Immunosuppression with Mycophenolic Acid: One Size Does Not Fit All

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Over the past decade, immunosuppression for renal transplantation has shifted from predominantly azathioprine-based regimens to those containing mycophenolic acid (MMF, CellCept) (1). In most centers, MMF is combined with cyclosporine or tacrolimus (calcineurin inhibitors) plus corticosteroid therapy. These combinations have led to unprecedented patient and graft survivals over the near term (1 to 3 yr) and low rates of acute rejection. The recommended MMF dose is standard for all patients at 1 g twice daily.

Long-term survivals of patients and grafts are also improving but are suboptimal. Donor factors such as age, prolonged cold ischemia, and delayed graft function are associated with shortened graft half-life. The occurrence of acute rejection episodes remains a strong predictor of shortened allograft half-life and chronic allograft nephropathy. In this issue of JASN, Knoll et al. (2) present a retrospective study showing the rather obvious fact that there is a decreased time to first acute rejection if the recommended dose of MMF is reduced because of side effects. Furthermore, there is a quantitative relationship between the time the patient spends at less than the recommended dose and the risk for acute rejection.

Although the study is flawed in design by its retrospective nature and its failure to examine important variables such as cytomegalovirus (CMV) status and the length of time the patient was on dialysis, this study does illustrate the difficulty clinicians have in using drugs that have no biologic end points for dose adjustment. The situation with MMF dosing is analogous to prescribing warfarin anticoagulation with no knowledge of INR but instead having to wait for bleeding or thrombosis before making dose adjustments. The consequences of long-term corticosteroid use and the nephrotoxic/metabolic side effects of calcineurin inhibitors are related to total drug exposure. For calcineurin inhibitors, we use pharmacokinetic parameters to allow individualization of therapy. With MMF, the current practice is that one size fits all. The data of Knoll et al. suggest that this is inadequate. It is difficult to ascribe cause and effect to the reduced MMF dose and acute rejection for several reasons. Cyclosporine and tacrolimus each have different pharmacokinetic interactions with mycophenolate mofetil, and they were used sequentially in the study. There is no adjustment for length of renal failure, which could influence bone marrow tolerance of MMF, particularly with second transplants. CMV infections, which can be associated with dose-limiting leukopenia, thrombocytopenia, and acute rejection, were not examined in this analysis, nor were renal function, liver function, and decreased drug-protein binding, all factors that increase mycophenolic acid exposure (3).

Mycophenolic acid is prescribed as a morpholinoethyl ester, mycophenolate mofetil (MMF, CellCept). The ester linkage is rapidly cleaved to the active compound, mycophenolic acid. MMF blocks de novo purine biosynthesis by inhibition of inosine monophosphate dehydrogenase (IMPDH), thus decreasing the proliferation of T and B lymphocytes (4,5). The pharmacokinetics of MMF are complex; some patients achieve a peak in 1 to 2 h and a second peak at 5 to 6 h due to enterohepatic circulation. In some patients, the second peak (Cmax) is as much as 50% of the total peak concentration. A maximum concentration of >10 μg/ml is associated with side effects. There is little correlation with area under the concentration curve (AUC) and dose. The AUC in the first 12 h does correlate with propensity to reject if it is < 30 μg · h/ml or toxicity if it is >60 μg · h/ml. The desired exposure is 35 to 60 μg · h/ml (6,7). Mycophenolic acid AUC is increased by renal dysfunction, which may be clinically relevant early after transplantation or during rejection episodes (8,9). When heart transplant patients who had rejection were compared with patients who did not reject, doses were the same but rejecters had low AUC and trough levels (10).

Most strategies to reduce steroids or to eliminate long-term nephrotoxic effects of calcineurin inhibitors presume adequate patient exposure to mycophenolic acid. This was true in the prematurely stopped NIH steroid withdrawal trial, where an excess of rejection episodes was seen in the patients who had steroids withdrawn. In African-American subjects in that trial, the dose of mycophenolic acid was only 200 mg more than in white patients; however, the rejection rate with steroid withdrawal was 40% in African Americans and 16% in non-African Americans. If indeed African Americans have increased propensity to reject and thus require larger doses of mycophenolate, one interpretation consistent with the data could be that inadequate mycophenolate was given to African-American patients (11). This type of analysis begs the question as to whether there are pharmacogenetic or gender differences in mycophenolate metabolism. Limited studies comparing pharmacokinetics parameters between African-American and white renal transplant patients have shown few differences, suggesting that the differences in rejection rates between

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these two populations are not explained by pharmacokinetic differences alone but are more likely related to differences in innate immunologic response (12).

It is a common sense notion that a fixed dose is inadequate for patients with large interindividual variations in pharmacokinetics and pharmacodynamics. To use the same 2-g daily dose of mycophenolate given to a 100-kg man and a 50-kg woman does not seem logical.

The frequency of adverse reactions both gastrointestinal (GI) and hematologic seen by Knoll et al. fit other series in the literature. It is common clinical experience that few patients, even African-American patients, can tolerate 3 g/d MMF. The GI side effects of MMF can be serious. Erosive enterocolitis can be seen. In some patients, infectious etiologies can be found, but dose reduction is usually required for symptomatic relief (13,14).

Another interesting aspect of mycophenolic acid pharmacology is the increase in AUC with time from transplant despite a constant dose (15). Adequate exposure to the drug in the first 3 mo is important to prevent rejection, whereas GI and hematologic side effects may occur later with the same dose. In practice, most clinicians start at 1 g twice daily and titrate the patient to diarrhea or cytopenias, ending with the maximum dose that avoids these complications.

Are there better ways to give this valuable drug? There has been some anecdotal success in preparing emulsions of mycophenolate instead of capsules. Also splitting the dose 3 to 4 times in a 24-h period instead of twice with the same dose. In practice, most clinicians start at 1 g twice daily and titrate the patient to diarrhea or cytopenias, ending with the maximum dose that avoids these complications.

Most of the rejection reactions that were seen in the study of Knoll et al. were mild and reversible without any change in 1-yr graft survival (2). Whether these rejections compromise long-term graft function is unknown. In a recent analysis of the UNOS database, rejection rates in a cohort from 1998–2000 ranged between 21 and 32%, thus the rejection rate of 24% in this study appears consistent with those numbers (16).

The major metabolite of mycophenolic acid is mycophenolic acid glucuronide (MPG). MPA is metabolized by an enzymatic process mediated by UDP-glucuronosyl transferase (UDPGT) (17). Although cyclosporine exhibits a dose-dependent inhibition of this reaction, thus increasing mycophenolic acid concentrations, tacrolimus is 60-fold more efficient as an inhibitor of this reaction (18,19). In patients with delayed graft function, AUC of MPG, the free fraction of MPA and the AUC of free-MPA are all increased. These perturbed pharmacokinetics improve with resumption of normal renal function (8).

We might improve the therapeutic index of MMF by pharmacokinetic modeling. There are as yet no agreed-upon guidelines or target levels for such monitoring. Furthermore, the optimal timing of drug monitoring, whether Cmax, trough, or AUC, correlate better with clinical events is unclear. There have been pharmacodynamic studies to look at reductions in IMPDH, but no clinically relevant information is currently available (20,21).

There are a host of studies examining steroid avoidance, steroid withdrawal, calcineurin inhibitor withdrawal, and dose minimization. The available data are summarized nicely by Bodziak et al. (22) and Vincenti et al. (23) The primary end point for these trials is usually percent acute rejection episodes after drug withdrawal. Even though these episodes are generally reversible, the long effects of these minimization strategies on graft half lives are unknown. The role of sirolimus (Rapamune) in minimization regimens is also under investigation. While patients usually improve renal function when calcineurin inhibitors are withdrawn and sirolimus is substituted, the long-term effects of these strategies are also unknown. It should be remembered that there may be pharmacokinetic and/or pharmacodynamic interactions that could reduce renal function when sirolimus and calcineurin inhibitors are used together. In fact, the pivotal studies used for sirolimus approval showed worse renal function at 1 yr, despite reduction of acute rejection episodes (24–26). Since long-term results continue to improve, the burden of proof for any new regimen is high.

Studies defining appropriate pharmacokinetic targets and correlation with efficacy and toxicity are urgently needed to maximize the therapeutic potential of mycophenolic acid.

We are living in an era with increasing choices for immunosuppressive regimens. The federal government is the main payor for immunosuppressive medications for the first 44 mo after transplantation under Medicare (hopefully extended by political persuasion from our professional societies); therefore, nephrologists have a responsibility to be good stewards of the government’s money. Therapeutic decisions should be based on well-designed clinical trials. Most trials of new drugs are by necessity funded by drug manufacturers. In addition, generic versions of Sandimmune and Neoral are now available with other patented drugs to follow. Minor formulation changes for tacrolimus (Prograf) are in the works. In a free marketplace, competition should reduce prices for the government and consumers. The experience to date has been disappointing in that the cost savings are not passed on to either the payor or consumers.

With the results of renal transplant being excellent now, we hope that real therapeutic advances will be corroborated by controlled, blinded studies. The data reported by Shah et al. (27) comparing blinded and open studies with Neoral versus Sandimmune are instructive. Blinded studies showed little difference in efficacy and toxicity, while open studies favored the newer agent made by the same manufacturer. We foresee this scenario replayed with Prograf compared with an extended release preparation of the same drug, the closely related drugs sirolimus and everolimus, and certainly for mycophenolic acid in the CellCept formulation versus an enteric-coated formulation (Myfortic). Generic alternatives to all these immunosuppressive drugs will be available as patents expire. It is imperative that physicians, patients, and dispensing pharmacists be acquainted with the guidelines set out by the recent American Society of Transplantation Consensus Conference on generics, which urge caution in switching from one preparation to another without adequate bioequivalence data being obtained in transplant recipients (28).
In 2003, we are doing well in renal transplantation outcomes even with our nonspecific immunosuppressive therapy. Improvements in efficacy and long-term safety will come from tolerance protocols that minimize the need for generalized immunosuppression and by obtaining sound scientific evidence for any changes in our basic protocols. While using one dose for all patients is simple, it runs the risk of toxicity and underimmunosuppression. For now, refinements in therapy using the drugs already available should make good results even better.

References


