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543

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SECOND CADAVER KIDNEY TRANSPLANTS: IMPROVED GRAFT SURVIVAL IN SECONDARY KIDNEY TRANSPLANTS USING CYCLOSPORIN A

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ABSTRACT

A total of 42 patients who had failed prior renal transplantation underwent repeat cadaveric transplantation using cyclosporin A and low dose steroid immunosuppression. Patient survival at 1 year was 100 per cent. Over-all graft survival was 83 per cent at 1 year, which was significantly better than had been obtainable previously in this high risk group. Repeat cadaver transplantation with cyclosporin A is safe and offers those who have failed previous transplantation an opportunity for existence free of dialysis.

Patients undergoing repeat renal transplantation after failure of a first kidney transplant are at high risk for graft failure. Cyclosporin A is a new, potent immunosuppressant that has been shown to be superior to conventional immunosuppression with azathioprine and predisone in early clinical trials.[1-3] From March 1981 to March 1982 all patients undergoing repeat kidney transplantation were managed with a regimen of cyclosporin A and low doses of steroids to determine if the beneficial effects of this new agent could be extended to this high risk group.

MATERIALS AND METHODS

From March 1981 to March 1982, 42 patients underwent repeat cadaver kidney transplantation. Of these patients 34 had received 1, 6 had received 2 and 2 had received 3 prior cadaver transplants, and 27 had lost the previous transplant in <12 months. HLA (A and B loci) and DR matching were random between donor and recipient, and averaged 1.3 (A and B loci). Average patient age was 33 years, with a range of 9 to 61 years. Ten patients had antibodies reactive against >70 per cent lymphocytes from a panel of 50 random donors at the time of transplantation, including 4 who had antibodies against 99 per cent of all lymphocyte panel donors on current and all historical sera. Two patients had nonconcurrent sera that killed kidney donor lymphocytes (T and B cells at 4C and 37C, respectively). Current sera for crossmatch were negative in all patients. Complete blood transfusion histories were available on 39 of the 42 patients who underwent transplantation with cyclosporin A and 16 of 22 with azathioprine immunosuppression. Of 39 patients who received cyclosporin A 37 had had ≧3 whole blood transfusions before transplantation, compared to 14 of 16 who received azathioprine.

Immune suppression consisted of 17.5 mg./kg. oral cyclosporin A 5 hours before transplantation and daily thereafter for the first 1 to 2 months. The dosage was tapered to 8 to 12 mg./kg. depending on the serum creatinine. Methylprednisolone (1 gm.) was given intravenously before transplantation. Prednisone was tapered from 200 to 20 mg. daily during the first 5 days after transplantation. Rejection was diagnosed clinically on the basis of 2 consecutive daily creatinine increases of >1 mg. per cent with no other demonstrable cause of reduced renal function, and was treated by recycle of prednisone to 200 mg. daily, tapered during 5 days to 20 mg. daily. Followup ranged from 12 to 22 months, with a mean of 14 months.

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RESULTS

Figure 1 shows the actual 1-year graft survival rates for the entire group compared to historical controls, with over-all graft survival rates of 83 per cent versus 36 per cent in the historical controls ($p = 0.005$). There have been no deaths. However, 7 kidneys were lost during followup: 6 from rejection and 1 from an arterial thrombosis. Of the 6 patients who lost the kidney because of rejection 3 had reactive antibodies against 99 per cent lymphocyte donors (preformed reactive antibodies) and the remaining 3 were complete HLA mismatches. Graft survival in recipients with a prior graft survival of >12 months was compared to that in recipients with a prior graft survival <12 months and was not significantly different (fig. 2).

DISCUSSION

Previous studies of repeat cadaver kidney transplantation have shown 1-year graft survival rates of 40 to 50 per cent.[4,5] Our 1-year graft survival for repeat cadaver kidney transplants in the 2½ years prior to this study was 36 per cent. Our patients were not randomized because of the previous poor graft failure with azathioprine and prednisone, and because of the early results of improved graft survival in patients with primary cadaveric transplants using cyclosporin A. The over-all graft survival of 83 per cent with no patient deaths is significantly better than historic controls at our institution. Patients who

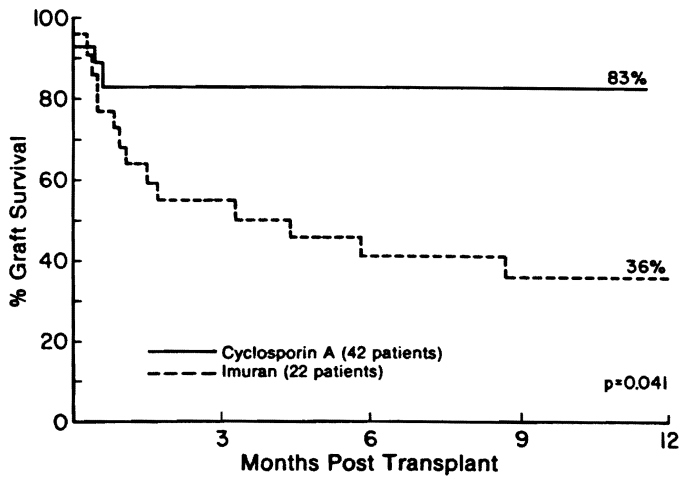

FIG. 1. Graft survival with cyclosporin versus azathioprine

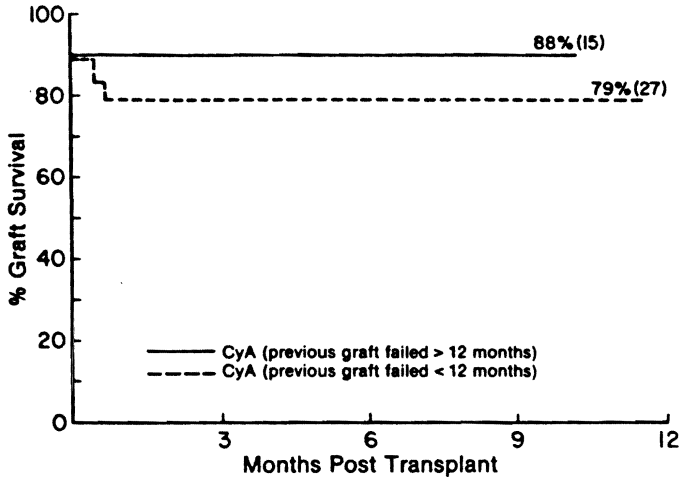

FIG. 2. Graft survival as function of time to previous graft loss

lost previous grafts quickly had a lower graft survival than those whose previous graft loss was >12 months irrespective of the cause of loss. However, if those patients who lost kidneys in <12 months who also had 99 per cent preformed reactive antibodies are excluded there is little difference in graft survival (about 90 per cent in patients who lost the previous kidney in >12 and <12 months). This finding is similar to that obtainable in patients who underwent primary cadaver transplantation with cyclosporin A.[6]

Others have demonstrated the efficacy of cyclosporin A in high risk patients.[7,8] Cyclosporin A nephrotoxicity and its management have been discussed previously.[9] Nephrotoxicity has not resulted in any recognized graft loss in our patients. High responding patients are a large part of most cadaver transplant lists with high levels of preformed antibodies, in whom it is difficult to achieve a negative lymphocyte crossmatch against donor kidneys. In the 10 patients with preformed reactive antibodies >70 per cent who received cyclosporin A and prednisone the graft survival was 5 (50 per cent), which is comparable to those who received conventional immunosuppression but less than the 90 per cent graft survival that has been observed using cyclosporin A. Humoral rejection may have been important, since 4 of the 6 patients who lost the grafts owing to rejection did so in an accelerated fashion 1 week after transplantation. Control of this form of rejection may require additional treatments, such as thoracic duct drainage or plasmapheresis, if this especially troublesome group of patients can undergo transplantation. The use of cyclosporin A and low dose steroid has improved early graft survival in patients who had failed previous renal transplants.

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EDITORIAL COMMENTS

Cyclosporin A has been shown to be more effective than azathioprine in preventing renal allograft rejection and, as indicated by the authors, first cadaver graft survival improved markedly with this agent. The authors now report a similar improvement in graft survival in repeat cadaver graft recipients. They rightly have not performed this study in a prospective randomized trial because of the marked improvement in outcome with cyclosporin A when compared to historical controls. If the few patients in their study who had high levels of preformed antibody are excluded from the calculation, then the results achieved with second cadaver grafts is almost the same as that achieved with first cadaver grafts. Cyclosporin A is without doubt an important new addition to the immunosuppression regimen of transplant recipients. The authors are to be commended for helping to define better the role of this potent new agent in renal transplantation.

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Cyclosporin A is a remarkably potent immunosuppressive drug whose advent had led deservedly to enhanced expectations in renal transplantation. Nevertheless, the most appropriate manner for its use in defined clinical settings has not yet been resolved. Although substitution of cyclosporin A for azathioprine has yielded excellent results in first renal transplants, recent studies suggest that it may be possible to achieve comparable graft survival rates with existing immunosuppressive regimens that incorporate antilymphocyte globulin.[1,2] However, in re-transplantation, even with adjunctive antilymphocyte globulin, graft survival has been extremely poor when the duration of initial graft function was <12 months (reference 4 in article). This report demonstrates that excellent results can be obtained when patients in this immunologically high risk subgroup are managed with cyclosporin A. This is an important contribution toward elucidating the most useful applications of this new agent in renal transplantation.

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