Kidney transplantation provides improved vitality and longevity compared with dialytic therapy. Successful transplantation has been greatly enabled by the development of immunosuppressive regimens with an improved therapeutic index. Current transplant recipients can anticipate a >90% success rate at 1 year and a graft half-life of ≥13–14 years. However, failure of a kidney transplant remains the fourth leading cause of ESRD in the United States.1 With >100,000 patients on the waiting list, the holy grail of transplantation remains having all allografts serve their owners for their remaining life expectancy.

After months or years of successful engraftment, many patients display a slow but steady loss of kidney function that is characterized by increasing accumulation of collagen in the renal interstitium with associated atrophy of the kidney tubules. In the past, this was called chronic allograft nephropathy but is now typically referred to as interstitial fibrosis/tubular atrophy. Calcineurin inhibitors (CNIs) have been blamed as a cause of this process, but recent data indicate that chronic antibody-mediated rejection plays an important role in this obliterative process.2

The critical relationship between the renin-angiotensin system and profibrotic processes, such as those mediated by TGF-β,3 has led investigators to use renin-angiotensin inhibitors as an antifibrotic therapy in experimental models of renal disease.4 The development of fibrosis in kidney biopsy–based trials of diabetic nephropathy, such as the Diabep:is trial from the 1990s, suggests an association with loss of kidney function and, of note, indicates that such fibrotic accumulation appears preventable by the use of angiotensin-converting enzyme inhibition with perindopril.3 The therapeutic advantage of renin-angiotensin system blockers in human diabetic and nondiabetic nephropathy has been recognized for years. Thus, it made sense to perform a randomized, controlled trial in recipients of a kidney transplant to see whether renin-angiotensin inhibition would slow the loss of kidney function, possibly by attenuating fibrosis.

As reported in this issue of JASN, Ibrahim and colleagues enrolled 153 patients within 3 months of their first or second kidney transplant.6 They all underwent a kidney biopsy at baseline. They were then randomly assigned to losartan, 100 mg daily (n=77), or placebo (n=76), along with usual transplant care. The goal was to have 58 evaluable patients in each group at the end of the study. Thus, enrolling 77 patients in the losartan and 76 in the placebo group would seem an appropriate hedge to have 58 patients finish in each group and hopefully demonstrate a difference in the primary outcome, defined as a doubling of fibrosis in the kidney cortex or ESRD. At the end of the trial, the original 77 in the losartan group, 47 had a final kidney transplant biopsy, and 44 of 76 in the placebo group had similar paired biopsy data. The investigators anticipated that 60% of the placebo group would demonstrate the buildup of fibrotic tissue in the interstitium or ESRD compared with 20% in the losartan group, as measured by histomorphometric analysis. After 5 years of therapy, their results showed that the fibrotic endpoint or ESRD was reached by 6 of 47 patients in the losartan group compared with 12 of 44 in the placebo group (P=0.08). Said another way,
13% of the losartan group compared with 27% of the placebo group reached trial endpoints.

As the authors note, the study had a lower-risk, largely white population and was a prevention trial, which accounts for some of the shortfall in the anticipated number of participants reaching primary trial endpoints. Additionally, BP control was reasonably good in both treatment groups. We suggest that several other factors may have diminished the likelihood that the investigators could capably evaluate a possible difference between the therapies.

Perhaps the most important confounding factor is the known erratic development of allograft fibrosis and decay of kidney function. This is probably related to the many putative factors involved in this destructive process, some of which may occur early after transplantation within the scope of a 5-year study, but many may also occur later, which would be missed. Another important factor is proteinuria. The development of proteinuria in transplant recipients is an ominous sign of progressive loss of function and could indicate recurrent disease, or the development of chronic antibody-mediated rejection. Very few patients had clinical proteinuria, a factor that limited the power of the study to examine renal endpoints. Although renin-angiotensin system inhibition may not treat rejection or CN1 nephrotoxicity, it may modify the profibrotic effects of both disease processes. Lower doses of CNIs, which are potential contributors to interstitial fibrosis, may have factored in the lower rates of renal endpoints. Finally, the increasing attention paid to cardiovascular risk factors (lipids, salt intake, use of low-dose aspirin, encouragement of physical activity) in patients with kidney disease probably contributed to some of the unmeasured confounding in this trial.

It is important, however, not to lose sight of the findings of this study. Although the P value for the primary outcome was not statistically significant, there was a halving of endpoints in the losartan group. The large dropout rate in both groups testifies to the challenge of undertaking such a study in this population, while at the same time providing an invaluable basis for planning future studies addressing important questions in kidney transplant outcomes with hard endpoints. Certainly, it would have been potentially helpful to have measures of donor-specific antibody and c4d staining in the biopsy samples because these data may provide a clue about ongoing immunologic activity.

We believe there are two take-home messages here. The first is that in planning intervention trials in patients with CKD or transplants, it is important to use the most current information on endpoint occurrence so as to assess outcome likelihoods with planned treatments or placebo. Second, it is also important to anticipate collateral improvements in care from other disciplines (such as cardiology or surgical techniques) that will probably occur during the trial. Thus, it is mandatory for future trials in kidney disease to broaden our thinking about recruitment goals as nephrologists into the minds of our cardiologic brethren; in cardiology trials, group sizes are typically in 3 or 4 significant-digit values, rather than the typical group sizes of less than 1000 in kidney-related trials. This will naturally increase clinical trial costs. However, because it takes about $70,000 US per year to dialyze a patient, the $5000 US per year cost to manage participants in clinical trials would seem to be a bargain. In current endeavors, such as SPRINT, the size of the CKD group is anticipated to be about 3000 participants. Although it took collaboration among several institutes at the National Institutes of Health to make this possible, we submit it is vital to maintain this mindset of enrolling the large numbers needed to definitely answer the pressing questions in the treatment of kidney disease.

DISCLOSURES

None.

REFERENCES


