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Therapeutic Monitoring of Mycophenolic Acid in Liver Transplant Patients

Raman Venkataramanan[1] and Leslie M. Shaw[2]

Mycophenolate mofetil (MMF) is a relatively new immunosuppressive drug normally used in combination with cyclosporine, tacrolimus, or steroids in kidney, heart, liver, lung, and bone marrow transplant patients. A fixed dose of 1 or 1.5 g twice a day is typically used in transplant patients for prevention or treatment of rejection. Several publications have recommended individualization of MMF therapy based on plasma concentration measurements because of (1) large variability in the pharmacokinetics of mycophenolic acid (MPA), the active metabolite of MMF in patients; (2) time-dependent changes in the pharmacokinetics of MPA within patients; (3) lack of a correlation between dose and plasma MPA concentrations; (4) variability in the MPA concentration / pharmacokinetics based on coadministered immunosuppressive drugs; (5) a decrease in the incidence of rejection with an increase in area under the plasma concentration vs. time curve (AUC) of MPA, and to a lesser extent with predose trough plasma MPA concentrations; (6) increased incidence of side effects in patients with higher AUC of MPA; (7) a relationship between MPA concentration and activity as measured by suppression of DNA synthesis or expression of T cell activation markers, *in vitro*; (8) difficulty in assessing the clinical response to MMF therapy; (9) narrow therapeutic index of MPA; and (10) the significant consequences of therapeutic failure (rejection).[1–5] Most of the studies published to date have been carried out in renal and cardiac transplant patients.

A thorough evaluation of the benefits of therapeutic monitoring of MPA in liver transplant patients has not been previously reported. The publication in this issue by Tredger and coworkers makes an attempt to fill this gap. This investigation was carried out in 147 adult and 63 pediatric liver transplant patients and measured 2501 predose plasma MPA concentrations using an enzyme multiplied immunoassay. This study provides documentation to support monitoring predose MPA levels, in agreement with previous publications in other patient populations. This is based on lack of a relationship between MMF dose and MPA levels; and an association of MPA levels with adverse events such as leucopenia, infection, and neurological complications (at >3 μg/mL), and acute rejection (at <1.0 μg/mL). Greater than 90% of the patients in this study eventually required less than 1 g twice-daily MMF dosing, and only 6.3% percent of the patients required the recommended dose of 1.5 g twice-daily MMF, leading the authors to conclude that a significant cost saving can offset the cost of therapeutic monitoring of MPA. In agreement with studies in other patient populations, a therapeutic range of 1 to 3.5 mg/L of MPA as measured by enzyme multiplied immunoassay is being recommended for liver transplant patients. Establishment of a therapeutic range for a drug that is typically used in combination with another primary immunosuppressive drug in a liver transplant patient population is difficult, and the authors must be acknowledged for their attempt to address this complex issue.

While this study has provided some interesting observations, it also points to the need for better experimental design to establish the therapeutic range for MPA in future studies. A heterogeneous group of patients were included in this study, with MMF being introduced from 0 to159 months posttransplantation. Since the incidence of acute rejection is higher during the early transplant period, it is likely that there will be differences in the incidence of rejection based on the time after transplantation and that it is reasonable to assume that "therapeutic range" is also likely to be different at different time points after transplantation, and therefore, among the different patient populations included as a single group in this study. Combining patients on different immunosuppressive regimens (cyclosporine and tacrolimus) or patients who received MMF for different reasons (secondary to calcineurin

Abbreviations: MMF, mycophenolate mofetil; MPA, mycophenolic acid; AUC, area under the plasma concentration vs. time curve; IMPDH, ionosine monophosphate dehydrogenase.

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toxicity *vs* supplemental immunosuppression), especially when doses and levels of other coadministered immunosuppressive drugs are different, makes the data difficult to interpret. Differences in serum albumin levels between patients who received MMF for renal sparing effect versus those who received it for other indications also confounds some of the observations. In this type of study it is important to collect trough plasma concentrations at an appropriate time, and inclusion of samples taken several hours after the normal trough concentrations will lead to misleading conclusions. While a determination of side effects or toxicity (the upper end of the therapeutic range) may be less influenced by the experimental design used, its appropriateness in the determination of the lower end of the therapeutic range for preventing rejection is in question.

While some of the conclusions are consistent with previous publications, others are clearly different from what is known about MPA in other patient populations. While the previous studies indicate a higher clearance of MPA in pediatric patients, this study suggests a higher apparent relative clearance in adults. The observation that the dose of MMF required per unit MPA concentration is higher in patients receiving tacrolimus is also different from what has been reported in several studies in renal transplant, lung transplant patients, and pediatric patients, when studies were carried out in two separate groups of subjects or when studies were carried out within the same subjects at different time periods after discontinuation of the calcineurin inhibitors. It is clear in the literature that patients on tacrolimus tend to have a higher MPA level per unit dose of MMF compared with those on cyclosporine. A likely cause for this apparent difference, as also recognized by the authors, is the increased clearance of MPA, secondary to lower albumin and increased unbound fraction of MPA in the patients studied. Interestingly neurological complications have been reported as adverse effects of MPA. It is not clear to what extent tacrolimus or cyclosporine contributed to this observation. The therapeutic range for a drug such as MPA that is used in different combinations with other immunosuppressive drugs may be dependent on the combination of drugs used. While the authors acknowledge the need for a therapeutic range based on the coadministration of other immunosuppressive drugs, this study does not provide that critical information.

Several important questions still need to be answered in order to optimize MMF therapy in liver transplant patients. (1) Is there any added benefit to monitoring unbound MPA concentrations? This is of particular importance in liver transplant patients in whom the unbound fraction of MPA changes with a change in albumin over time after transplantation, and also in patients with impaired renal function. The pharmacokinetic properties of MPA suggest that while changes in plasma protein binding alone will change the concentration of the total drug, the unbound MPA concentration is expected to be unaltered. Under certain circumstances, such as in chronic renal failure, the unbound MPA concentrations may increase without any change in total MPA concentrations. We hypothesize that this is due to a decrease in the intrinsic clearance of MPA associated with chronic renal failure. Since ionosine monophosphate dehydrogenase (IMPDH) activity is a function of unbound MPA concentration, unbound concentration may be a better index of the activity of MPA. (2) What is the therapeutic range to be achieved when MMF is used alone versus when it is used in combination with other agents? (3) What is the optimal therapeutic range for MPA early after transplantation compared with a later time after transplantation? (4) Does the trough MPA level provide a proper estimate of drug exposure, especially when it is more sensitive to enterohepatic recycling? Several studies suggest that an MPA AUC_{0-12} hour of >30 μg/mL/hr but <60 μg/mL/hr may be associated with optimal immunosuppression. With AUC being the most accurate measure of drug exposure, what is the role of MPA AUC monitoring in liver transplant patients? Can a limited sampling strategy be successfully used in liver transplant patients to estimate the AUC_{0-12} hours? (5) Is there a role for IMPDH activity measurement in liver transplant patients? What is the degree of inhibition of IMPDH necessary to prevent acute rejection? IMPDH is the target enzyme for MPA. The acyl glucuronide of MPA is known to inhibit IMPDH and may also contribute to the pharmacologic activity. (6) How significant is the interference by other metabolites of MPA in the enzyme multiplied immunoassay of MPA, especially in patients with poor renal and/or liver function?

While monitoring trough plasma concentrations of MPA in liver transplant patients is the first step in the right direction, the optimization of MMF therapy may require measurement of unbound MPA concentrations and/or estimation of AUC (total or unbound) based on a limited sampling strategy. Further studies are needed to evaluate these possibilities.

References

1. Shaw LM, Korecka M, Venkataramanan R, Goldberg L, Bloom RD, Brayman KL. Mycophenolic acid pharmacodynamics and

pharmacokinetics provide a basis for rational monitoring strategies. Am J Transplant 2003;3:534–542.
2. Shaw LM, Holt DW, Oellerich M, Meiser B, van Gelder T. Current issues in therapeutic drug monitoring of mycophenolic acid: Report of a round table discussion. Ther Drug Monit 2001;23:305–315.
3. Cox VC, Ensom MHH. Mycophenolate mofetil for solid organ transplantation: Does the evidence support the need for clinical monitoring? Ther Drug Monit 2003;25:137–157.
4. Nicholls AJ. Opportunities for therapeutic monitoring of mycophenolate mofetil dose in renal transplantation suggested by the pharmacokinetic/pharmacodynamic relationship for mycophenolic acid and suppression of rejection. Clin Biochem 1998;31:329–333.
5. Weber LT, Shipkova M, Armstrong VW, Wagner N, Schutz E, Mehls O, et al. The pharmacokinetic-pharmacodynamic relationship for total and free mycophenolic acid in pediatric renal transplant recipients: A report of the German study group on mycophenolate mofetil therapy. J Am Soc Nephrol 2002;13:759–768.