Mycophenolate Mofetil: A Promising Immunosuppressive Agent

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Abstract

With availability of newer immunosuppressive agents, incidence of acute graft rejection has decreased. Mycophenolate mofetil is one such new drug, now available in the Indian market. It has been found to be useful in prevention and treatment of acute and chronic rejection after transplantation. Besides transplant it has been used successfully in primary and secondary glomerulopathies (e.g. SLE) and other autoimmune diseases. The drug is well tolerated with side effects limited mainly to gastrointestinal system in the form of epigastric pain, vomiting and diarrhoea.

INTRODUCTION

Successful long-term outcome of a kidney transplant recipient depends on properly balanced immunosuppression. Azathioprine and steroids were standard immunosuppressants until introduction of cyclosporine in 1980s. Cyclosporine, although a potent immunosuppressant, is nephrotoxic and may play a role in chronic allograft nephropathy. So need for a good and safe immunosuppressant that balances immunosuppression and side effects has always been there. Mycophenolate mofetil (MMF) is a promising advance in transplant immunosuppression whose side effect profile is mainly limited to gastrointestinal system and infection.

Mycophenolate mofetil is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexanoate (Fig. 1). It is an ester prodrug of the immunosuppressant mycophenolic acid [MPA]. Although it was first derived in 1896 by Gozio from several Penicillium species, its antibacterial and antifungal properties were identified in 1940s. Mitsui and Suzuki first studied its immunosuppressive properties in mice in 1969. Allison rediscovered MPA in 1980 and found the answer to improve its bioavailability and tolerability in morpholinoethyl ester, i.e. mycophenolate mofetil.

Sollinger conducted phase 1 and 2 clinical trials in 1986 proving safety and promising efficacy. Phase 3 clinical trials began in 1993 which were conducted successfully and established the safety and efficacy of mycophenolate mofetil over azathioprine to prevent rejection.

Registration of mycophenolate mofetil for prevention of rejection in renal transplant recipients was done in 1995 in United States and in other countries thereafter.1

MECHANISM OF ACTION

Mycophenolic acid, an active component of MMF, inhibits inosine-monophosphate dehydrogenase (IMPDH) which controls the synthesis of guanosine monophosphate (GMP).1 Lymphocytes depend upon GMP, an important nucleotide in de novo purine pathway, for proliferation and normal function unlike other cells that can use salvage pathway (Fig. 2).

There are two isoforms of IMPDH, 1 and 2. Isoform 1 is present in all leukocytes and isoform 2 is present only in activated lymphocytes. MMF is a noncompetitive and selective inhibitor of IMPDH isoform 2. This selectivity of IMPDH may theoretically result in an inhibition of proliferative responses of T and B lymphocytes with less potential for inducing myelotoxicity than azathioprine.

Another advantage of MMF is that it inhibits purine synthesis at a late stage in the proliferation process; thus cell proliferation rapidly resumes and adverse effects quickly reverse after discontinuation of the drug.
Absorption and Distribution

The absorption of mycophenolate mofetil is complete and same by oral and I.V. administration. Mean bioavailability is 94%. Area under curve (AUC) of MPA is directly proportional to dosage ranging from 100 mg to 3.5 gm per day. After an oral dose, plasma MPA peaks at 1 hour, declines rapidly and peaks again at around 6-12 hours leading to terminal half-life of about 16 hours. Cause of second peak at 6-12 hours is enterohepatic circulation. MPA is metabolised to mycophenolic acid glucuronide [MPAG] in the liver. MPAG is deconjugated by colonic bacteria to MPA so that it gets absorbed to enter enterohepatic circulation.

Although food has no effect on total MMF absorbed, with food the Cmax for MPA is reduced by 40% and delayed to about 2 hours. Binding of MPA to plasma albumin is concentration-dependent. Increasing concentration will lower binding to albumin. Normally MPA and MPAG are 97% and 82% respectively bound to albumin.

Metabolism and excretion

MMF is rapidly and completely converted to the active metabolite MPA. MPA is subsequently converted to MPAG in the liver by glucuronidation. The excretion of MMF is largely through urine as MPAG [87%] and MPA [6%]. Only 6% is excreted in feces. No dose adjustment is required in patients with renal impairment.

DRUG INTERACTIONS

Acyclovir, Probenecid

Both these drugs increase AUC of MPAG and MPA because they compete with MPAG for secretion by the renal tubules. Although dose adjustment is not required, careful monitoring is recommended.

Cyclosporine

Concomitant cyclosporine administration is known to decrease the MMF level. The exact level at which this interaction occurs is not known.

Tacrolimus

In vitro studies suggest that tacrolimus inhibits conversion of MPA to MPAG which results in an increase in AUC of MPA. Also it has been observed that adverse effects of MMF are more common when given with tacrolimus. This necessitates dose reduction of mycophenolate mofetil in the presence of tacrolimus.

Antacids with Magnesium and Aluminium Hydroxide

There is a 33% reduction in AUC and 17% reduction in Cmax when antacids containing magnesium and aluminium hydroxide are given with mycophenolate mofetil.

Dose

Usual oral dose recommended is 1gm twice daily with or without food. Maximum daily dose is 3 gm/d. No dose adjustment is required in heart, renal or hepatic failure. MMF has not been used as monotherapy. It has been used in conjunction with additional immunosuppression, usually cyclosporine or tacrolimus and steroids.

Children

Doses of 600mg/m² body surface area twice a day is advised in children. Gastrointestinal side effects are predominant.

Old Age

Extremes of age have always been less tolerant as far as infection and immunosuppression is concerned. In a study conducted by Johnson DW et al in elderly (>55 years) renal transplant patients, the combination of MMF, cyclosporine and prednisolone appeared to result in a worse outcome compared with less potent combination of azathioprine, cyclosporine and prednisolone. In this study two years survival rates for azathioprine and MMF treated patients were 100 and 87% respectively. The principal cause of death in MMF cohort was infection.

Pregnancy

Mycophenolate mofetil is relatively contraindicated in pregnancy. Patient should be advised to avoid conception for 6 weeks after withdrawal.

Drug monitoring

There is growing interest as regards monitoring the drug level. It has been observed that there is variability of MPA area under curve (AUC) within and between patients. Conditions like liver disease and low albumin alter the drug level. Concomitant cyclosporine is known to decrease MPA level and tacrolimus is known to increase the level.

Pilot study conducted by Takahishi et al showed the rate of acute rejection was highest with the lowest post-transplant MPA AUC values.
MPA pre-dose trough level is usually measured by high performance liquid chromatography (HPLC). Proposed target concentration strategy for MPA is as follows.10

Pre-dose trough level 1 - 3.5 µg/ml
MPA AUC 30 - 60 µg/hr/ml

Ideally, evaluation of MPA AUC provides a more precise estimate of MPA exposure than a single trough level, but for practical purposes single trough level may be appropriate on out-patient basis.

USE OF MMF IN RENAL TRANSPLANTATION

The currently available immunosuppressive regimes control acute rejection so well that therapeutic issue today has become reduction in short term and long term morbidity and premature mortality. Currently expected 1 year graft survival rates from living donors and cadaveric donors are 93.9% and 87.7% respectively. Use of azathioprine is limited by occurrence of bone marrow suppression manifested by leukopenia, thrombocytopenia, megaloblastic anemia and pure red cell aplasia. Cyclosporine contributes to hypertension, nephrotoxicity, and lipid disturbances. Steroids cause hypertension, diabetes mellitus, lipid disturbances etc. and rapamycin causes dyslipidemia. All these side effects make these agents imperfect for long term management. Mycophenolate mofetil has no side effects mentioned above and seems to be a promising candidate for long term use.

When considering the new immunosuppressive regimens, ultimate aim is host acceptance of the graft with minimal adverse effects. MMF is one such drug that can be used in renal transplant at various stages like prophylaxis of rejection, at the time of first acute rejection, for refractory acute rejection and for chronic allograft dysfunction.

MMF FOR PROPHYLAXIS OF REJECTION

With earlier regimens, most renal allografts were lost because of acute rejection episodes.12 This has significantly reduced with introduction of MMF in the immunosuppressive protocols. The European Mycophenolate Mofetil Co-operative Study Group in 1995 enrolled 491 patients and used two different doses MMF 2 gm and 3 gm, which they compared with placebo. All patients received cyclosporine and corticosteroids. Patients were followed up for six months. Data showed that 46.4% of patients in placebo group had biopsy proven rejection as compared to 17% patients in MMF 2 gm and 13.8% patients in MMF 3 gm groups. By six months incidence of subsequent rejection was 25% in MMF group as compared to 19.8% and 17.5% in patients receiving MMF 2gm and 3gm/d respectively. Incidence of graft loss / death was 6% in azathioprine group as compared to 3% and 2% In MMF 2 gm/d and MMF 3 gm/d group.14

Third study, known as Tricontinental Study compared MMF 2 gm and 3 gm with azathioprine (1-2 mg/kg/d) in patients who also received corticosteroids and cyclosporine in the first six months following cadaveric renal allograft. Incidence of biopsy proven rejection was 35.5% in azathioprine group as compared to 19.7% and 15.9% in MMF 2 gm/d and 3 gm/d respectively. At 1 year after transplantation graft survival in MMF group was marginally superior but statistically insignificant to that in azathioprine group.15

In a pooled analysis of these three trials, mycophenolate Mofetil reduced significantly the incidence of biopsy proven rejection episodes in the first year from 40% for placebo/azathioprine group to 19.8% for MMF 2 gm/d and 16.5% for MMF 3 gm/d (Fig. 3). Also the need for second course of steroid was reduced and the use of antilymphocyte therapy for severe rejection was reduced by 55%.16

In pediatric population, administration of MMF 600mg/m2 BID is effective in prevention of acute rejection, provides predictable pharmacokinetics and is associated with an acceptable safety profile in renal transplant recipients. Adverse effects in pediatric patients had similar frequencies as adults. However, diarrhea, leukopenia, sepsis and anemia were more frequent in < 6 years age group.17

MMF AT THE TIME OF FIRST REJECTION EPISODE

MMF can be used for treatment of first rejection, as it reduces the incidence of subsequent rejection by 25%. MMF Acute Renal Rejection Study Group, carried out a study on 221 renal transplant recipients who had developed first rejection episode between seven days and six months after transplant. Patients enrolled in study group received MMF whereas in control group received I.V. corticosteroids. By six months incidence of subsequent rejection was 25% in MMF group as compared to 58% in control group.18 All these patients were followed up for three years for patient and graft survival, chronic allograft dysfunction (CAD) and malignancy. Out of 221 patients enrolled in first study, 123 patients completed study. At three years cumulative incidence of rejection was 42.2% in MMF group and 68.8% in control group. At 3 years
19.6% in study group and 24.1% in control group lost their graft or died.19

**MMF FOR REFRACTORY ACUTE REJECTION**

Although data for treatment of refractory acute rejection are limited, primary results are encouraging.20,21 An initial noncomparative study was carried out on 75 patients who had developed biopsy proven rejection. All patients had received at least one course of muromonab CD3 or antilymphocyte globulin with or without steroids but response was unsatisfactory. Rescue was achieved in 69% of these patients when treated with MMF 2 - 3.5 gm/d.22 In a randomized controlled study, 150 patients who had biopsy proven rejection and who were refractory to at least one course of antilymphocyte agent were randomly given MMF 3 gm/d or I.V. methylprednisolone 5 mg/kg/d for five days. Incidence of subsequent rejection was 39% in MMF group as compared to 64% in steroid group. Also graft loss and death were reduced by 45% in MMF group.21

**MMF FOR CHRONIC ALLOGRAFT DYSFUNCTION**

While reduction in the rate of acute graft loss has been dramatic over the last 30 years with the advent of cyclosporine-based regimens; there has been little change in the rate of chronic dysfunction.

Chronic allograft dysfunction is one of the most important impediment to improved graft and patient survival, and MMF is a promising agent in this context. MMF therapy decreases the risk of developing chronic allograft dysfunction by 27%. This improvement is not only caused by decrease in incidence of acute rejection; but is also caused by an effect independent of acute rejection.23

Cyclosporine toxicity is a nonimmunological factor of chronic allograft dysfunction. MMF allows safe withdrawal of cyclosporine in such patients thereby resulting in improved renal function, a more favorable lipid profile and beneficial effects on post-transplant hypertension.

In a pilot study carried by Weir et al.,24 28 renal transplant recipients with progressively declining renal function on cyclosporine and azathioprine at the end of two years had azathioprine replaced by MMF and cyclosporine dose halved. Renal function improved in 21 out of 28 patients and only one patient continued to show deterioration of renal function over a mean period of seven months.

**MYCOPHENOLATE MOFETIL IN OTHER ORGAN TRANSPLANTS**

**Heart**

In a study done by Kobashigawa et al., mycophenolate mofetil significantly reduced mortality (6.2% vs. 11.4%) at the end of one year. It also decreased the incidence of rejection (65.7% vs 73.7%).25

**Other organs**

Results with the use of mycophenolate mofetil in liver, lung, and simultaneous pancreas and kidney transplant are small but encouraging. It has been reported to be useful in reducing rejection episodes.26

**USES OF MMF IN SITUATIONS OTHER THAN TRANSPLANT**

MMF is a potential new treatment for autoimmune mediated diseases. Use of MMF in several of these diseases is described. In addition to its effects, in modulating the autoimmune response, MMF reduces adhesion molecule expression on lymphocytes.

**Primary Glomerular Diseases**

MMF inhibits both T and B lymphocyte proliferation. It has been shown to inhibit vascular smooth cell and mesangial cell proliferation. It is a selective inhibitor of nitric oxide (NO) synthetase and can induce apoptosis in T lymphocyte.27

Study conducted by Choi et al showed that MMF therapy in patients with primary glomerulopathies like focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN) and minimal change disease (MCD) is well tolerated, causes improvement in renal function and allows safe steroid withdrawal. It can also lead to improvement of nephrotic syndrome.28 Although large scale randomised studies are required, MMF proves its short term efficacy in glomerular diseases.

**Resistant Lupus Nephritis**

Long term cyclophosphamide therapy for lupus nephritis is associated with gonadal toxicity, malignancy and hemorrhagic cystitis. MMF in dosages of 0.5 - 1.5 gm/d is equally effective to treat lupus nephritis. Its side effect profile is mainly limited to gastrointestinal toxicity and bone marrow suppression which reverse immediately after stopping drug.

A randomised controlled study done by Chan et al in patients with diffuse proliferative lupus nephritis showed combination of MMF and prednisolone to be equally effective and relatively safe than regimen of cyclophosphamide and prednisolone followed by azathioprine and prednisolone.29 Mycophenolate mofetil has also been successfully used in cyclophosphamide- and cyclosporine-resistant lupus nephritis in children.30

**Other Diseases**

Other diseases for which MMF has been used are neuromuscular diseases like myasthenia gravis, inflammatory myopathy and chronic acquired demyelinating neuropathy;31 collagen vascular diseases like dermatomyositis, discoid lupus erythematosus and scleroderma;32,33 vasculitic diseases like Wegener’s granulomatosis, microscopic polyangiitis, Takayasu’s arteritis,34,35 and skin diseases like psoriasis, atopic dermatitis, cicatrical pemphigoid, and pemphigus vulgaris.36,37

MMF has been used even in autoimmune hemolytic anemia, primary biliary cirrhosis, and Crohn’s disease.38-40

**ADVERSE EFFECTS**

Adverse reaction profile for mycophenolate mofetil is largely restricted to hematopoietic and gastrointestinal
system. The larger dose 3 gm/d is less tolerated as compared to 2 gm/d.

**Gastrointestinal Side Effects**

Abdominal pain, vomiting, diarrhea are the commonest significant and reversible adverse effects. These are due to direct gastric irritation and can be reduced by dosing with food or dividing the same total daily dose into smaller doses.

**Anemia / Leukopenia**

Usually it occurs in 10% of individuals. Agranulocytosis and pancytopenia is rare. Almost all abnormalities revert within 1 week.

**Infections**

Renal transplant patients receiving MMF have a higher incidence of CMV disease as compared to those receiving azathioprine-based immunosuppression.\(^4\)\(^1\) MMF also increases morbidity of CMV infection warranting use of effective anti-CMV prevention regimens while patients are treated with MMF.\(^6\)\(^2\)

**Malignancy**

According to ANZDATA registry, all renal transplant recipients have at least one malignancy after 35 years.\(^4\)\(^3\) Overall pattern of malignancy with mycophenolate mofetil in the early years doesn’t raise particular concern. In patients receiving MMF incidence of post-transplant lymphoproliferative disorder (PTLD) is 0.6% to 1% at the end of 12 months. These findings are well within expected incidence of PTLD in protocols not including mycophenolate mofetil.

Skin and non-skin carcinomas are noted in 4% of patients on mycophenolate mofetil (4.2% in Azathioprine group).

In summary, MMF is potent and selective immunosuppressive drug. It has significantly improved results of organ transplantation. It has also been used in different autoimmune diseases with good results. Adverse effects are few which is mainly limited to gastrointestinal system and increased susceptibility to infection.

**REFERENCES**

21. Mycophenolate mofetil refractory rejection study group. MMF


