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SMALL BOWEL TRANSPLANTATION

Clinical Small Bowel or Small Bowel Plus Liver Transplantation Under FK 506

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AS AN extension of multivisceral abdominal organ transplantation,¹ a clinical trial of intestinal transplantation under FK 506 was instituted at the University Health Center of Pittsburgh in May 1990. From that time until the end of August 1991, nine patients received either an isolated small bowel graft ($n = 1$) or combined small bowel and liver grafts ($n = 8$). The results as of May 1991 in the initial five cases were reported earlier this year.² We will describe here a 2-month longer follow-up of these five recipients and brief clinical notes on an additional four liver-intestinal transplantations.

METHODS

Case Material

Three recipients were adults and 6 were children (Table 1). All of the recipients had been maintained preoperatively by total parenteral nutrition (TPN) from 6 months to 4 1/3 years preoperatively, and had experienced life-threatening TPN-related complications repeatedly. Septic episodes had been seen in all of the recipients

and eight had liver failure. Causes of the short-gut syndrome in the nine patients are listed in Table 1.

Operative Procedures

Donor Operation. Grafts were obtained from ABO-compatible cadaveric donors, of which two (cases 5 and 9) had positive cytotoxic crossmatches with the recipients. The principles of the donor operation were described elsewhere.³ Selective decontam-

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Table 1. Clinical Features of the 9 Patients

Case	Age	Sex	Cause of Short-Gut Syndrome	Duration of TPN (Months)	Remaining Intestine	Transplantation		Survival (Days)	Current Grant Function*	Comments
						Date	Graft			
1	31.1	M	Gun-shot wound	6	Transverse colon-rectum	5/2/90	Small bowel	486	Under treatment of rejection	Chronic renal failure on dialysis
2	2.3	F	Necrotizing enterocolitis	38	Transverse colon-rectum	7/24/90	Liver/small bowel	403	Good	
3	26.7	F	SMA thrombosis	30	Jejunum (20 cm) whole colon	8/3/90	Liver/small bowel	393	Good	Femoral arterial graft
4	4.3	M	Gastroschisis	52	Jejunum (10 cm) whole colon	11/24/90	Liver/small bowel	280	Good	Spinal cord injury
5	2.8	M	Intestinal atresia	33	Transverse colon-rectum	3/24/91	Liver/small bowel	159	Under treatment of rejection	Respiratory support, ICU
6	0.5	F	Intestinal atresia	6	Transverse colon-rectum	8/9/91	Liver/small bowel	22	Under TPN	In ICU
7	1	F	Volvulus	12	Transverse colon-rectum	8/10/91	Liver/small bowel	21	Under partial TPN	On floor
8	1.5	F	Volvulus	18	Jejunum (5 cm) whole colon	8/12/91	Liver/small bowel	19	Under TPN	In ICU
9	21	M	Traffic accident	12	Transverse colon-rectum	8/21/91	Liver/small bowel	10	Under TPN	In ICU

*Follow-up to 1 September 1.
ICU: intensive care unit.

ination of the donor GI tract was attempted in all cases. Irradiation or ALG administration to alter graft lymphoid tissues were not performed. The isolated intestinal graft was preserved by simple immersion in an ice bath without vascular flushing. The liver and intestine grafts were cooled first by aortic infusion of University of Wisconsin (UW) solution (0.5 to 1 L), and subsequently by portal infusion of the liver with only UW solution (1 to 2 L) on the back table. The intestinal lumen of the first three grafts was irrigated with cold-lactated Ringer's solution, while no such attempt was made with the last six grafts. The grafts were preserved from 3 to 10.5 hours.

Recipient Operations. The surgical techniques were reported previously.²⁻⁴ With liver-intestine transplantation, liver venous outflow was provided onto the intact retrohepatic inferior vena cava with the piggyback technique in seven recipients, and by the standard vena caval substitution method in one patient. Prior to the recipient hepatectomy, a portacaval shunt to decompress splanchnic venous congestion of the upper abdominal organs was performed in six cases, and retained permanently in two patients (cases 2 and 3). In the remaining six cases, the portacaval shunt was taken down after the transplantation was completed and the recipient portal vein was anastomosed to the side of graft portal vein. The intestine was vented at both ends by a chimney-type jejunostomy and ileostomy in the first five patients, but only by an ileostomy in the last four. The spleen had been removed in one patient (case 2) before transplantation; three other patients had splenectomy during the operation because of splenic injury.

Postoperative Management

Postoperative immunosuppression was with FK 506 and low-dose steroids as currently applied in our center for all organs,⁵ except for a smaller continuous IV dose of FK 506 (0.1 mg/kg per day) than originally described. When enteral feeding became possible after 2 to 4 weeks, oral FK 506 was started at 0.3 mg/kg per day in divided doses. A low dose of Imuran (1 to 2 mg/kg per day) was added in combination with FK 506 in patients 7 and 9 from the outset. Dose adjustments of FK 506 were strongly influenced by the quality of liver graft function.⁶ Histopathologic study of serial biopsies collected through the stomas or through a rectal endoscope was used to monitor intestinal graft rejection.

TPN was continued during the immediate postoperative period and gradually reduced while enteral feeding was started after 2 to 4 postoperative weeks. Selective decontamination was continued for 4 weeks while stool and blood cultures were carefully monitored.

Intestinal graft function was estimated principally by the amount and nature of stomal discharge, the ability to maintain body weight, serial serum protein analyses, D-xylose absorption results, and periodic G-I series.

RESULTS

Survival

All of the 9 recipients are currently alive. The first 5 patients have been followed for 4 to 15 months postoperatively. Two (patients 2 and 3) are at home and gaining weight without parenteral support. Two more were rehospitalized recently for the treatment of graft rejection (patient 1), and for a medical complication (patient 4). Patient 5 has been in the hospital continuously because of respiratory insufficiency and recurrent rejection. The 4 recipients operated on at 1 to 3 weeks earlier are in the hospital.

Complications

Postoperative complications in the first five recipients were renal failure (case 1), femoral artery graft pseudoaneurysm at an arterial line insertion (case 3), and paraplegia secondary to a lumbar tap (case 4) which did not confirm suspected meningitis. The fifth patient has been on ventilatory support because of paralysis of right hemidiaphragm, which apparently occurred after injury of the phrenic nerve during the upper vena anastomosis.

Rejection and Treatment

The first five recipients experienced one to five episodes of intestinal graft rejection during the follow-up. Most rejections occurred during the initial hospitalization, and were treated mainly by FK 506 dose augmentation and, less frequently, by bolus steroid therapy. The most serious and persistent graft rejections were in the isolated small bowel recipient (case 1) at .5, 5, and 14 postoperative months, and required steroid recycle treatment and OKT3 administration. The last two episodes in this patient followed drug noncompliance after discharge. Prominent graft rejection was also seen in patient 5 at the fourth postoperative month, soon after the reduction of immunosuppression for the management of a respiratory infection.

The frequency and severity of hepatic graft rejection was similar to that in simple liver graft recipients.

Graft versus host disease (GVHD) was not diagnosed in any patient.

Bacterial Translocation

Three of the first five recipients had a total of five bouts of bacterial translocation, as judged by bacteremia with the same organism found in the stool. One of these episodes only was associated with rejection.

Graft Function

The first five recipients were freed from TPN between 1.5 and 9 months after transplantation. The patient who was TPN-dependent the longest was the isolated small bowel recipient. All but this patient (case 1) gained body weight during the follow-up and had normal absorption of D-xylose. Currently, patients 2, 3, and 4 have normal intestinal function 13, 12, and 9 months after transplantation, respectively. Patients 1 and 5 were placed back on TPN support because of late intestinal rejection after long periods of oral nutrition.

DISCUSSION

Experimental transplantation of the small bowel, as an isolated graft⁷ or as a composite of multiple abdominal organs,⁸ was described in dogs more than 30 years ago. However, compared to the progress of the other organ transplants during succeeding years, clinical small bowel transplantation under conventional immunosuppression has been unsatisfactory,^{9,10} except for isolated exam-

ples.^{11,12} Our experience suggests that small bowel transplantation in humans could become more widely used. Our first four patients are either approaching or beyond the first postoperative year and three of them are healthy. The exceptional patient, an isolated small bowel recipient, had a stormy postoperative course and more vigorous graft rejection than most of the recipients of the small bowel plus liver. A simultaneously transplanted hepatic graft may protect the intestine from immunological attack as suggested from the results of animal experiments,^{13,14} and the pioneering observations of Wall et al¹² who were the first to succeed with clinical intestine-liver transplantation.

A phenomenon seen previously in rats^{14,15} and in all of our human recipients studied to date^{2,16} was lymphoreticular repopulation, whereby these cells in the graft became those of the recipient, beginning within a few days after operation. What has happened to the lymphoreticular cells leaving the graft is under study and is of considerable interest in connection with the late risk of GVHD.

It is apparent that intestinal transplantation, alone or in combination with the liver, is a complex and hazardous undertaking. The good survival figures in our FK 506 series tend to obscure the difficulties which one may expect as these trials proceed. The convalescence of all of our patients was difficult, requiring protracted hospitalization, even if the operation was done successfully and there were no major complications.

A total of 28 patients, 8 adults and 20 children, have been referred to our center during the last 15 months for small bowel ($n = 5$) or small bowel plus liver ($n = 23$) transplantation. They tended to be gravely ill when first seen, and 4 died of liver failure or sepsis while waiting. The 9 who came to transplantation had protracted further dependence on TPN before their GI tract became free from ileus and was able to support oral nutrition. Yet, it seems clear that success can be expected in more than the isolated case.

CONCLUSIONS

Nine patients with the short-gut syndrome and liver failure in eight cases were treated with isolated small bowel

transplantation ($n = 1$) or small bowel plus liver transplantation ($n = 8$) under FK 506. All are alive after 10 days to 15 months. In the first 5 recipients with the follow-up of 5 to 15 months, TPN was discontinued between 1.5 and 9 months postoperatively. Immunosuppression with FK 506 appears to have been a significant factor in the improved outlook after intestinal transplantation, as was predicted from the prior demonstration of this drug's effectiveness in rats.^{14,17-19}

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