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RESULTS WITH CYCLOSPORINE IN RENAL TRANSPLANTATION IN PATIENTS WHO HAVE LOST TWO PREVIOUS ALLOGRAFTS

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We investigated the fate of the cadaver renal transplant done with cyclosporine and prednisone immunosuppression into a recipient who had suffered the loss of at least two prior allografts. Nineteen cadaver renal allografts were transplanted into 18 recipients. All 18 recipients had previously rejected at least two prior allografts. One of these rejected an allograft done at our institution with cyclosporine and prednisone and was included a second time in this series when a fourth allograft was received.

Nine of 19 allografts were successfully transplanted. Average follow-up time was 39 months. Eight allografts were rejected. One graft was lost to technical complications. In one instance, the recipient died with a functioning graft.

Duration of function of previous allografts was not found to be a critical determinant of third or fourth graft survival. Human leukocyte antigen matching was not a statistically significant determinant. Panel reactive antibody was higher in those who rejected the third or fourth allograft, but not with statistical significance. Recipients with the blood type A were less likely to enjoy successful third or fourth cadaver renal transplantation. We concluded that the "two time loser" renal allograft recipient should not be systematically denied subsequent transplantation.

THE PATIENT who suffers loss of a renal transplant to rejection is at increased risk of rejecting a subsequent cadaver kidney transplant (CKT) performed under azathioprine and prednisone immunosuppression (1, 2). Retransplantation after two failed transplant attempts has been found to have a prohibitive failure rate, and at least one center has advocated withholding a third transplant from those patients who have a history of early rejection of antecedent grafts (3). Cyclosporine, in conjunction with low dose prednisone, has been shown to have superior immunosuppressive properties (4). This combination has been used for CKT at the University of Pittsburgh since 1980 and has been found to yield superior results in patients who have required a second attempt at renal transplantation (5). To investigate the fate of the third or fourth kidney transplant, we reviewed the records of all recipients at our institution who had failed at least two previous transplantation attempts and underwent CKT with cyclosporine and prednisone immunosuppression (C+PI).

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MATERIALS AND METHODS

From February 1981 to February 1985, 16 patients, each of whom had previously suffered two graft failures, underwent CKT at the University of Pittsburgh. An additional two patients underwent CKT after each had lost three previous grafts. One of the patients included in the 16 who received a third transplant rejected the CKT and went on to receive a fourth transplant. With the exception of this patient, all of the antecedent allografts were done prior to the use of C+PI. Review of the 19 instances of CKT done in these 18 patients ensured a minimum follow-up period of one year for each CKT.

Warm T-cell cross matches between donor and recipient were negative in all instances. Human leukocyte antigen (HLA) A and B mismatching did not preclude transplantation. Immunosuppression consisted of cyclosporine and low dose prednisone, as previously described (6).

The records of these 18 patients were reviewed to determine the cause of failure for each antecedent graft. The HLA mismatches between recipients and their most recent respective allografts were reviewed. The blood type of the recipient

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TABLE I.—HUMAN LEUKOCYTE ANTIGEN, PANEL REACTIVE ANTIBODY, BLOOD TYPE AND CAUSE OF ANTECEDENT GRAFT FAILURE IN UNSUCCESSFUL TRANSPLANT GROUP

Patient No.	Previous transplants	No. of HLA (A and B) matching loci	PRA, per cent—Historical highest	PRA, per cent—Most recent	Blood type recipient/donor	Cause of antecedent graft failure—No. 1	No. 2	No. 3
1	2	0	80	56	A/A	IR	AR	
1	3	0	80	56	A/A	IR	AR	AR*
2	2	2	99	98	O/O	CR	AR	
3	2	1	17	00	A/A	CR	AR	
4	2	1	87	41	A/A	CR	AR	
5	2	0	22	00	O/O	AR	AR	
6	2	0	99	68	A/A	AR	AR	
7	2	2	84	80	A/O	TC	AR	
Average		0.8	71	50				

*Performed with cyclosporine and prednisone immunosuppression.
AR, Acute rejection; IR, intermediate rejection; CR, chronic rejection; TC, technical complications; HLA, human leukocyte antigen A and B, and PRA, panel reactive antibody.

and each respective donor was noted. In addition, the status of presensitization of each recipient, as reflected by the panel reactive antibody (PRA), was reviewed. In an effort to determine if any of the factors influenced the outcome of a third or fourth allograft, the patients who rejected the allografts were compared with those who underwent successful transplantation.

RESULTS

To date, nine of 19 allografts are functioning. The duration of graft survival time for these nine successful transplants ranges from 13 to 58 months, with an average of 39 months. Seven patients rejected a total of eight CKT. Seven of the eight CKT were rejected within one month. The remaining graft was rejected within one year of transplantation. One patient who had previously undergone three unsuccessful transplantations lost the transplant to technical complications. One patient died with a functioning CKT within one month of transplantation. The cause of death was myocardial infarction and represents the only operative mortality. These latter two patients were excluded from analysis of the recipients who lost the grafts to rejections. The total graft survival rate was 46.0 per cent and the operative mortality rate was 5.3 per cent.

In Tables I and II, the donor to recipient HLA matching loci, the PRA determinations of the recipient and the blood types of each recipient and respective donor are tabulated. The number of matched HLA (A and B) loci are out of a possible four. The highest historical PRA and most recent pretransplantation PRA of the patient are both recorded. In addition, the cause of failure for the antecedent allografts for each recipient is listed.

The designation "acute rejection" refers to those episodes of antecedent graft rejection which occurred within three months of the transplantation. The term "chronic rejection" signifies episodes of rejection which required the return of the recipient to dialysis after one year. To further differentiate duration of antecedent graft survival time, a classification of "intermediate rejection" was used to define those grafts which had been rejected between three months and one year after transplantation. In one instance, an antecedent graft was lost due to the noncompliance of the recipient with the immunosuppressive regimen. In another instance, an antecedent allograft was sacrificed to rejection by abandoning immunosuppression in order to treat a life-threatening infection. Two antecedent allografts were lost to technical complications.

In Table I, seven patients who lost the CKT done with C+PI are presented. In Table II, the patients who received successful CKT with C+PI are listed.

The successful transplants were performed with a slightly better HLA (A and B) match between recipient and donor than the unsuccessful transplants (1.7 matched loci versus 0.8). The average highest historical PRA was greater for the recipients who rejected the CKT (71 per cent) than it was for those who received successful CKT (52 per cent). The average most recent PRA was also different between the two groups (50 versus 23 per cent). These differences are not statistically different.

Six of eight CKT which were rejected were transplanted into recipients with blood type A. Only one successful recipient demonstrated this phenotype.

The nine patients who underwent successful CKT with C+PI received a total of 19 antecedent allografts. Three had been lost to chronic rejection, two to intermediate rejection, one graft to technical complications and 13 grafts were acutely rejected. The seven patients who rejected

TABLE II.—HUMAN LEUKOCYTE ANTIGEN, PANEL REACTIVE ANTIBODY, BLOOD TYPE AND CAUSE OF ANTECEDENT GRAFT FAILURE IN SUCCESSFULLY TREATED TRANSPLANT GROUP

Patient No.	Previous transplants	No. of HLA (A and B) matching loci	PRA, per cent— Historical highest	PRA, per cent— Most recent	Blood type recipient/donor	Cause of antecedent graft failure— No. 1	No. 2	No. 3
1	2	0	89	49	O/O	AR	AR	
2	2	2	16	02	B/B	CR	AR	
3	2	1	57	57	O/O	AR	AR	
4	2	3	88	85	O/O	AR	IR*	
5	3	1	00	00	A/A	AR	AR	AR
6	2	0	48	10	AB/B	AR	TC	
7	2	3	90	00	O/O	AR	AR	
8	2	2	05	00	O/O	CR	AR†	
9	2	4	74	03	O/O	CR	IR	
Average		1.7	52	23				

*Rejected secondary to noncompliance, five months post-transplant.
†Rejected secondary to withdrawal of immunosuppression during infection.
AR, Acute rejection; IR, intermediate rejection; CR, chronic rejection; TC, technical complications; HLA, human leukocyte antigen A and B, and PRA, panel reactive antibody.

the CKT done under C+PI received 15 antecedent allografts. One of these was the CKT done in Patient No. 1 under C+PI. Three allografts had been lost to chronic rejection, one to intermediate rejection, one to technical complications and ten were acutely rejected.

DISCUSSION

Lower second graft success rates have been reported in those patients who reject an antecedent first graft within three months. Those recipients who have a history of rejecting the first graft after three months have been found to have a greater likelihood of success with a subsequent CKT (7). In a single center study, it was found that the recipient who suffers chronic rejection of an allograft (defined as one year of graft function) and receives a subsequent allograft fares better than the recipient who suffers acute rejection and receives a second allograft (8).

Using conventional immunosuppression, results with transplantation in the patient who has rejected two previous kidneys have been poor. In a multicenter study, it has been reported that a mere 18 per cent one year graft survival rate can be expected if a preceding allograft was rejected within three months. In those patients who rejected the preceding allograft after one year, retransplantation was met with a 50 per cent one year graft survival rate (9). Similar observations of a single center with a smaller number of patients have led others (3) to discourage retransplantations if the recipient has a history of early rejection of antecedent grafts. Our results, using cyclosporine, do not support the distinction between chronically rejected and acutely rejected antecedent grafts. Three of 19 antecedent grafts were chronically rejected in the patients who went on to successful CKT. Similarly, three of 15 grafts were chronically rejected in the patients who went on to reject a third or fourth allograft. The incidence of acute rejection of antecedent grafts was 68 per cent in the successfully transplanted group. A similar incidence of 67 per cent acutely rejected antecedent grafts was found in the recipients who rejected a subsequent CKT under C+PI.

In the primary CKT performed under cyclosporine and prednisone immunosuppression, recent PRA levels have been shown to be a significant prognostic indicator (10). Recent PRA levels have also proved prognostically significant for secondary transplants performed with conventional immunosuppression (11, 12). In addition, the most recent pretransplant PRA level has been shown to predict outcome of the CKT that occurs after a previous failed attempt, when the secondary CKT is performed with the aid of cyclosporine (10).

In the patients who undergo a third transplant under conventional immunosuppression, population size has not been adequate to investigate statistical significance of this prognostic indication (3). Although our successful transplant population enjoyed a lower historical and recent PRA than those who failed transplantation, these differences are not significant. Determination of the significance of these differences must await accumulation of a larger patient population.

Degree of HLA matching between donor and recipient was not a statistically significant factor in determining outcome of the third or fourth allograft in this small series. It is interesting to note, however, that the three grafts which matched the HLA loci of the recipient at three or four positions were all successfully transplanted. None of the failed grafts matched the recipients at more than two loci.

One apparent difference between the recipients who received a successful CKT and those who rejected the CKT is the prevalence of the blood type A in the group who failed CKT. Eight allografts transplanted under cyclosporine and prednisone immunosuppression were rejected. Of these eight, six were transplanted into recipients with the blood type A. Nine allografts were successfully transplanted. Of these nine, only one was transplanted into a recipient with the blood type A. This may reflect dependency upon a smaller donor pool for the potential recipient with the blood type A. This smaller pool may yield allografts with a lesser chance of matching the recipient at antigens other than blood type. In no instance did an A type recipient receive a CKT with greater than 2 HLA (A and B) matching loci. While the HLA (A and B) loci themselves may not statistically influence the graft outcome, this mismatch may reflect mismatches at other significant loci.

SUMMARY

In order to investigate the fate of the CKT transplanted under cyclosporine and prednisone immunosuppression into a recipient who has suffered the loss of at least two prior allografts, we reviewed our experience with 19 such CKT into 18 recipients. One recipient rejected a CKT which was done with C+PI and went on to have a fourth allograft. Nine of 19 grafts were successfully transplanted with an average follow-up period of 39 months. Eight allografts were rejected. One graft was lost to technical complications. In one instance, the graft was functioning one month postoperatively but the recipient died of a myocardial infarction.

Unlike others, we could not identify a poorer outcome for those CKT transplanted into a recipient who had previously rapidly rejected a allograft. Although function duration of prior allograft might be a determinant of third or fourth graft survival, our data indicates that it is not a critical determinant. Since few institutions will accumulate large numbers of patients in whom two previous grafts have failed, it is premature to exclude such patients from consideration for other transplants. Optimal tissue matching, a goal which is difficult to achieve in these high PRA patients, might improve graft survival.

Although the average HLA (A and B) match for the successfully transplanted CKT was greater than that for the failed CKT, this difference was not statistically significant in our small patient population. An interesting finding of unknown significance is the poorer prognosis for the recipient with blood type A who loses two allografts. It would appear from our data that these patients are less likely to enjoy a successful third or fourth allograft under C+PI.

In conclusion, the graft survival time for patients failing two or more prior grafts is about 50 per cent with cyclosporine and steroids, significantly less than the graft survival time for patients receiving the first transplant. Nevertheless, such patients should not be systematically denied subsequent transplants.

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