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Conversion to Prolonged-Release Tacrolimus for Pediatric Living Related Donor Liver Transplant Recipients

T. Ueno, Y. Takama, K. Masahata, S. Uehara, S. Ibuka, H. Kondou, Y. Hasegawa, and M. Fukuzawa

ABSTRACT

Prolonged-release tacrolimus allows for once-daily dosing. Although many adult recipients have been switched from standard tacrolimus, prolonged-release tacrolimus has not been popular for pediatric patients despite the potential benefits for medication compliance. We report on prolonged-release tacrolimus for 11 pediatric living related donor liver transplant (LRDLT) recipients. Patients under 18 years of age who were receiving standard tacrolimus-based immunosuppression and steroid taper underwent conversion from standard to prolonged-release tacrolimus. We monitored tacrolimus trough levels and liver function tests (LFTs). We also assessed adverse effects and satisfaction levels for prolonged-release tacrolimus. Mean age at transplantation was 4.3 years. The mean duration of follow-up was 12 months. The ratios of trough levels with prolonged-release vs standard tacrolimus were 0.97, 0.95, and 0.92 at 1, 2, and 4 weeks post conversion, respectively. Two patients discontinued prolonged-release tacrolimus owing to abnormal LFTs and neurological abnormalities, respectively; but symptoms resolved after reconversion. One patient returned to standard tacrolimus and the other was converted to cyclosporine. Once-daily administration satisfied 89% of patients. In the overall assessment, conversion to prolonged-release tacrolimus satisfied all patients. Prolonged-release tacrolimus was useful for pediatric patients after LRDLT. Trough levels after conversion were compatible with those before conversion. Most patients were satisfied with prolonged-release tacrolimus. However, some patients failed conversion because of unexpected responses. Close observation after conversion is required even if patients have previously had an uneventful course on standard tacrolimus.

PROLONGED-RELEASE tacrolimus, which is now commercially available, allows for once-daily dosing. It is widely used in adults; however, the new formulation is currently not popular for pediatric patients. Immunosuppression can be withdrawn in some pediatric patients after living related donor liver transplantation (LRDLT), but most subjects require life-long immunosuppression. Once-daily administration is potentially beneficial in terms of medication compliance for pediatric patients. Herein we have reported on prolonged-release tacrolimus in pediatric patients after LRDLT.

MATERIALS AND METHODS

Patients who were less than 18 years old at the time of conversion and who underwent LRDLT at our institution were included in this study. They had originally received the standard tacrolimus formulation with a steroid taper. Our tacrolimus taper was a target tacrolimus trough level of 10–15 ng/mL for the first month after transplantation; 5–10 ng/mL for 1 year, and 3–5 ng/mL thereafter. Steroids were administered to all patients. Patients received a bolus dose of methylprednisolone (20 mg/kg) at the time of transplantation, and were tapered off by 4 months thereafter. Prednisolone was continued for patients who had an episode of biopsy-proven acute cellular rejection or posttransplant hepatitis. Mycophenolate mofetil was administered to selected patients who experienced a steroid-resistant acute

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cellular rejection episode proven by another biopsy following steroid therapy. No patients were withdrawn from immunosuppressive therapy.

Prolonged-release tacrolimus at twice the dose of standard tacrolimus was given in the morning immediately before the switch. All subsequent prolonged-release doses were taken daily in the morning. Because once-daily prolonged-release tacrolimus was only available in capsule form, capsules were prescribed even if patients had taken the granule form of standard tacrolimus.

Blood samples to measure tacrolimus trough levels were taken just before the morning dose of prolonged-release or standard tacrolimus. Trough levels were measured 12 hours after the previous standard tacrolimus dose; prolonged-release tacrolimus levels were measured 24 hours after the previous dose. Samples were collected in the clinic at 1, 2, and 4 weeks following conversion. Whole blood samples were placed in tubes containing EDTA and stored at 4°C. Concentrations were measured within 4 hours using the Architect i2000 (Abbott Laboratories).

Serum aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGTP), and total bilirubin levels were measured concurrently with the tacrolimus trough levels. We assessed adverse effects of prolonged-release tacrolimus and levels of patient and parent satisfaction.

Data were analyzed using the JMP Ver. 8.0 software package (SAS, Cary, NC). Continuous variables presented as median values with ranges were compared using nonparametric tests or Student t test if the data were normally distributed; categorical variables, as numbers with percentages were evaluated with Pearson's χ^2 test or Fisher Exact Test. A p value less than .05 was considered to be statistically significant.

RESULTS

The characteristics of the 11 patients switched from standard to prolonged-release tacrolimus are shown in Table 1 Mean age at transplantation was 4.3 years (range, 1.1–8.2). Mean age at conversion was 11.3 years (range, 6.9–16.3). The mean duration of follow-up was 12.0 months (range, 2.4–20.4). Underlying diseases included biliary atresia (n = 9), Wilson's disease (n = 1), and ornithine transcarbamylase deficiency (n = 1). Tacrolimus trough levels are shown in Fig 1. Trough levels just before conversion did not correlate with prolonged-release values at 4 weeks thereafter (P = .21). The average ratios of standard to prolonged-release tacrolimus trough levels at 1, 2, and 4 weeks after conversion are shown in Fig 2. Mean tacrolimus trough levels after conversion decreased gradually. The trough level 4 weeks post conversion was 0.92 of standard tacrolimus, a difference that was not significant (P = .26). The outcomes of conversion are shown in Fig 3. Two patients discontinued prolonged-release tacrolimus owing to abnormal liver function tests and neurological abnormalities, respectively (Fig 4). One patient returned to standard tacrolimus and the other was switched to cyclosporine, with resolution of symptoms soon after discontinuation.

Of the 9 children who continued with prolonged-release tacrolimus, 89% of patients were satisfied with once-daily administration and the capsule formulation, although younger patients needed training on how to swallow capsules. In the overall assessment, all patients were satisfied with conversion to prolonged-release tacrolimus.

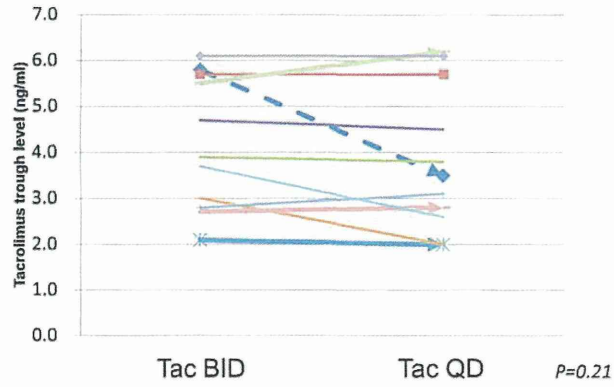

Fig 1. Prolonged-release tacrolimus trough levels 4 weeks after conversion. Each line indicates the change in the tacrolimus trough level for an individual patient. Standard tacrolimus (Tac BID) trough levels were measured just prior to conversion, and prolonged-release tacrolimus (Tac QD) trough levels were measured 4 weeks after conversion (P = .21; paired t test).

Table 1. Patient Characteristics

Patient	Gender	Age at Tx	Original Disease	Age at CV	BW (kg)	Observation (mo)	Tac BID Dose (mg)	Other IS
1	Male	4.1	Biliary Atresia	16.3	53	14.3	1.5	PSL
2	Male	1.3	Biliary Atresia	11.4	38	20.4	2.5	PSL
3	Female	1.1	Biliary Atresia	10.3	28	14.3	1.5	MMF
4	Female	8.2	Wilson's disease	15.8	49	14.3	2	None
5	Male	5.9	Biliary Atresia	13.3	45	10.1	3	PSL
6	Female	1.6	Biliary Atresia	8.3	23	3.6	0.5	PSL
7	Female	1.4	Biliary Atresia	7.6	21	2.4	0.8	PSL
8	Female	7.2	Biliary Atresia	13.2	39	2.4	2	PSL
9	Female	6.0	Biliary Atresia	8.8	26	20.0	3	PSL + MMF
10	Male	4.7	Biliary Atresia	7.7	29	18.3	1	PSL
11	Female	5.6	OTCD	6.9	20	3.1	1.2	None

Tx, transplant; CV, conversion; BW, body weight; IS, immunosuppression; PSL, prednisolone; MMF, mycophenolate mofetil; OTCD, ornithine transcarbamylase deficiency.

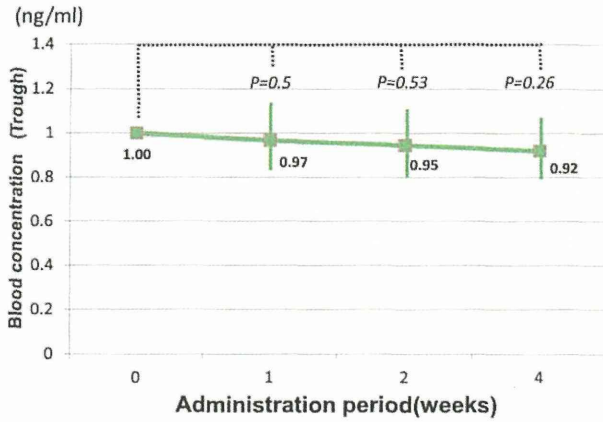

Fig 2. Mean prolonged-release tacrolimus trough levels over time. Tacrolimus trough level ratios were plotted for 1, 2, and 4 weeks postconversion. Week 0: standard tacrolimus trough level = 1. Each number corresponds to (prolonged-release tacrolimus trough level)/(standard tacrolimus trough level). Each *P* value represents a comparison with the standard tacrolimus trough level (week 0).

DISCUSSION

Prograf, an immediate-release formulation, is administered twice daily to prevent and treat allograft rejection in liver transplant patients. A prolonged-release formulation (Graceptor) has been developed to provide once-daily dosing; however, it is only available in capsule form.

Liver transplant patients are generally monitored with routine blood tests that include liver function tests (LFTs). Some patients may no longer require immunosuppression. However, pathological changes are sometimes detected even when blood test results are within the normal range.[1] Therefore, patients require life-long immunosuppression. Once-daily administration is also beneficial for drug compliance in pediatric patients who require continued immunosuppression.

This study was designed to determine the efficacy, safety, and level of patient satisfaction from a switch from the standard tacrolimus to the prolonged-release formulation. Trunečka et al studied the safety and efficacy of dual-therapy regimens of twice-daily tacrolimus and once-daily tacrolimus (Advagraf) administered with steroids among 475 adult primary liver transplant recipients who did not receive antibody induction.[2] The rate of biopsy-proven acute rejection episodes at 24 weeks was 33.7% for standard vs 36.3% for the prolonged-release tacrolimus group. At 12 months, the number of episodes requiring treatment was similar for patients on both standard and prolonged-release forms (28.1% and 24.7%, respectively). Twelve-month patient and graft survivals were 90.8% and 85.6% vs 89.2% and 85.3% for the standard vs prolonged-release tacrolimus groups, respectively. Adverse event profiles were similar. Prolonged-release tacrolimus was well tolerated with similar efficacy and safety profiles as standard tacrolimus. In our study, 2 patients experienced unexpected reactions. Close observation after conversion is required even if patients have had an uneventful course on standard tacrolimus.

Beckebaum et al reported that switching of adult liver transplant recipients from twice-daily to once-daily tacrolimus on a 1:1 mg basis was associated with lower tacrolimus trough levels in nearly two-thirds of patients (>25% lower in 28.8% of patients) at 1 week postconversion. Tacrolimus concentrations were approximately 10% lower than baseline at week 1 without any dose changes, remaining significantly lower at week 2 and prompting us to increase the dosage of tacrolimus with once-daily dosing in the corresponding patients. These observations suggested that close monitoring of tacrolimus trough levels is essential during the early postconversion period. In our study, pediatric liver transplant recipients displayed lower tacrolimus trough levels after conversion, consistent with results among adults.[3]

Satisfaction levels were excellent among both patients and their parents. In general, medication adherence tends to decrease during adolescence. So far only a capsule form is available on the market. Therefore, only patients who can take capsules can benefit from once-

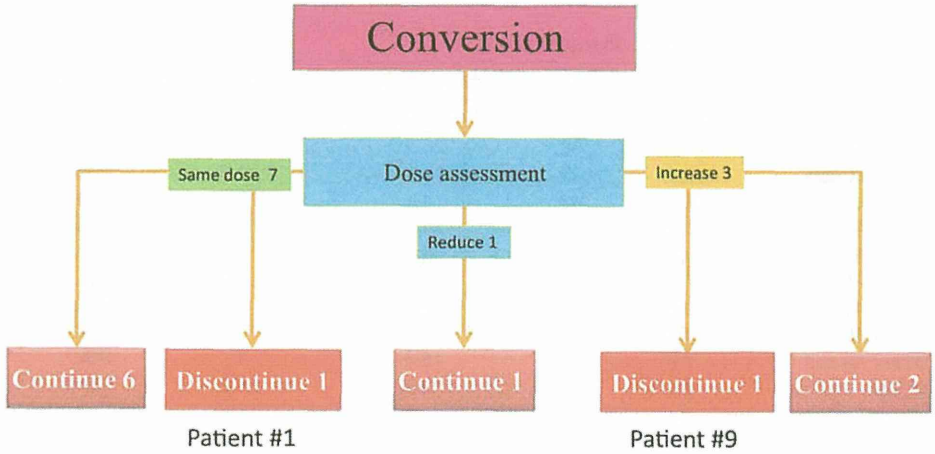

Fig 3. Summary of outcomes after conversion. The flowchart shows patient outcomes after conversion. The numbers at each step represents the number of patients. Patients 1 and 9 discontinued tacrolimus.

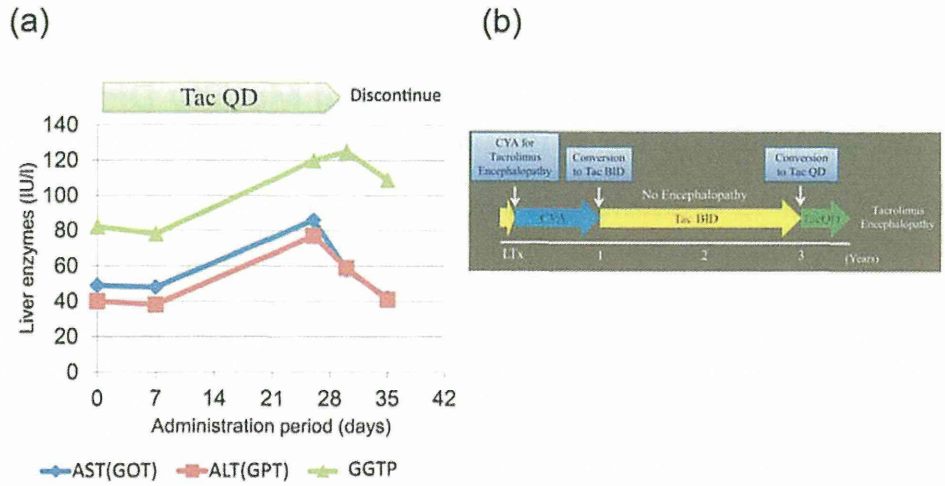

Fig 4. Clinical courses of the patients who discontinued prolonged-release tacrolimus. (a) Patient 1 had abnormal liver function tests after switching to prolonged-release tacrolimus, which normalized after prolonged-release tacrolimus was switched back to standard tacrolimus. (b) In Patient 9, tacrolimus encephalopathy recurred after conversion to prolonged-release tacrolimus, although the patient did not experience neuropathy for more than 2 years on standard tacrolimus. Tac BID: standard tacrolimus; Tac QD: prolonged-release tacrolimus; CyA: cyclosporine; AST: aspartate aminotransferase; ALT: alanine transaminase; GGTP: gammaglutamyl transpeptidase; LTx: liver transplant.

daily dosing. A granule-type formulation is awaited for once-daily tacrolimus, as is available with standard tacrolimus.

In conclusion, prolonged-release tacrolimus was useful for pediatric patients after LRDLT. Trough levels after conversion were compatible with those before conversion. Most patients were satisfied with prolonged-release tacrolimus. However, some patients failed conversion because of unexpected responses. Close observation after conversion is required even if patients have had an uneventful course on standard tacrolimus.

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A National Survey of Patients With Intestinal Motility Disorders Who Are Potential Candidates for Intestinal Transplantation in Japan

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ABSTRACT

Intestinal motility disorders are a major cause of intestinal failure. Severe cases such as idiopathic pseudo-obstruction represent life-threatening illnessed. Intestinal transplantation is a treatment for severe motility disorders with irreversible intestinal failure. However, the prevalence of severe motility disorders is unknown. We performed a national survey to identify patients with intestinal motility disorders who require an intestinal transplant. The national survey of 302 institutions treating intestinal motility disorders identified 147 patients treated from 2006 to 2011 at 46 institutions. The mean patient age was 12.1 years (range, 0.3–77.5). The mean age of onset was 3.0 years (range, 0.0–68.8). Diagnoses included chronic idiopathic intestinal pseudo-obstruction (n = 96), Hirschsprung disease (n = 29), megacystis microcolon intestinal hypoperistalsis syndrome (n = 18), and other (n = 6). There were 126 survivors and 21 patients who died during the last 5 years. The mortality rate was 14.3%. Eighty-five percent of patients required parenteral nutrition for more than 6 months, which was defined as irreversible intestinal failure. Among surviving patients with irreversible intestinal failure, 8 (9.4 %) developed hepatic failure with jaundice and 27 (31.8%) 2 or more central vein thromboses. In all, at least 35 patients (41%) with irreversible failure due to intestinal motility disorders may be candidates for transplantation. The prevalence of severe intestinal motility disorders was elucidated in Japan. Severe cases should be referred to transplant centers.

INTESTINAL MOTILITY DISORDERS are a major cause of intestinal failure. Severe cases such as idiopathic pseudo-obstruction are life-threatening. Causes of intestinal motility disorders seem to be multifactorial, and only a few have been elucidated. The prognosis is poor for patients with severe illness. The outcome for intestinal failure has improved dramatically due to the development of parenteral nutrition (PN). However PN-related complications, such as central venous catheter infection, thrombosis of venous access points, and PN-associated cholestasis of the liver, are still major problems for patients with intestinal failure. Intestinal transplantation is a treatment for irreversible intestinal failure due to severe disorders of intestinal motility that can significantly improve the prognosis and quality of life for patients. Progress in intestinal transplantation has improved survival. However, the prevalence of severe intestinal motility disorder is unknown. The Therapeutic Guidelines for Intestinal Failure Study Group performed a national survey to identify patients with intestinal motility disorders requiring an intestinal transplant.

METHODS

This national survey was designed as a 5-year retrospective observation study involving 302 institutions that treat intestinal motility disorders. These institutions were members of the Japanese Society of Pediatric Surgeons, the Japanese Society for Small Bowel Transplantation, and the Japanese Study Group for Home Parenteral and Enteral Nutrition. After an initial survey, a questionnaire about each patient was sent to responding institutions from the data center based at Osaka University. Patients with intestinal

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failure treated at each institution from 2006 to 2011 were included. Exclusion criteria were: (1) final diagnosis other than intestinal failure, (2) intestinal failure ultimately resolved, (3) intestinal failure resulting from malignancy, and (4) intestinal failure secondary to diseases in other organs. There were 354 patients reported by 69 institutions. Irreversible intestinal failure was defined as dependence on PN for more than 6 months. Out of these 354 patients, patients with intestinal failure due to motility disorders were identified. The following factors were assessed for possible associations with indications for intestinal transplantation: diagnosis, patient age, age of onset, sex, patient outcome, PN status, liver function tests (LFTs), and central line access. This study was approved by the Osaka University Hospital institutional review board and was supported by Health Science Research Grants from the Ministry of Health, Labor and Welfare of Japan.

RESULTS

There were 147 patients with intestinal motility disorders identified from 46 institutions. The prevalence was approximately one in one million. There were 55 male and 92 female patients. The female-to-male ratio was about 2:1. The mean patient age was 12.1 years (range, 0.3–77.5 years). The mean age of onset was 3.0 years (range, 0.0–68.8 years). Causes of intestinal failure are shown in Fig 1. During the observation period, 126 patients survived and 21 patients died. The mortality rate was 14.3%.

Detailed analysis was added for survivors to determine indications for intestinal transplantation. Of the surviving patients, 91 (62.0%) needed PN at least once a week, and 85 (57.8%) required PN for more than 6 months. Those 85 patients were defined as having irreversible intestinal failure. The following analyses were carried out for patients with irreversible intestinal failure. Catheter-related complications were assessed. The site of central vascular access (internal jugular vein, subclavian vein, and femoral vein) was reported. The number of venous access failures is shown in Fig 2. Twenty-seven patients (31.9%) had 2 or more instances of central vascular access loss.

There were 61 patients (71.8%) who developed abnormal LFTs suggestive of liver injury from PN, including 8 patients (13%) with jaundice. They were considered to have severe liver injury resulting from PN.

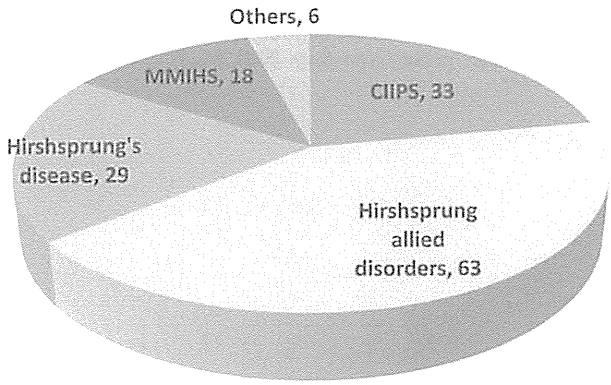

Fig 1. Causes of intestinal failure (n = 147). CIIPS, chronic idiopathic intestinal pseudo-obstruction; MMIHS: megacystis microcolon intestinal hypoperistalsis syndrome.

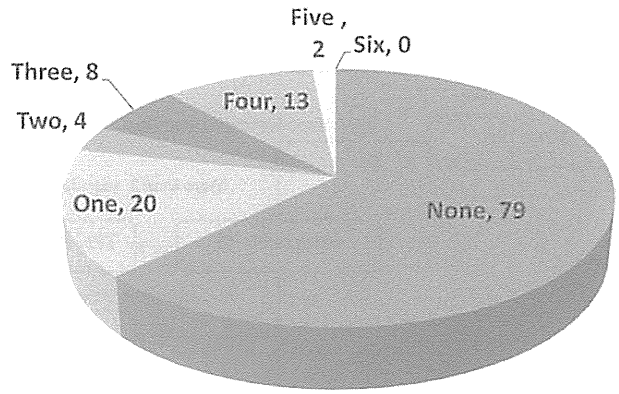

Fig 2. Number of central vascular access losses (n = 126). The number on the left indicates the number of vascular access losses.

Fifty-eight patients required at least 1 hospitalization in the previous year. Nineteen patients (22.4%) required hospitalization for more than 6 months over the previous year. Their quality of life was severely impaired.

A flowchart for identifying possible candidates for intestinal transplantation is shown in Fig 3. Patients dependent on PN for more than 6 months were defined as having irreversible intestinal failure. Those with more than 2 central vascular access losses, and abnormal LFTs with jaundice were considered for candidates for intestinal transplantation. Patients who died from liver failure or infection might be saved by intestinal transplant. They might be candidates for intestinal transplant too. In total, 45 patients were potential candidates for intestinal transplantation. Additionally, the 19 patients who were hospitalized for more than 6 months can be potential candidates given their poor quality of life.

DISCUSSION

Intestinal motility disorders include a wide range of diseases. Chronic intestinal pseudo-obstruction, the most common type of intestinal mobility disorder, is caused by ineffective intestinal contraction. It is characterized by symptoms and signs of intestinal obstruction.[1] Intestinal transplantation can significantly improve the prognosis and quality of life of patients with intestinal motility disorders in Japan.[1] Survival rates in Japan are comparable with rates from the international intestinal transplant registry.[2]

Previously, the prevalence of intestinal motility disorders in Japan was unknown. It was estimated that there were 100 severe cases nationwide. This study supports this figure because surveillance was of a large enough scale to cover the entire nation.

There were over 40 patients who may need intestinal transplantation. However, only 3–4 a year intestinal transplants are performed in Japan, even if 10 times as many patients may be cured by intestinal transplantation.

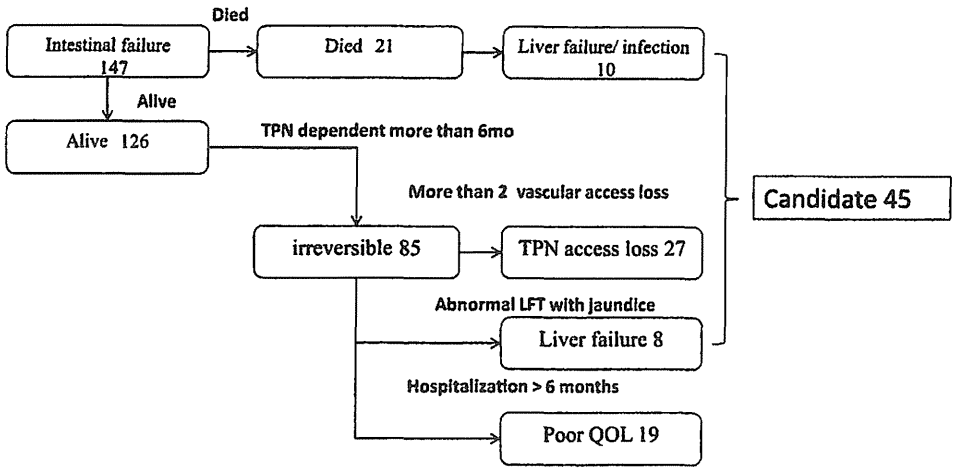

Fig 3. Candidates for intestinal transplantation. TPN, total parental nutrition; QoL, quality of life.

There were 2 major reasons for the relative paucity of intestinal transplants in Japan. One reason is the lack of available organs. For a long time, very few organs from deceased donors were obtainable in Japan. As with other solid organs, most intestinal transplants in Japan are performed with living donors. The shortage of organs has been alleviated due to a new act on organ transplantation that went into effect in 2010. However, the number of intestinal transplant has remained steady.

The financial barrier is the other, more profound reason preventing greater use of intestinal transplantation in Japan. Since the procedure is not covered by health insurance, either the patient or the transplant institution must pay the considerable costs out of pocket.

Some patients develop liver failure with intestinal motility disorders. These patients need simultaneous liver-intestine transplants. A combined liver-intestine transplant has less risk of acute rejection than an isolated intestinal transplant because the liver may have protective effects on the intestine. Current organ allocation guidelines do not allow for simultaneous combined liver-intestine organ retrieval; thus, a simultaneous liver-intestine transplant is impossible from deceased donor sources.

Previously, the laws on organ transplantation banned donors below 15 years of age. Intestinal transplants were not previously possible in infants because of organ size mismatch. Such patients will benefit from intestinal transplants in the future. Moreover, younger patients sometimes develop liver failure.[3] Multiorgan transplantation is a good option for such patients.[4]

It is difficult to determine the optimal timing for intestinal transplants to treat intestinal failure associated with intestinal motility disorders. Severe cases of intestinal motility disorders should be referred to institutions with expertise in transplantation.

In conclusion, the prevalence of severe motility disorders in Japan was elucidated. Patients with irreversible intestinal failure from intestinal motility disorders may be candidates for intestinal transplantation. Severe cases of motility disorder should be referred to transplant centers. Further investigation for patient details is required.

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Histology of Intestinal Allografts

Lymphocyte Apoptosis and Phagocytosis of Lymphocytic Apoptotic Bodies Are Diagnostic Findings of Acute Rejection in Addition to Crypt Apoptosis

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Abstract: Acute rejection of a small-bowel transplant is often difficult to diagnose due to complicated immune responses. The present study aimed to elucidate the specific immune responses involved in intestinal transplant rejection. We correlated immunohistologic findings with an increase in crypt apoptosis, which has been commonly accepted as a criterion for the diagnosis of acute cellular rejection (ACR). Of 8 patients who received an intestinal allograft at Kyoto University Hospital, biopsy specimens from 7 patients were assessed immunohistologically with antibodies against 20 types of lymphocytic antigens including CD3, CD4, CD8, CD79a, CD20, IgG, and T-cell receptor, along with assessment of the patients' clinical courses. It was revealed that, in addition to apoptotic crypts, T-lymphocyte apoptosis and phagocytosis of apoptotic bodies in the lamina propria of villi were findings of ACR; both were observed in all cases. Immunostaining of the Fas ligand, one of the apoptosis-inducing molecules, was useful for the identification of the apoptotic bodies in the lamina propria of villi. Apoptotic body phagocytosis may be a surrogate diagnostic finding of grafts undergoing ACR.

Key Words: intestinal transplantation, apoptosis, Fas ligand, lymphocyte, phagocytosis, acute cellular rejection

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BACKGROUND

Intestinal transplantation is a commonly accepted standard therapy for patients with irreversible parenteral nutrition complications associated with short-bowel syndrome,[1–8] Hirschsprung disease, and related diseases such as chronic idiopathic intestinal pseudo-obstruction syndrome or megacystis-microcolon-intestinal hypoperistalsis syndrome.[9,10] One-year patient survival rate after transplantation has improved, and more than half of the children who survive a transplant can now be weaned off parenteral nutrition.[1–8] However, acute cellular rejection (ACR), which may be detected by histopathologic methods, remains the major cause of intestinal graft failure after transplantation. Histopathologic diagnosis is useful in the detection of ACR.[11–15] In fact, for most patients who experience severe acute rejection, sufficient recovery of mucosal absorption function remains difficult, and bacterial infection is inevitable.[6] Therefore, the diagnosis and treatment of acute rejection in the early phase are critical for postoperative care.

The major histologic finding of acute rejection is a mixed cellular inflammation infiltrate including activated large lymphocytes and crypt apoptosis.[12,15] In the current study, we applied a grading system of acute rejection according to criteria defined at an international meeting.[12] Crypt apoptosis involves epithelial stem cell injury, and its development inhibits sufficient recovery of mucosa. The level of mucosal damage caused by ulceration due to apoptosis is therefore critical in terms of transplant success. The aim of this study was to precisely evaluate immune responses in an intestinal allograft before the appearance of crypt apoptosis in order to prevent the development of rejection.

MATERIALS AND METHODS

Case Selection

In the 15 years between May 1997 and February 2012, 8 patients underwent orthotopic intestinal transplantation at

TABLE 1. Clinical Profiles of Patients and Donors

Patient	Patient: Age (y)/Sex	Donor: Age (y)/Sex	ACR (POD)	Steroid Pulse	Immunosuppressants	Etiology	Induction
1	2/M	20-30/F	12	+	Tacro/azatio/steroid	SB	
2	0/F	20-30/F	12	+	Tacro/cyclo/steroid	SB	OKT3
			18	+			
			20	+			
			25	+			
3	4/M	20-30/F	66	+	Tacro/steroid	SB	
4	4/F	20-30/F	22	+	Tacro/steroid	SB	
5	12/F	20-30/F	27	+	Tacro/steroid	CIIP	Daclizumab
6	19/M	40-50/M	12	+	Tacro/cyclo/steroid	SB	Daclizumab
7	10/F	30-40/M	11	+	Tacro/cyclo/steroid	CIIP	Basiliximab
			19	+	Thymoglobulin		

Etiology: status of native intestine of the patient.
Steroid pulse: 10 to 20 mg/kg/d.
CIIP indicates chronic idiopathic intestinal pseudo-obstruction syndrome; F, female; M, male; SB, short-bowel syndrome.

Kyoto University Hospital. All of the protocols of this study were approved by the Committee of Medical Ethics of the Graduate School of Medicine, Kyoto University, and the study was performed with the informed consent of the patients' parents.

The patients commonly received immunosuppressant therapy consisting of tacrolimus for suppression of immune responses to the allograft. In brief, intravenous tacrolimus (baseline, 5 to 15 ng/mL) and methylprednisolone were commonly used as maintenance therapy for immunosuppression in patients 2 to 7.[16] Mycophenolate mofetil was transiently administrated for treatment of ACR in patients 5 to 7 after the present histologic examination.

To evaluate the degree of rejection and the effect of immunosuppressive therapy, daily endoscopic examinations were performed for the first 2 months. Specifically, endoscopic examination, including biopsy, was performed every day or every other day from posttransplantation operative day (POD) 7 to 20 (Table 1). From POD 21 to 50, biopsy examination was performed once or twice a week, and endoscopic examination was performed when patients complained of fever (> 37°C) and had an increased peripheral blood C-reactive protein level of > 1.0 mg/0.1 L. Frozen sections were prepared for immunohistochemical analysis, and hematoxylin and eosin (H&E)-stained sections of formaldehyde-fixed paraffin-embedded specimens were prepared from residual frozen samples. We examined the immunohistology of frozen biopsied specimens in addition to the H&E-stained paraffin-embedded specimens and investigated the early histologic features of ACR to determine the appearance of ACR before the development of crypt apoptosis. When ACR was diagnosed pathologically, the patients received steroid pulse therapy (15 to 20 mg/kg/d). The profiles of the patients and donors are shown in Table 1.

Immunohistochemistry

A total of 282 frozen biopsy specimens were taken from intact and damaged mucosa and used for histologic diagnosis. The immunohistochemistry protocol was previously reported.[17]

The following antibodies, obtained from the indicated sources, were used for immunostaining: anti-CD3 (Dako, Glostrup, Denmark); anti-CD4 (Dako); anti-CD8 (Dako); anti-CD20 (Dako); anti-CD79a (Dako); antileukocyte common antigen (Dako); anti-CD45RO (Dako); anti-Ki67 (Dako); anti-p53 (Dako); anti-PCNA (Dako); anti-cyclin D1(Dako); anti-Fas (Dako); anti-FasL (Nichirei, Tokyo, Japan); anti-IgG and anti-IgM, used to determine nonspecific binding (Dako); anti-C4d; and anti-T-cell receptor αβ chain (Immunotech Inc., Marseille, France). All antibodies were diluted to 1:100. 3,3'-Diaminobenzidine or phycoerythrin-labeled streptavidin and fluorescein isothiocyanate-labeled/phycoerythrin-labeled streptavidin (Vector Labs, Burlingame, CA) staining was used for visualization of the immunohistochemical signal. Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end-labeling (TUNEL) staining of apoptosis was performed using an in situ apoptosis detection kit (Takara, Otsu, Japan).

Diagnosis of ACR

The histology of the intestinal graft was diagnosed according to previously reported criteria.[11,12,15] To identify ACR, the following histologic criteria were used: inflammatory infiltrate, increased crypt epithelial apoptosis (usually with >6 apoptotic bodies/10 crypts), architectural distortion of villi, and mucosal ulceration changes. To accurately detect apoptotic bodies, TUNEL staining of the graft specimens was additionally performed.

Statistical Analysis

Interindividual differences in the responses to high-dose steroid therapy (> 15 mg/kg/d) were assessed using the Student *t* test (SPSS 10.0.5 from SPSS Inc., Chicago, IL), as this test provides the most conservative estimates. All *P* values were 2-sided and were considered to be statistically significant if <0.01. *P* values were not adjusted for multiple testing.

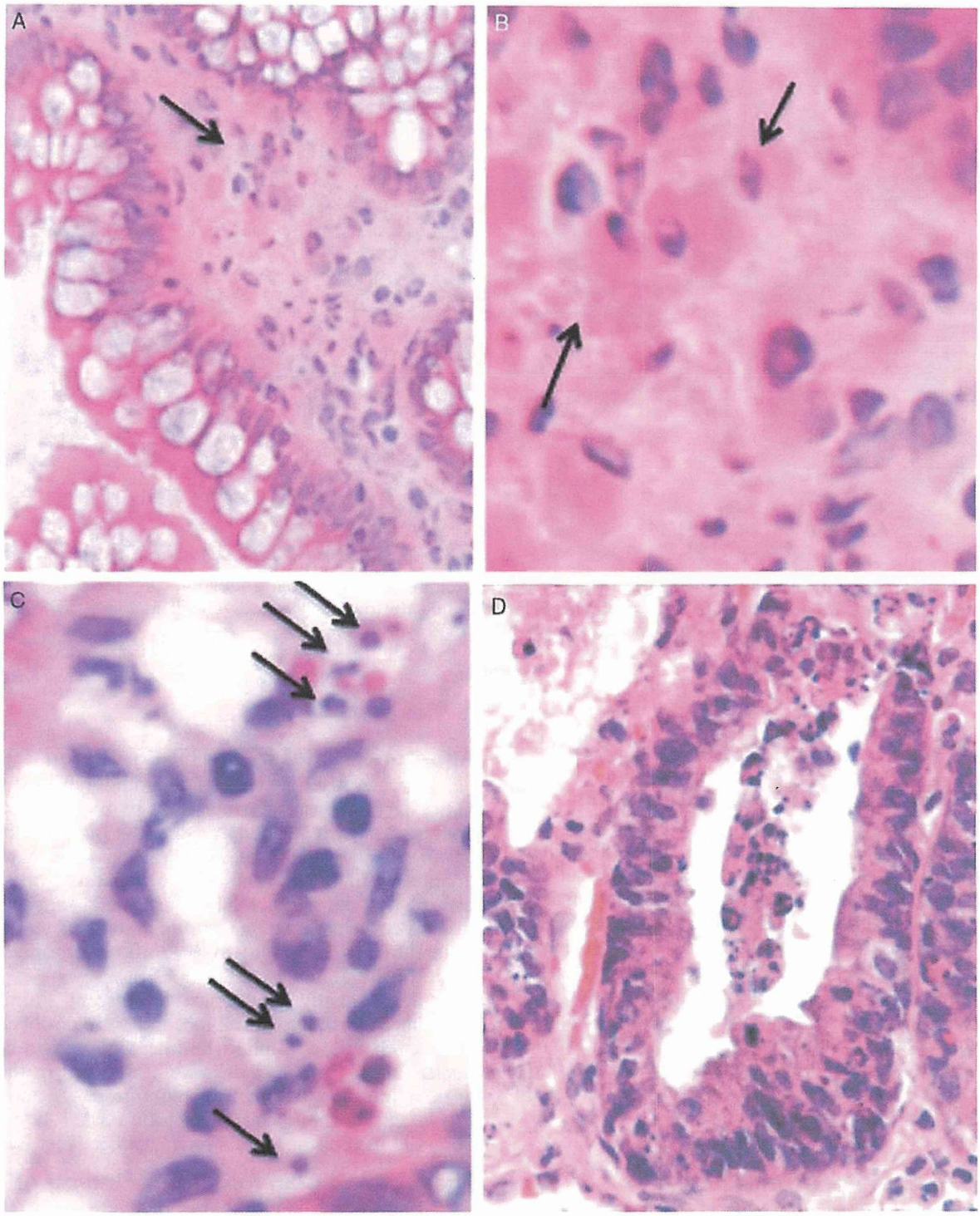

FIGURE 1. Collection of macrophages and apoptotic bodies in the LP of villi. H&E and immunohistochemical staining of biopsy specimens of intestinal transplants at POD 9 to 13 were analyzed. A–B, Collection of macrophages (indicated by arrows in A and B with apoptotic bodies in the LP. A, B, patient 7. C, Apoptotic bodies in the LP are indicated by arrows. Six apoptotic bodies were observed. D, Crypt apoptosis that appeared 2 days after the collections of LP macrophages containing apoptotic bodies appeared in patient 5.

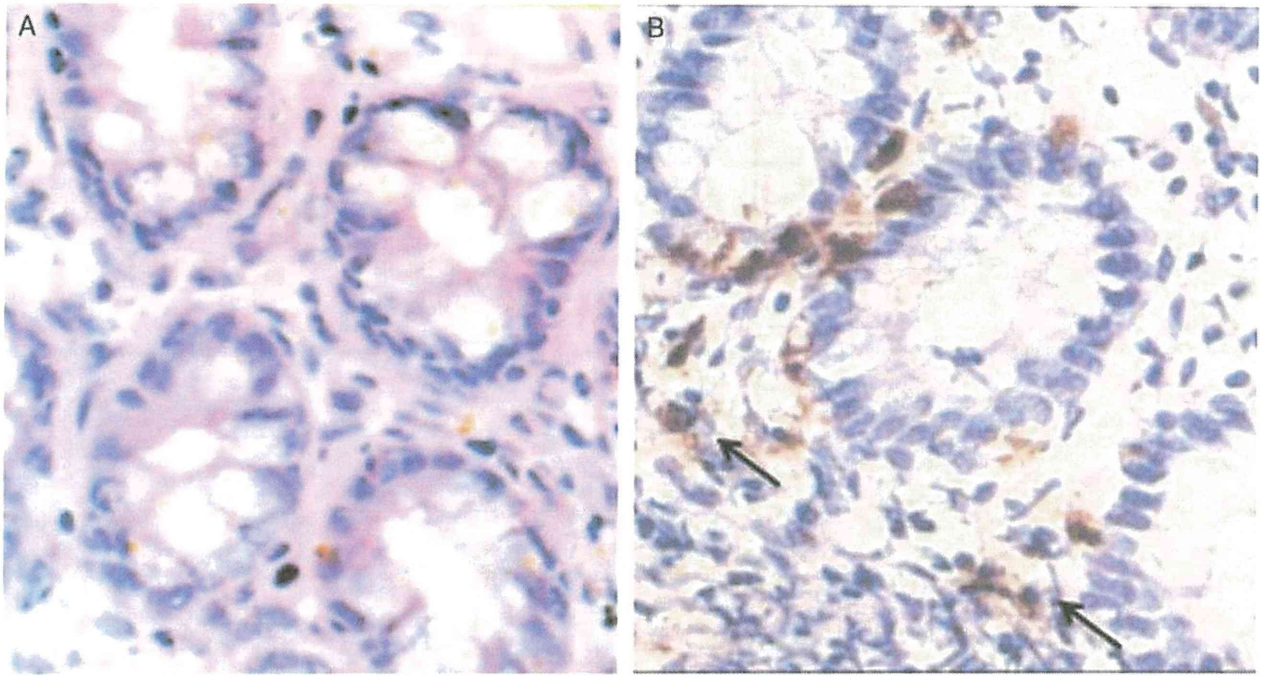

FIGURE 2. TUNEL staining of apoptotic bodies in the LP. TUNEL staining of the normal donor intestine for patient 2 (A) and transplanted intestine with ACR on POD 12 are shown. B, Arrows indicate the TUNEL-positive cells in the LP. The signal was visualized with 3,3′-diaminobenzidine. Counter staining was performed with H&E.

RESULTS

Apoptotic Bodies and Phagocytosis in the Lamina Propria of Villi

The transplanted intestines were assessed through H&E staining and immunohistochemical analysis of sections. We commonly observed apoptotic bodies when crypt apoptosis was present in the lamina propria (LP) of villi (Figs. 1A–C). These apoptotic bodies were localized around capillary veins and were frequently eosinophilic. In addition, the macrophages were weakly eosinophilic and their collections in the LP of villi contained the apoptotic bodies. The macrophage collections and apoptosis in the LP (LP apoptosis) was followed by the appearance of >6 crypt apoptoses per 10 crypts, which is diagnostic of ACR, in all 7 of the allografts studied (Fig. 1D).

Identification of Apoptotic Bodies

To confirm LP apoptosis, we stained the apoptotic bodies using the TUNEL method. The normal intestine, that is intestinal grafts before transplantation, was weakly stained at the crypt (range, 0.1 to 1.3 per 10 crypts; median, 0.4 per 10 crypts; $n = 7$) (Fig. 2A). In contrast, apoptotic crypts in the grafts undergoing ACR were intensely stained (range, 6.2 to 8.5 per 10 crypts; median, 6.3 per 10 crypts; $n = 7$) and apoptotic bodies in macrophages in the LP were additionally stained (Fig. 2B).

Apoptotic Bodies in the LP Contained T Cells

To identify the types of cells undergoing apoptosis in the LP of the graft during ACR, immunohistochemical analysis using an antibody against the Fas ligand (FasL), an apoptosis-related molecule, was carried out to detect apoptosis. In the normal control, that is grafts before transplantation, intact cells showed FasL signals (Fig. 3A); in contrast, apoptotic signals were positively stained by FasL antibody in the graft undergoing ACR in addition to the intact cells (Fig. 3B).

Subsequently, multicolor fluorescent staining was performed. FasL and T-cell receptor were doubly stained, and 4′,6-diamidino-2-phenylindole was used to stain the nuclei. Intact FasL+ T cells were observed in the donor normal intestine before transplantation. In addition to this intact FasL+ T cells, apoptotic FasL+ T cells were observed in the transplants during ACR (Fig. 3C, D).

Phagocytosis is an Additional Finding of ACR

In addition, macrophages phagocytosing the apoptotic FasL+ cells were frequently observed in the LP (Fig. 4A). Immunohistochemical analysis of a serial section of the same tissue using an anti-CD68 antibody also showed that $CD68^+$ macrophages phagocytosed FasL+ apoptotic bodies in the LP of villi in allografts ongoing ACR (Fig. 4B). Thus, FasL staining is useful for the identification of apoptotic bodies in allografts and TUNEL staining (Table 2).

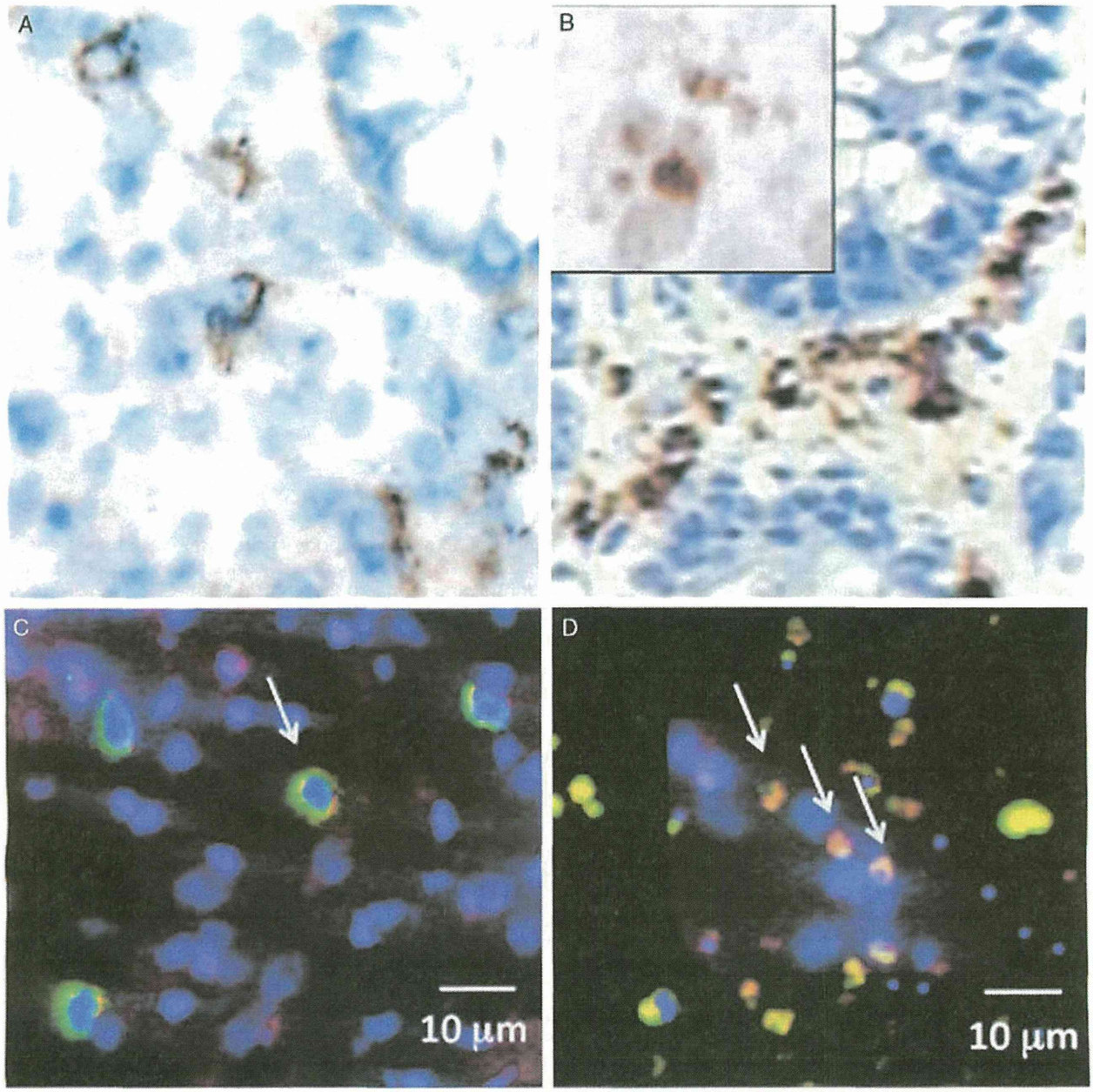

FIGURE 3. Apoptotic bodies containing T cells. (A, B) FasL immunostaining of donor intestine (A) and transplant tissues in ACR (B). The inset in (B) shows a high-power magnification of an apoptotic body aggregation. The FasL signal in apoptotic clusters was visualized with 3,3′-diaminobenzidine around the crypt. Counter staining was performed with hematoxylin. C and D, Co-staining of apoptotic clusters by fluorescent immunostaining of FasL and T-cell receptor. Phycoerythrin-streptavidin-stained FasL (red) and fluorescein isothiocyanate-streptavidin (green) (T-cell-receptor staining) can be seen. Nuclei were visualized using 4′,6-diamidino-2-phenylindole. C Triply stained intact FasL+ T cells in the donor intestine before transplantation (patient 7). The arrow indicates intact FasL+ T cells. D, Triply stained FasL+ apoptotic T cells in the donor intestine before transplantation (patient 7). Arrows in (D) indicate the apoptotic fragments. Scale bars are shown.

LP Apoptosis may be a Surrogate Finding of Crypt Apoptosis

On the basis of this staining, we semiquantitatively scored the apoptosis in the LP (score 0, no signals; score 1, scant and isolated signals; score 2, a few signal aggregations; score 3, signal aggregates surrounding the crypt). A total of 150 specimens did not contain the sufficient number of crypt (> 10) architecture for the diagnosis of ACR, and the LP apoptosis score closely correlated with the crypt apoptosis count in the remaining 132 sections ($R^2 = 0.87$, $P < 0.001$), indicating that LP apoptosis can be a surrogate finding of crypt apoptosis (Fig. 5).

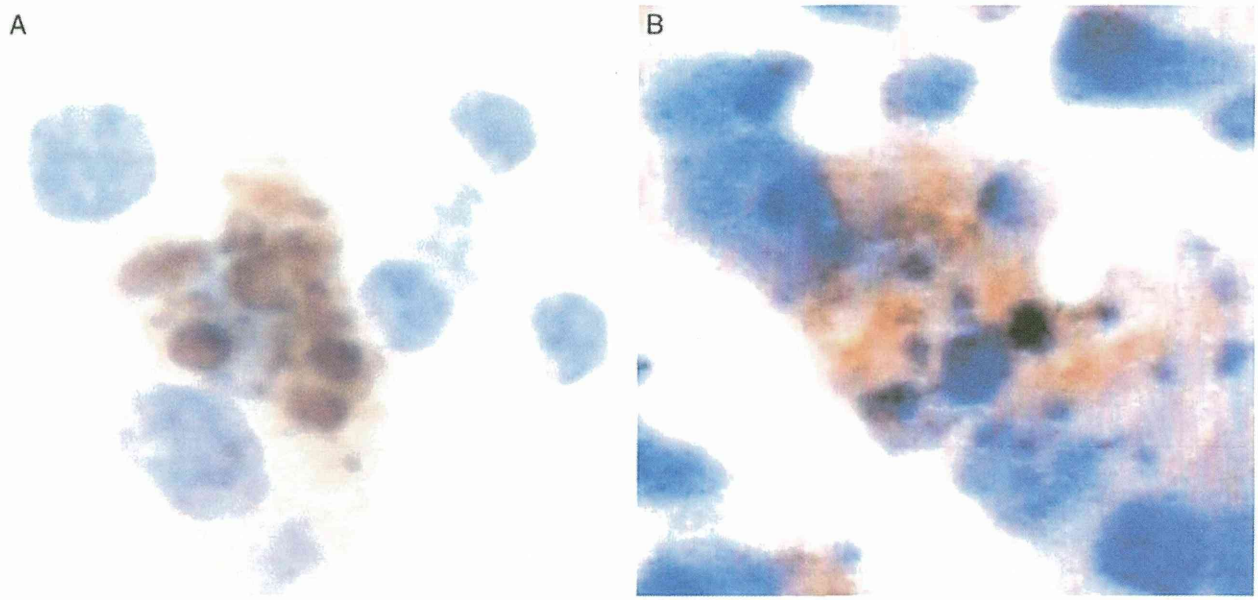

FIGURE 4. Phagocytosis of apoptotic bodies. A, FasL immunostaining of an apoptotic body cluster that was phagocytosed by a macrophage. The FasL signal was visualized with 3,3′-diaminobenzidine. Brown-stained FasL-containing apoptotic bodies surrounding the nucleus of the phagocytosing macrophage. B, Immunostaining of macrophages using anti-CD68, and visualization of the signal with 3,3′-diaminobenzidine. An apoptotic body cluster that was phagocytosed by a macrophage (brown stain) can be seen.

DISCUSSION

The present study includes only 7 transplants, but histologic assessment was performed using 20 types of immunohistochemical markers and was correlated with the clinical courses. FasL was selected as a marker of apoptosis in intestinal transplants on the basis of the immunohistochemical study.

For the long-term period, novel immunologic suppressants, such as mycophenolate mofetil, have been popularized. In the present cases, mycophenolate mofetil was transiently administrated after our histologic follow-up. The treatment protocol for the therapy and follow-up has been constitutively stable using tacrolimus and steroids. Although there have been previous reports regarding T-cell apoptosis in the intestine in ongoing ACR or graft-versus-host disease, its clinical significance has not been evident.[18–20] In the current study, FasL+ T-cell apoptosis was a useful indicator of evident transplant rejection.

TABLE 2. Histologic Profiles of Patients and Donors

Patient	ACR (POD)	Mixed Inflammatory Infiltrate	Apoptotic Crypt Counts	Villous Architecture	LP Apoptosis (Score)	Phagocytosis in LP	FasL+ T Cell in LP	Other Findings	ACR Grade
1	12	Marked	8.5	Distortion	3	+	Marked increase and apoptosis	Chronic rejection	3
2	12	Marked	6.3	Soughing	3	+	Marked increase and apoptosis	Neutrophilic infiltrates	2
	18		5.9		2	+	Modest increase		2
	20		6.1		2	+	Modest increase		2
	25		6.2		2	+	Modest increase		1
3	66	Mild	6.1		2	+	Modest increase		1
4	22	Moderate	7.5	Distortion	2	+	Modest increase		2
5	27	Marked	6.2	Distortion	2	+	Marked increase		2
6	12	Moderate	6.4	Soughing	2	+	Marked increase and apoptosis		2
7	11	Moderate	6.5	Ulceration	1	+	No significant increase	C4d immunostaining+	3
	19		7.6	Shortening	3	+	No significant increase		2

Apoptotic crypt count: per 10 crypts
ACR grades 0 to 3 according to the International grading scheme.[12]
LP apoptosis indicates lymphocytic apoptosis (in the LP) in ACR; phagocytosis in LP, phagocytosis (of the apoptotic bodies) in LP.

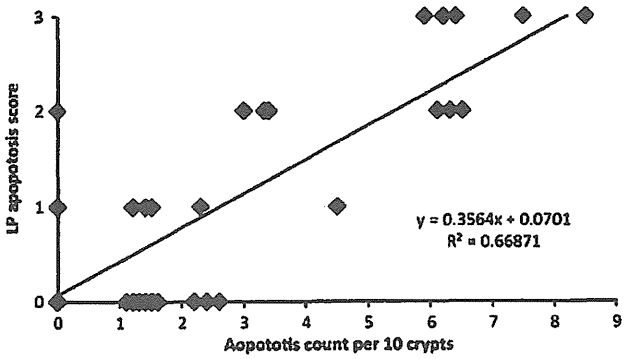

FIGURE 5. Correlation between the LP apoptotic score and the count of apoptotic crypts. A regression analysis of the LP apoptotic score and the count of apoptotic crypts was carried out. The shown equation shows the close correlation between the LP apoptotic score and the count of apoptotic crypts.

It remains unclear how T cells undergoing apoptosis in the LP result in indeterminate ACR. Because T cells commonly express both FasL and Fas, 1 plausible mechanism of T-cell apoptosis is that FasL produced by some of the T cells interacted with the Fas on other T cells to induce their apoptosis.[21,22] In contrast, it was not evident whether this expressed FasL directly contributed to the crypt apoptosis that was observed during ACR. Our previous cytokine measurements suggested that a variety of cytokines increased at the onset of ACR[10] and that tumor necrosis factor-α contributed to mucosal damage in graft-versus-host disease.[20] In the present study, we suspect that FasL, in addition to tumor necrosis factor-α, is the major factor in mucosal damage of the graft. The phagocytosis of apoptotic T cells by macrophages that was observed in the intestinal allografts of the current study was also previously observed in a liver allograft.[23] Thus, these phagocytic findings may be common to all allografts in ACR.

Because crypt apoptosis is probably irreversible,[24,25] mucosal damage cannot be prevented once crypt apoptosis has become evident. However, when only surface mucosa was biopsied, there was often insufficient specimen for the detection of crypt apoptosis. In this case, accurate evaluation of crypt apoptosis requires TUNEL or other examination methods that are not routine and take time to complete. Therefore, identification of the initial and subsequent responses of intestinal allografts leading to ACR is essential for better prognosis. In the present study, T-cell apoptosis in the LP was as good an indicative finding as crypt apoptosis. Although more studies will be necessary for understanding this T-cell response, T-cell apoptosis appears to be a useful finding for diagnosing ACR in intestinal allografts. Although the study population remains small in the current study, because there are few comprehensive immunohistochemistry studies that are correlated with clinical findings in patients who have undergone intestinal transplants, our study provides novel information of intestinal transplant histology.

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■ 特集 ここまで来た小児小腸移植

腸管不全患者における小腸移植の適応

上野豪久* 福澤正洋

はじめに

経静脈栄養（parenteral nutrition：PN）の発達により，腸管不全患者の予後は飛躍的に改善した。腸管不全に対しては内科的，外科的治療を試み，いわゆる intestinal rehabilitation を行いできるだけ腸管機能の回復を試みるが，PN から離脱できない場合も少なくない。しかし，PN に関連した合併症，カテーテル感染や中心静脈の血栓，そして腸管不全関連肝障害（intestinal failure associated liver disease），いわゆる IFALD によって生命の危険に曝される場合も少なくはない。そのため腸管不全の究極の治療として正常な腸管を移植する，小腸移植が行われている[1]。これは腸管不全の患者の予後を改善し，また生活の質（quality of life：QOL）を上げるために非常に有効な治療手段といえる。本稿では腸管不全における小腸移植の適応を概説し，わが国における小腸移植適応患者の全国調査の結果について報告する。

Ⅰ．小腸移植の適応

適応となる疾患については，大きくわけると短腸症候群と腸管運動機能障害がある。短腸症候群をきたす疾患として代表的なものでは中腸軸捻転，壊死性腸炎，小腸閉鎖などがある。また，腸管運動機能不全の代表的疾患としては慢性特発性仮性腸閉塞症（chronic idiopathic intestinal psudo-obstruction syndrome：CIIPS）があげられる。これら以外にも，微絨毛萎縮症のような難治性下痢なども小腸移植の適応疾患となりえる。

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現在の小腸移植の成績を考えると，腸管不全は直ちに小腸移植の適応とはならない。このことが，肝不全が肝移植の適応になっているなどほかの臓器移植とは大きく異なる点である。そのため，小腸移植の適応時期の判断が難しくなる。

現在の小腸移植の適応は，腸管不全を原因として PN から離脱できる見込みがなく，PN の合併症によって生命が脅かされる，もしくは QOL が著しく悪いときに小腸移植が検討される。

具体的には PN から離脱できる見込みがなく，以下の状態となったときである。

絶対的適応としては，

1）PN を行う中枢ルートがなくなることが予測されること。小児の場合は頸部の中枢ルート，すなわち左右の内頸，鎖骨下静脈の合計 4 本のうち 2 本がなくなった時点。

2）PN，もしくは腸管不全のため，肝障害をはじめほかの臓器に障害がもたらされている，またはもたらされることが予測されること。具体的には肝障害においては肝線維化が進行している（Metavir 分類で F 2 以上が目安），腎障害においてはクレアチニンクリアランスが 60 ml/分以下が小腸移植を検討する目安となるであろう。

相対的適応としては，

3）腸管不全のため著しく QOL が落ちている場合。腸炎，カテーテル感染などで 1 年のうち半年以上の入院を余儀なくされる。もしくは生活の大半をベッド上となることが目安となるであろう。

4）著しい苦痛を伴う場合。腹痛が強くて我慢ができない状態などが考えられる。

ただし，小腸移植後にもしばらくは中枢ルートが必要なため，中枢ルートを完全に失った場合は

適応外と考えられる。

以前は，肝硬変にいたった場合も適応外であったが，現在では肝・小腸同時移植が選択される。また，小腸移植は免疫抑制剤を多量に必要とし腎障害をきたしやすいため，腎障害が進行し小腸移植後に透析が必要な場合も，慎重に適応を考える必要がある。

もちろん，ほかの臓器移植と同様に活動性の感染症がある場合は適応とならないので，感染症，カテーテル敗血症が持続している場合も慎重に判断する必要がある。

II．腸管不全の全国調査

腸管不全の究極の治療が小腸移植であるが，小腸移植はまだ保険適用となっておらず，実施数は20例を超えたにすぎない。それ以前に腸管不全，ときに運動機能障害によるものは診断治療に難渋しているのが現状で，全体像の把握すらされていない。そのため，腸管不全のため小腸移植を必要としている患者がどの程度存在しているかも明らかになっていない。

そのため，平成23年度より厚生労働科学研究費にもとづき，全国に分布する小腸移植の適応疾患である腸管不全の全国調査（福澤正洋研究班）が行われている[2)]。

この調査は腸管不全症例に対しての，過去5年の後方視的観察研究として行われた。日本小児外科学会認定施設，日本小腸移植研究会，日本在宅静脈経腸栄養研究会の会員施設に対して，多施設共同研究としての症例登録が行われた。

腸管不全と診断された全症例を対象として，生存，PN離脱，中枢ルートに関する所見，臓器合併症の所見，入院日数，パフォーマンスステータス（PS）についての観察研究を行った。

63施設より354例の調査票を得ることができた。このうち，発症年齢が15歳以下と考える52施設264例に対して検討を加えた。

1．症例と予後

発症時の平均年齢は1.2歳であった。210例（80%）は1歳以下で乳児発症例が多かった。調査時の平均年齢が7.9歳で，観察期間中の5年間のうちに34例が死亡しており，調査時に230例が生存していた。

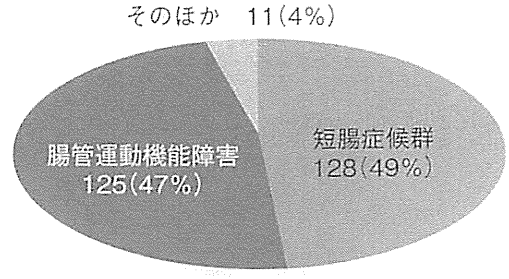

図1　原疾患の分布

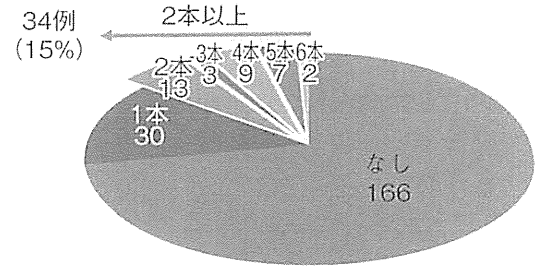

図2　閉塞血管の本数（N＝230）

2．原疾患

原疾患の分布を図1に示す。腸管不全の原因としては，短腸症候群と腸管運動機能障害がおよそ半数ずつであった。

生存例230例中の137例（60%）はPNから離脱しておらず，そのうち127例は6カ月以上PNに依存しており，不可逆的腸管不全と考えられた。

PNに使用できるルートは，小児の場合は左右の内頸静脈，鎖骨下静脈である。このうち，2本以上失った場合は将来的に中枢アクセスを失う可能性がある。生存例のうち64例がなんらかの中枢ルートの閉塞をきたしていた。生存例の閉塞血管の本数を図2に示す。不可逆的腸管不全症例のなかで2本以上の静脈が閉塞した症例は20例あり，小腸移植を考慮するべきだと考えられる。

3．肝障害

生存例のうちの肝障害について図3に示す。肝障害をきたしている症例が110例（48%）に認められた。不可逆的腸管不全のなかでは127例中82例の肝障害を認め，このうち10例には黄疸が認められ，肝障害がより進んだものと考えられる。IFALDは腸管不全の合併症の大きなもので，とくに欧米では小腸移植適応の要素となる。そのため，

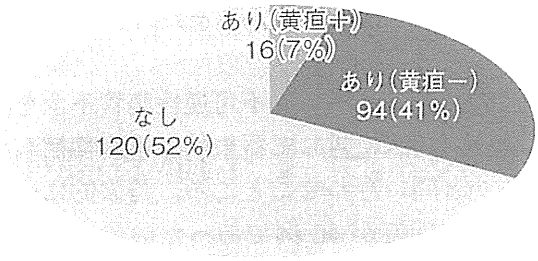

図 3 肝障害（N＝230）

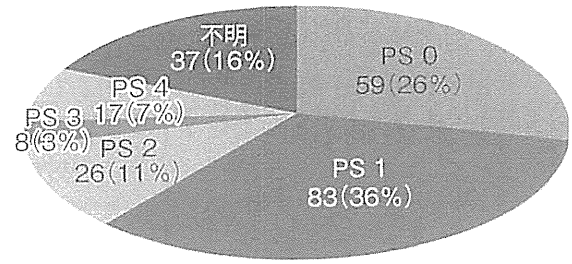

図 4 パフォーマンスステータス（N＝230）
0：無症状で社会活動ができ，制限を受けることがない。
1：軽度の症状があり，肉体労働は制限を受けるが，歩行，軽労働や座業はできる（軽い家事，事務など）。
2：歩行や身の回りのことはできるが，ときに少し介助がいることもある。軽労働はできないが，日中の 50%以上は起居している。
3：身の回りのある程度のことはできるが，しばしば介助がいり，日中の 50%以上は就床している。
4：身の回りのこともできず，常に介助がいり，終日就床を必要としている。

黄疸を認めた 10 例については小腸移植を考慮するべきだと考えられる。

4．日常生活の質（QOL）

生存例のうちの PS を図 4 に示す。不可逆的腸管不全のうち一日 50%以上のベッド上の臥床を必要とする PS であり，PS 3，ないしは PS 4 である症例を 15 例認めた。これらは著しく QOL が阻害されていた。

生存例における診療形態を図 5 に示す。過去 1 年間に入院を要した患者は 45 例であった。不可逆的腸管不全症例においては 30 例の入院を認め，そのうち 20 例は年間 6 カ月以上の入院を余儀なくされており，極端に QOL が低いと考えられる。これらの患者も小腸移植の適応となると考える。

5．小腸移植

小腸移植に関する適応のまとめを図 6 に示す。127 例は 6 カ月以上 PN より離脱ができずに不可逆的腸管不全と判断した。現在生存している不可逆的腸管不全患者のうち ① 黄疸を伴った肝障害，② 中枢ルートが 2 本以上閉塞のどちらかを満たす 29 例は，小腸移植の適応だと考えられる。

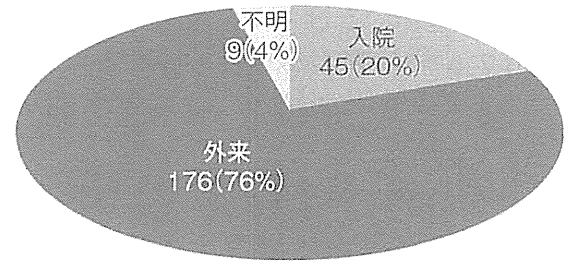

図 5 診療形態（N＝230）

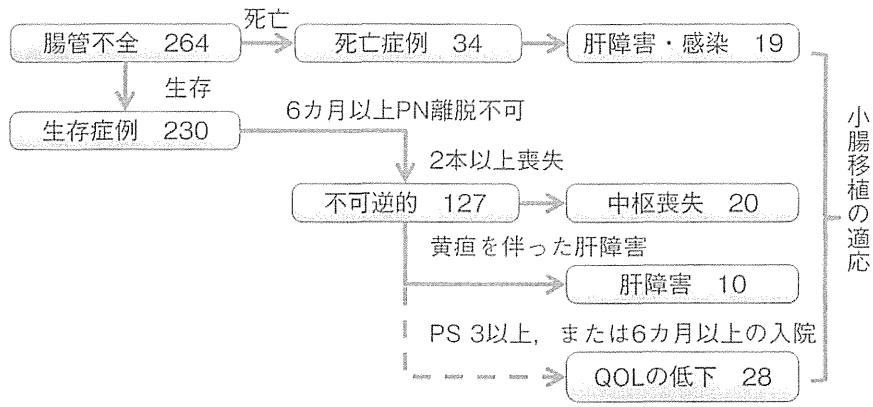

図 6 小腸移植適応

また，死亡患者のうち肝不全と感染症で死亡した患者 19 名も，小腸移植で救命できた可能性がある。

①PS 3 以上の，②6 カ月以上の長期入院を必要とする，のどちらかを満たす 28 例も相対的な小腸移植の適応と考えられる。

ま と め

小腸移植の適応である，

1．中枢ルートの欠如

2．進行した肝障害

の観点からこのうち小腸移植の適応患者を推計すると，29 症例が小腸移植の適応になると考えられる。また，相対的な小腸移植の適応である QOL の著しい悪化について検討すると，長期入院が必要である 28 症例についても，相対的に小腸移植の適応となると考えられる。

また，今回は詳細な検討を加えていないが，死亡症例も小腸移植が実施できたら救命できた可能性も否定できない。そのことも考えると，小児症例で 50 例程度の小腸移植の適応患者が存在すると考えられる。

しかし，小腸移植は現在でも年間数例程度にとどまっている。原因の一つには，保険適用になっていないために医療経済的な問題があると考えられる。

今回の調査のなかで，不可逆性腸管不全を診察している担当医に対して将来的に小腸移植が必要であるかと問い合わせたところ，将来的には必要であるとの回答が 46 例であったので，小腸移植に対する認識はあると考えられる。しかし，現在小腸移植の適応であるとの回答が 15 例にとどまっているのは，適応の判断に苦慮しているものと考えられる。そのため，患者を治療している施設と小腸移植施設との連携が重要であると考えられる。いずれにせよ，小腸移植が適応であったとしても保険適用がなければ治療は経済的な観点から困難であるので，小腸移植の保険適用は速やかになされるべきである。

文 献

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報告

本邦小腸移植症例登録報告

日本小腸移植研究会

A Report from the Japanese Intestinal Transplantation Registry

The Japanese Society for Intestinal Transplantation

【Summary】

Twenty-four intestinal transplants were performed since 1996 in 5 institutions. There were 13 deceased donor and 12 living related donor transplants. Primary causes of intestinal transplants were short gut syndrome (n=9), intestinal mobility function disorder (n=12), others (n=1) and re-transplantation (n=3). One-year patient survival was 86%, and 10-year patient survival was 65%. They were excellent results for a standard therapeutic option for intestinal failure if patients fail to maintain total parental nutrition.

Keywords: small bowel transplant, short gut syndrome, intestinal failure

I. はじめに

臓器移植法が改正されてから3年が経過したが，小腸移植はいまだに保険適用となっておらず，実施件数も限られている。本邦にも少なからず腸管不全の患者が治療を待ち望んでいるが，すべての患者に恩恵がいきわたっているとは言い難い。

日本小腸移植研究会では，国内での小腸移植の実態を把握し，今後の小腸移植の発展のために小腸移植登録事業を2007年より開始した。これは2013年6月末までの小腸移植実施症例に関するデータをまとめたものである。また，本年度の調査については平成25年度厚生労働科学研究費補助金「腸管不全に対する小腸移植技術の確立に関する研究」に基づいて行われた。

II. 対象と方法

各小腸移植実施施設に調査依頼状を送付して，各施設よりデータセンターのWeb上の症例調査票に入力を行い，その回答を基に調査を行った。本邦における小腸移植は1996年に第1例目がなされたが，2013年6月末までに，脳死小腸移植，あるいは生体小腸移植を受けた症例に対して，患者数，年齢，性別，死亡原因，術式，原疾患，免疫抑制剤，術後生存率，移植の効果を調査した。

III. 結果と考察

2013年6月末までの小腸移植は22名に対して25例の移植が実施された。ドナー別では脳死小腸移植が13例，生体小腸移植が12例であった。年次ごとの脳死，生体ドナー別の小腸移植の実施件数を**図1**に示す。年次の実施小腸移植の件数は臓器移植法の改正後立て続けに4例実施されたが，2012年は1件も実施されなかった。臓器移植法改正後8例の脳死小腸移植が実施されているが，脳死小腸移植の待機患者は2013年9月30日現在2名にとどまっている。平成23年度の厚生労働科学研究費による調査によると，小腸移植

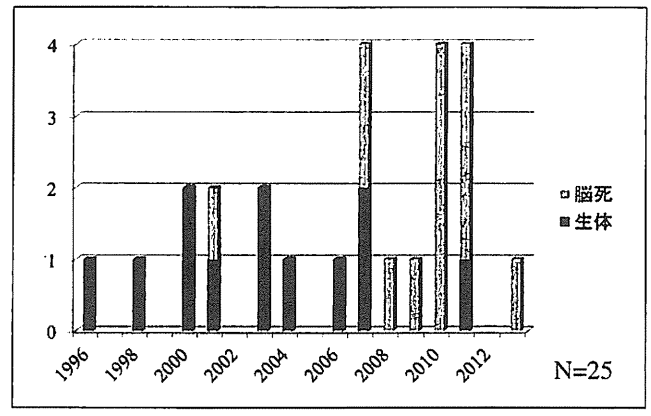

図1　小腸移植実施件数

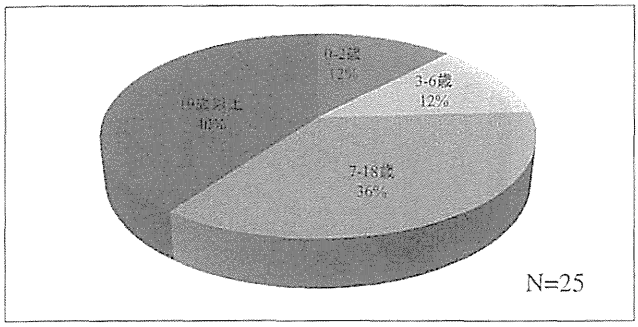

図2　レシピエントの年齢分布

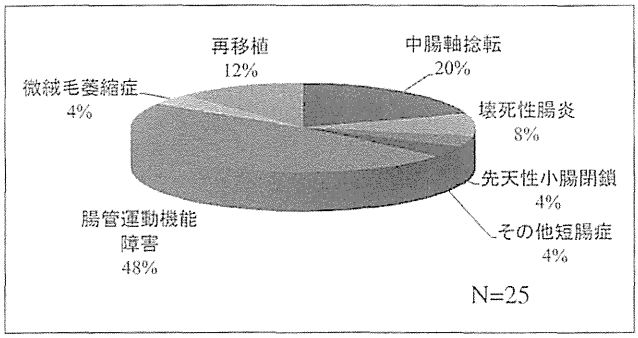

図3　原疾患

の潜在的待機患者は全国で200名弱と推計されている。しかし，保険適用がなされていないことなど経済的要因により，依然として件数がのびないものと考えられる。脳死小腸移植の先進医療が認められ，プログラフ®やネオーラル®の公知申請が認められたものの，小腸移植には必須である抗胸腺グロブリンなどの製剤は依然として適用が認められていないことも問題であると考える。

レシピエント22名の性別は男性が14名，女性8名であった。症例数に対する年齢分布を図2に示す。本邦での小腸移植症例は小児期の疾患に基づくものが多いが，19歳以上の成人症例が4割を占める。これは，依然として小児のドナーが極めて少ないことから，成人期まで待機した患者のみ移植を受けることができるのが原因と考える。

原疾患を図3に示す。3分の1が小腸の大量切除による短腸症候群であったが，海外に比べるとやや小腸運動機能障害によるものが多い。また，移植後グラフト不全に伴う再移植も増加してきた。術式は，肝小腸同時移植が1例の他は，全例単独小腸移植であった。

小腸移植適応患者には，肝小腸同時移植を必要とする患者が存在するが，2臓器の摘出は生体ドナーからは医学的，倫理的に難しい。また，脳死ドナーにおいては肝小腸同時移植を想定した臓器配分が行われていなかった。そのような中で，肝移植と小腸移植を合わせて行うため生体肝移植を先行して行い，その後に脳死小腸移植を行った異時性肝・小腸移植が実施されている。この移植も本登録においては単独小腸移植となっている。しかし，小腸移植後待機中に中心静脈栄養を行わなければいけないこともあり，移植肝への影響を考えると肝小腸同時移植が望ましい。2011年よりは肝臓と小腸を同時に登録し肝臓の提供を受けられれば優先的に小腸の提供を受けられることとなったが，現在のところは肝臓，小腸と同時に待機している患者はいない。

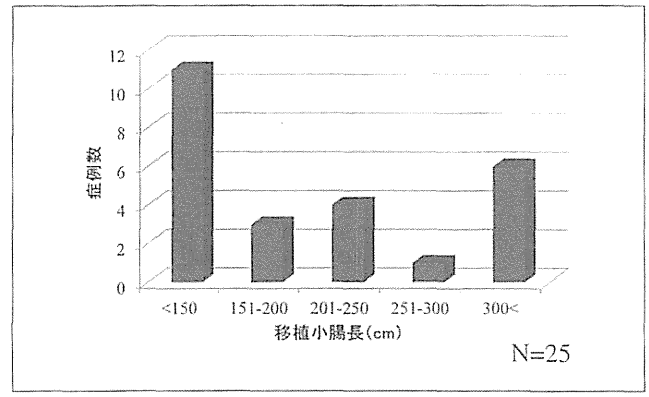

図4　グラフト小腸の長さ

小腸移植では一致のほうが望まれるので，本邦の実施例でもドナーのABO血液型は一致が22例で，適合が3例であった。グラフトとして使用された小腸の長さを図4に示す。150 cm以下が半数を占めるのは，生体ドナーを反映していると思われる。グラフトの回盲弁の有無を図5にしめす。脳死よりのグラフト提供が増えたことより回盲弁付のグラフトも増加したが，回盲弁の有無と成績についはまだ議論の余地がある。

血行再建については図6に静脈再建方法，図7に動脈再建用法を示す。現状では静脈再建については systemic return と portal return がほぼ同数となっている。

免疫抑制剤は全例 tacrolimus を主体とした免疫抑制剤が使用されている。また，小腸移植は拒絶反応を起こしやすいことから，induction が使用されている。その使用薬剤を図8に示す。以前は daclizumab が主に用いられていたが，販売中止になったことから basiliximab と rATG が主流になってきている。

2013年6月までの累積患者生存率を図9aに示す。