Renal Transplantation

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Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. *Lancet* 370: 59–67, 2007

Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM

Immunodeficiency is known to predispose to malignancy in populations with HIV/AIDS and with therapeutic immunosuppression for solid organ transplantation. The types of cancer that have arisen seem to be related to specific viral infections. For ascertainment of whether these types of malignancies were a product of the immunosuppressed state or specific for these disease entities, cancer incidence was compared in large population-based cohort studies between people with HIV/AIDS and solid organ transplant immunosuppression. The methods used were meta-analyses of log standardized incidence ratios (SIR) for specific tumors in both populations.

Findings. Seven studies of patients with HIV/AIDS totaling 44,172 individuals were compared with five studies of transplant recipients (97% of which were renal transplant recipients) involving 31,977 transplants. Of the 28 types of cancer examined, there was an increased incidence in both populations for 20. Most of these cancers were related to known viral infections in both populations. The most common epithelial cancers did not occur at greatly increased rates, although some specific tumors did show increases in the renal transplant population as compared with those seen in HIV/AIDS.

Commentary. It is known to most nephrologists who care for transplant recipients that the incidence of posttransplantation malignancies is increased. Thus, a thorough search is made for malignancy risk before transplantation by serologic workup of patients who are about to undergo immunosuppression to look for immunity to Epstein-Barr virus, human papillomavirus, and other viruses. This article is the work of a large group of Australian epidemiologists and follows their study in 2006 examining the cancer incidence before and after kidney transplantation (1). This study showed that cancer incidence was markedly increased after transplantation with a SIR of 3.27 compared with 1.35 in dialysis patients and potential transplant recipients. In the previous study, there was increased incidence of 25 types of cancer with a relative risk >3 for 18 of these tumors. Most of the tumors were of suspected viral cause. This study shows that most likely the immunosuppressed state is responsible, because the incidence of these virally related tumors is increased similarly in both HIV/AIDS and immunosuppressed transplant patients. In the latest study, the SIR for breast and prostate cancer were similar in both populations and not >1; however, colorectal, ovarian, and lung tumors were greater in both populations with SIR of 1.69, 1.55, and 2.18, respectively. As has been reported before, renal cancer has a large relative risk in transplant recipients of 6.78 compared with a lesser incidence of 1.50 in HIV/AIDS. These analyses do not include nonmelanoma skin cancers, which are exceedingly common in renal transplant recipients (2). Patients with these tumors may benefit from the use of sirolimus as a drug in maintenance immunosuppression, although proper studies need to be done in this regard. The "take-home message" for nephrologists who are caring for transplant patients is that malignancies are increased and that some patients at particular risk (*e.g.*, those who are Epstein-Barr virus negative at the time of transplantation). Patients who have risk factors for human papillomavirus and are unvaccinated should be followed very closely. All recipients should at least get the cancer surveillance recommended for the general population. This if often not done by busy nephrologists who care for such patients. In the renal transplant patient with retained native kidneys, renal cell carcinoma remains a significant risk (3,4). Annual screening for cervical and breast cancer and colonoscopy at suggested intervals should be done. Renal imaging every 2 yr and yearly prostate assessments seem reasonable. Patients would also benefit from careful skin examinations with expert follow-up of all suspicious lesions. We rely heavily in our program on skilled transplant-aware dermatologists.

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carcinoma in transplant recipients with acquired cystic kidney disease. *Clin J Am Soc Nephrol* 2: 750–756, 2007

The impact of UGT1A8, UGT1A9, and UGT2B7 genetic polymorphisms on the pharmacokinetic profile of mycophenolic acid after a single oral dose in healthy volunteers. *Clin Pharmacol Ther* 81: 392–400, 2007

Levesque E, Delage R, Benoit-Biancamano M-O, Caron P, Bernard O, Couture F, Guillemette C

Mycophenolate mofetil (MMF) is a component of most modern immunosuppressive medication regimens for solid organ transplantation and is increasing used in renal diseases of immune pathogenesis. The pharmacokinetics are complex, and there is wide interindividual variation in drug metabolism and exposure. The target for mycophenolic acid, the active metabolite, is *de novo* purine biosynthesis limiting T cell proliferation capacity in response to stimuli. For other narrow therapeutic index drugs, therapeutic drug level monitoring has proven utility, but with MMF, no simple approach has proved useful. Perhaps knowing metabolism genotype might provide a better insight into dosing in patients before starting immunosuppression with mycophenolic acid. In this study, 17 healthy volunteers with no polymorphisms were compared with 17 carriers of UGT1A9 (−275/−2152) after a single 1.5-g oral dose of MMF).

Findings. Compared with control subjects, the patients who were carriers for the specific UGT1A9 polymorphism showed significantly lower exposure to mycophenolic acid and lower estimated enterohepatic recycling. There was no apparent change in metabolism. Compared with the control subjects, carriers of a different UGT1A9 polymorphism, UgT1A9*3, had higher mycophenolic acid maximum concentrations. The results of this study indicate that mycophenolic acid dosage would be significantly affected by the UGT genotype of an individual. This provides at least a partial explanation for why "one size fits all" does not apply to dosing patients with MMF.

Commentary. The information in this article, although somewhat peripheral to the day-to-day practice of nephrology, gives insight as to the complexity of mycophenolic acid exposure and thus efficacy and toxicity in individual patients. Clearly, the current practice of starting with a fixed dosage of 1 g twice daily and titrating down to the maximum dosage tolerable by adverse effects such as gastrointestinal intolerance and cytopenias is somewhat primitive. Disappointing is that simple trough level monitoring has not found much utility. Furthermore, there are differential effects of cyclosporine to block enterohepatic recycling and tacrolimus-based regimens to leave this process relatively unaffected. Area-under-the-curve monitoring is simply not practical for most transplant patients in long-term follow-up settings. Also, it is not even known whether the area under the curve is stable over time.

Having a signature genotype on the patient's drug-metabolizing enzymes might provide a useful clue to dosing initial therapy with MMF. Further studies on this approach will be forthcoming. For now, therapy with MMF will continue to be empiric. It should be recognized that patients with renal dysfunction have reduced protein binding of mycophenolic acid, leading to higher free concentration and enhanced adverse effects. Thus, nephrotic patients with low serum albumin may be at increased risk for adverse consequences, particularly cytopenias, if dosage adjustment is not made. Although studies that largely were supported by the manufacturers of MMF and the enteric-coated sodium salt have shown that reducing the dosage enhances rejection activity, none of these studies has provided a pharmacokinetic basis for these observations. The enteric-coated formula has shown no superiority in terms of efficacy or gastrointestinal adverse effects, and thus the foregoing discussion most likely applies to both drugs.

Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant* 7: 1506–1514, 2007

Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, Uchida K, Pescovitz MD, Marchetti P, Tuncer M, Citterio F, Viecek A, Chadban S, El-Shahawy M, Budde K, Goto N, on behalf of the DIRECT (Diabetes Incidence after Renal Transplantation: Neoral C_2 Monitoring Versus Tacrolimus) investigators

New-onset diabetes is a significant comorbidity in patients who undergo what otherwise would be a life-extending procedure, namely resumption of normal kidney function by transplantation. The differences between standard immunosuppressive calcineurin inhibitors cyclosporine and tacrolimus have been pointed out before. Somewhat paradoxic, cyclosporine increases other risk factors for cardiovascular disease, such as hypertension and LDL cholesterol, compared with tacrolimus, which increases new-onset diabetes. This study compared *de novo* renal transplant patients who were on a regimen of basiliximab, mycophenolic acid, steroids, and either cyclosporine microemulsion or tacrolimus. The cyclosporine therapy was monitored by C_2 sampling, and the tacrolimus was monitored by trough levels. This study was an attempt to compare the two most commonly used calcineurin inhibitors in terms of their metabolic consequences because cardiovascular death, presumably associated with abnormal risk factors in these patients, is the most common cause of death with a functioning transplant.

Findings. This was an intention-to-treat study of 682 patients, 336 of whom were treated with cyclosporine microemulsion and 346 with tacrolimus. A total of 567 did not have diabetes at the baseline visit, and their risk for diabetes including steroid doses was similar at baseline. The end point was new-onset diabetes after transplantation or impaired fasting glucose at 6 mo. This was a multicenter study, and a variety of steroid protocols were used in these patients. It is pointed out by an editorialist for these articles that the dosages of steroids and target tacrolimus trough levels may be higher than is currently used in clinical practice and may partially account for the results obtained (1). The primary efficacy end point was biopsy-proven acute rejection, graft loss, or patient death at 6 mo. Renal function was estimated by the Cockcroft-Gault formula.

There was statistically more diabetes in the tacrolimus patients, 96 of whom developed the end point of new-onset diabetes or fasting glucose intolerance. This represents 33.6% of the patients. Seventy-three cyclosporine microemulsion patients achieved this end point for a 26% prevalence. Efficacy was no different between the groups with an end point occurring in 43 (12.8%) cyclosporine microemulsion patients and 34 (9.8%) tacrolimus patients. Renal function as estimated by the formula was no different. BP was no different, but total cholesterol and LDL cholesterol were higher in cyclosporine compared with tacrolimus patients. It should be noted that the study was supported financially by Novartis.

Commentary. This large, well-done clinical study points out what has been thought by transplant physicians, namely that the price for effective immunosuppression with both calcineurin inhibitors is an increased incidence of posttransplantation diabetes, which is obviously a major risk factor for cardiovascular disease. A recent review of this subject has appeared in the pages of the *Clinical Journal of the American Society of Nephrology* (2). Efficacy between the two immunosuppressive drugs is similar as noticed in previous studies. The trend toward less rejection with tacrolimus is again noted. The major criticism of this study is the higher steroid burden and the trough levels and thus the increased exposure to tacrolimus provided by the protocol. Both steroids and tacrolimus cause insulin resistance, contributing to the risk for posttransplantation diabetes. Thus, the differences between the two drugs are not terribly surprising and do favor the sponsor's compounds. For the physician contemplating which calcineurin inhibitor to use, the choice should be based on individual patient factors. These include the immunologic risk of the patients *versus* the risk for cardiovascular and metabolic complications. Individual choices can then be rationalized. We have two effective calcineurin inhibitors, and their differences and similarities should be considered in prescribing for the individual patient.

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Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: The CAESAR Study. *Am J Transplant* 7: 560–570, 2007

Ekberg H, Grinyo J, Nashan B, Vanrenterghem Y, Vincenti F, Voulgari A, Truman M, Nasmyth-Miller C, Rashford M, on behalf of the CAESAR study group

Calcineurin inhibitors have revolutionized renal transplantation. The drugs cyclosporine and tacrolimus have led to improved renal allograft survivals and patient survivals and enabled the emergence of extrarenal organ transplantation in the 1980s and 1990s. The downside of calcineurin inhibitors is their widely known adverse effects, the most prominent of which is nephrotoxicity. Much of this nephrotoxicity is mediated by impairment of renal hemodynamics, but chronic tubulointerstitial disease has also been shown both experimentally and clinically (1). This has led to protocols to try to minimize the exposure of renal transplant recipients to calcineurin inhibitors after an initial period of more intense immunosuppression. The Cyclosporine Avoidance Eliminates Serious Adverse Renal Toxicity (CAESAR) study is an attempt to withdraw or minimize calcineurin exposure after 6 mo after engraftment.

Findings. A total of 536 patients who were receiving their first renal transplant were randomly assigned to one of three regimens. All patients received induction with daclizumab, a CD25 mAb, mycophenolate mofetil, and corticosteroids. Withdrawal from cyclosporine starting at month 4 and completed by month 6 was given to one group, another had low-dosage cyclosporine continued but targeting a lower-than-usual trough blood level of 50 to 100 ng/ml, and a final group received a standard dosage of cyclosporine. There was significant increase in biopsy-proven acute rejection in the group that was withdrawn from cyclosporine of 38% *versus* the low- or standard-dosage cyclosporine groups, which were 25.4 and 27.5%, respectively. Renal function as measured by GFR was not different in all three groups. The authors concluded that maintenance of cyclosporine probably is useful in avoiding higher rejection rates and that low-dosage cyclosporine as indicated by this protocol targeting lower trough levels is safe.

Commentary. As pointed out by the editorialists for this article, this study does document a lower level of rejection when calcineurin inhibitors are maintained *versus* their withdrawal at 4 to 6 mo (2). This begs the question of whether the addition of a presumably nonnephrotoxic immunosuppressive agent such as sirolimus would provide lower rates of rejection comparable to the calcineurin inhibitor arms of the study. Left unexplained is the higher-than-usual rejection rates of all groups in this study *versus* what is reported by other transplant centers usually experiencing 10 to 15% acute rejection rates. Deficiencies in this study are again noted by the editorialist. Cyclosporine levels in the standard arm approach the low-dosage arm, perhaps accounting for the minor differences in rejection between these two groups. The lack of effect on renal function may be due to short-term follow-up. Translation of these data to the longer term effects of calcineurin inhibitors to reduce renal function gradually over time cannot be addressed by this short-term study. It is not known whether exposure to cyclosporine in lower-than-conventional dosages is beneficial over the long haul. Also, the effect of more potent induction before calcineurin withdrawal is left up in the air. Because excellent results are obtained in renal transplantation at the present time using triple drug regimens, the standard protocols for cyclosporine and tacrolimus maintenance therapies should aim for 6-mo trough calcineurin levels between 100 and 150 and tacrolimus levels between 5 and 10. This should remain the standard of care until well-controlled, long-term clinical results are available from CAESAR or other studies.

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