combined with mycophenolate mofetil (MMF) at an initial dose of 1,000mg b.i.d, and corticosteroids which was started with 1,000mg of methyl prednisolone during anhepatic period, 100mg methyl-prednisolone on day 1, tapered to 20mg on day 6, and 5mg on day 60. Anti-CD25 mAb (basiliximab) was administered twice on days 0 and 4.

Control group

Eleven patients of the control group received either normal dosage of CNI (CsA 250-350ng/mL, FK 10-15ng/mL, N group) or low-dose CNI (LD group), each without anti-CD25 mAb, which was not available at the time of the study. MMF and steroids were administered using the same doses as for LD-B group.

Postoperative renal function, incidence of acute cellular rejection (ACR), patient survival, and other clinical data were compared among these groups. De novo hypertension was defined as hypertension requiring anti-hypertensive drugs after LDLT without previous history of hypertension. De novo diabetes mellitus was defined as new-onset diabetes that required anti-diabetic drugs after LDLT without previous history of diabetes mellitus.

To evaluate CNI concentration, the trough level of tacrolimus was converted to 25x (FK trough) as a CsA equivalent of tacrolimus to compare with the C0 of CsA.

Continuous data were expressed as mean±SD. Group data sets were compared using student t-test or Mann-Whitney U test. Categorical data were presented as percentages, and differences between proportions were compared using the chi-square test. A p value less than 0.05 was considered significant.

RESULTS

Six patients received low-dose CNI immunosuppressive regimen with anti-CD25 mAb (LD-B group), whereas 8 patients received normal dosage of CNI with or without MMF (N group) and 3 patients received low-dose CNI without anti-CD25 mAb (LD group). Patients' characteristics were similar among the three groups, except that CNI was mainly CsA in the LD-B and LD group, whereas it was mainly FK in the N group. Preoperative CrCl was similar among the three groups (37.1±10.0, 44.9±2.5, and 34.4±10.6mL/min in LD-B, LD, and N group, respectively, **Table 1**). CNI concentrations were significantly higher in the N group than the LD-B group and LD group at days 7 and 14 after LDLT, but were similar after 1 month post-transplantation (**Figure 1A**). GFR was similar in the three groups preoperatively, and it tended to improve 1 month after LDLT in the LD group and LD-B group while it slightly deteriorated 1 month after LDLT in the N group, although the change was not statistically significant (**Figure 1B**). The incidence of ACR was similar among the three groups (40%, 33% and 35%, for the LD-B, L and N group, respectively, **Figure 2A**).

The morbidity and mortality rates in the early period after LDLT (less than 6 months) are shown in

TABLE 1 Patients' Characteristics

	LD-B (n=6)	LD (n=3)	N (n=8)
Recipient age	49.8±10.4	55.0±3.5	49.8±14.3
Gender (M/F)	5/1	2/1	6/2
Primary diagnosis			
Virus cirrhosis (HBV, HCV)	5	3	6
PSC	0	0	1
Laennecs	1	0	0
Cryptogenic	0	0	1
MELD score	21.8±6.5	22.3±3.1	26.5±12.8
PreOP Crn	1.44±0.46	1.15±0.07	1.48±0.62
PreoOP Ccr	37.1±10.0	44.9±2.5	34.4±10.6
Donor age	40.0±12.4	44.0±10.6	39.4±13.6
CNI (FK/CsA)	1/5	0/3	7/1
Graft (Left/Right)	1/5	2/1	1/7
GLV	633.7±91.0	598.0±29.7	666.3±89.3
GW/SLV (%)	48.8±4.1	49.6±2.1	53.5±8.5
WIT (min)	55.8±15.6	46.7±7.4	46.8±12.9
CIT (min)	83.2±29.5	80.0±44.2	71.4±57.1

Data are mean±SD or number of patients.
PSC: Primary sclerosing cholangitis, MELD: model for end-stage liver disease, PreOp Crn: preoperative serum creatinine, PreOP Ccr: preoperative creatinine clearance, CNI: calcineurin inhibitors, GLV: graft liver volume, GW/SLV%: graft weight/recipient standard liver volume (GW/SLV) ratio (%), WIT: warm ischemic time, CIT: cold ischemic time

TABLE 2. Morbidity and Mortality Within 6 Months after LDLT

	LD-B group (n=6)	LD group (n=3)	N group (n=8)
Chronic renal failure (Crn> 4mg/dL)	0	0	1 (12.5%)*
Infection			
CMV infection	1 (17%)	0	0
Bacterial infection	0	0	2 (25%) (MDRP, MRSA)
Surgical complication	0	0	2 (25%) (PVT, Biliary stenosis)
De novo Diabetes Mellitus	1 (33%)	0	0
De novo hypertension	1 (25%)	0	2 (25%)

*Died 5 months after LDLT

The incidence of acute cellular rejection was similar between renal sparing patients and control patients, suggesting that the renal sparing protocol (LD-B group) was safe and effective enough to suppress immunological response after LDLT. One patient of the control group (N group) died of chronic renal failure, while none of the LD-B group did, suggesting that even the difference in CNI dose during the first month post-transplantation might contribute to renal dysfunction in patients with preoperative chronic renal impairment.

One patient from the LD group developed severe persistent acute rejection that could not be controlled despite treatment. Although any conclusion drawn from a single case could be viewed as an overstatement, it is possible that the combination of low-dose calcineurin inhibitor without anti-CD25 mAb is too weak to suppress the immunological response even in living donor liver transplantation.

To our knowledge, this is the first report of renal sparing immunosuppressive protocol for patients with living donor liver transplant recipients with preoperative renal dysfunction. Although our study consisted of a small number of patients, the results suggest that low-dose CNI combined with immunosuppressive agents including anti-CD25 mAb is feasible and effective for LDLT patients with preoperative renal dysfunction, and could improve prognosis and quality of life after LDLT.

The limitation of this study is that it is only a pilot and non-randomized study of a small number of patients, making it difficult to conclude the effectiveness of our renal sparing protocol for patients with preoperative chronic renal dysfunction. Further studies should be conducted that include a larger patient population and longer follow-up period.

In conclusion, our renal sparing protocol using minimal dosage of CNI as an induction immunosuppression was safe and effective in LDLT recipients with preoperative renal dysfunction.

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Once-Daily Prolonged-Release Tacrolimus in *De Novo* Liver Transplantation: A Single Center Cohort Study

Shigeru Marubashi[1], Hiroshi Wada[1], Shogo Kobayashi[1], Hidetoshi Eguchi[1], Masahiro Tanemura[1], Koji Umeshita[2], Yuichiro Doki[1], Masaki Mori[1] and Hiroaki Nagano[1]

[1]Department of Surgery and [2]Division of Health Science,
Graduate School of Medicine, Osaka University, Osaka, Japan

Corresponding author: Shigeru Marubashi, MD, PhD, Department of Surgery, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka (E2), Suita city, Osaka 565-0871, Japan; Tel.: +81-6-6879-3251, Fax: +81-6-6879-3259; E-mail: smarubashi@gesurg.med.osaka-u.ac.jp

KEY WORDS: Tacrolimus; Once-daily formula; Liver transplant; Dose adjustment; Biopsy-proved acute cellular rejection.

ABBREVIATIONS: Biopsy-Proven Acute Cellular Rejection (BPAR); Estimated Glomerular Filtrating Rate (eGFR); Living Donor Liver Transplantation (LDLT); Postoperative Day (POD); Tacrolimus (TAC); Tacrolimus Prolonged Release (TAC-PR).

ABSTRACT

Background/Aims: The feasibility of oral administration of once-daily prolonged-release tacrolimus (TAC-PR) in *de novo* liver transplantation is not clear and therefore was investigated further. **Methodology:** The clinical profiles of 16 consecutive primary living donor liver transplantation (LDLT) recipients, who received oral TAC-PR once daily (TAC-PR group) between January 2009 and August 2010, were compared with those of 14 consecutive liver transplantation recipients given twice-daily tacrolimus (TAC; TAC group) between August 2006 and January 2009. Of the 14 patients in the TAC group, 9 received LDLT (TAC-L subgroup). **Results:** Patient characteristics were similar between groups. Trough levels of TAC during the first 3 months after liver transplantation were well-adjusted in both groups. Dose adjustment was more frequently required (31.3%) in the TAC-PR group and the total amount of TAC was significantly higher in the TAC-PR group (181.1±75.3mg) than in the TAC-L group (100.2±53.8mg, p=0.014). The incidence of biopsy-proven acute cellular rejection, renal dysfunction, other morbidities and hospital stay length were similar between groups. **Conclusions:** Oral administration of TAC-PR for *de novo* liver transplantation recipients was well tolerated with similar safety and efficacy profiles as traditional twice-daily TAC with closely controlled adjustment of the TAC-PR dose.

INTRODUCTION

Calcineurin inhibitors, which emerged in the 1970s, are the most potent immunosuppressants available. Organ transplant recipients receive calcineurin inhibitors twice daily in an oral formula of either tacrolimus (TAC) or cyclosporine A as a primary immunosuppressive regimen. Recently, a prolonged-release formulation of TAC (Graceptor, Astellas Pharma Japan Ltd, Tokyo, Japan; hereafter referred to as TAC-PR) was developed to provide once-daily dosing with efficacy and safety similar to those of the twice-daily formulation (1). After the initial trial however, there have been no studies reported in the field of liver transplantation. Moreover, it is not clear from the available data whether there are any difficulties in adjusting doses during the early post-transplant period in *de novo* liver transplantation recipients. The aim of the present study was to compare the feasibility, safety and efficacy of a regimen of oral administration of TAC-PR with that of traditional twice-daily TAC in *de novo* living donor liver transplantation (LDLT) recipients.

METHODOLOGY

Sixteen consecutive primary adult-to-adult LDLT recipients during the period between January 2009 and August 2010 received one dose of TAC immediately after the transplant, followed by oral TAC-PR in a once-daily protocol (TAC-PR group) from postoperative day 1 (POD 1). In contrast, 14 consecutive primary adult liver transplantation recipients (TAC group) during the period between August 2006 and January 2009 received TAC twice daily. Nine of these patients underwent LDLT (TAC-L group) and 5 patients underwent deceased donor whole liver transplantation (TAC-D group).

The initial daily dose of TAC, 0.5mg/kg in both the TAC-PR and TAC groups, was given through a nasogastric tube immediately after arrival in the intensive care unit after liver transplantation

and then the tube was clamped for 1 hour. The dose of TAC-PR given on POD 1 was calculated using the following formula: TAC-PR POD 1 dose (mg) = 2×amount of TAC on POD 0 (mg) × target trough level (ng/mL) × (0.6-0.8)/trough level on POD 1 (ng/mL).

The dose was adjusted based on the morning trough level from POD 1 to 3 and then the dose of TAC-PR for POD 4 was determined by the trough level on POD 3. The evening dose of TAC was adjusted based on the morning trough level on each day after POD 1. The dose was held when the trough level was over 20ng/mL and additional doses were administered when the trough concentration of TAC was suboptimal. The target trough level of TAC was 8-12ng/mL within 28 days after liver transplantation and 6-10ng/mL between 29 to 90 days after liver transplantation in both groups.

The immunosuppression regimen comprised TAC-PR or TAC and corticosteroids, starting with 1g methylprednisolone during the transplant, then tapering from 100mg/day to 5mg/day in patients with primary biliary cirrhosis, primary sclerosing cholangitis or autoimmune hepatitis, or tapering off in recipients with liver failure of other etiologies. Mycophenolate mofetil was added in patients with renal impairment, rejection episodes or others as needed. Patients with hepatitis C virus (HCV) received corticosteroid-free immunosuppression, comprising TAC or TAC-PR, mycophenolate mofetil and basiliximab (anti-CD25 monoclonal antibody, Novartis Pharma K.K., Tokyo, Japan).

An elementary diet (ED) tube (8Fr, silicon, Create Medic Co., Ltd, Yokohama, Japan) was placed into the jejunum during the transplant surgery and an ED was started as soon as possible. Oral intake of medicine including TAC was started when water intake was fully possible and followed oral intake of food. A biliary drainage tube (pancreatic tube, 5Fr, Sumitomo Bakelite, Tokyo, Japan) was placed in all recipients and drained until the serum total bilirubin level was below 3mg/dL after cholangiography using the drainage tube.

The incidence of holding TAC or adding TAC, biopsy-proven acute cellular rejection (BPAR), renal toxicity evaluated by estimated GFR (eGFR) (2), infection and other morbidities during the first 3 months after liver transplantation was compared between TAC-PR group and TAC group or between the TAC-L group and TAC-D subgroups.

Statistical analysis

Continuous data are expressed as mean ±SD and group data sets were compared using Student's *t* test, a Mann-Whitney U test or the Kruskal-Wallis test. Categorical data are presented as percentages and differences between proportions were compared using the chi-squared test. The cumulative risk of BPAR was estimated by Kaplan-Meier analysis (log rank test). A p value of less than 0.05 was considered to be significant.

RESULTS

Background and characteristics of recipients were similar between the TAC-PR group and TAC groups, except for recipient age and graft volume (**Table 1**). Age of recipients in the TAC-PR group was 55.3±7.9 years, significantly higher than that of recipients in the TAC group (45.5±14.9 years, p=0.030) and tended to be higher than that of recipients in the TAC-L group (47.4±13.0 years, p=0.071). Graft weight was 554±117g in the TAC-PR group, 892±485g in the TAC group (p=0.014, *vs.* TAC-PR group) and 563±98g in the TAC-L group (n.s. *vs.* TAC-PR group). Preoperative model of end-stage liver disease score and eGFR were similar between the groups. Seven (43.8%) patients with HCV in the TAC-PR group and 3 (21.4%) patients with HCV in the TAC group received steroid-free immunosuppression.

Trough levels of TAC were similar between the TAC-PR and TAC-L groups throughout the study period while those of the TAC-D group were slightly higher than those of the TAC-PR group,

although there was no statistical difference between them except on POD7 and POD90 (**Figure 1A**). Trough levels in the TAC-PR group were well controlled within the target level even in the early post-transplantation period.

The incidence of holding TAC was 1/16 (6.3%, POD1) in the TAC-PR group and 3/14 (21.4%, POD1, POD2 and POD6) in the TAC group due to high trough levels. The incidence of additional TAC (**Figure 2**) due to low trough levels was 5/16 (31.3% POD2-7) in the TAC-PR group, while in the TAC group all of the adjustments were managed by increasing the evening dose.

The administered dose of TAC was higher in the TAC-PR group compared with the TAC-L group and similar to that in the TAC-D group (**Figure 1B**). The daily dose of TAC was increased until POD 21 when it peaked, then decreased in both the TAC-PR and TAC groups. The total amount of TAC was 1.8-fold higher in the TAC-PR group than in the TAC-L group and slightly less than that in the TAC-D group (**Figure 1C**).

The start time of the ED after transplant was similar between groups and initiation of oral intake of food was also similar between groups. Gastrointestinal symptoms such as diarrhea and vomiting were uncommon (6.3% in the TAC-PR group, 14.3% in the TAC group) in both groups (**Table 2**).

Cumulative incidence of BPAR by POD 90 was 18.7% in the TAC-PR group and 50.0% in the TAC group. There was no statistically significant difference in the incidence of BPAR within POD 90 (**Figure 3**).

Preoperative eGFR was not different between groups. The ratio of the lowest eGFR within POD 90 to preoperative eGFR was almost identical between groups (75.3% in TAC-PR group, 70.5% in TAC group and 75.2% in TAC-L group) (**Table 2**).

Postoperative surgical morbidities, such as postoperative intra-abdominal bleeding or portal vein

thrombosis, were similar between groups (**Table 2**). Postoperative non-surgical morbidities such as infection were not specific to the TAC-PR group, although two recipients developed intracranial bleeding which was not considered to be a side effect of TAC. Duration of hospital stay after liver transplantation was similar between groups (TAC-PR 93.7±58.5 days, TAC 103.7±114.5 days; **Table 2**).

DISCUSSION

Once-daily administration of TAC is better for recipients because of easy handling with less stress than the mandatory scheduled intake of the twice-daily formula. Oral administration of twice-daily TAC for *de novo* liver transplantation recipients is widely accepted in clinical practice, however, because of its simplicity and efficacy in stable post-transplantation recipients (3-7). In contrast, oral administration of TAC-PR for *de novo* liver transplantation carries a risk of inappropriate control of the drug concentration, which can cause graft damage or graft loss. Therefore, in some programs, intravenous TAC is administered concurrent with oral TAC in the early post-transplantation period due to the fear of suboptimal drug concentration (personal communication). Another regimen for TAC-PR in liver transplantation recipients is oral administration of twice-daily TAC or temporary intravenous administration of TAC at first, then conversion to a TAC-PR formula. As long as the concentration is well controlled, once-daily oral administration of TAC is better for *de novo* liver transplantation recipients than methods that require conversion because of its simplicity and unnecessary conversion of the TAC formula.

To date, there has been only one clinical trial of TAC-PR for *de novo* liver transplantation recipients (1) but the authors did not mention the management of the TAC-PR dose and its clinical outcome. In the present single center cohort study of the use of once-daily TAC-PR in *de novo* liver transplantation, we investigated the feasibility of oral administration of TAC-PR and

the incidence of holding or adding TAC-PR early after liver transplantation to evaluate the difference between TAC-PR and the traditional TAC protocol.

We presented a formula for calculating the first dose of TAC-PR on POD1 based on the trough level of TAC after one dose immediately after liver transplantation, which proved to be very accurate. The trough level of early post-transplantation recipients (POD 2 to POD 7) was quite well controlled within the target level of TAC. The incidence of holding the dose of TAC-PR was low. In contrast, dose adjustment by adding a dose due to a suboptimal concentration of TAC was required in 5/16 (31.3%) recipients from POD 2 to POD 7 in the TAC-PR group, while all dose adjustments were managed by increasing the evening dose of TAC in the TAC group. Thus, the dose adjustment for TAC-PR was not difficult but careful attention was required, especially within the first week after liver transplantation. This procedure of "adding a dose" could be prevented if the dose is determined after establishing the TAC trough level of the day; however we chose to determine the scheduled dose for POD 4 and after, based on the trough levels of the day before for fear of missing a dose. Our method may be more acceptable in the clinical setting due to the certainty.

The actual dose of TAC was generally higher in the TAC-PR group than in the TAC group and it was 1.8-fold higher in the TAC-PR than in the TAC group for the first 90 days after liver transplantation, consistent with previous studies (1,8). This is probably due to the reduced absorption of TAC from the intestine. TAC is absorbed mainly from the proximal jejunum, while the prolonged release particles of TAC-PR interfere with absorption, which is important for the once-daily oral administration protocol.

The incidence of acute cellular rejection tended to be higher in the TAC group than in the TAC-PR group. The deviation of the incidence of acute cellular rejection is likely due to the small number of recipients in both groups. The incidence of other morbidities

post-transplantation, including infection and renal dysfunction, was also similar.

This study was a non-randomized cohort study comparing the TAC-PR and TAC protocols with only a small number of cases in both groups. The results clearly demonstrate, however, that the TAC-PR protocol is more feasible and effective with strict adjustment compared to the traditional twice-daily TAC protocol. Future studies should clarify the long-term feasibility and efficacy, especially the rate of reduction of non-compliance and reduction of renal dysfunction when using the TAC-PR formula.

In conclusion, oral administration of TAC-PR for *de novo* liver transplantation recipients was well tolerated with a safety and efficacy profile similar to that of the traditional twice-daily TAC with closely controlled adjustment of the TAC-PR dose.

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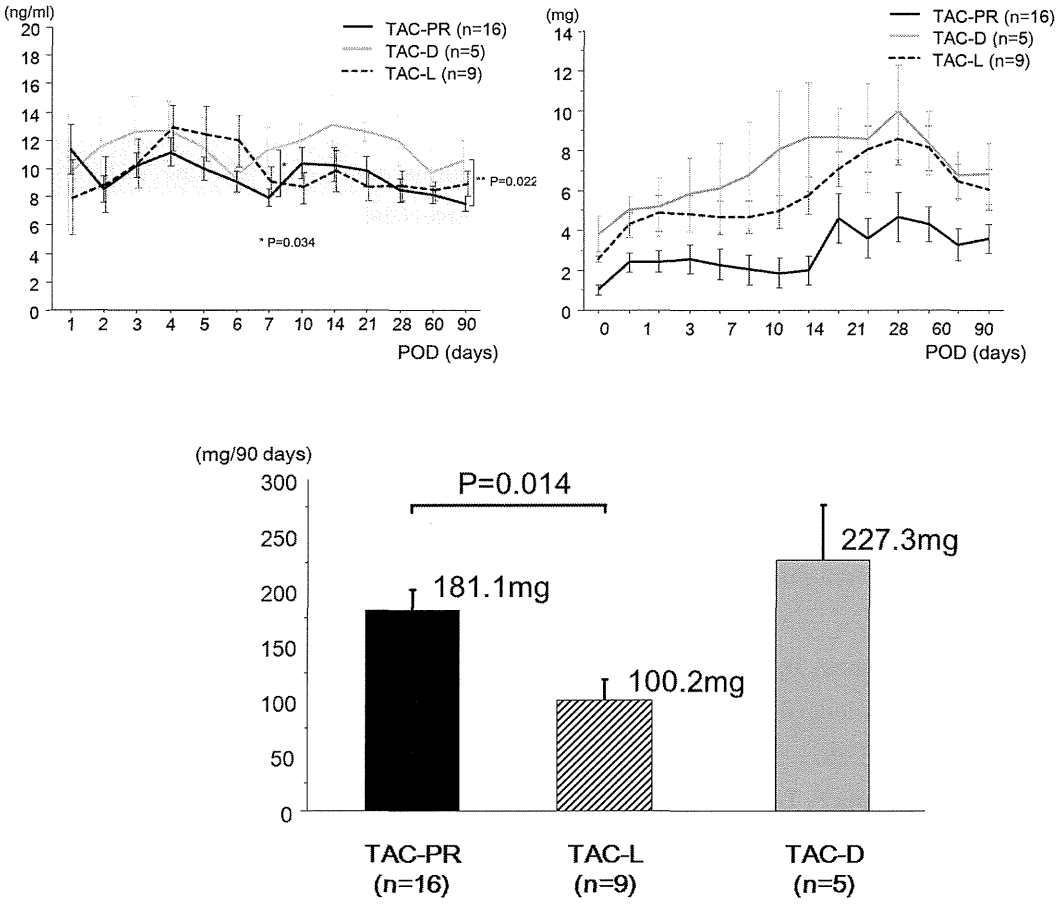

FIGURE 1. Trough level and administered amount of tacrolimus. (**A**) Trough level of tacrolimus. *p=0.034 (TAC-PR vs. TAC-D), **p=0.022 (TAC-PR vs. TAC-D); (**B**) Administered amount of tacrolimus; (**C**) Total amount of tacrolimus during first 90 days after liver transplantation. p=0.014 TAC-PR vs. TAC-L.

TAC-PR: Tacrolimus Prolonged Release; TAC-D: deceased donor liver transplant with traditional twice-daily tacrolimus; TAC-L: Living donor liver transplant with traditional twice-daily tacrolimus; POD: Postoperative Day. Gray zone: target trough level.

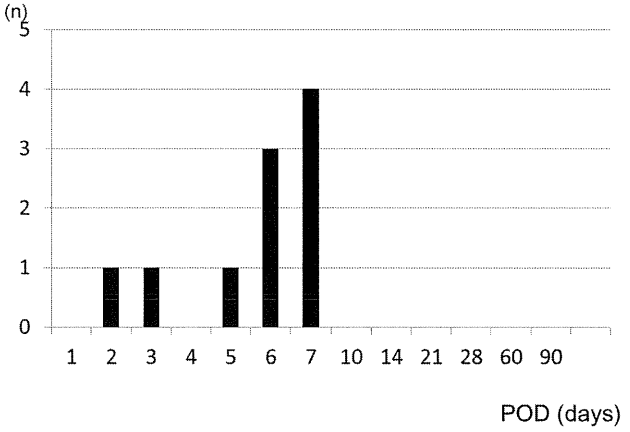

FIGURE 2. Incidence of additional tacrolimus in the TAC-PR group (n=16). Additional TAC-PR was required due to suboptimal levels within the first week after liver transplantation, but there was no need for additional TAC-PR after POD 10. POD: Postoperative Day.

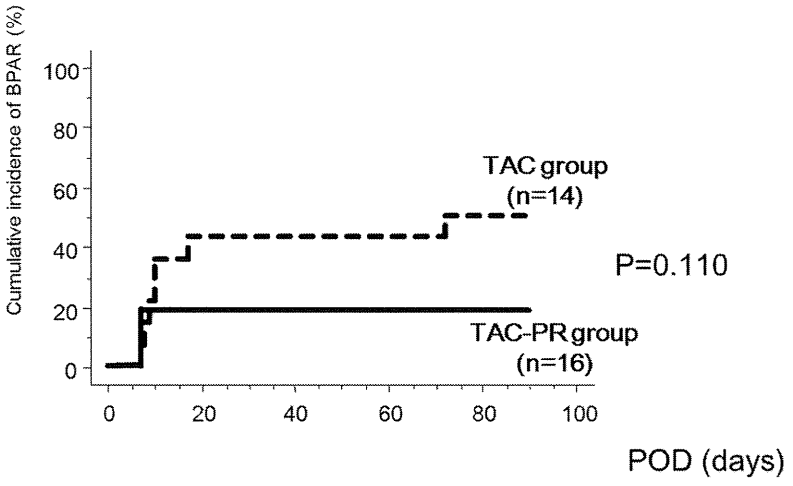

FIGURE 3. Incidence of biopsy-proven acute cellular rejection within 3 months after LDLT. There was no statistical difference between TAC-PR and TAC groups (p=0.110) BPAR: Biopsy-Proven Acute Cellular Rejection; POD: Postoperative Day.

TABLE 1. Patient characteristics.

		TAC-PR	TAC	TAC-L	TAC-D	*p* value	
		(QD)	(BID)	(BID)	(BID)		
		(n=16)	(n=14)	(n=9)	(n=5)	TAC-PR *vs.* TAC	TAC-PR *vs.* TAC-L
Age (y)		55.3±7.9	45.5±14.9	47.4±13.0	42.0±19.1	0.030	0.071
Gender (M/F)		7/9	8/6	4/5	4/1	0.464	0.552
Primary diagnosis							
	HCV	7	3	1	2	0.088	0.170
	HBV	2	2	2	0		
	PBC/PSC	2	2	1	1		
	Wilson disease	0	1	0	1		
	Badd-Chiari	1	0	0	0		
	EtOH	1	0	0	0		
	Fulminant	1	1	1	0		
	Others	2	5	4	1		
Type of donor							
	Deceased	0	5	0	5	0.009	0.999
	Living	16	9	9	0		
Type of graft							
	Left lobe with caudate	7	4	4	0	0.832	0.303
	Right lobe	9	3	3	0		
	Right lateral section	0	2	2	0		
	Whole liver	0	5	0	5		
	Graft weight (g)	554±117	892±485	563±98	1485±250	0.014	0.852
Preoperative MELD score		21.8±10.4	20.1±6.7	23.3±6.0	14.4±3.4	0.603	0.704
Preoperative eGFR (mL/min)		83.4±35.2	70.9±33.5	62.7±34.8	85.8±28.4	0.333	0.171
Operative time (min)		709±87	808±225	819±261	791±176	0.140	0.161
Blood loss (mL)		7303±4645	5014±3128	4190±2461	6498±3925	0.138	0.080

TABLE 2. Postoperative course and morbidities.

		TAC-PR	TAC	TAC-L	TAC-D	*p* value	
		(QD)	(BID)	(BID)	(BID)		
		(n=16)	(n=14)	(n=9)	(n=5)	TAC-PR *vs.* TAC	TAC-PR *vs.* TAC-L
Starting ED diet (POD)		2.8±0.7	3.6±3.0	3.0±1.0	4.0±4.1	0.668	0.343
Starting of oral intake (POD)		14.4±11.2	16.0±13.6	17.9±16.5	13.0±8.0	0.727	0.543
Diarrhea and other abdominal symptoms (%)		1 (6.3%)	2 (14.3%)	0	1 (20%)	0.464	0.444
Acute cellular rejection (%)		3 (18.8%)	7 (50.0%)	4 (44.4%)	3 (60%)	0.07	0.17
Ratio of postoperative-minimal-eGFR/preoperative-eGFR		75.3%	70.5%	75.2%	62.0%	0.798	0.996
Morbidities							
	Postoperative intra-abdominal bleeding	0	3	2	1		
	Portal vein thrombus	0	1	0	1		
	Hepatic artery stenosis	0	2	1	1		
	Acute renal failure	0	1	0	1		
	Infection	1	4	3	1		
	Intracranial bleeding	2	0	0	0		
Hospital stay (day)		93.7±58.5	103.7±114.5	125.7±150.2	72.8±14.6	0.778	0.486

脳死肝移植の現状と問題点

永野浩昭　丸橋　繁　小林省吾
和田浩志　江口英利　種村匡弘
梅下浩司　土岐祐一郎　森　正樹

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今月のテーマ●これからの脳死移植

脳死肝移植の現状と問題点

永野浩昭　丸橋　繁　小林省吾
和田浩志　江口英利　種村匡弘[1)]
梅下浩司[2)]　土岐祐一郎　森　正樹[1)]

要旨：末期肝疾患に対する根治手段である「肝臓移植」は，本邦においては，1997年に脳死臓器移植法が成立したにもかかわらず，生体部分肝移植がその主流を占めてきた．しかしながら，2008年5月の「イスタンブール宣言」などの国際的事情により，2009年7月に臓器移植法改正案が成立し，翌2010年7月からの施行後，現在までに約半年が経過した．この間の脳死肝移植症例数はたしかに増加したが，①国際的に見た提供者不足，②提供者不足による脳死肝移植・待機時間，③MELD基準導入など肝移植適応基準の改正，④肝移植実施施設における移植外科医の減少と労働環境整備，などの諸問題を依然として包括している．

索引用語：脳死肝移植，提供者不足，待機時間，肝移植適応基準，移植医不足

はじめに

肝臓移植は，末期肝疾患，先天性代謝疾患，劇症肝不全，肝細胞癌，などに対する根本的治療手段として定着してきた．欧米では，脳死ドナー（臓器提供者）からの肝臓移植が一般的であるが，日本では，1997年に脳死臓器移植法が成立したにもかかわらず，脳死肝移植はほとんど発展せず，健常な親族からの肝臓の一部を提供していただく，生体部分肝移植がその主流を占めてきた．しかし，肝移植を望むすべての患者さんに生体提供者が存在するわけではない．このような状況は，残念ながら肝移植を望む患者さんに対して自国内での移植が制限され，海外での渡航移植患者の増加という現象をまねいた．しかしながら近年，臓器移植を取り巻く環境は激変した．2004年，世界保健機関（WHO）は，臓器売買など，弱者からの移植を求めて海外に渡航して移植を受けることを「移植ツーリズム」と規定し，これに対して対策を講じるように加盟各国に呼びかけた．次いで，2008年5月，WHOの後援のもとに国際移植学会および国際腎臓学会が，いわゆる「イスタンブール宣言」[1)]を公表し，海外渡航移植が禁止されることになった．さらに，2009年1月のWHO執行理事会においては，「自国民の移植は自国内で行うこと（self-sufficiency），そのために国内での臓器提供を増加させるべく努める」よう，日本をはじめ加盟各国に求める決定がなされた[2)]．これらの国際的な事情により，脳死臓器移植法改正に対する気運が高まり，2009年7月3日に臓器移植法改正案が成立し，翌2010年7月より施

1）大阪大学大学院消化器外科学　2）大阪大学大学院周手術期管理学
Current status and problem about cadaveric liver transplantation in Japan
Hiroaki NAGANO, Shigeru MARUBASHI, Shogo KOBAYASHI, Hiroshi WADA, Hidetoshi EGUCHI, Masahiro TANEMURA[1)], Koji UMESHITA[2)], Yuichiro DOKI and Masaki MORI[1)]
1) Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, 2) Division of Health Science, Graduate School of Medicine, Osaka University
Corresponding author：永野　浩昭（hnagano@gesurg.med.osaka-u.ac.jp）

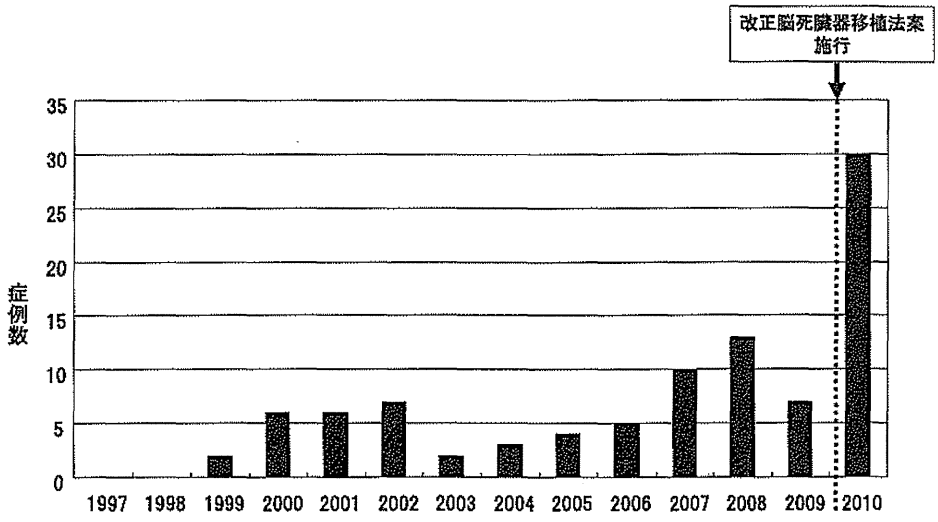

Figure 1. 脳死下の肝移植症例の年次推移（1997～2010年）.

行されるに至り，施行後現在までに約半年が経過した.

本稿においては，この改正臓器移植法案施行後半年間の脳死肝移植における現状と問題点について，①提供者不足，②脳死肝移植・待機時間，③肝移植適応，④肝移植実施施設，について概説する.

1 提供者不足

本邦での脳死肝移植における最大の問題点は，臓器提供施設，移植施設，日本臓器移植ネットワーク，など関係各所の尽力にもかかわらず，脳死臓器提供数がきわめて少ないことにある．世界各国における100万人あたりの脳死下の臓器提供数は，日本は0.5人と一番少なく，スペインが33人と最多である．たしかにスペインなどは，“オプティングアウト”，つまり「臓器提供を拒否しないかぎり，臓器提供に至る国」であることより提供数が多いことは十分に予想される．しかし，アメリカのように“オプティングイン”，つまり「本人が生前，臓器提供の意思を示していた場合，または家族が臓器提供に同意した場合，臓器提供が行われる国」であっても，20人程度になる．また，アジアの中では韓国の臓器提供数が2008年頃より増加しており，100万人あたり19人となっている．したがって，アメリカでは年間約6000人，また隣国の韓国では約280人の脳死下の肝移植が施行されている一方で，本邦では1997年の脳死臓器移植法案成立後2009年までに，わずか83例の脳死肝移植が施行されたにとどまる（Figure 1）．脳死下の肝移植が普及しなかった原因の1つとして，何よりも臓器提供に関する国民の意識の違いがある．先日，韓国での脳死下での臓器提供者が日本より多いことや最近増加していることについて，韓国人医師に伺う機会があった．その答えの1つが「韓国人の50%はキリスト教である」とのことであった．たしかに，カトリック教会は1985年に「脳死は人の死」と結論し，「臓器移植は“愛の行為”」とした．さらに，ローマ法王，故ヨハネ・パウロ2世は1990年に「死後に自分の臓器を提供する行為は，キリスト教的な美しい愛の表現である．カトリック信者は臓器遺贈に協力すべきだ」と語り[3]，2000年8月29日，第8回国際移植学会・世界会議で演説された．筆者も学会に参加していたが，病をおしてバチカンからローマの国際移植学会会場に駆けつけられた姿は記憶に新しい.

ただ，本邦の提供者不足という状況は，改正脳死臓器移植法案施行後かなり変化したように思われる．2010年8月以降，現在までに39例の肝移植が施行されている，つまり，1カ月あたり5.6症例の脳死肝移植が成立していることになり，その数は明らかに増加してきている（Figure 1）.

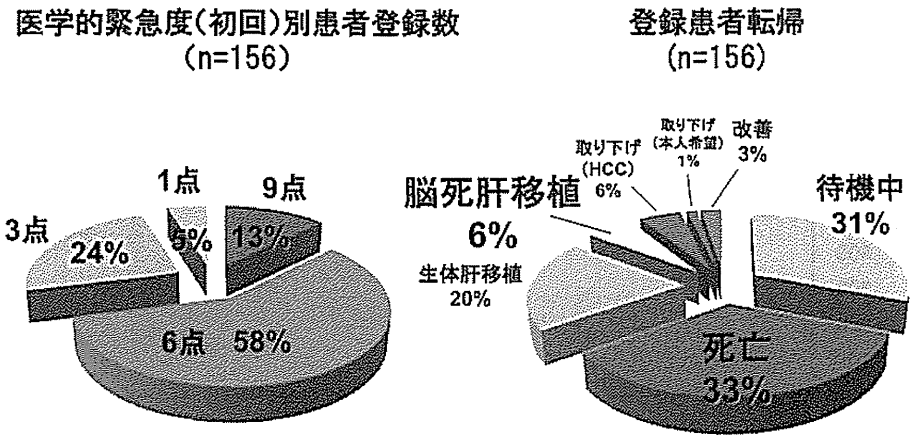

Figure 2. 大阪大学における2009年末までの脳死登録症例（156名）の医学的緊急度別患者登録数（左）と登録患者転帰（右）．登録患者156名のうち，脳死移植施行患者は6%にとどまる．医学的緊急度および予測生存期間は，9点：1カ月以内，6点：6カ月以内，3点：1年以内，1点：1年以上．

単純計算すると年間約67症例になる．この数が多いか少ないかは，アメリカ，韓国に比較すると議論の分かれるところではあるが，少なくとも年間の脳死肝移植症例数が平均6症例（2〜13例）であった臓器移植法改正前と比較すると，増加していることは間違いない．当然，先述した日本における宗教観・死生観と改正臓器移植法案との接点は不明であるが，少なくとも法律改正により提供者数が増加したことは事実である．今後は，諸外国と比較しても少なくない状況になることで，次項の待機期間に対する問題点への解決になる可能性がある．

II 脳死肝移植・待機時間

日本臓器移植ネットワーク資料（(社)日本臓器移植ネットワークhttp//www.jotnw.or.jp/index.html）では，2011年1月31日現在，脳死肝移植待機症例308例中，1年以上待機している症例が170例（55%），2年以上待機している症例が108例（35%）と3割以上の患者さんが登録から2年以上肝移植を待機していることになる．また，脳死肝移植を希望して登録された症例で肝移植を受けられた症例は106例であったが，その一方で待機中に死亡された患者さんは450例と，約4倍の患者さんが待機中に死亡している．たしかに，腎移植の登録期間も非常に長く，5年以上の長期待機を要するという現状はあるものの，「人工透析」という生命維持のための代替治療が存在することで，待機期間中に死に直結することは少ない．一方，肝移植においては，代替治療は存在しない．そのため，登録後肝移植を受けることがかなわず死亡される方も少なくないことは，日本臓器移植ネットワークのデータが示すとおりである．つまり移植によってしか救命できない末期肝不全の患者さんは，移植を受けることが可能であった患者さんの4倍程度いるということである．教室のデータも全く同じ傾向にある（Figure 2）．2009年末までに，大阪大学附属病院において，脳死肝移植待機登録を行った患者さんの数は156名であった．そのうち，現在も待機中の患者さんは31%にすぎず，すでに33%は死亡され，20%は待機中に肝機能の増悪を認めたため，生体部分肝移植を施行した．待機症例の中で，脳死肝移植を施行できた患者さんは9人，6%にすぎない．また，幸いにも移植を受けられた患者さんの待機時間は，平均708日，約2年間である（Figure 3）．後述するように，脳死肝移植待機患者さんの適応の原則は，「不治の末期状態にあり原則として従来の治療方法では余命1年以内と予想されること」であるにもかかわらず，患者さんは移植を受けるまで約2年間待機する必要がある．つまり，

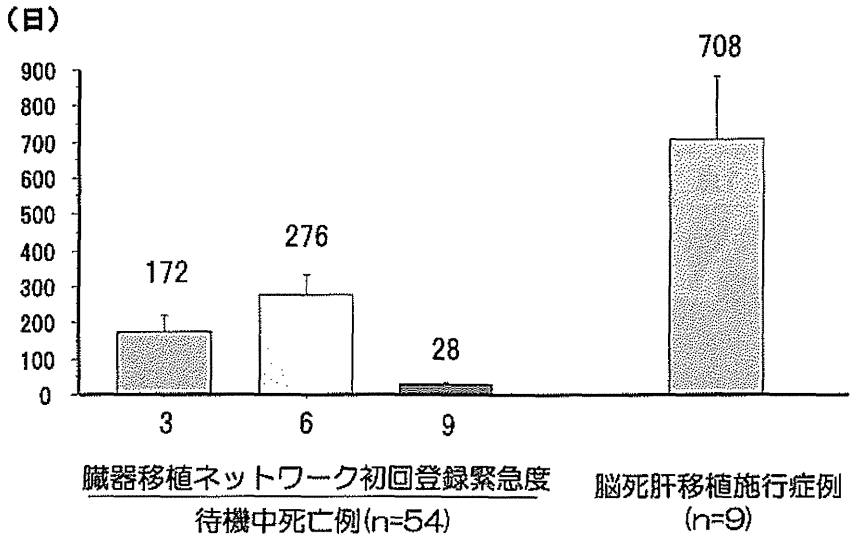

Figure 3. 脳死肝移植待機中死亡症例（n＝54）と脳死肝移植施行症例（n＝9）の待機期間の比較．死亡症例54例の死因は，全員肝不全関連死亡（100%）．

われわれは肝移植を希望する患者さんが外来に紹介されてきた時に，「肝不全状態ですので，肝移植が必要です．ただ，登録から約2年間お待ちいただくことになります」という説明をしないといけない現状にある．これが，本当に現場の医療として成立するのかというと，きわめて疑問に感じる．移植する側の筆者らがそう思うのであれば，なおさら患者さんの思いは？？ということであろう．また，紹介する消化器（肝臓）内科医にとっても，この提供者不足や脳死肝移植登録症例などの現状の中では，簡単に肝移植医療を患者さんに勧めることはできない気持ちになることは間違いないであろう．よく，消化器内科の先生方と患者さんの紹介についてお願いすることがあるが，「紹介すべき気持ちはあるが，医療として現実問題成立するのか否か」ということから，患者さんに説明することの“虚無感”がある，とのご意見をいただく．まさに本音であると思われる．ただ，その一方では，肝移植医療について説明しなかったことで，患者さんのご家族より告訴されることも現実問題としては存在する．

このような状況で，かなり進行した状態で受診された患者さんの場合には，脳死肝移植の普及事情と前述した提供者不足の状況に鑑み，登録の手続きはしていただくものの並行して生体部分肝移植の説明をする．本邦での肝移植は諸外国と完全に異なり[4]，脳死ドナーからの臓器提供数はきわめて少なかったため，手技的にはより煩雑な生体部分肝移植[5]が成人での成功例[6]を契機にして急速に国内に普及した．この結果，わが国で施行された肝移植件数は，99% が生体ドナーで施行されるという国際的に見るとかなり極端な状況になった．欧米においても生体ドナーは一時的に脳死提供者不足に対する解決策の1つとして期待され，全肝移植症例数の10% を占めるまでに増加したが，生体ドナーの死亡例が報告されたことにより[7]，その安全性が問題視され急速に件数は減少し，2009年の時点では4% 未満となっている．

生体部分肝移植については，教室でも毎年約20症例ほど施行しており，そのものを否定することはないどころか，現状においては必要不可欠な医療であることはいうまでもない．したがって全例とまでは行かないが多くの症例において，脳死・生体肝移植の準備を並行して開始することになる．そのため，当科でも脳死肝移植に登録し待機されている患者さんの22% が待機期間中に生体肝移植を施行している（Figure 2）．

このように，提供者不足，待機時間，生体部分肝移植優先など種々の問題点より，脳死肝移植医療推進のかなりの妨げになっていることは想像に