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Small Bowel Transplantation Alone or With the Liver in Children: Changes by Using FK506

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AFTER the successful results of experimental studies using cyclosporine A (CsA) in animals, we started small bowel transplantation (SBTx) in pediatric patients 10 years ago. During the period from 1987 to 1990, nine isolated SBTx have been performed in seven children aged 5 months to 9 years with short bowel syndrome. CsA was used as the main immunosuppressive agent associated with methylprednisolone and antilymphoglobulines. Two graft underwent early failure (1 death); five grafts were removed within 2 months after transplantation for uncontrolled acute graft rejection. One patient died after 6 months from sepsis and multiorgan failure. Two additional grafts were removed 6 and 17 months after transplantation for chronic rejection. Finally, only the youngest recipient having received a small bowel graft from ananencephalic neonate remains with a functioning graft 9 years later. She is enjoying normal life at home, free of TPN, growing normally. She is the longest isolated small bowel survival worldwide. Her current immunosuppression includes low doses of steroids and Neoral.[1] Of the four patients who have survived after graft removal, three died within 2 years with end-stage liver cirrhosis. The last one is currently on long-term home parenteral nutrition (PN) waiting for isolated small bowel retransplantation.

POPULATION AND METHODS

The recent introduction and proven therapeutic efficacy of FK506 (Tacrolimus) with solid organ transplantation led us to restart the program.[2] From November 1994 until October 1997, 13 children (2.5–14 years) received a jejunoileal graft either alone (n = 6) or in combination with the liver (n = 7). The first five patients required a combined small bowel–liver transplant (SBLTx) as a life-saving procedure because of hepatointestinal failure. The last four patients received a right colon graft (2 SBTx and 2 SBLTx). Indications for transplantation are summarized in Table 1 and include short bowel syndrome, intractable diarrhea from enterocyte disease, and motility disorders. All grafts were harvested from cadaveric donors (1.5 to 40 years), and were ABO identical and HLA mismatched. Donor/recipient were CMV−/CMV− (n = 7), CMV+/CMV− (n = 3), and EBV−/EBV− (n = 2), EBV+/EBV− (n = 6). Surgical procedure included the placement of 2 to 4 meters small bowel length after 2 to 10 hours cold ischemia time using UW solution. The entire liver was transplanted in all seven SBLTx cases. Proximal intestinal end of the graft was anastomosed to the native dodenum or remaining segment of jejunum. The distal end of the graft was exteriorized as stoma.

Table 1. Indications for Transplantation

	SBTx	SBLTx	Age (y)
Intractable diarrhea			
Microvillous inclusion disease	1	1	3–12
Epithelial dysplasia	1	2	2.5–12
Short bowel syndrome	2	2	2–12
Motility disorders			
Extensive	0	2	5–6
Hirschsprung disease			
Intestinal pseudo-obstruction	2	0	12–14

Immunosuppression included: (1) tacrolimus (Prograf, Fujisawa, Japan) given intravenously during the first 2 days and then orally or enterally to maintain through blood levels around 15 to 20 ng/mL during the first month, 10 to 15 ng/mL during the 5 following months, and 5 to 10 ng/mL thereafter; (2) methylprednisolone given as initial bolus, and then at the dose of 2 mg/kg/d during the first month and then tapered to 1 mg/kg/d for 2 months with a maintenance dose of 0.5 mg/kg/d to the 6th month; (3) Azathioprine (Imuran) was added to all patients at a dose of 1 to 2 mg/kg/d. Anti-infective prophylaxis included systemic antibiotics during the first postoperative week, total bowel decontamination during the first months, and acyclovir during the first 3 months. All patients were monitored for graft rejection by performing routine small bowel mucosal graft biopsies from the stoma every other day from postoperative day 6 to the end of the 3rd week, and according to clinical events thereafter. All specimen were examined histopathologically and immunohistochemically.

RESULTS

Current follow up ranges from 2 to 37 months. Three patients died: one (SBTx) immediately after transplantation

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0041-1345/98/$19.00
PII S0041-1345(98)00360-1

Table 2. Infectious Complications

	SBTx	SBLTx	Treatment
EBV-related PTLD	0	3	Decrease tacrolimus
Parvovirus B19	0	1	Immunoglobulines
Herpes encephalitis	0	1	Acyclovir
Cytomegalovirus	2	0	DHPG
Severe rotavirus diarrhea	1	3	Acetorphan
Gram negative sepsis	0	3	Antibiotics (1 death)
Candida sepsis	0	1	Amphotericin B
Catheter related sepsis	0	1	Vancomycin

from hemodynamic shock; the second case (SBTx) who was referred to us with total lack of venous access died on the 25th day from liver and renal failure with normal graft; and the third patient died after 5 weeks with gram-negative sepsis and *Candida* infection following treatment of acute intestinal rejection. Acute liver allograft rejection was diagnosed in three patients during the first 2 months, while five episodes of acute intestinal rejection were recorded during the first 3 months in five patients. All episodes of rejection were successfully treated by increasing tacrolimus dose and/or 3 days of methyprednisolone bolus. Surgical complications occurred six times after SBLTx and only once after SBTx and were as follows: two intestinal perforations, one hemorrhage, one biliary leack, one biliary stenosis, one graft volvulus, and one abdominal wall defect. The infectious complications are listed in Table 2, and were more frequent in SBLTx recipients. Three patients presented with PTLD-related EBV infection. Complete resolution of PTLD was achieved with reduction of immunosuppression (discontinuation of azathioprine and reduction of the tacrolimus daily dosage).

All patients were started with oral and/or enteral feeding from postoperative day 7 by using either normal food or protein hydrolysate diet respectively. Digestive autonomy was achieved after 5 to 30 weeks in seven patients while the three remaining are currently partially TPN-dependent (20% to 30%) because of high water-electrolyte losses from the graft. All recipients gained weight while growth velocity remains reduced during the first 6 months because of the steroid therapy.

DISCUSSION

These results, which reflect a single-center experience of two different phases, confirm the superior therapeutic index of tacrolimus for intestinal transplantation as has already been demonstrated from the data of the international transplant registry.[3] Our results show a 6-month patient and graft survival of 86% in SBLTx recipients with an overall survival rate of 77%. Combined liver and intestinal transplant is a life-saving procedure for patients with end-stage intestinal failure associated with liver disease. Hepatic failure should be avoided by using appropriate monitoring and care when liver dysfunctions appear in patients with intestinal failure who are treated with long-term TPN.[4] Isolated SBTx should be considered in patients with irreversible intestinal failure who are suffering from PN-related complications such as recurrent sepsis and/or venous thrombosis, impending liver failure, or significant psychological disorders.[5] Long-term follow-up is needed before considering isolated SBTx for patients with chronic intestinal before the development of PN-related disorders.

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