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Liver Transplantation, 1980, With Particular Reference to Cyclosporin-A

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THIRTEEN years ago this month, liver replacement with extended patient survival was accomplished for the first time. That little recipient lived for more than a year before dying of metastases from the hepatoma for which she originally had been treated.[1]

RESULTS WITH CONVENTIONAL IMMUNOSUPPRESSION

The demonstration of its feasibility did not make orthotopic liver transplantation a widely used clinical procedure, and in fact, only we[2] and Calne and Williams of England[3] have persisted in large scale trials. Two years ago in Rome, we summarized our experience and that of the British group using conventional immunosuppression with azathioprine and prednisone, to which in the Colorado series we had added lymphoid depletion with antilymphocyte globulin (ALG) or, more recently, thoracic duct drainage.

Our results have been so thoroughly reported that I will dwell on them in summary only, and then mainly to emphasize how unsatisfactory they have been. By early summer of 1976, we had treated 111 consecutive patients. Thirty-one (28%) of these recipients had survived for at least a year (Fig. 1). Now, with follow-ups of 4.5–10.5 years, 13 patients are still living. The flatness of the late life survival curve has been an important stimulus to persist in these efforts, and so has the very acceptable quality of life of these chronic survivors. Chronic graft rejection has been the single most common cause of late death.[2]

A second Colorado series of 30 patients was compiled in the subsequent 18 months, ending in early 1978. Half (50%) of these patients survived for at least 1 year, and today, after 2.5 to almost 4 years, 13 (43%) are still living (Fig. 1). It was thought that improvements in surgical technique (especially biliary tract reconstruction), better diagnosis of postoperative hepatic dysfunction, and refinements in immunosuppression were responsible for the better results.

It is distressing to report that we were unable to maintain these gains in a further series of 30 patients, of whom the first 23 have been documented elsewhere.[4] Instead of using ALG, many of these last 30 patients had lymphoid depletion with thoracic duct drainage[4] or lymphaphoresis. All 30 were given azathioprine and prednisone. The projected 1-year survival is only 33% (Fig. 1). Many of the early deaths in the last series were attributable to technical or management errors, as in the past. These misadventures often were not intrinsically lethal but became so because of the need for high-dose steroid therapy.

The preoperative use of thoracic duct drainage (TDD) as a steroid-sparing device which had been shown to be valuable in cadaveric kidney transplantation[5] proved impractical for conditioning of liver recipients.[4] The amount of thoracic duct lymph drained in patients with chronic liver disease was always large and sometimes it was prodigious.

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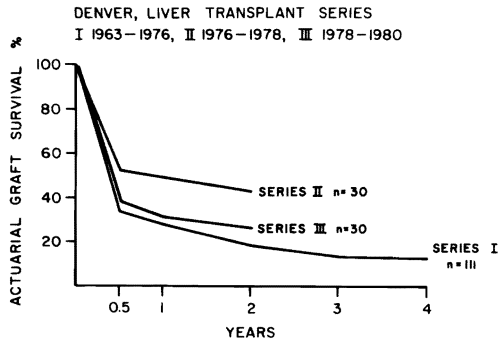

Fig. 1. Life survival curves of three successive series of patients who were given orthotopic liver homografts at the University of Colorado.

In Fig. 2 is shown a progressive increase in the volume of thoracic duct lymph, which rose to nearly a liter an hour during the 2 weeks preceding transplantation at the same time as the cell yield fell. After successful transplantation, the lymph volumes were halved (Fig. 2). This patient had a good result, but two patients died during preparation for transplantation because of our inability to manage fluid exchange of as much as 2 liters/hr.

THE JUSTIFICATION FOR CHANGE

By the end of 1979, we had concluded that no real movement of liver transplantation toward an acceptable risk was going to be possible without a drastic change in immunosuppressive techniques. Thus, when the possibility arose of using cyclosporin-A, we had no hesitation in proceeding. As everyone here knows, cyclosporin-A was the product of a Sandoz Corporation research team. The powerful immunosuppressive qualities of cyclosporin-A were accurately delineated in rodents by Borel et al.[6] Calne and his associates of Cambridge, who were the first to use cyclosporin-A in larger animals and humans, reported these trials to this Society in Rome almost 2 years ago.[7] In Calne's most recent comprehensive publication,[8] he described the administration of cyclosporin-A to two liver recipients, of whom both were then alive with follow-ups of a few weeks. By personal communication 2 weeks ago, the number of cyclosporin-A liver cases in Cambridge had increased to five. Three were still alive (longest follow-up 10 months), although one of the three had been switched to azathioprine-prednisone because of nephrotoxicity. The deaths were due to rejection in one instance and an unexplained cardiac arrest 3 weeks postoperatively in the other.

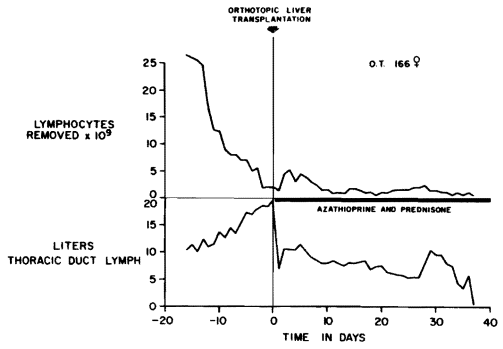

Fig. 2. Daily lymph volumes and lymphocytes obtained by TDD in an orthotopic liver recipient whose original hepatic disease was primary biliary cirrhosis.

CYCLOSPORIN-A AND RENAL TRANSPLANTATION IN COLORADO

When cyclosporin-A became available for clinical trials in the United States in late 1979, we began its evaluation in the simple kidney transplant model. From the beginning, it was obvious that unless some hidden problem surfaced, cyclosporin-A would change the face of transplantation. Between December 1979 and 1 month ago, we treated 36 recipients of 37 cadaveric kidneys with cyclosporin-A and prednisone. Eleven of the patients also had preoperative lymphoid depletion with thoracic duct drainage (10 examples) or lymphaphoresis (1 example).[9] After 1–6.5 months, 89% of the patients have been liberated from dialysis (Table 1). Two patients died with well functioning kidneys, for a mortality of 5.6%. Two kidneys were lost to rejection, and a third organ was removed because of ureteral necrosis. Even though the follow-ups are still short, the early results (Table 1) have been superior to those achieved by us in the past with any other kind of immunosuppression, particularly consider-

Table 1. Cadaveric Renal Transplantation at the University of Colorado Under Cyclosporin-A and Steroid Therapy (Eleven of the 36 Patients Also had Preoperative Lymphoid Depletion With Thoracic Duct Drainage or Lymphapheresis)

	Patients	Grafts	Deaths*	Kidneys Lost Other Than Death	Patients off Dialysis
Primary transplantation	30	30	2	1†	27 (90%)
Retransplantation	6	7	0	2‡	5 (83%)
Total	36	37	2 (5.6%)	3	32 (89%)

*One death from pneumonitis; one death from complication of coronary artery bypass.

†Loss from rejection.

‡One loss from ureteral necrosis, the other from rejection.

ing the fact that retransplantations were included in the statistics.

Thus, we reinforce Calne's optimistic projections about the future role of cyclosporin-A in transplantation. However, our views about how to best use this valuable agent[9] are divergent from those of the Cambridge team, which has warned against combining cyclosporin-A with other agents. In constrast, we have concluded that cyclosporin-A alone, even in doses of 15–20 mg/kg/day, does not consistently prevent rejection, that it should be combined with steroid therapy for optimal use, and that the proper amount of prednisone when cyclosporin-A is used is much smaller than when steroids are combined with azathioprine. Finally, cyclosporin-A has been safely combined with thoracic duct drainage.

Conceptually, we have substituted cyclosporin-A for azathioprine in what is a modern-day version of the time-honored double-drug immunosuppression introduced in 1962 and 1963.[10] Having learned that rejection usually can be expected, we now start the steroids on the day of operation and reduce the prednisone in adults by 20 or 40 mg/day until a maintenance dose of 20 mg/day is reached (usually within 5 or 6 days). The amount of prednisone needed in the first 3 months has been between one-fifth and one-tenth that which we used to give when prednisone was combined with azathioprine.

Besides learning from kidney recipients how to provide immunosuppression, this experience gave insight into the hepatotoxicity that has been seen with cyclosporin-A. We have seen significant hepatotoxicity, including jaundice in 15% of our kidney recipients, always with daily cyclosporin-A doses of about 17.5 mg/kg.[9] This information in kidney graft recipients has been important in making decisions about how to give cyclosporin-A in liver transplant recipients. The patient whose course is shown in Fig. 3 developed jaundice 4 weeks after renal transplantation, while being given 17.5 mg/kg/day of cyclosporin-A. The hepatic dysfunction promptly reversed when the cyclosporin was reduced to 7.3 mg/kg/day. At the new low dose of cyclosporin-A, the kidney graft began to reject, requiring an adjustment of steroids. After weeks of drug juggling, a good result was obtained.

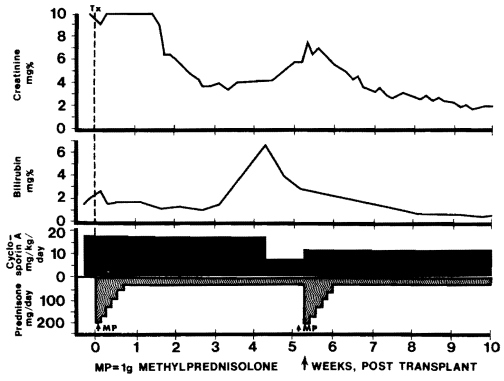

Fig. 3. The development of jaundice in the recipient of a cadaveric kidney who was being treated with cyclosporin-A. Note decline of the bilirubin after reduction of the cyclosporin-A dose, but with the penalty of renal homograft rejection. Eventually, the combination of prednisone plus an increased dose of cyclosporin-A allowed control of the rejection.

Table 2. Orthotopic Liver Transplantation at the University of Colorado Under Cyclosporin-A and Steroid Therapy

OT No.	Age (Years)	Diagnosis	Lymphoid Depletion	Date of Operation	Outcome	mg/dl Bilirubin 7/1/80	mg/kg/Day Cyclosporin-A 7/1/80	mg/Day Prednisone 7/1/80
171	29	Chronic aggressive hepatitis	2 month, TDD	3/9/80	Alive	1.2	12	20
172	24	Hepatoma	No	3/10/80	Alive	4.0	10	25
173	34	Secondary biliary cirrhosis	1.5 month Lymphapheresis	3/21/80	Alive	0.6	11	20
174	20	Budd-Chiari syndrome	No	3/25/80	Alive	0.6	8	10
175	41	Primary biliary cirrhosis	No	4/13/80	Alive	1.8	10	15
176	33	Sclerosing cholangitis	No	5/13/80	Alive	3.0	10.5	20
177	26	Chronic aggressive hepatitis	No	5/17/80	Alive	2.0	10	20
178	37	Secondary biliary cirrhosis	No	5/30/80	Operative death			
179	23	Budd-Chiari syndrome	No	6/5/80	Alive: neurologic damage	3.0	8	10

CYCLOSPORIN-A AND LIVER TRANSPLANTATION

The first liver transplantation under cyclosporin-A was not attempted until experience had been acquired with 22 cadaveric kidney graftings. Since then, nine orthotopic liver transplantations have been performed (Table 2). There was one operative death, when the abdominal incision could not be closed despite repeated attempts during a 48 hr period. Postoperative therapy with cyclosporin-A was not provided. Of the eight survivors, all are being treated with cyclosporin-A. One has serious residual neurologic injury from a cardiac arrest. The others are well, although not all have perfect liver function. The eight survivors are being treated with 8–12 mg/kg/day of cyclosporin-A plus 10–25 mg/day of prednisone.

We mentioned earlier our conclusions about the optimal way to use cyclosporin-A in kidney graft recipients. It was not surprising that these conclusions seemed to apply in liver transplantation. Five of the eight patients who survived operation were suspected of having rejection within 1–4 months postoperatively. In two cases there were increases in serum transaminases and alkaline phosphatase, but

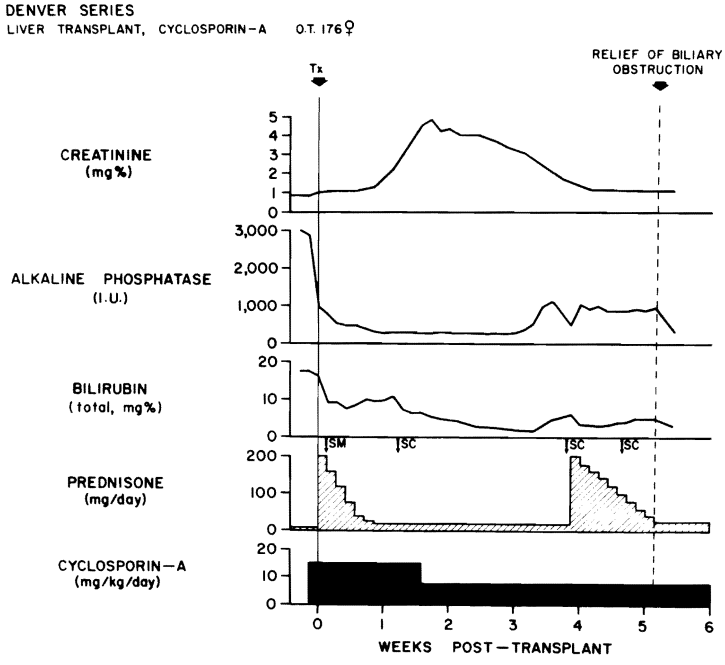

Fig. 4. The development of uremia in an orthotopic liver recipient treated with cyclosporin-A. Kidney function returned to normal after a reduction in cyclosporin-A dose. Note that prednisone was given from the beginning, but in rapidly decreasing amounts. Later (not shown), the penalty of decreasing immunosuppression was liver homograft rejection as judged by liver biopsy. An increase of the cyclosporin-A dose plus steroid therapy seemed to control the rejection, but subsequently it was found that the liver homograft was partly constructed. The cholecystojejunostomy was converted to a choledochojejunostomy, with amelioration of the low-grade jaundice.

no jaundice. Three other patients also had increases in serum bilirubin.

One to five liver biopsies were obtained in these five patients. In every case the grafts contained mononuclear cells and other findings compatible with cellular rejection. Eosinophiles were more prominent than in rejecting livers under conventional immunosuppression. The liver function abnormalities were promptly ameliorated with steroid therapy, thus reinforcing the histopathologic impression of rejection.

The high incidence of rejection in liver recipients treated with cyclosporin-A but not initially given prednisone has caused us to adopt the same policy of prophylactic steroid immunosuppression (Fig. 4) described earlier for adult renal graft recipients, namely, 200 mg prednisone on the first postoperative day, reduction by decrements of 40 mg/day until 40 mg is reached. On the next day, the maintenance dose of 20 mg is reached from which further slow reductions (or increases) are individualized (Fig. 4). The development of rejection in spite of such treatment signals a need for more steroids. We do not respond by drastically increasing doses of cyclosporin-A, since we have learned from kidney graft recipients that the hepatotoxicity range is entered with daily doses of 15–20 mg/kg. Furthermore, nephrotoxicity could be the price of such adjustments. Three of our eight liver recipients under cyclosporin-A have developed renal dysfunction, which promptly improved after a dose reduction (Fig. 4).

SUMMARY

The field of liver transplantation, which had reached a state of tantalizing but incompletely fulfilled promise, has been revitalized by experience with the new immunosuppressive drug, cyclosporin-A. For optimal value, cyclosporin-A in both kidney and liver recipients has required steroid therapy, but the amounts of prednisone have been a small fraction of those used in the past. It seems to us that the cyclosporin-A–prednisone combination should permit a new chapter to be opened in transplantation.

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