuricaemia, hypercholesterolaemia, lipid disorders and structural bone loss.

Based on preliminary information, a positive benefit-risk ratio has been demonstrated with the use of mycophenolate mofetil in the prophylaxis of rejection in cadaveric renal allograft transplantation. Data from studies in other types of organ transplants are promising, but are too limited to draw clear conclusions. Long term follow-up studies are required to confirm these observations. Although mycophenolate mofetil is expensive, the beneficial effects on the reduction of rejection, treatment failure and related expenses suggest that it is most likely to be cost effective.

Short term patient and graft survival rates in solid organ transplantation continue to improve with the introduction of new immunosuppressive agents. Immunosuppressive drugs can be categorised based on the mechanism by which they disrupt normal immune system activity. The full immune system response requires: (i) a favourable local environment; (ii) antigen presentation and costimulation leading to cytokine release from activated T cells; and (iii) synthesis of *de novo* nucleotides.[1] Each drug provides varying degrees of benefits, but also has an inherent risk of toxicity. Mycophenolate mofetil is a selective immunosuppressant developed to prevent and treat transplant rejection. It was approved in the US in 1995 for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants and is also available in a number of European markets including Belgium, Denmark, France, Germany, Switzerland and the UK. Mycophenolate mofetil is the morpholinoethyl ester prodrug of mycophenolic acid – an isolate from the fermentation of several penicillin species.[2,3] Mycophenolate mofetil was designed to enhance oral bioavailability and was later found to have important immunological properties. Mycophenolic acid has been evaluated for its unique properties in the past as an anticancer[4] and antiviral[5] agent, as well as for its therapeutic use for psoriasis[6,7] and rheumatoid arthritis.[8]

Allison et al.[9] first recognised the utility of the properties of mycophenolic acid, and later proved that lymphocytes were suppressed by the inhibition of inosine monophosphate dehydrogenase (IMPDH). Mycophenolic acid was later shown to be a potent, non-nucleotide, noncompetitive, reversible inhibitor of IMPDH, which is the rate limiting step of *de novo* purine synthesis.[10,11] This discovery led to transplantation experiments in ani-

mals in the late 1980s and early 1990s[12-15] with human clinical trials beginning shortly thereafter.

Comprehending the risks and benefits associated with mycophenolate mofetil in transplant patients necessitates an understanding of its unique properties including its mechanism of action, pharmacokinetics, pharmacodynamics, interactions, experimental data, clinical efficacy, toxicity and cost of therapy. Since mycophenolate mofetil has only recently been incorporated into clinical immunosuppressive regimens, this article provides an overview of the known properties and published studies to form the basis of the preliminary risk-benefit evaluation.

1. Mechanism of Action

Mycophenolic acid has a very specific mechanism of action on the antiproliferation of lymphocytes, avoiding interference with purine synthesis in other cell lines. Purine synthesis is accomplished by 2 separate pathways: the *de novo* pathway and the salvage pathway (fig. 1).[16]

Most cells are able to utilise the salvage pathway, which basically recycles sugars and other products. Hypoxanthine guanine phosphoribosyl transferase (HGPRTase) is a catalyst, converting guanine to guanine monophosphate (GMP). This proceeds on to either (i) deoxyguanosine triphosphate (dGTP) and on to DNA synthesis; or (ii) guanosine triphosphate (GTP), used in RNA and glycoprotein synthesis.[16] Some of these glycoproteins are adhesion molecules. Human cells rely on a varying combination of these pathways; however, activated lymphocytes predominately depend on the *de novo* pathway.[16] In the *de novo* pathway ribose and ATP form phosphoribosyl pyrophosphate (PRPP), which is then converted to inosine monophosphate (IMP). IMP is then acted on by IMPDH to form GMP.[16]

IMPDH exists as 2 distinct isoforms. Type I isoform is expressed by resting lymphocytes; type II is up-regulated by activated lymphocytes. Mycophenolic acid asserts its effect by inhibiting the action of IMPDH, especially the type II isoform, which is approximately 5-times more susceptible than type I.[17] As IMPDH is inhibited, IMP levels increase, resulting in a build-up of adenosine and deoxyadenosine nucleotides. This, coupled with the decrease in guanosine and deoxyguanosine nucleotides, down-regulates enzymes in human lymphocytes. This results in a decrease in PRPP and DNA polymerase activity, causing a restriction of

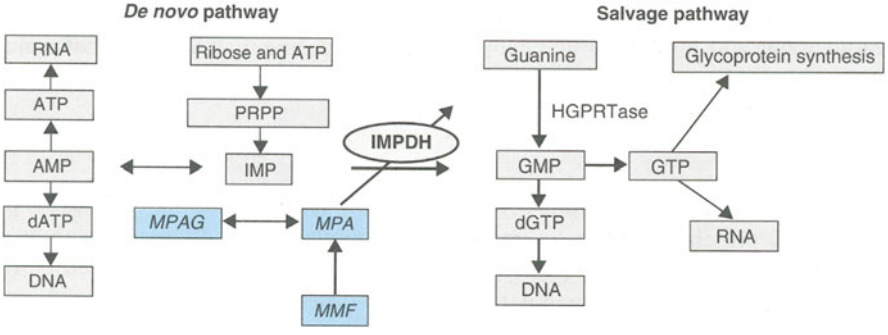

Fig. 1. The inhibitory effect of mycophenolate mofetil (MMF) and its relationship to the *de novo* and salvage metabolic pathways of purine nucleotide biosynthesis. MMF is quickly converted to mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase (IMPDH), preventing inosine monophosphate (IMP) conversion to guanine monophosphate (GMP). This depletes GMP, guanosine triphosphate (GTP), deoxyguanosine triphosphate (dGTP), and increases adenosine monophosphate (AMP), adenosine triphosphate (ATP) and deoxyadenosine triphosphate (dATP). The imbalance inhibits 2 rate-limiting enzymes, leading to a decrease in phosphoribosyl pyrophosphate (PRPP) and DNA polymerase activity. *Abbreviations*: HGPRTase = hypoxanthine guanine phosphoribosyl transferase; MPAG = mycophenolic acid glucuronide.

lymphocyte proliferation.[16] Lymphocytes are locked in the S-phase of the cell cycle if guanine nucleotides are reduced.[18]

2. Pharmacokinetics

Mycophenolate mofetil undergoes complete oral absorption and is rapidly hydrolysed by esterases to mycophenolic acid, with an oral bioavailability of 94% in healthy volunteers.[19] Following oral administration of mycophenolate mofetil, mycophenolic acid plasma concentrations peak at approximately 1 hour.[20] Mycophenolic acid is converted, mainly in the liver, by glucuronyl transferase to an inactive metabolite, mycophenolic acid glucuronide. Undergoing enterohepatic recirculation, mycophenolic acid glucuronide is deglucuronidated to mycophenolic acid and is reabsorbed, contributing to mycophenolic acid plasma concentrations.[21] A secondary mycophenolic acid peak plasma concentration occurs 6 to 12 hours after oral administration of mycophenolate mofetil. The mean apparent half-life of mycophenolic acid and mycophenolic acid glucuronide is about 16 hours.[20] The majority of the drug, approximately 85% of the dose, is recovered as mycophenolic acid glucuronide in the urine.[22]

Active tubular secretion adds considerably to the total renal clearance.[20] Chronic renal impairment will reduce plasma mycophenolic acid glucuronide clearance but will produce little change in the clearance of mycophenolic acid.[23] It is suggested that doses should be limited to 2 g/day in patients with long term severe renal impairment.[20]

Mycophenolic acid and mycophenolic acid glucuronide are highly protein bound to serum albumin.[22] As with many highly bound drugs, the pharmacological activity of mycophenolate is a function of the free mycophenolic acid concentration in the plasma.[22] Mycophenolic acid and mycophenolic acid glucuronide are not significantly removed by haemodialysis, and are unlikely to be affected by peritoneal dialysis.[20]

The maximum concentration (C_{max}) and area under the concentration-time curve (AUC) for mycophenolic acid in stable renal allograft recipients at least 120 days post-transplant was nearly twice that of patients who were less than 40 days post-transplant. It is suggested that this is due to distribution or metabolic factors,[23] rather than differences in absorption. Healthy volunteers had pharmacokinetic measurements that were similar to stable, late postoperative patients.[23] In patients with cirrhosis and hepatic oxidative impairment, limited data concerning the pharmacokinetics of mycophenolate mofetil suggest that no change in administration is necessary.[24]

Therapeutic drug monitoring is being evaluated for its utility in calculating the proper dosage of mycophenolate mofetil. Studies are being performed to determine whether bound or unbound mycophenolic acid and/or mycophenolic acid glucuronide concentrations are best suited as monitoring tools. Initial studies have not demonstrated a relationship between the plasma mycophenolic acid AUC and mycophenolate mofetil toxicities.[22] A consensus panel[22] has suggested a need for further examination of drug monitoring to evaluate: (i) the correlation between the risk of rejection and drug exposure; (ii) patients with highly variable pharmacokinetics, i.e. paediatric patients and early liver transplant recipients, those patients with suspected altered oral absorption or drug/drug, drug/diet interactions; (iii) patients in whom therapy is unsuccessful; (iv) compliance with medication regimen; and (v) taper of concomitant immunosuppressants after graft stabilisation.

3. Interactions

Mycophenolate mofetil has the potential to have a number of important interactions, including food, antacid, drug class and specific drug interactions. In order to enhance the beneficial effects and to improve the tolerability of the drug these interactions must be considered in depth.

Food reduces and delays peak mycophenolic acid plasma concentrations for up to 1 hour without changing the total mycophenolic acid AUC profile.[20] Although the manufacturer recommends mycophenolate mofetil be taken on an empty stom-

ach,[19] for those patients who experience gastrointestinal upset with mycophenolate mofetil the dose is often given with food to reduce the high peak concentrations, which in turn may decrease intolerance. Also, in clinical practice, the drug has been given in 3 or 4 divided doses with food to improve compliance.

Antacids, consisting of magnesium and aluminum hydroxide, administered at the same time as mycophenolate mofetil, produce a decrease in C_{max} (33%) and AUC (17%).[19] It is recommended that antacids should be administered 1 to 2 hours before or after mycophenolate mofetil administration to avoid this interaction. Although not tested, this may suggest that concomitant administration of other divalent cations, such as calcium and iron compounds, should be avoided.

The concomitant administration of tacrolimus and mycophenolate mofetil can significantly increase the AUC of mycophenolic acid and may have greater than additive effects.[25] Cyclosporin does not appear to interact with mycophenolate mofetil.[19]

Medications which interrupt enterohepatic recirculation can reduce the reabsorption of mycophenolic acid. Cholestyramine, a bile acid sequestrant, reduces the AUC of mycophenolic acid by 40%.[19] Antibacterials, and other agents which disrupt normal intestinal flora, may also affect enterohepatic recirculation.[19]

Agents competing for renal tubular secretion may inhibit mycophenolic acid glucuronide elimination. These can increase mycophenolic acid glucuronide AUC, as well as increase the plasma concentrations of competing drugs. For example, the concomitant administration of aciclovir and mycophenolate mofetil causes an increase in mycophenolic acid glucuronide concentrations by 10.6%, and an increase in aciclovir plasma AUC by 21.6%.[19] In animals, probenecid was shown to triple the AUC of mycophenolic acid glucuronide and double the AUC of mycophenolic acid.[19]

As previously mentioned, mycophenolic acid is highly protein bound to serum albumin. Coadministration with other highly protein bound drugs may displace mycophenolic acid and mycophenolic acid glucuronide from serum albumin and vice versa. Furosemide (frusemide) and sodium salicylate cause a decrease in mycophenolic acid binding;[23] this may cause clinically important increases in the concentration of the active form of mycophenolic acid.

It is important to remember that pharmacodynamic interactions can occur and these can increase the efficacy of mycophenolate mofetil when this agent is combined with other immunosuppressants. However, this must be tempered by the problems associated with an overly suppressed immune system. In addition, additive toxicity must be considered, such as a possible increased risk of leucopenia occurring with the combination of mycophenolate mofetil and ganciclovir.

4. *In Vitro* and Animal Pharmacodynamics

4.1 Selective Antiproliferative Effects on Lymphocytes

Mycophenolic acid depletes GTP in human peripheral blood monocytes, but not in neutrophils.[16] This allows for a reduction of lymphocyte function while maintaining normal phagocytosis and bactericidal activity by the neutrophils.[16] In mice, mycophenolic acid prevented DNA synthesis in lymph nodes but DNA continued to be synthesised in testicular germinal cells and basal epithelial cells of the small intestine.[16] It was also noted that mycophenolate mofetil did not affect platelet or neutrophil counts.[16]

Eugui et al.[26] exposed human endothelial cells, fibroblasts and peripheral blood mononuclear cells to known mitogens in the presence of physiological concentrations of mycophenolic acid. They found that mycophenolic acid was able to prevent lymphocyte proliferation but had no effect on the proliferation of endothelial cells and fibroblasts. This confirmed the theoretical specificity of mycophenolic acid that was predicted from its mechanism of action.

4.2 Prevention of Antibody Formation

Mycophenolic acid was able to inhibit antibody formation by activated human B cells and secondary responses of human spleen cells to tetanus toxoid.[26,27] In mice and rats, mycophenolate mofetil prevented antibody formation in a dose dependent manner.[26]

47 patients with primary cadaveric renal transplants were evaluated for antithymocyte globulin antibodies in a prospective, randomised, double-blinded study.[28] All patients were induced with methylprednisone and antithymocyte globulin. Maintenance immunosuppression consisted of cyclosporin, prednisone and mycophenolate mofetil 2 g/day (1g twice daily) or 3 g/day (1.5g twice daily) or azathioprine 1 to 2 mg/kg/day. In 2 to 3 g/day dosages, mycophenolate mofetil produced a statistically significant reduction in the incidence and titre of IgG antithymocyte globulin antibody formation compared with azathioprine. This proved that mycophenolate mofetil significantly decreased human B cell responses in the clinical setting.

4.3 Combination with Interleukin-2 Inhibitors

In vitro, mycophenolic acid has been shown not to inhibit interleukin (IL)-1β or IL-2 in mitogen-stimulated lymphocytes.[26] This demonstrates that mycophenolic acid does not prevent early T cell signal transduction.[26,29] This is beneficial because the action of mycophenolic acid is sequentially different from either tacrolimus or cyclosporin. Thus, mycophenolate mofetil may be extremely effective in combination with these agents. In rats, a combination of mycophenolate mofetil and cyclosporin improved efficacy without additive toxicity.[30]

4.4 Reversibility

Peripheral blood mononuclear cells of patients taking mycophenolate mofetil were not suppressed when separated from plasma, but were strongly antiproliferative in the presence of plasma.[16] This suggests that inhibition is not permanent; reversibility is a positive trait when correction of over-immunosuppression is desired and a liability in noncompliant patients.

4.5 Lymphocyte Adhesion

Mycophenolic acid decreased glycosylation of adhesion molecules or their ligands.[31] If GTP is depleted, ongoing transfer of fucose and mannose to glycoproteins may not occur. This could affect the selectins, vascular cell adhesion molecule (VCAM)-1 and very late activation antigen (VLA)-4 involved in the enhancement of lymphocyte adhesion during acute rejection.[31]

4.6 Reversal of Rejection

In vitro, mycophenolic acid was shown to prevent the binding of activated human lymphocytes to activated endothelial cells, demonstrating its ability to inhibit recruitment and subsequent actions at the potential sites of rejection. This may be the reason why mycophenolate mofetil can treat ongoing rejection.[16]

In rats, efficacy was displayed even after delaying the initiation of mycophenolate mofetil until significant mononuclear cell infiltration into the graft had occurred.[30] Later studies confirmed this observation in dogs.[32] This suggests that mycophenolate mofetil may be useful for treatment of rejection episodes in humans. In addition, the ability of mycophenolate mofetil to prevent on-going antibody response may prove to be a means to reduce chronic graft rejection.[16]

4.7 Chronic Rejection

Obliterative arteriopathy, characterised by intimal hyperplasia with infiltration of macrophages and smooth muscle cells, is commonly seen in chronic rejection.[16] Therapeutic concentrations of mycophenolic acid have antiproliferative effects on human arterial smooth muscle cells in culture. This has also been demonstrated in rats and primates.[16] In rat aortic allograft models, mycophenolate mofetil inhibited intimal proliferation.[33] Mycophenolate mofetil may reduce proliferative

and obliterative arteriopathy and may be effective for the treatment of chronic rejection.

4.8 Tolerance

With the short term administration of mycophenolate mofetil, donor specific tolerance was achieved with atrial tissue in rats, and with pancreatic islet transplants in mice and rats.[16] Reduction or elimination of long term administration of immunosuppressives may be possible if tolerance can be demonstrated in future clinical practice.

4.9 Target Site

Activated lymphocytes and macrophages increase glucuronidase levels, which in turn may lead to greater mycophenolic acid transformation from mycophenolic acid glucuronide at the site of rejection and inflammation.[16] This may be an additional measure to maximise the amount of the active form of drug at the target site.

5. Clinical Pharmacodynamics

A study in renal transplant patients to evaluate IMPDH inhibition with mycophenolate mofetil therapy has been described.[34] A group of patients (n = 5) treated with mycophenolate mofetil, when compared with an azathioprine control group (n = 7), had a comparatively significant decrease in IMPDH activity for 8 hours after administration. An inverse relationship between mycophenolic acid concentration and IMPDH activity has been demonstrated. Mycophenolic acid, in a concentration of 2 to 5 mg/L in whole blood and lymphocytes, caused a 50% inhibition of IMPDH. In intact cells, complete inhibition could not be achieved even at much higher concentrations. This proved that only down-regulation of IMPDH activity, not complete inhibition, is required for immune suppression. In disrupted lymphocyte cell membranes complete inhibition was nearly achieved. Thus, it appears that mycophenolic acid uptake into the cell is a saturable process and this may affect future administration regimens.

Currently, studies are being performed to delineate the utility of pharmacodynamic markers in determining the degree of immunosuppressant activity for individual patients. These trials are in the early developmental stages and further work is needed before they can be evaluated.

6. Efficacy

6.1 Clinical Renal Transplant Rescue

In a phase I, open label, nonrandomised study, Sollinger et al.,[35] administered oral doses of mycophenolate mofetil to 48 patients with primary cadaveric renal transplants. Mycophenolate mofetil dosages of 100 to 3500 mg/day were given in combination with cyclosporin, prednisone and antilymphocyte globulin. This study revealed an inverse relationship between mycophenolate mofetil dosage and, (i) the number of rejection episodes; (ii) number of patients with rejection episodes; (iii) total number of corticosteroid and muromonab CD3 (OKT3) courses; and (iv) 4-month serum creatinine levels. It also showed that patients taking a mycophenolate mofetil dosage of 2g or more per day had significantly fewer rejection episodes.

In an open label, multicentre study, the use of mycophenolate mofetil was evaluated in 75 patients with biopsy-proven kidney transplant rejection.[36] To be included in the study, all patients must have experienced a previous rejection episode which had not responded to corticosteroids, muromonab CD3 or antilymphocyte globulin treatment. Mycophenolate mofetil 1 to 1.5g twice daily was started within 48 hours after biopsy. Long term rescue was achieved in 69% of all patients. This was even more impressive in patients with a serum creatinine level of 4 mg/dl or less, who experienced a 79% rescue rate.

6.2 Clinical Renal Transplant Rejection Prophylaxis

Mycophenolate mofetil entered phase III trials for the prophylaxis of renal allograft rejection in 3 separate study groups. These were multicentre, double-blind studies investigating safety and effi-

cacy. In all 3 studies, mycophenolate mofetil was administered as either a 2g (1g twice daily) or 3g (1.5g twice daily) regimen. Lack of response to treatment, defined as biopsy-proven rejection, graft loss, death or lack of response caused by any other reason, was evaluated.

The European Mycophenolate Mofetil Cooperative Study Group (EUR study)[37] combined results from 20 European transplant centres (table I). 491 patients with first or second cadaveric kidney transplants were enrolled. The group was randomised such that 166 patients received placebo, 165 patients were randomised to mycophenolate mofetil 2 g/day and 160 patients to 3 g/day. In addition, all patients received corticosteroid and cyclosporin without induction therapy. At 6 months significant differences in treatment failure rates were found. The placebo group had a 56% rate compared with 30.3% ($p \leq 0.001$) for the 2 g/day group and 38.8% ($p \leq 0.001$) for the 3 g/day group. The biopsy-proven rejection rate was found to be 46.4% for the placebo group, while rates of 17 and 13.8% were found for the 2 g/day and 3 g/day groups, respectively. Antirejection medication was reduced with mycophenolate mofetil use. The study also found that in the placebo group, 17.5% of the patients required multiple courses of corticosteroid, in contrast to 4.2% for the 2 g/day and 5.0% in the 3 g/day cohorts. Antilymphocyte agents were used in 21.1% of the placebo group, compared with 5.5% in the 2 g/day and 3.1% in the 3 g/day group.[38]

The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group (TRI study)[39] involved 21 sites in Europe, Canada and Australia (table II). Enrollment consisted of 503 patients with either first or second cadaveric renal transplants. The azathioprine group received 100 to 150 mg/day of orally administered drug. All patients were concomitantly treated with a corticosteroid and cyclosporin without induction therapy. At 6 months, the azathioprine group had a 50% treatment failure rate compared with 38.2% ($p = 0.0287$) in the mycophenolate mofetil 2 g/day group and 34.8% ($p = 0.0045$) in the 3 g/day group.

Table I. Comparative efficacy of placebo versus mycophenolate mofetil in the European Mycophenolate Mofetil Cooperative Study Group (EUR) study (n = 491)[37,38]

Parameter	Placebo (%) [n = 166]	Mycophenolate mofetil (%)	
		2g[a] (n = 165)	3g[b] (n = 160)
Treatment failure	56.0	30.3[c]	38.8[c]
Biopsy-proven rejection	46.4	17.0	13.8
Multiple courses of corticosteroids	17.5	4.2	5.0
Antilymphocyte usage	21.1	5.5	3.1

a 1g twice daily.
b 1.5g twice daily.
c $p \leq 0.001$ difference from placebo.

Biopsy-proven rejection developed in 35.5% of patients taking azathioprine compared with 19.7% in the 2 g/day and 15.9% in the 3 g/day groups. In the azathioprine group, 12.4% of patients took multiple courses of corticosteroids, compared with 9.9% for the 2 g/day and 4.3% for the 3 g/day group. Antilymphocyte agents were used in 15.4% of azathioprine group, compared with 8.8% for the 2 g/day and 4.9% for the 3 g/day groups.[38] A trend towards improved 1-year graft survival with mycophenolate mofetil therapy over azathioprine was found.

The US Renal Transplant Mycophenolate Mofetil Study Group (US study)[40,41] had 14 participating sites (table III). Only primary cadaveric renal transplant recipients were enrolled in the study. All patients received cyclosporin, corticosteroid therapy and were induced with antithymocyte globulin. The study compared patients receiving azathioprine 1 to 2 mg/kg/day with those receiving mycophenolate mofetil 1g twice daily or 1.5g twice daily. At 6 months, the azathioprine group had a 47.6% treatment failure rate compared with 31.1% ($p = 0.0015$) for the 2 g/day and 31.3% ($p = 0.0021$) for the 3 g/day groups. Biopsy-proven rejection occurred in 38% of the azathioprine treated group, compared with 19.8% in the 2 g/day group and 17.5% in the 3 g/day group. In the azathioprine group, 6.7% of the patients required

Table II. Comparative efficacy of azathioprine versus mycophenolate mofetil in the Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group (TRI) study (n = 503)[38,39]

Parameter	Azathioprine (%) [n = 166]	Mycophenolate mofetil (%)	
		2g[a] (n = 173)	3g[b] (n = 164)
Treatment failure	50.0	38.2[c]	34.8[d]
Biopsy-proven rejection	35.5	19.7	15.9
Multiple courses of corticosteroids	12.4	9.9	4.3
Antilymphocyte usage	15.4	8.8	4.9

a 1g twice daily.
b 1.5g twice daily.
c p = 0.0287 difference azathioprine.
d p = 0.0045 difference from azathioprine.

multiple courses of corticosteroids compared with 3.0% of the 2 g/day and 0.6% of the 3 g/day groups.

Antilymphocyte agents were used in 20.1% of the azathioprine patients, compared with 10.3% for the 2 g/day and 5.4% for the 3 g/day groups.[38]

Overall, these 3 studies reveal statistically significant reductions in treatment failure rates with the use of mycophenolate mofetil compared with either azathioprine or placebo. The similarity in the efficacy rates in the studies substantiates the validity of these findings. Early acute rejection has been implicated in reduced 1-year[42] and 5-year[43] graft survival, as well as in chronic rejection.[44] Mycophenolate mofetil has now been documented to reduce early acute rejection, further studies are required to prove long term benefits. An important point with regard to cost considerations is that mycophenolate mofetil was able to reduce the need for multiple courses of corticosteroids and antilymphocyte globulin to treat rejection episodes.[38]

6.3 Clinical Renal Transplant Treatment of Rejection

In another study, mycophenolate mofetil was more effective than high dose intravenous corticosteroids for the treatment of refractory, acute renal transplant cellular rejection episodes.[45] 150 patients were enrolled in a 6-month randomised, multicentre, open label trial comparing mycophenolate mofetil with high dose intravenous corticosteroids. 77 patients were given oral mycophenolate mofetil 1.5g twice daily, typically in addition to cyclosporin and corticosteroids. Of these, 73 patients received intravenous methylprednisolone 5 mg/kg for 5 days tapered to 20 mg/day or down to the baseline dose, typically in addition to cyclosporin and azathioprine. The mycophenolate mofetil group had a reduction in the number of rejection episodes (presumptive or biopsy-proven) and patients who did not respond to treatment (39%) compared with the intravenous corticosteroid group (64.4%). Antilymphocyte therapy was used twice as often in the intravenous corticosteroid group. In the mycophenolate mofetil group, graft loss and death were decreased by 45% at 6 months and 42% at 1 year.

6.4 Cardiac Transplantation

Animal studies have shown mycophenolate mofetil to be effective in both cardiac allograft and xenograft models. In rat cardiac allografts, mycophenolate mofetil produced a dose dependent prolongation of survival, reversed rejection episodes,[30] induced donor specific tolerance[16] and prevented graft coronary disease.[46] Mycophenolate mofetil aids in the prolongation of cardiac xenograft transplantation survival in many different animal models, including primates.[15,47-49]

The earliest human cardiac allograft study involving mycophenolate mofetil was a small, open label, unrandomised phase I safety study.[50] 30 patients who had developed mild cellular rejection while on azathioprine, cyclosporin and a corticosteroid were enrolled. Mycophenolate mofetil in dosages of 500mg to 3 g/day replaced azathioprine. Rejection abated in two-thirds of the patients within 4 weeks. One-third of the patients receiving the 500 mg/day dosage went on to develop moderate rejection.

In another small study (n = 16),[51] mycophenolate mofetil was substituted for azathioprine in patients with persistent cardiac allograft rejection. Dosages were initiated at 1.5g twice daily and adjusted down to 1g twice daily or increased to 1.75g

Table III. Comparative efficacy of azathioprine versus mycophenolate mofetil in the US Renal Transplant Mycophenolate Study Group (US) study[38,40,41] (n = 499)

Parameter	Azathioprine (%) [n = 166]	Mycophenolate mofetil (%)	
		2g[a] (n = 167)	3g[b] (n = 166)
Treatment failure	47.6	31.1[c]	31.3[d]
Biopsy-proven rejection	38.0	19.8	17.5
Multiple courses of corticosteroids	6.7	3.0	0.6
Antilymphocyte usage	20.1	10.3	5.4

a 1g twice daily

b 1.5g twice daily.

c p = 0.0015 difference from azathioprine.

d p = 0.0021 difference from azathioprine.

twice daily based on gastrointestinal tolerance with mycophenolate mofetil therapy. The rate of rejection episodes per patient per month was statistically reduced from 0.67 to 0.27 with mycophenolate mofetil.

33 cardiac transplant patients were enrolled in a long term follow-up study with mycophenolate mofetil for an average of 240 ± 46 days.[52] 28 episodes of mild rejection occurred; 68% of these resolved after increasing the mycophenolate mofetil dosage alone and 32% resolved after increasing the dosage of mycophenolate mofetil and adding cyclosporin or a corticosteroid to the regimen. Only 9 episodes of moderate rejection were found, all of which resolved with bolus administration of a dose of intravenous corticosteroid.

These studies suggest that mycophenolate mofetil is more effective than azathioprine in the prophylaxis and resolution of rejection in cardiac allograft transplantation. The optimal dose range is 3 to 3.5 g/day; dosages of less than 1 g/day are not as effective.[53]

6.5 Liver Transplantation

Mycophenolate mofetil alone, or in combination with cyclosporin, extended canine hepatic allograft survival.[53] In addition, mycophenolate mofetil alone or in combination with tacrolimus extended the xenograft survival in hamster-to-rat liver transplants.[49]

Mycophenolate mofetil has been evaluated in an open label study involving 23 liver allograft recipients.[54] These patients exhibited persistent acute rejection while medicated with azathioprine, cyclosporin and a corticosteroid. 21 of these patients had documented biopsy-proven rejection and had not responded to high dose corticosteroid and muromonab CD3 therapy. Oral administration of mycophenolate mofetil 1.5 to 1.75g twice daily were substituted for azathioprine. 21 of the 23 patients responded. Complete resolution of rejection occurred in 14 patients.

In 4 case reports involving liver allograft recipients,[55] mycophenolate mofetil in dosages of 1 to 2g twice daily eliminated or reduced the need for cyclosporin and azathioprine. All patients were maintained on cyclosporin, azathioprine and prednisone. In 3 cases, cyclosporin toxicity developed and this agent was discontinued and rejection occurred while the patients were treated with azathioprine and prednisone. Following a corticosteroid bolus, mycophenolate mofetil was substituted for azathioprine and the patients were free from rejection at follow up. In the fourth report, rejection occurred while the patient was being treated with cyclosporin, azathioprine and prednisone. Following rejection therapy, cyclosporin was stopped because of toxicity, and mycophenolate mofetil was replaced by azathioprine. The patient developed mild rejection and low dose cyclosporin was reinitiated, preventing further episodes.

A dose escalation study to evaluate the maximum tolerability of mycophenolate mofetil in primary prophylaxis of hepatic allograft transplantation was reported.[56] Patients on prednisone and low dose cyclosporin were given mycophenolate mofetil in oral dosages of 1.75 to 2.5g twice daily. At 3 months, 7 of the 17 patients were rejection-free. Of the patients experiencing rejection, 7 needed high dose corticosteroids to halt the rejections and another 3 needed corticosteroids and muromonab CD3.

6.6 Pancreatic Transplantation

In mice, mycophenolate mofetil allowed for pancreas islet allograft survival and led to donor specific tolerance.[57] Mycophenolate mofetil was found to prolong pancreas allograft survival in rat models, both alone and in combination with cyclosporin.[58]

In a small study involving human simultaneous pancreas-kidney allografts, mycophenolate mofetil was prospectively studied in combination with a corticosteroid and cyclosporin or tacrolimus.[59] This combination produced a statistically significant reduction in rejection rates when compared, retrospectively, with the combination of azathioprine, corticosteroid and cyclosporin.

6.7 Intestinal Transplantation

Mycophenolate mofetil, combined with cyclosporin at therapeutic dosages, significantly prolonged heterotopic and orthotopic canine intestinal allograft transplants.[60] Intestinal transplantation in humans has not been adequately described in the literature. Unlike other organ transplants, small bowel transplant recipients continue to experience frequent acute rejections despite treatment with cyclosporin and a corticosteroid. Adding mycophenolate mofetil to this regimen may prove effective.

7. Risk

7.1 Clinical Trials

The *in vivo* studies mentioned earlier in this manuscript suggest that mycophenolate mofetil is generally well tolerated and that the most common adverse effect is gastrointestinal intolerance. This discussion will concentrate on the results of 3 large, randomised, double-blind, multicentre, phase III, renal allograft transplant rejection prophylaxis studies, which are representative of the findings of the other studies. The results are summarised in table IV which represents a compilation of adverse reactions seen in the EUR,[19,37] TRI[19,39] and US[19,40] studies (see section 6.2).

The results shown in table IV were obtained from data from patients who were followed for 1 year and who accounted for more than 50% of the study population. The actual incidence of toxicity seen in the EUR study differed greatly from the US and TRI studies, but the trends in adverse reactions were quite similar.

Mycophenolate mofetil was well tolerated and did not demonstrate a major safety difference from placebo or azathioprine in the categories of metabolic, cardiovascular, skin or nervous system toxicities. Gastrointestinal adverse affects and abdominal pain were most common in the mycophenolate mofetil groups (especially in patients receiving the 3 g/day dosage). A number of the gastrointestinal symptoms reported may be attributable to an infectious aetiology, such as cytomegalovirus (CMV) enteritis.

Haemorrhage also occurred more frequently in patients receiving mycophenolate mofetil and it appeared to be dosage related. However, overall the number of patients involved was small. The majority of haematological adverse effects appeared to correlate with increasing immunological suppression. Placebo was associated with the lowest incidence, while mycophenolate mofetil 3 g/day was associated with the highest incidence of haematological adverse effects. The exception to this rule was thrombocytopenia, which had an inverse relationship to mycophenolate mofetil dosage. The haematological adverse effects generally reversed upon discontinuation of the drug. Overall, infection, sepsis and opportunistic infection rates were only minutely increased with mycophenolate mofetil administration. CMV tissue invasive disease was slightly increased with mycophenolate mofetil, occurring to a greater extent with the 3 g/day than the 2 g/day dosage. *Pneumocystis carinii* infections were slightly more frequent in the placebo and azathioprine cohorts. Infection patterns will need to be followed in great detail in future clinical practice and studies.

Whenever the immune system is suppressed, there is an increased risk of malignancy formation. Malignancy rates were examined by combining

Table IV. Adverse reactions reported in renal allograft rejection prophylaxis studies.

Adverse effect	European study (%)[19,37]			Tricontinental and US combined studies (%)[39,40]		
	placebo (n = 166)	MMF 2g[a] (n = 165)	MMF 3g[b] (n = 160)	AZA (n = 326)	MMF 2g[a] (n = 336)	MMF 3g[b] (n = 330)
Body overall						
Abdominal pain	10.8/11.4[c]	11.5/12.1[c]	11.3/11.9[c]	23.0	24.7	27.6
Sepsis	13.9	21.8	17.5	15.6	17.6	19.7
Infection	13.3	12.7	15.6	19.9	18.2	20.9
Fever	NR	NR	NR	23.3	21.4	23.3
Asthenia	NR	NR	NR	19.9	13.7	16.1
Oedema	NR	NR	NR	13.5	12.2	11.8
Haematological						
Leucopenia	4.2	10.9/11.5[c]	13.8/16.3[c]	24.8	23.2	34.5
Anaemia	1.8	4.2	6.8	23.6	25.6	25.8
Thrombocytopenia	4.8	4.2	3.1	13.2	10.1	8.2
Pancytopenia	0	1.8	0	NR	NR	NR
Leucocytosis	NR	NR	NR	7.4	7.1	10.9
Agranulocytosis	0	0	1.3	NR	NR	NR
Gastrointestinal						
Diarrhoea	12.7/13.9[c]	12.7/16.4[c]	15.6/18.8[c]	20.9	31.0	36.1
Constipation	NR	NR	NR	22.4	22.9	18.5
Dyspepsia	5.4	3.0	5.0	13.8	17.6	13.6
Nausea	2.4	4.2	6.3	24.5	19.9	23.6
Vomiting	1.2	2.4	3.8	9.2	12.5	13.6
Nausea and vomiting	NR	NR	NR	10.7	10.4	9.7
Oral moniliasis	NR	NR	NR	11.3	10.1	12.1
Haemorrhage	0	1.2	1.9	NR	NR	NR
Pancreatitis and gastritis	0	0	0.6	NR	NR	NR
Urogenital						
Urinary tract infection	37.3	45.5	44.4	33.7	37.2	37.0
Haematuria	NR	NR	NR	11.3	14.0	12.1
Renal tubular necrosis	NR	NR	NR	5.8	6.3	10.0
Urinary tract disorder	4.2	6.7	10.6	NR	NR	NR
Cardiovascular						
Hypertension	19.3	17.6	16.9	32.2	32.4	28.2
Respiratory						
Infection	9.0	15.8	13.1	19.6	22.0	23.9
Bronchitis	8.4	8.5	11.9	NR	NR	NR
Pneumonia	10.8	3.6	10.6	NR	NR	NR
Dyspnoea	NR	NR	NR	16.6	15.5	17.3
Pharyngitis	NR	NR	NR	8.0	9.5	11.2
Skin						
Acne	NR	NR	NR	6.4	10.1	9.7
Rash	NR	NR	NR	10.4	7.7	6.4
Nervous system						
Tremor	NR	NR	NR	12.3	11.0	11.8
Insomnia	NR	NR	NR	10.4	8.9	11.8
Dizziness	NR	NR	NR	11.0	5.7	11.2

Table IV. Contd

	European study (%)[19,37]			Tricontinental and US combined studies (%)[39,40]		
	placebo (n = 166	MMF 2g[a] (n = 165)	MMF 3g[b] (n = 160)	AZA (n = 326)	MMF 2g[a] (n = 336)	MMF 3g[b] (n = 330)
Metabolic						
Hypokalaemia	NR	NR	NR	8.3	10.1	10.0
Hyperkalaemia	NR	NR	NR	16.9	8.9	10.3
Hyperglycaemia	NR	NR	NR	15.0	8.6	12.4
Hypophosphataemia	NR	NR	NR	11.7	12.5	15.8
Hypercholesterolaemia	NR	NR	NR	11.3	12.8	8.5
Opportunistic infection						
CMV viraemia/syndrome	13.3	15.2/15.8[c]	15.0	13.8	13.4	12.4
CMV tissue invasion	2.4	3.0/3.6	6.9/7.5[c]	6.1	8.3	11.5
Herpes simplex	6.0	14.5/15.2[c]	11.3/12.5[c]	19.0	16.7	20.0
Herpes zoster	1.8/2.4[c]	6.7	5.0/6.9[c]	5.8	6.0	7.6
Candida	7.8	9.7	5.6	NR	NR	NR
Fungaemia/disseminated	0	0	0.6	0.3	0.6	0.6
Tissue invasion	0	0	0.6	0.3	0.6	0.6
Pneumocystis carinii	2.4	0	0	1.2	0.3	0
Aspergillus/Mucor	0.6	0	0	0.3	0.3	0.9

a 1g twice daily.

b 1.5g twice daily.

c Two figures are given, reflecting differences in the data presented in the 2 published reports of this study.

Abbreviations: AZA = azathioprine; CMV = cytomegalovirus; MMF = mycophenolate mofetil; NR = data not reported.

the results of the 3 studies.[19] Malignancies were rarely found in any group. Lymphoma and lymphoproliferative disease was not found in the EUR study placebo group, while it was found in 0.3% in the azathioprine group, 0.6% in the mycophenolate mofetil 2 g/day group and 1.0% in the mycophenolate mofetil 3 g/day group. Non-melanoma malignancies were not documented in the placebo group in this study, but were present in 2.4% of the azathioprine group, 4.0% of the 2 g/day group and only 1.6% in the 3 g/day group.

Other types of malignancies were noted in 1.8% of the placebo and azathioprine groups, 0.8% in the mycophenolate mofetil 2 g/day and 1.4% in the 3 g/day groups. Of these, skin cancer was the most common malignancy, especially in trial participants in Australia where there is a particularly high incidence of this cancer. The risk of malignancy continues with prolonged therapy, thus this is an area which will need long term follow-up with maintenance doses.

Withdrawal rates from the 3 studies, due to adverse events, were highest in the mycophenolate mofetil 3 g/day group. At 6 months in the TRI[39] and the US[40] studies, the withdrawal rates for azathioprine were 4.2 and 3.6%, respectively; for the mycophenolate mofetil 2 g/day group they were 8 and 4.2%, respectively; and they were 9.1 and 9.6%, respectively, for the 3 g/day group. At 1 year in the EUR study,[37] the withdrawal rate for placebo was 13.9%, for 2 g/day it was 17.6% and for the 3 g/day group it was 25.6%.

The number of deaths after 6 months was similar and not significantly different with regard to the drug regimen. In the EUR study,[37] there were 6 deaths in the placebo group, compared with 4 deaths in the mycophenolate mofetil 2 g/day group and 5 in the 3 g/day group. In the TRI[39] and US[40] study groups, the numbers of deaths in the azathioprine group were 2 and 5, respectively, in the 2 g/day they were 1 and 6, respectively, and in the 3 g/day groups they were 3 and 9, respectively.

7.2 Miscellaneous Risk

Mycophenolate mofetil was shown not to be carcinogenic in mice or rats, nor mutagenic in the standard assays.[19]

Mycophenolate mofetil is rated category C for pregnancy because it has been shown to be teratogenic in rats and rabbits.[19] No studies on the administration of this agent in pregnant women have been published; therefore, effective contraception must be used. Mycophenolate mofetil is excreted in rat milk, but no human studies of excretion into breast milk during breast feeding have been performed.[19]

Due to the teratogenic effects of mycophenolate mofetil, opening or crushing the capsules is not recommended in the package insert.[19] However, in clinical situations, the capsules are often opened for extemporaneous preparation for paediatric administration and administration through nasogastric tubes. The recommendations found in the safety data sheets should be followed; inhalation and physical contact should be avoided. The wearing of gloves, gowns and masks should help to reduce contact. There have been no published reports of harm to caregivers.

The pharmacokinetics of mycophenolate mofetil powder versus capsules has not been studied. Opening the gelatin capsules to expose the powder is unlikely to alter the absorption characteristics of mycophenolate mofetil, other than to avoid the time required for capsule dissolution. Anecdotal experiences with mixing chocolate syrup, grape jelly or apple sauce to reduce the unpleasant flavour of mycophenolate mofetil powder have been reported.

8. Cost-Benefit

Cost is a major concern with all new immunosuppressants, and thus may present a financial risk to patients and third-party payers. The average wholesale prices (AWPs) quoted in this section were sourced from the 1997 Drug Topics Redbook. Mycophenolate mofetil is expensive, with an average AWP of $US1.8750 per 250mg capsule. This corresponds to a yearly maintenance therapy cost of $US5475 for a dosage of 2 g/day and $US8213 for a dosage of 3 g/day. These costs may be adjusted as optimal individual dosage schedules are defined. Mycophenolate mofetil cost reductions would be realised if future studies confirm that the dose can be lowered for late stable renal transplant recipients, in whom previous studies indicated a higher mycophenolic acid AUC compared with early renal transplant recipients.

Mycophenolate mofetil would be considered a replacement medication for azathioprine in many triple and quadruple drug regimens. Generic azathioprine has an AWP of $US1.1663 per 50mg tablet. This represents a yearly cost of $US851 to $US1277 for a dosage of 100 to 150 mg/day.

As shown earlier in clinical trials of renal allograft transplants, mycophenolate mofetil reduced treatment failures, acute rejection episodes, antilymphocyte use and courses of high dose corticosteroids. Corticosteroid boluses are relatively inexpensive in terms of drug cost – approximately $US100 per course. Antilymphocyte agents, typically antithymocyte globulin and muromonab CD3, are very expensive. The AWP of antithymocyte globulin is $US52.448 per 50mg. For a 70kg patient at a dose of 15 mg/kg, antithymocyte globulin costs over $US1100 per day or $US7700 to $US15 400 for a 7- to 14-day course. The AWP of muromonab CD3 is $US672 for a 5mg vial. Thus, the cost is $US4704 to $US9408 for a 7- to 14-day course, and the cost may escalate to $US18 816 if a dosage of 10 mg/day is needed for 14 days. Reducing the use and associated cost of antilymphocyte agents for treatment of rejection should help balance the higher yearly cost of mycophenolate mofetil.

Drug costs are only part of the overall expense of rejection episodes. Increases in the number or severity of rejection episodes leads to increased costs. Hospital charges are based on length of stay, in addition to laboratory, nursing, physician and pharmacy costs. Mycophenolate mofetil has been shown to reduce rejection episodes, which have been estimated to cost almost $US25 000 per cycle

of treatment.[61] Mycophenolate mofetil can reduce treatment failures and graft loss, thus eliminating the need for dialysis.

The annual cost of medical care for a patient on dialysis can be $US50 000.[62] Mycophenolate mofetil may eliminate the cost of another transplant, which is estimated at nearly $US66 000 in the US.[61] In addition to these costs, physician and other health professional costs, laboratory and clinic costs must be factored into the equation in the event of a failing graft.

These observations are confirmed in an economic impact study involving the analysis of the 3 multinational trials.[63] Seven independent experts, from 6 different institutions, compared the direct cumulative healthcare costs of each of the regimens in 1003 evaluable patients. The use of mycophenolate mofetil resulted in an estimated 19 to 38% cost reduction during the first 6 months after transplantation. The cost savings resulted from fewer rejection treatments, nephrectomies and dialysis sessions. The greatest cost reduction factors were length of stay in the hospital and the cost of each hospitalisation day. Long term, prospective, cost-benefit studies need to be performed to identify the most cost-effective immunosuppressive regimen in each type of organ transplant.

Cyclosporin and tacrolimus therapeutic drug concentrations need to be monitored because of the narrow therapeutic window of the drugs. The charges for these drug assays are expensive, approximately $US35 for each at our institution. Typically, these assays are initially performed on a daily basis, then weekly, biweekly, monthly and quarterly to establish a maintenance concentration. Periodic measurement is necessary throughout treatment. Mycophenolate mofetil drug concentrations are not routinely monitored in current clinical practice although studies are ongoing to evaluate the use of these measurements in a subset of patients.

9. Conclusions

Mycophenolate mofetil has many beneficial effects with regard to transplant rejection. Among these is its unique mechanism of action – the inhibition of IMPDH and consequent selective inhibition of T cell and B cell proliferation, preventing antibody formation. Mycophenolate mofetil does not directly inhibit IL-2 or IL-1β, and can be useful in combination with agents that do inhibit these interleukins. Its reversible cytostatic effects are clinically useful because serious toxicity, or an overly suppressed immune system, can be avoided by dose reduction or drug discontinuation.

Mycophenolate mofetil does have activity when used alone, but is most often used in combination therapy. Its unique mechanism of action makes it a good choice for use in combination with corticosteroids and immunophilin-binding drugs, such as cyclosporin and tacrolimus. Since mycophenolate mofetil asserts its main effects on *de novo* purine synthesis, it works on a different step of immune response. However, due to overlapping activity, it is not used in combination with azathioprine, but as a replacement for this agent.

Clinical trials evaluating the utility of mycophenolate mofetil are ongoing in solid organ transplantation. Initial information is encouraging but limited, except in renal transplant recipients. Mycophenolate mofetil has been shown to be more effective than placebo and azathioprine in the prophylaxis of acute rejection in renal allograft transplantation and has demonstrated significant activity in suppressing ongoing rejection. Due to the recent excellent short term success rates in renal transplantation, it is difficult to detect differences in effectiveness between the various immunosuppressant medications. Despite the large number of patients in the clinical renal rejection prophylaxis trials, these studies still did not have enough power to detect significant differences in graft survival at 1 year. However, there was a trend for increased graft survival in mycophenolate mofetil–treated patients at 1 year.[38]

The prevention of acute rejection may be a surrogate marker for predicting long term graft survival. *In vitro* animal and human studies are starting to suggest a role for mycophenolate mofetil in chronic rejection prophylaxis. The role of myco-

phenolate mofetil in reducing the severity and incidence of acute rejection episodes, coupled with the inhibitory effects on T and B cell proliferation, antibody formation and synthesis of adhesion molecules, makes the concept of chronic rejection prophylaxis intriguing. These findings need to be confirmed in long term follow-up studies.

The safety of mycophenolate mofetil over the short term has been well established. Reports of long term use need further evaluation. However, mycophenolate mofetil has been prescribed safely in 85 patients for up to 13 years for the treatment of psoriasis.[7] Considering the strong immunosuppressant activity of mycophenolate mofetil, it has relatively few adverse effects. The most common patient health risks include gastrointestinal toxicity and haematological suppression. Dose reduction or discontinuation can usually quickly reverse the toxicities.

Infection, notably CMV tissue invasive disease, is a concern in higher mycophenolate mofetil doses. CMV infection may become known as the most noxious complication associated with mycophenolate mofetil therapy. Malignancy, especially post-transplant lymphoproliferative disease, needs to be carefully monitored in long term studies.

The safety profile of mycophenolate mofetil also makes it a good choice to combine with other clinically available immunosuppressive agents. Corticosteroids, cyclosporin and tacrolimus can cause hypertension, skin disorders, nervous system disturbances, electrolyte abnormalities, hyperglycaemia, hypercholesterolaemia, lipid disorders and structural bone loss.[64-66] Mycophenolate mofetil is not known to cause these adverse effects. In addition, cyclosporin and tacrolimus are nephrotoxic.[67] Cyclosporin should be avoided in patients with delayed graft function;[68] this may also prove true with tacrolimus administration. Mycophenolate mofetil is not associated with nephrotoxicity allowing it to be given immediately after transplantation.

Unlike azathioprine, mycophenolate mofetil has a selective effect on lymphocyte purine synthesis. Theoretically then, in order to achieve the same desired immunosuppressive effect, the myelotoxicity would be greater with azathioprine than with mycophenolate mofetil. In addition, in contrast with mycophenolate mofetil, azathioprine has a risk of hepatotoxicity.

Despite differences in mycophenolate mofetil absorption and elimination, standard doses of mycophenolate mofetil, across various indications and different adult body mass characteristics, have led to a good clinical response without the expended time and cost of pharmacokinetic drug assay monitoring. Pharmacokinetic mycophenolic acid monitoring may be clinically available in the future to delineate the dose in patients with therapeutic failures or overly suppressed immune systems. Pharmacodynamic measurements of IMPDH activity have been performed clinically. Perhaps this, or another biological marker, may be a better measure of proper immunosuppression.

Mycophenolate mofetil is an expensive immunosuppressant. Comparative cost-benefit ratios for mycophenolate mofetil have not been thoroughly studied. Mycophenolate mofetil appears to be cost effective in renal transplant recipients based on present evaluable data. Prospective cost-benefit analysis needs to be performed with a variety of immunosuppressive regimens for each type of organ transplantation.

Thus, based on the preliminary available studies, mycophenolate mofetil therapy appears to have a positive benefit-risk ratio in primary cadaver renal allograft transplant. It remains to be seen whether the data will bear this out in long term studies. This equation is still unknown in other solid organ transplants because of a shortage of data. Clinical trials are being done at this time and initial studies look promising.

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