

1355
xP

Clinical Intestinal Transplantation: Focus on Complications

A.G. Tzakis, S. Todo, J. Reyes, K. Abu-Elmagd, A. Casavilla, T. Ohya, J.J. Fung, E. Yunis, A.J. Demetris, S. Kocoshis, D.H. Van Thiel, and T.E. Starzl

NINE intestinal transplants (three adults, six children) have been performed at the University of Pittsburgh since the advent of FK 506.

Eight patients had a combined liver-intestinal transplant, one had a solitary intestinal graft. Four of these were performed 3 to 5 weeks before this report, the other five are presented with 5- to 16-month follow-ups. The clinical profiles of the patients at transplantation are presented in Table 1.

Eight patients are alive with the original grafts including the patient with the solitary intestinal graft. One patient died. The methods and techniques have been previously reported.¹⁻⁴

Briefly, the solitary intestinal transplant was arterialized from the infrarenal aorta and drained into the recipient superior mesenteric vein. In the case of the liver-intestinal combination, seven were placed piggyback⁵ onto the recipient inferior vena cava (IVC) and, in one case, the retrohepatic IVC was replaced by the respective donor

cava. Arterialization was from the infrarenal aorta with the use of fresh vascular grafts.

A portocaval shunt provided permanent drainage of the recipient portal vein (PV) in two cases. In the remaining cases, the PV of the recipient was drained into the PV of the donor. A temporary portocaval shunt during the pro-

From the Departments of Surgery, Pathology and Pediatrics, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania.

Supported by Research Grants from the Veterans Administration and Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, Maryland.

Address reprint requests to Thomas E. Starzl, MD, PhD, Department of Surgery, 3601 Fifth Avenue, University of Pittsburgh, Pittsburgh, PA 15213.

© 1992 by Appleton & Lange
0041-1345/92/\$3.00/+0

Table 1. Patient Characteristic and Outcome

Patient	Sex	Age (y)	Cause of Short Gut Syndrome	Transplantation			Hospital Stay (w)			Survival [†] (d)
				Graft	Cytotoxic Crossmatch	Current Immunosuppression*	ICU	Ward	Current TPN	
1	M	31.1	Gun shot injury of SMA	Small bowel	Negative	FK 506, steroids, azathioprine	2	40	Partial 36	498
2	F	2.3	Necrotizing enterocolitis	Small bowel-liver	Negative	FK 506	0.7	29	None 8 wk	416
3	F	26.7	Thrombosis	Small bowel-liver	Negative	FK 506, steroids, azathioprine	0.6	21	None	407
4	M	4.3	Gastrochisis	Small bowel-liver	Negative	FK 506	0.4	>36	Partial 6	296
5	M	2.8	Intestinal atresia	Small bowel-liver	Doubtful positive	FK 506, steroids	12.4 [‡]	>12	Partial	171
6	F	0.6	Intestinal atresia	Small bowel-liver	Negative	FK 506	3.1 [§]	—	—	22 [¶]
7	F	1.1	Volvulus	Small bowel-liver	Negative	FK 506, steroids	0.4	>4.6	Partial	35
8	F	1.7	Volvulus	Small bowel-liver	Negative	FK 506	3	>1.7	Partial	33
9	M	22.4	Motor vehicle accident (injury of SMA right nephrectomy)	Small bowel-liver	Strongly positive	FK 506, steroids, azathioprine	2	>1.5	Partial	24

*Patient 1 received a 7-day course of OKT3, and patients 1, 5, and 9 received steroid recycle.

[†]Follow-up to September 15, 1991.

[‡]Respirator-dependent because of paralyzed left diaphragm.

[§]Patient died of possible acute GVHD.

Table 2. Clinical Course

Patient	Technical Complications	No. of Rejection Episodes		No. of Infectious Episodes				Other Significant Complications
		Small Bowel	Liver	Bacterial	Viral	Fungal	Translocation	
1	None	6	—	0	0	1	1	Noncompliant
2	None	3	1	3	1	0	2	Refused to eat
3	Pseudoaneurysm of the femoral artery—required femoral artery graft	2	1	0	0	0	0	Pancreatitis, gastric stony + pylorospasm, pseudomembranous colitis
4	Spinal cord injury after spinal tap	1	6	3	2	0	2	Pylorospasm
5	Paralysis of the right hemidiaphragm	4	1	1	2	0	0	Prolonged assisted ventilation
6	Anastomotic bowel leak	0	0	1	0	0	0	Died of possible acute GVHD
7	None	0	0	0	0	0	0	None
8	Hemophilic required BD reconstruction	0	0	0	0	1	0	None
9	None	1	1	1	0	0	0	Pancreatitis

cedure was used in three cases, because test clamping caused unacceptable congestion.

Intestinal continuity was established at the time of the surgery in all cases but one who had a double enterostomy. Both ends of the intestinal graft were exteriorized in the first five cases and closed 8 to 16 weeks later. In the latter four cases in the series, only the distal end was exteriorized.

Immunosuppression was with FK 506 and prednisone supplementation.⁶ Azathioprine was given when sufficient FK 506 could not be administered mainly because of renal impairment.

Patient characteristics at transplantation and outcome are shown in Table 1. Three patients are living at home, two of them are totally independent of any form of intravenous (IV) therapy.

The difficulties encountered during the postoperative course are summarized in Table 2.

REJECTION

This complication presented with fever, malaise, dysmotility (ileus or diarrhea) of the graft, and malabsorption. All patients with longer follow-up (cases 1 to 5) developed at least one biopsy-confirmed episode of rejection of their intestinal graft.

Seventeen such episodes were diagnosed in total. On five occasions, pathogens from the intestinal lumen produced septicemias (translocation).

Augmented immunosuppressive therapy resulted in complete resolution of the syndrome. Rejection caused sloughing of all identifiable mucosa in two cases. Control of rejection resulted in regeneration.

Liver rejection occurred in five cases (Table 2). When liver rejection was contemporaneous to the intestine, the liver allograft responded to treatment and resumed normal

function before the intestine. Patient 4 developed five liver rejections not accompanied by intestinal rejection.

GRAFT-VERSUS-HOST DISEASE (GVHD)

Patient 6 died of GVHD. The patient had an unsuspected *Pneumocystis pneumonia* at the time of transplantation and developed an anastomotic leak at the gastrojejunostomy. Fear of fatal infection prompted reduction of the FK 506 dosage.

At approximately 1 week postoperatively, she developed cellulitis of the abdominal wall. Skin biopsies at day 11 failed to reveal GVHD. Repeated skin biopsy at postoperative day 20 showed unequivocal histological evidence of the disease. The patient went on to develop a multiorgan failure in spite of aggressive immunosuppressive treatment.

INFECTION

All patients with longer follow-ups (cases 1 to 5) developed at least one episode of infection during the postoperative course.⁷ On five occasions, the cause was thought to be translocation, because the same organisms, bacterial in 4 and fungal in 1, which were found in the lumen of the intestine, produced septicemia 1 to 2 days later.

One patient (2) developed CMV enteritis, which resolved with reduction of immunosuppression and IV DHPG treatment.

Patient 5 developed *Adenovirus enteritis* which also is thought to have resolved.

ENTERAL ALIMENTATION

Enteral alimentation was attempted within a few weeks of transplantation. All patients with long follow-ups (cases 1 to 5) have been independent of IV nutrition and gained weight on enteral alimentation for various periods of time.

Nevertheless, IV nutrition is a remote memory in only two patients, who live at home and enjoy eating. Failure to maintain enteral nutrition long term has been due to:

1. *Rejection.* Rejection resulted in dysmotility and malabsorption which necessitated interruption of the enteral feedings. Enteral nutrition could be reinstated after the rejection was controlled.
2. *Infection.* Systemic infections resulted in ileus which necessitated interruption of enteral nutrition. CMV or adenovirus enteritis had the same result. Resolution of these complications allowed resumption of enteral alimentation.
3. *Refusal to eat.* It was assumed that, given the choice, all patients would prefer to eat rather than be fed IV or enterally with feeding tubes. Contrary to this assumption, the pediatric patients in particular demonstrated a recalcitrant refusal to eat, even if this meant a well-understood inconvenience of IV line placement and insertion or maintenance of nasal feeding tubes.

The cause of this phenomenon probably lies with the unpleasant experience which the patients have had in association with food preoperatively or lack of experience with feeding.

An adult patient (3) described that, although she forced herself, she had no desire to eat whatsoever for 7 months after transplantation and did not enjoy eating until after then.

In one of our pediatric patients (2), refusal was followed by hesitation over a period of 4 to 5 months, and she has now developed normal eating patterns which she seems to enjoy.

RENAL FAILURE

Two patients (cases 1 and 9) have required hemodialysis within the first week after surgery. The first patient's renal failure was thought to be the result of a complicated postoperative course and the use of nephrotoxic agents, primarily antibiotics and FK 506. The same causes are suspected in case 9, in addition to the fact that the patient lost function of the left kidney at the time of the injury which necessitated the transplant. Patient 9 subsequently recovered from renal failure and patient 1 is awaiting kidney transplantation.

All patients developed some renal dysfunction during the postoperative course which responded to reduction of FK 506 and withdrawal of other nephrotoxic agents.

Inability to administer therapeutic doses of FK 506 because of renal dysfunction was the main cause of adjuvant treatment with azathioprine.

OTHER IATROGENIC COMPLICATIONS

This group of patients suffered an unprecedented number of iatrogenic complications, which precipitated a cascade of life-threatening or compromising events.

Patient 3 developed a pseudoaneurysm of the left femoral artery as a result of an arterial line. Repair of the pseudoaneurysm resulted in recurrence, presumably due to suture line infection which necessitated an extraanatomical bypass. There is no permanent disability.

Patient 4 developed paraplegia after a spinal tap. The spinal tap was performed 6 months after transplantation to rule out meningitis and resulted in a hematoma of the spinal cord. Emergency decompression was performed, but the prognosis for recovery is poor.

Patient 5 developed paralysis of the right hemidiaphragm presumably due to right phrenic nerve injury at the time of transplantation. He has been ICU-bound since the time of transplantation and is currently intermittently respirator dependent.

Patient 8 developed hemobilia after a percutaneous liver biopsy which necessitated bile duct reconstruction for evacuation of clots.

COSTS

The cost of transplantation of these patients has or is expected to exceed \$500,000 per case.

Considering the high cost of IV nutrition and its complications, a successful intestinal transplant should still offer a savings in the long run.

Nevertheless, the cost of these transplants has been extraordinarily high and may limit access to the procedure by the less wealthy patients.

CONCLUSIONS

Successful intestinal transplantation is now possible. Wide clinical application is tempered by the complex postoperative course.

Rejection, infection, inability to eat, and other complications seemingly unrelated to the procedure caused significant morbidity. GVHD was most likely the cause of the only mortality in our series and stemmed from a technical complication.

REFERENCES

1. Starzl TE, Todo S, Tzakis A, et al: Surg Gynecol Obstet 172:335, 1991
2. Todo S, Fung JJ, Starzl TE, et al: Ann Surg 212:295, 1990
3. Todo S, Tzakis A, Reyes J, et al: Transplant Proc (in press)
4. Tzakis AG, Todo S, Reyes J, et al: Transplantation Sci 1:27, 1991
5. Tzakis A, Todo S, Starzl TE: Ann Surg 210:649, 1989
6. Abu-Elmagd KM, Fung JJ, Alessiani M, et al: Transplant Proc (in press)
7. Reyes J, Abu-Elmagd K, Nour B: Transplant Proc (in press)