

Report card on renal transplantation

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Technology: Renal transplantation

Use: The second half of the 20th century witnessed the rapid evolution of both dialysis and transplantation as treatment options for end-stage chronic renal failure. Comparative studies of the 2 modalities have demonstrated that renal transplantation is associated with better quality of life and prolonged patient survival.^{1,2} As a result, it has become the treatment of choice for many patients with end-stage renal failure.

History: Lowering the immunological barriers to transplantation has taken many years. In 1948, when effective anti-rejection drugs were unavailable, the first successful human kidney transplantation was performed between identical twins in order to avoid rejection. In the 1960s the use of prednisone and azathioprine to modify immunological responses allowed successful kidney transplantation between humans who were not genetically identical. Severe acute rejection remained a problem, and in the 1970s antilymphocyte preparations were developed to prevent and treat rejection. Outcomes improved in the 1980s with the introduction of cyclosporine, which further restricted T-cell activation in the recipient and substantially reduced the incidence of early graft loss because of rejection. Cyclosporine enters the cell and binds to cyclophilin, an intracellular protein, and inhibits calcineurin, a key enzyme in the T-cell activation cascade. In the late 1980s an antibody directed against the CD3 complex on T cells (anti-CD3) was the first monoclonal antibody to be licensed for clinical use and was shown to be effective in the treatment of severe acute rejection. In the early 1990s tacrolimus, mycophenolate mofetil and sirolimus were shown to reduce the rate of acute rejection.³ Tacrolimus is similar to cyclosporine in that it inhibits calcineurin, but it binds to a different intracellular protein (FK-binding protein).³ Mycophenolate mofetil decreases lymphocyte proliferation and acts selectively on lymphocytes to inhibit inosine monophosphate dehydrogenase, which is crucial in the de novo biosynthesis of guanine nucleotides.³ Sirolimus (also known as rapamycin) is an antiproliferative drug that binds to the FK-binding protein but does not inhibit calcineurin; it does prevent cycle progression by mechanisms that are as yet unknown.³ In the late 1990s humanized anti-IL-2 receptor monoclonal antibodies were developed; these antibodies bind to the α -chain of the IL-2 receptor and prevent T-cell activation after allo-antigen stimulation. These drugs not only prevent early rejection but are easier to use and have fewer side effects than the other antilymphocyte preparations.³

Problems: The 2 main problems of renal transplantation are the limited supply of donor kidneys and the failure to improve

long-term survival. In 1996 a total of 963 renal transplantations were performed in Canada. At the end of the same year 2390 patients were waiting for a kidney, and that number rises each year.⁴ This discrepancy in supply and demand is due to the low cadaveric organ donor rate in Canada (about 14 donors per million population⁵). Long-term survival has not improved despite the marked increase in the 1-year graft survival rate, which now approaches 90%.⁶ The half-life of cadaveric renal transplants (7–9 years) has not increased substantially in the last 25 years because of late graft loss owing to chronic allograft nephropathy and because of patient death with or without a functioning graft. Chronic allograft nephropathy is a progressive process that damages the transplanted kidney and is due in part to pre-existing disease in the donor and to both immunological and nonimmunological processes in the recipient.⁷ Cancer, infection and cardiovascular disease are major complications of immunosuppressive therapy and are the main causes of death after transplantation. However, renal transplantation at any age offers a survival advantage when compared with dialysis.² Transplant recipients have a projected increase in survival of 6 to 10 years compared with those who do not undergo transplantation.

Prospects: Solutions to the low organ donor rate in Canada remain elusive. The application of successful strategies such as a government-organized program (Spanish model) or required referral of all deaths in a hospital (Pennsylvania model) has not occurred. In Spain, the government-sponsored National Transplant Organization has achieved more than twice the organ donor rate of that in Canada.⁸ This success has been achieved by a well-financed infrastructure and a strong public relations program. In Pennsylvania a plan to provide financial assistance in the form of stipends to funeral homes for the funeral expenses of donors has been implemented.⁹ The impact of this initiative on organ donor rates will be closely monitored. In addition, Pennsylvania has legal statutes to compel hospitals to request referral for organ donation. Transplant programs have improved transplantation rates because of the increased use of kidneys from living donors and from older, high-risk adult cadaveric donors.¹⁰ Xenotransplantation — the transplantation of animal organs — is a potential solution to the organ donor shortage, since there would be an unlimited supply of kidneys.¹¹ However, there are still many barriers to this approach, such as the ethical implications of using animal organs in humans, the risk of disease transmission from animals to humans and the significant unresolved immunological problems.

Improving long-term renal transplant survival is a difficult

problem because the cause of progressive renal damage is poorly understood and the trials needed to test new therapies will require large numbers of patients and several years to complete. Nevertheless, trials to test the efficacy of newer drug combinations have begun. Until new evidence is available, transplant centres try to minimize the long-term toxicity of antirejection drugs by optimizing blood pressure control, normalizing lipid levels and screening for cancer and infection.

Conclusion: Renal transplantation has progressed from an experimental to a highly effective therapy. With this success comes an increased demand for donor kidneys and a severe organ shortage. Long-term improvement in survival has lagged behind the significant improvement in short-term survival. Increasing the number of donor organs and improving antirejection therapy are goals for the next century.

Competing interests: None declared.

References

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