Update on kidney transplantation: Increasing clinical success, expanding waiting lists

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ABSTRACT

Short-term and long-term renal allograft survivals have improved in recent years for several reasons. Improvements in immunosuppression have reduced acute cellular rejections to about 15% to 25%. The use of erythropoietin to treat anemia allows patients to avoid transfusions, thereby reducing sensitization and hyperacute rejections. Advances in the management of cardiovascular disease and infection have also been significant factors in improved patient and allograft survival. Although living donations are helping to increase the number of transplants, their effect on rapidly growing waiting lists is relatively small.

SUCCESS RATES in renal transplantation are improving significantly, and the number of patients receiving transplants is increasing. However, optimism about our successes in renal transplantation is counterbalanced by pessimism surrounding a chronic shortage of organ donors.

This paper reviews some of the highlights of the recent transplant experience.

RENAL TRANSPLANTATIONS INCREASING

In the 20 years from 1970 and 1990, about 100,000 renal transplantations were performed in the United States. In comparison, in the 10 years between 1990 and 2000, approximately 109,000 were performed. At the current rate of more than 13,000 per year, there will be as many transplants done in the next 15 years as were done in the previous 30 years.

Unfortunately, the need for organs for transplantation continues to far exceed the supply. In 1988 there were approximately 15,000 people waiting for a kidney, in 2000 there were nearly 50,000. The waiting period for a cadaver kidney varies somewhat from place to place, but averages about 3 years.

Survival has improved, but the need for organs far exceeds the supply

INCREASED USE OF LIVING UNRELATED DONOR KIDNEYS

Much of the surge in kidney transplantation over the last decade has been in transplants from living, unrelated donors, mostly spouses of the patients. Currently, about 24% of all living donors are not blood relatives of the recipient. In 2000, there were 1,200 renal transplants performed with organs from living, unrelated donors. Unfortunately, the marked increase in the number of transplants from living donors has hardly made a dent in the need for organs.

Five-year graft survivals show that kidneys from living donors have a substantial advantage over cadaver kidneys, almost regardless of how well the human lymphocyte antigens (HLA) of the donor and recipient are matched. According to data from the United Network for Organ Sharing (UNOS), the 5-year survival rate is 62% for cadaver kidneys, while the rate is 75% for

This paper discusses therapies that are not yet approved by the Food and Drug Administration for the use under discussion or that are still investigational.

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kidneys from spousal donors, 72% for other living, unrelated donors, and 75% for mismatched living, related donors.[1] In this circumstance, the physiologic advantage of even an unrelated living donor kidney is greater than that of an immunologically advantaged cadaver kidney.

EPO, FEWER TRANSFUSIONS HAVE NEARLY ELIMINATED HYPERACUTE REJECTIONS

Hyperacute rejections, manifested by diffuse intrarenal coagulopathy occurring within the first 24 hours after transplantation, have nearly disappeared in the past 10 years. This trend is probably due to use of recombinant erythropoietin (EPO; Epogen, Procrit) introduced in 1990, which stimulates the bone marrow to produce red blood cells. Because of EPO, transplant candidates can usually avoid blood transfusions and therefore have a lower percentage of preformed HLA antibodies induced by HLA-incompatible cells in the transfusion.

For example, among patients waiting for cadaveric kidney transplants in 1988, 28% were highly sensitized, as measured by panel reactive antibody (PRA) higher than 80%.[2] In comparison, only 14% of patients in 1999 had a PRA over 80%. Conversely, the percentage of patients with minimal sensitization (PRA lower than 20%) rose from 48% in 1988 to 70% in 1999. The absence of detectable preformed HLA antibodies reduces the risk of not only hyperacute rejection but also early vascular rejections. Those antibodies that do occur can almost always be detected by sensitive crossmatching techniques, and a transplant destined for a hyperacute rejection can be avoided.

Half-life of cadaver kidney transplants: In 1991—8 years Today—12 years

ACUTE REJECTIONS ALSO DECREASING

As immunosuppressive regimens have improved, the frequency of acute cellular rejections within the first 6 to 12 months after transplantation has declined, from approximately 40% in the cyclosporine/azathioprine/prednisone era to about 28% in the cyclosporine/mycophenolate mofetil/prednisone era, and recently to a range of about 8% to 15% with the newest immunosuppressant protocols.

LONG-TERM GRAFT SURVIVAL IS INCREASING

Up until the mid-1990s, the improvement in early graft survival had not been translated into a concomitant improvement in long-term survival. For example, the $T_{1/2}$ (the time at which half the kidneys functioning 1 year after transplantation have failed) remained about 7.5 to 8 years from 1975 until at least 1991. Since then, however, the $T_{1/2}$ of cadaveric kidney transplants has increased to 11.5 to 12 years, thanks to several developments.[3]

Lower cyclosporine doses. Cyclosporine, introduced into general use in 1984, caused significant nephrotoxicity that was nullifying any long-term benefit, despite a decrease in early acute rejections. Consequently, initial dosages of cyclosporine after kidney transplantation were reduced from 14 mg/kg/day (or even higher in some centers) to 8 mg/kg/day or less. Recently, lower doses of cyclosporine are being used with low doses of rapamycin.

Better cyclosporine formulations. Early cyclosporine formulations in liquid form and then capsule form (Sandimmune) had variable absorptions, and blood levels were difficult to control in many patients. It was authoritatively reported that approximately 60% of cases of cyclosporine nephrotoxicity occurred within a therapeutic range of 150 to 400 ng/mL, as did 60% of rejections. The current formulation of cyclosporine (Neoral) has more predictable bioavailability. An important corollary is that cyclosporine formulations are not equivalent, and blood levels should be monitored if switching from one formulation to another or to a generic.

New initial and maintenance immunosuppressive agents include FK-506 (tacrolimus; ProGraf), used originally for rescue therapy with rejection; mycophenolate mofetil (CellCept), which is a more potent purine antagonist than azathioprine (Imuran) and is gradually replacing it; rapamycin (sirolimus, Rapamune); and monoclonal antibodies directed at the IL-2 receptor (see below).

Better control of hypertension in transplant recipients has only relatively recently been recognized as having a major impact on allograft survival. For each 10-mm Hg incre-

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ment in systolic blood pressure from less than 120 mm Hg to greater than 180 mm Hg, a decrease in graft survival can be seen. For example, patients with systolic blood pressures up to 140 mm Hg have 8-year allograft survivals of about 70%, whereas those with systolic blood pressures from 160 up to 180 mm Hg have 8-year survivals of approximately 55%.[4] This finding holds true even in renal transplant recipients who have diastolic blood pressures less than 90 mm Hg and have not experienced allograft rejection, so it is not merely a reflection of impaired allograft function.

More emphasis on preventing and aggressively treating coronary artery disease. Annual cardiovascular mortality per 1,000 patient-years is approximately twice as high in transplant recipients (0.54) as in the general population (0.28), but is still only about 6% of that seen in dialysis patients (9.12).[5] Coronary disease is the leading cause of death in recipients with a functioning graft. Consequently, risk-factor reduction is even more important in transplant recipients than in the general population and should include tight control of hypertension, hyperlipidemia, hyperglycemia, and hyperhomocysteinemia, as well as smoking cessation.

CURRENT TRENDS

Sunset for cyclosporine?

Because the calcineurin inhibitors (cyclosporine and FK-506) have a significant potential for nephrotoxicity, new immunosuppression protocols have been designed to reduce or eliminate their use. These protocols involve newer potent immunosuppressants, such as rapamycin (sirolimus), monoclonal antibodies directed against the alpha chain of interleukin 2R (anti-CD25) (daclizumab [Zenapax] and basiliximab [Simulect]), and the polyclonal antibody thymoglobulin.[6,7] Although early studies using FTY 720 (a sphingosine-like compound that redirects T and B lymphocyte traffic so that they preferentially "home" to lymph nodes and Peyer's patches and thus are less available to infiltrate the renal allograft) were promising, cardiac toxicity has become a major obstacle.

Withdrawing glucocorticoids early

Because corticosteroids cause considerable side effects, it is desirable to minimize their use.

Withdrawing glucocorticoids is easier if done sooner rather than later. Studies are in progress to demonstrate that rapid elimination of prednisone within 1 week is safe and associated with a low risk of allograft rejection, in sharp contrast to later steroid withdrawal.[8]

Why would avoiding glucocorticoids altogether or withdrawing them sooner be safer than withdrawing them later?

Glucocorticoids have been shown to directly inhibit T-cell proliferation by suppressing production of the cytokines IL-1, IL-6, and interferon alpha. Concurrently, glucocorticoids also enhance cytokine receptor expression on activated T cells, thereby conferring a higher stimulation capacity upon reactivation. Consequently, when glucocorticoids are withdrawn, T-cell proliferation is increased.[9]

Cyclosporine may be easier to withdraw than prednisone

In a meta-analysis of immunosuppression withdrawal trials in renal transplantation, Kasiske et al[10] found that withdrawing either prednisone or cyclosporine was associated with an increased risk of acute rejection, but only prednisone withdrawal was associated with an increased risk of graft failure.

In nine prednisone studies (which included 1,461 patients), the proportion of patients with acute rejection was increased by 14% ($P < .001$) and the relative risk of graft failure after prednisone withdrawal was 1.4 ($P = .012$).

In contrast, in 10 cyclosporine withdrawal studies (with 1,049 patients), the proportion of patients with acute rejection was increased by 11% ($P < .001$), and in 12 trials (N = 1,151) the relative risk of graft failure after cyclosporine was withdrawn was only 1.06 (P = NS).

In three trials comparing cyclosporine and prednisone withdrawal (N = 259), there was a nonsignificant trend for less graft failure with cyclosporine withdrawal (relative risk 0.63, range 0.8 to 1.16, P = NS).

5-year graft survival for kidneys: From living, unrelated donors—75% From cadaver donors—62%

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'Secondary' benefits of some currently used medications may be extremely important

Experimental studies have shown that some antihypertensive and antihyperlipidemic agents may have secondary benefits in reducing the risk of progression of renal disease. These effects may ultimately be their dominant benefit and may prove to be especially valuable in renal transplant recipients.

For example, HMG-CoA reductase inhibitors (statins) have an antiproliferative effect (against epidermal growth factor) and an anti-inflammatory effect (lowering C-reactive protein).[11] In addition, angiotensin-converting enzyme inhibitors are renoprotective by decreasing TGF-beta and proteinuria, are cardioprotective by reducing mortality in acute myocardial infarction with or without congestive heart failure, and also appear to protect high-risk adults from developing type 2 diabetes mellitus.[12–14] Rapamycin has potent antiproliferative effects that have been used to prevent neointimal proliferation in coronary artery stents and is being explored for its antineoplastic effects.[15]

Coronary disease is the leading cause of death in patients with a functioning graft

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