EDITORIALS

The Growing Problem of Chronic Renal Failure after Transplantation of a Nonrenal Organ

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The clinical introduction of the immunosuppressive drug cyclosporine in the early 1980s revolutionized the field of organ transplantation. The adoption of cyclosporine-based immunosuppressive regimens dramatically improved survival among patients who received nonrenal allografts. Twenty years later, cyclosporine and tacrolimus (another inhibitor of calcineurin — a key enzyme involved in T-cell activation)[1] remain the cornerstone of immunosuppressive therapy for most patients who receive nonrenal transplants.

Not surprisingly, given the procedures involved, transplantation of nonrenal organs can be associated with acute renal failure. During the past two decades, however, it has become apparent that chronic renal failure is also an important complication. Whatever type of organ is transplanted, the clinical features are quite similar: a decrease in the glomerular filtration rate — by 30 to 50 percent during the first six months after transplantation — followed by stabilization or a slower rate of loss of renal function.[2] Hypertension is present in the majority of affected patients. The urine sediment is usually unremarkable, although proteinuria may be present. Laboratory studies may show evidence of low-grade thrombotic microangiopathy.[3] Renal biopsies (rarely performed unless the clinical presentation is atypical) usually demonstrate interstitial fibrosis and tubular atrophy, arteriolar hyalinosis, and sclerosis or collapse of glomeruli.[4]

The predominant cause of these clinicopathological abnormalities is the long-term use of calcineurin inhibitors — either cyclosporine or tacrolimus. Similar abnormalities have been found when these drugs are used in settings other than organ transplantation — for example, in patients with psoriasis.[5] Unfortunately, a late reduction in the dose of calcineurin inhibitors appears to have limited benefit in improving renal function — a finding that is not unexpected, since the histologic changes may be irreversible. In addition to the direct nephrotoxic effects of these drugs, other factors can contribute to post-transplantation chronic renal failure: perioperative renal damage, hypertension, diabetes mellitus (a relatively frequent complication of immunosuppression with corticosteroids and calcineurin inhibitors), hepatitis C infection, and the use of other nephrotoxic drugs.[2]

In this issue of the *Journal*, Ojo et al.[6] report an analysis of renal outcomes in almost 70,000 recipients of nonrenal organ transplants — the largest cohort that has been studied to date. Data were obtained regarding recipients of heart, lung, heart–lung, liver, or intestine transplants in the United States between 1990 and 2000. The results are cause for concern: after a median follow-up of 36 months, severe chronic kidney disease (defined, according to the current consensus guidelines,[7] by a glomerular filtration rate of 29 ml per minute per 1.73 m^2 of body-surface area or less) had developed in 16.5 percent of the patients, and almost one third of these patients had end-stage renal disease (ESRD) requiring dialysis or renal transplantation. Overall, ESRD occurred at a rate of 1.0 to 1.5 percent per year. Chronic kidney disease was significantly associated with increased mortality — a finding similar to that observed in the general population. It is likely that kidney disease in the patients who had received a nonrenal transplant was also associated with increased risks of conditions such as anemia, hypertension, and bone disease.

Ojo et al. do not report the prevalence of moderate chronic renal impairment (a glomerular filtration rate of 30 to 59 ml per minute per 1.73 m^2) among recipients of nonrenal transplants, but a conservative estimate based on data from the gen-

eral population suggests that its prevalence would be several times as high as the prevalence of severe chronic kidney disease in this population.[8] Such renal dysfunction may be clinically relevant, since even moderate chronic kidney disease has been associated with adverse outcomes.[9]

What are the implications of this study? First, it demonstrates that severe chronic kidney disease is relatively common after the transplantation of a nonrenal organ and is associated with increased mortality. Therefore, as the authors suggest, their findings underscore the need to counsel potential transplant recipients (particularly those with preexisting renal dysfunction, hypertension, diabetes mellitus, or hepatitis C) about the significant long-term risk of this complication. Clearly, the risk of severe chronic kidney disease must be added to the list of other risks associated with the transplantation procedure, such as opportunistic infections, cancer, or bone disease.

Second, the study highlights the potential public health effect of transplant-related kidney disease. Improvements in immunosuppressive regimens and general medical care are allowing transplant recipients to live longer, and a yearly rate of ESRD of 1.0 to 1.5 percent may ultimately translate into a requirement for renal-replacement therapy (dialysis or renal transplantation) in many thousands of patients. The care of patients with ESRD is extremely expensive. For example, although such patients represent only 0.8 percent of the Medicare population, they account for almost 6 percent of Medicare expenditures.[8] These costs should be considered in the estimation of the true cost per patient of transplantation of a nonrenal organ.

Third, the study confirms data from single-center studies showing that renal transplantation can improve survival in the subgroup of transplant recipients in whom ESRD develops. Thus, when renal-replacement therapy is needed and there are no contraindications, renal transplantation should be strongly considered. Unfortunately, as with the transplantation of other organs, a shortage of available kidneys bedevils the field of renal transplantation.[10]

Most important, the findings of Ojo et al. should stimulate new studies to determine how the high incidence of chronic kidney disease among recipients of nonrenal transplants might be reduced. What interventions might be effective — and safe? Understandably, there has been some reluctance to pursue protocols without calcineurin inhibitors in recipients of nonrenal transplants, since a backup analogous to dialysis is not available if catastrophic rejection occurs. Moreover, because calcineurin inhibitors have been the cornerstone of immunosuppressive therapy for the past two decades, their complete elimination from current regimens would require a well-validated basis, and this is not available today for recipients of nonrenal transplants. What about the reduction of maintenance doses of calcineurin inhibitors, under the protection of the recently introduced nonnephrotoxic immunosuppressants mycophenolate mofetil and sirolimus? This strategy is currently being investigated extensively in renal transplantation, and it has been shown to improve renal function, at least in the short term.[11,12] Similar approaches might be effective in recipients of nonrenal transplants as well. Indeed, in small series of recipients of heart and lung transplants, the substitution of mycophenolate mofetil for azathioprine — with a concomitant reduction in the dose of calcineurin inhibitors — has been reported to improve renal function, without increasing the rate of allograft rejection.[13,14]

These preliminary data and a greater awareness of the magnitude of the problem of post-transplantation kidney disease should prompt randomized, controlled trials of these and other strategies. A useful starting point would be to study patients at the highest risk for chronic kidney disease. Another area that warrants investigation is the identification of genetic or phenotypic traits that might increase individual susceptibility to the toxic effects of calcineurin inhibitors. Finally, in the future, the induction of donor-specific immune hyporesponsiveness in the recipient may result in novel antirejection strategies with minimal need for maintenance immunosuppressive therapy — and therefore with fewer long-term toxic drug effects.[11,15]

Pending the results of such studies, much can still be done. The rate of development and progression of post-transplantation chronic kidney disease can probably be reduced with meticulous preoperative and perioperative care, avoidance of drug-induced acute renal failure in the early post-transplantation period, optimal long-term control of hypertension[16] and hyperlipidemia, and the use of angiotensin-converting–enzyme inhibitors or angiotensin II receptor blockers in patients with microalbuminuria or proteinuria. The many complications of chronic kidney disease, such as anemia and hyperparathyroidism, should also be identified and managed according to consensus guidelines.[7]

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Welcome to the Genomic Era

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> To him who devotes his life to science, nothing can give more happiness than increasing the number of discoveries, but his cup of joy is full when the results of his studies immediately find practical applications.
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> — Louis Pasteur

This issue of the *Journal* includes the last installment in a monthly series on genomic medicine that began in November 2002.[1-11] The series has focused on the ways in which the rapidly appearing tools of genomics have already begun to change the practice of medicine. In this issue, for instance, Burke explores how genomics has started to improve our understanding of the biology of health and disease in ways that were never before possible.[11] Although the series demonstrates that genomics has indeed begun to change the practice of medicine, it catalogues only the birth of the genomic era and thus no more captures in detail the ultimate effect of genomic medicine than does the examination of a newborn foretell what the mature adult will be like.

If the genomic era can be said to have a precise birth date, it was in the midst of the appearance of the series, on April 14, 2003. That was when the international effort known as the Human Genome Project put a close to the pregenomic era with its announcement (available at http://www.genome.gov/11006929) that it had achieved the last of the project's original goals, the complete sequencing of the human genome. The extent and pace of progress in genomics are suggested by the fact that this achievement occurred 11 days shy of the 50th anniversary of the publication of Watson and Crick's seminal description of the DNA double helix. If science, technology, and medicine have consistently demonstrated anything, it is that they proceed at an ever-quickening pace. That we have gone in the past 50 years from the first description of the structure of our DNA to its complete sequencing gives some indication of how much the impact of genomic medicine on the health care of today's neonates will increase by the time they turn 50 years of age.

However, it is not solely the next 50 years that will witness important advances in genomic medicine. Many such advances have already occurred, including some during the interval since the launch of the Genomic Medicine series. Indeed, one need look no further than the pages of the *Journal* to see potent additional examples of what has occurred during these past few months: the use of genomics for the rapid identification of newly discovered pathogens such as that involved in the severe acute respiratory