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Mycophenolate mofetil: Use in pediatrics

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Pharmacology Literature Reviews

In 1946, Sir Howard Florey first demonstrated the ability of mycophenolic acid (MPA) to inhibit bacteria, fungi, and leukocytes.[1] Investigated for its antineoplastic activity in the 1970's, MPA has since demonstrated additional benefit in treating psoriasis and has been further studied for its antimicrobial properties.[2-5] In the late 1980's, studies in animals demonstrated the immunosupressive characteristics of MPA. This work led to the formulation of a prodrug, mycophenolate mofetil (MMF), and human trials which established its efficacy in preventing acute rejection in renal, liver, and heart transplants.[6] Since that time, numerous protocols have been devised which substitute MMF for azathioprine, using it in combination with cyclosporine and corticosteroids.

Mechanism of Action

MPA, the active form of MMF, inhibits immunologically mediated inflammation, preventing organ rejection. The primary site for MPA activity is the *de novo* pathway responsible for adenosine and guanosine biosynthesis in human cells.

MPA blocks the rate-limiting enzyme inosine monophosphate dehydrogenase (IMPDH) in this pathway, depleting guanosine and causing a relative increase in adenosine, both of which ultimately inhibit the proliferation of *de novo* dependent T- and B-lymphocytes.[7] Other cell lines, capable of purine biosynthesis by shifting to the salvage pathway, are left relatively unaffected. Additionally, MPA impedes B-lymphocyte antibody production and, through suppressing glycoproteins responsible for cellular adhesion, inhibits leukocyte recruitment to inflammation and graft rejection sites.[8,9]

Current Indication

MMF is approved for the prevention of renal and cardiac allograft rejection when combined with cyclosporine and steroids in adults.[9]

Use in Children

Several reports of MMF use in pediatric patients have been published over the decade. These papers consist of a mix of retrospective reviews, clinical trials, case series, and case reports.[10-19]

There have been several papers targeting children under the age of 12 years. In 1997, Boucek and colleagues[10] reported success with a combination strategy of MMF and antithymocyte serum (ATS) in 18 consecutive children undergoing orthotopic heart transplantation. The authors compared this sample to the preceding 22 transplanted children who served as historical controls. Routine perioperative cyclosporine (CyA), azathioprine (AZA), and steroids were administered, followed by a protocol of ATS for 3 days and 6 weeks of 30-50 mg/kg/day MMF combined with CyA. For CMV-positive recipients or donors, ganciclovir was used during ATS and was followed by acyclovir during MMF. Seventeen patients completed the protocol. The number of rejection episodes per 100 days for the MMF patients was 0.23 versus 0.45 for the AZA and CyA controls. Infection rates were comparable. Gamma glutamyltransferase and absolute neutrophil counts were comparable to the controls. Mortality for the control group was 23% versus 5.5% for the MMF-treated group.[10]

Also last year, Ettenger and coworkers[11] published a 2 year retrospective review of MMF as maintenance immunosuppression in pediatric renal transplantation. Thirty-seven patients from 2 to 20 years of age received MMF with CyA and prednisone. The average length of therapy was 11 months, and the MMF dosage ranged from 16-60 mg/kg/day, in 2 divided doses. Reported toxicities included neutropenia (8%), diarrhea, and nausea (16% each). Cytomegalovirus (CMV) infection was observed in 19% of the patients, bacterial infection in 8%, and 5% had oral thrush or herpes stomatitis.

Nine of 12 available biopsy results from these children were normal or showed only borderline acute rejection changes. One patient had mild acute rejection and 2 patients had mild interstitial mononuclear cellular infiltrates with otherwise

insignificant clinical findings. Two of the 12 had moderate chronic nephropathy. Glomerular filtration rate studies and calculated creatinine clearance revealed no significant reduction or improvement in renal function. Mean daily prednisone doses were 0.098 mg/kg in the MMF group, compared to 0.17 mg/kg for the matched controls. The authors concluded that MMF was a useful addition to immunosuppressive therapy and are currently using a MMF dose of 600 $mg/M^2/day$.[11]

The use of MMF for intestinal transplantation was also reported in 1997. Of the 19 patients studied by Tzakis and colleages[12], 5 were children. MMF was started at a dosage of 30 mg/kg/day in two divided doses in 3 of the children initially after transplant. Two others were switched to MMF after being treated for rejection which occurred during CyA immunosuppression.

Additional reports of MMF use as rescue therapy after rejection have also been published. MMF doses of 18-50 mg/kg/day, given in two divided doses for 6 months, were described in a study of 37 liver transplantation patients. Four of the patients enrolled in this rescue protocol were under the age of 12.[13]

A case report published in *Lancet* in 1996 described a 2 year old renal transplant patient who received MMF after developing anuria and biopsy-proven acute rejection on her initial immunosupressive regimen of antithymocyte globulin, CyA and acyclovir. Eight days after initiating MMF, her renal function began to improve, eventually returning to baseline values. A subsequent episode of rejection was managed with muromonab-CD3 while she remained on MMF maintenance therapy. At last evaluation, 11 months post-transplant, the child was rejection-free on MMF 375 mg/day and CyA.[14]

In addition to these studies involving young children, several other studies have included preadolescent and adolescent patients. The children in these reports have been treated with MMF dosage regimens of 1000 mg to 1500 mg per day after kidney, lung, or liver transplantation.[15-19]

Pharmacokinetics

MMF is well absorbed after oral administration and rapidly hydrolyzed in the liver to MPA, the active drug. The time to maximum plasma concentration is approximately 2 hours following oral administration, with a secondary peak occurring within 6 to 12 hours. This secondary peak results from enterohepatic recycling of an inactive metabolite, mycophenolic acid glucuronide (MPAG). The volume of distribution of MPA in adults is approximately 4 L/kg. MPA is 97% bound to serum albumin. MPAG is also highly protein bound and may compete with MPA for binding sites, resulting in greater free drug.[9,20]

The conversion of MPA to MPAG takes place primarily in the liver, but may also occur via *b*-gluronidases in other cells.[7,9] Hepatic insufficiency due to alcoholic cirrhosis does not appear to alter the metabolism of MPA; however, other etiologies for hepatic disease may produce a different metabolic profile.

MPAG is eliminated by renal excretion. Less than 1% of an oral dose is eliminated as unchanged MPA. MPAG accumulates in patients with severe chronic renal impairment. Neither MPAG nor MPA are significantly removed by hemodialysis.

Drug Interactions

Pharmacokinetic

Decreased MPA concentrations have been observed with concomitant administration of MMF and antacids or cholestyramine, likely the result of interference with enterohepatic recirculation. Antibiotics which alter gastrointestinal flora may also impair this pathway. Competition for protein binding sites may elevate serum concentrations of theophylline or phenytoin when given with MMF, increasing free drug by 10%.

Since MPAG is eliminated by renal tubular secretion, administration with acyclovir, ganciclovir, or probenecid which compete for or alter renal tubular secretion, may increase serum concentrations of both drugs. This drug interaction is likely to be most pronounced in patients with high MPAG concentrations resulting from severe renal impairment or delayed graft function.

Pharmacodynamic

Immunosuppressive agents used in conjunction with MMF to prevent or treat allograft rejection may result in additive risk for severe bone marrow suppression.[9]

Adverse Reactions

The principal adverse reactions associated with MMF are vomiting, diarrhea, leukopenia, and an increased incidence of infection. Additionally, gastrointestinal hemorrhage has been observed in 2-3% of transplanted patients receiving MMF. Post-marketing experience has also revealed reports of colitis and pancreatitis. Care should be taken when administering MMF to patients with active digestive system disease.[9]

Data collected from 3 double-blind controlled trials for the prevention of renal transplant rejection and 1 double blind comparative trial for the prevention of cardiac transplant rejection have generated the following observations:

- Severe neutropenia occurred in up to 2% of the renal patients and 2.8% of the cardiac patients.
- In the cardiac population, opportunistic infections were approximately 10% higher in MMF-treated patients compared to those treated with AZA, but did not lead to an increase in mortality due to infection/sepsis.
- Patients with renal transplants who were treated with MMF had a higher incidence of sepsis, primarily CMV, than patients receiving AZA or placebo; cardiac patients showed no difference.

- Similar rates of fatal infection/sepsis (<2%) occurred in patients receiving either MMF or AZA after cardiac or renal transplantation.
- The incidence of malignancies for patients with renal transplants was similar in patients treated with MMF to previously reported data with other immunosuppressive regimens.
- Lymphoproliferative disease or lymphoma occurred in 1% of the population receiving MMF during clinical trials. This was a slight increase over previous data with AZA in renal patients. Non-melanoma skin carcinoma occurred in 1.6-4.2% of transplant patients treated with MMF, compared to 2.4% previously reported with AZA. Other malignancies were observed in 0.8-2.1% of MMF patients (both renal and cardiac), similar to values reported for AZA or placebo.[9,20]

Dosing and Monitoring in Pediatric Patients

The studies and cases previously described have established an initial MMF dosage range of 16 to 60 mg/kg/day, usually divided into two doses, for patients from 0.5 to 20 years of age.[10-13] The initial dose of MMF should be given as soon as possible following transplantation. Patients with severe renal impairment during the immediate post-operative period should be followed closely because of potential drug accumulation and bone marrow suppression.

Complete blood counts should be monitored at least weekly during the first month of MMF therapy, then twice monthly for 2 months, and then monthly for the remainder of the first post-transplant year. If the absolute neutrophil count falls to less than 1.3 x $10^3/\mu$ L, further diagnostic tests should be performed to evaluate the need for reduction or interruption of MMF therapy.

MMF is available as 250 mg capsules and 500 mg tablets (CellCept®; Roche Laboratories). Methods for preparing an extemporaneous oral liquid have been recently published, allowing more precise dosing adjustments in younger children. The 100 mg/ml suspension retains more than 90% potency for 4 months, whether refrigerated or stored at room temperature. Since MMF is a possible teratogen (pregnancy category C[20]), care should be taken when compounding or administering the suspension to avoid exposure of health care professionals and family members to the capsule powder or the resulting liquid.[21]

An injectable formulation of MMF was approved by the Food and Drug Administration earlier this month. The injection will also be sold under the brand name CellCept®by Roche.[22]

Conclusion

MMF appears to be an effective addition to the immunosuppressive armamentarium. Further studies need to be done to define the role of MMF in pediatric transplant patients. Areas for research include the long-term impact of MMF on graft survival in children, potential for steroid dose reduction, and reversal of resistant rejection episodes.

References

1. Florey HW, Gilliver K, Jennings MA, et al. Mycophenolic acid: An antibiotic from *Penicillium breicompactum*. Lancet 1946;1:46-9.
2. Williams RH, Lively DH, Delong DC, et al. Mycophenolic acid: Antiviral and antitumor properties. J Antibiot 1968;21:463-4
3. Carter SB, Franklin RJ, Jones DF, et al. Mycophenolic acid: An anticancer compound with unusual properties. Nature 1969;223:848-50.
4. Suzuki S, Kimura R, Ando K, et al. Antitumor activity of mycophenolic acid. J Antibiot 1969;22:297-302.
5. Jones EL, Epinette WW, Hackney VC, et al. Treatment of psoriasis with oral mycophenolic acid. J Invest Dermatol 1975;65:537-42.
6. Lee W, Gu L, Miksztal AR, et al. Bioavailability improvement of mycophenolic acid through amino ester derivatization. Pharm Res 1990;7:161-6.
7. Allison AC, Eugui EM. The design and development of an immunosuppressive drug, mycophenolate mofetil. Sem Immunopath 1993;14:358-80.
8. Allison AC, Eugui EM. Preferential suppression of lymphocyte proliferation by mycophenolic acid and predicted long-term effects of mycophenolate mofetil in transplantation. Transplant Proc 1994;26:3205-10.
9. Product information. CellCept. Roche Laboratories, Nutley, New Jersey. February 1998.
10. Boucek MM, Pietra B, Sondheimer H, et al. Anti-T-cell-antibody prophylaxis in children: Success with a novel combination strategy of mycophenolate mofetil and antithymocyte serum. Transplant Proc 1997;29(8A):16S-20S.
11. Ettenger R, Cohen A, Nast C, et al. Mycophenolate mofetil as maintenance immunosuppression of pediatric renal transplantation. Transplant Proc 1997;29:340-1.
12. Tzakis AG, Nery JR, Thompson J, et al. New immunosuppressive regimens in clinical intestinal transplantation. Transplant Proc 1997;29:683-5.
13. Gavlik A, Goldberg MG, Tsaroucha A, et al. Mycophenolate mofetil rescue therapy in liver transplant recipients. Transplant Proc 1997;29:549-52.
14. Songok EM, Libondo DK, Rotich MC, et al. Mycophenolate mofetil to rescue children with acute renal transplant rejection. Lancet 1996;347:1699-700. Letter.
15. Sollinger HW, Belzer FO, Deierhoi MH, et al. RS-61443 (mycophenolate mofetil): A multicenter study for refractory kidney transplant rejection. Ann Surg 1992;216:513-9.
16. Zuckerman A, Birsan T, et al. Mycophenolate mofetil in lung transplantation. Transplant Proc 1998;30:1514-6.
17. The Mycophenolate Mofetil Renal Refractory Rejection Study Group. Mycophenolate mofetil for the treatment of refractory, acute, cellular renal transplant rejection. Transplantation 1996;61:722-9.
18. Ringe B, Braun F, Lorf T, et al. Tacrolimus and mycophenolate mofetil in clinical liver transplantation: Experience with a steroid-sparing concept. Transplant Proc 1998;30:1415-6.

19. Filler G, Ehrich J. Mycophenolate mofetil for rescue therapy in acute renal transplant rejection in children should always be monitored by measurement of trough concentrations. Nephrol Dialysis Transplant 1997;12:374-5.
20. Mycophenolate mofetil. In: Olin BR ed. Drug Facts and Comparisons. St. Louis: Facts and Comparisons, Inc. 1998:737l-738.
21. Anaizi NH, Swenson CE, Dentiger PJ. Stability of mycophenolate mofetil in an extemporaneously compounded oral liquid. Am J Health-Syst Pharm 1998;55:926-9.
22. Roche CellCept. F-D-C Reports, "The Pink Sheet" 1998;60(33):31.

Pharmacology Literature Review

Tacrolimus Absorption During Enteral Feeds

While this study was conducted in adult organ transplant recipients, the results have application within the pediatric population as well. Ten liver or lung transplant patients receiving tacrolimus (FK 506) were given nasoduodenal feeds with Osmolite on two consecutive days. On one day, tacrolimus was administered during feedings; and on the other, the feeding was held from 1 hour prior to 8 hours after each dose. Serial serum samples were obtained to document drug absorption and the results were compared with a paired t-test. The authors found no significant difference in time to reach peak serum concentrations, dose-adjusted trough concentrations, maximum blood concentrations, or area under the concentration curves between the two feeding methods. As a result, they concluded that concurrent enteral feeding does not affect oral tacrolimus absorption. Murray M, Grogan TA, Lever J, et al. Comparison of tacrolimus absorption in transplant patients receiving continuous versus interrupted enteral nutritional feeding. **Ann Pharmacother 1998;32:633-6.**

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