significant (Table 6). Similarly, the incidence of harmful relapse was much higher, but not significantly so, when the donors were parents or siblings versus when the donors had other relationships with the recipients (Table 6).

TABLE 3. Comorbidities After Transplantation in 195 Patients

Comorbidities	Patients (n)
Biliary complications	41
Cytomegalovirus diseases	38
Bacterial infection	37
Acute cellular rejection	34
Intra-abdominal hemorrhage	26
Malignancies*	13
Vascular complications	12
Fungal infection	12
Permanent dialysis	8
Steroid-resistant acute cellular rejection	5
Chronic rejection	2

*Recurrence of hepatocellular carcinoma (n = 8), gastric cancer (n = 2), lung squamous cell cancer (n = 1), tongue squamous cell cancer (n = 1), and frontal sinus squamous cell cancer (n = 1).

TABLE 4. Causes of Hospital Deaths

Cause of Death	Patients (n)
Infection	10
Small-for-size syndrome	3
Acute cellular rejection	3
Chronic rejection	1
Hepatic artery thrombosis	2
Portal vein flow insufficiency	1
Cerebral hemorrhage	1
ABO-I AMR	1
Graft-versus-host disease	1
Multiorgan failure	1
Biliary stenosis	1
Graft injury	1

Impact of Alcohol Consumption After LT on Patient Survival

The survival rates were compared for recidivist patients and abstinent patients 18 months after LT. Five patients for whom the time of relapse was not obtained and 10 patients who had died within 18 months of LT were excluded from this analysis. The survival rates were 100.0%, 94.7%, 89.5%, 65.7%, and 21.9% at 1, 3, 5, 7, and 10 years, respectively, for recidivist patients and 100.0%, 98.6%, 96.4%, 92.7%, and 73.8% at 1, 3, 5, 7, and 10 years, respectively, for abstinent patients. There was a significant difference in survival ($P = 0.01$; Fig. 2).

Impact of Alcohol Consumption Status on Harmful Relapse

The impact of an early onset of drinking, frequent drinking, and the consumption of large amounts of alcohol after LT on the incidence of harmful relapse was analyzed in 32 recidivist patients. The incidence of harmful relapse was higher for patients who consumed alcohol 4 days or more per week (88.9%) versus patients who drank less frequently (35.7%, $P = 0.008$; Table 8), and it was higher for patients who binged (100%) versus patients who drank less (25%, $P = 0.002$; Table 8). One patient showed all 3 patterns of harmful drinking, and 5 patients showed 2 of the 3 patterns.

Histological Changes in the Liver After LT

Liver biopsy was performed for 20 recidivist patients and 53 abstinent patients. Results from biopsy samples obtained before hospital discharge were included. The incidence of fatty changes was greater in the recidivism group (45.0%) versus the abstinent group (13.2%; Table 9). In contrast, the incidence of rejection was greater in the abstinent group (30.6%) versus

TABLE 5. Causes of Death After Discharge

Cause of Death	Patients (n)	Survival Period (Days)
Infection	6	3802, 2256, 662, 517, 328, 295
Hepatocellular carcinoma recurrence	5	2588, 2057, 422, 357, 300
Gastric cancer	1	2309
Lung cancer	1	195
Cholangitis	2	3302, 1414
Alcoholic cirrhosis	2	2526, 4641
Arachnoid hemorrhage	1	246
Myocardial infarction	1	2983
DIC/lung edema	1	1990
Chronic rejection	1	528
Accident	1	3361
Intra-abdominal hemorrhage	1	373

TABLE 6. Univariate Analysis of Risk Factors for Recidivism and Harmful Relapse After Transplantation

Risk Factor	Patients (n)	Recidivism: Log-Rank Test [n/N (%)]*	*P* Value	Patients (n)	Harmful Relapse: Chi-Square Test [n/N (%)]†	*P* Value
Before transplantation						
HRAR score			0.48			0.24
0	8	1/8 (12.5)		8	1/8 (12.5)	
1	25	8/25 (32.0)		25	6/25 (24.0)	
2	40	8/40 (20.0)		40	4/40 (10.0)	
3	16	4/16 (25.0)		15	3/15 (20.0)	
4	9	1/9 (11.1)		9	0/9 (0.0)	
Unknown	42	—		42	—	
Duration of heavy drinking			0.41			0.50
≥25 years	41	9/41 (22.0)		41	4/41 (9.8)	
<11->25 years	32	7/32 (21.9)		31	6/31 (19.4)	
≤11 years	31	9/31 (29.0)		31	7/31 (22.6)	
Unknown	36	—		36	—	
Daily alcohol consumption‡			0.96			0.47
≤9 g	43	11/43 (25.6)		43	9/43 (20.9)	
<9->17 g	36	8/36 (22.2)		36	4/36 (11.1)	
≥17 g	23	5/23 (21.7)		22	3/22 (13.6)	
Unknown	38	—		38	—	
Pretransplant abstinence			0.39			0.68
≥6 months	100	19/100 (19.0)		99	13/99 (13.1)	
<6 months	31	9/31 (29.0)		31	5/31 (16.1)	
Unknown	9	—		9	—	
Pretransplant abstinence			0.77			0.19
≥24 months	31	5/31 (16.1)		30	1/30 (3.3)	
12-24 months	20	3/20 (15.0)		20	3/20 (15.0)	
6-12 months	49	11/49 (22.4)		49	9/49 (18.4)	
<6 months	31	9/31 (29.0)		31	5/31 (16.1)	
Unknown	9	—		9	—	
History of treatment for psychiatric diseases other than alcoholism			<0.01‡			0.17
Yes	9	5/9 (55.6)		9	3/9 (33.3)	
No	125	27/125 (21.6)		125	18/125 (14.4)	
Unknown	6	—		5	—	
Recipient sex			0.16			0.73
Male	88	23/88 (26.1)		88	14/88 (15.9)	
Female	52	9/52 (17.3)		51	7/51 (13.7)	
Smoking			0.12			0.43
Smoking	46	15/46 (32.6)		46	10/46 (21.7)	
No history	24	5/24 (20.8)		24	3/24 (12.5)	
Quit	59	8/59 (13.6)		58	6/58 (10.3)	
Unknown	11	—		11	—	
Living			0.08			0.03‡
With family	122	27/122 (22.1)		121	16/121 (13.2)	
Alone	9	4/9 (44.4)		9	4/9 (44.4)	
Unknown	9	—		9	—	
Marital status			0.04‡			0.04‡
Stable partner	106	24/106 (22.6)		105	15/105 (14.3)	
Widowed/divorced	10	1/10 (10.0)		10	1/10 (10.0)	
No marital history	13	6/13 (46.2)		13	5/13 (38.5)	
Unknown	11	—		11	—	
Living with donor			0.99			0.28
Yes	70	16/70 (22.9)		69	8/69 (11.6)	
No	53	14/53 (26.4)		53	11/53 (20.8)	
Unknown	17	—		17	—	
Occupational status			0.41			0.85
No	42	9/42 (21.4)		41	7/41 (17.1)	
Part time	13	2/13 (15.4)		13	1/13 (7.7)	
Full time	64	16/64 (25.0)		64	10/64 (15.6)	
Unknown	21	—		21	—	

TABLE 6. *Continued*

Risk Factor	Patients (n)	Recidivism: Log-Rank Test [n/N (%)]*	*P* Value	Patients (n)	Harmful Relapse: Chi-Square Test [n/N (%)]†	*P* Value
After transplantation						
Noncompliance with clinic visits			<0.01‡			0.03§
Yes	8	4/8 (50.0)		7	4/7 (57.1)	
No	131	8/131 (6.1)		131	17/131 (13.0)	
Unknown	1	—		1	—	
Followed by psychiatrists			0.78			0.78
Yes	29	7/29 (24.1)		29	5/29 (17.2)	
No	108	25/108 (23.1)		107	16/107 (15.0)	
Unknown	3	—		3	—	
Smoking			<0.01‡			0.09
Yes	24	11/24 (45.8)		24	7/24 (29.2)	
No	73	12/73 (16.4)		72	7/72 (9.7)	
Unknown	43	—		43	—	
Living			0.25			0.07
With family	107	25/107 (23.4)		107	17/107 (15.9)	
Alone	8	4/8 (50.0)		8	3/8 (37.5)	
Unknown	25	—		24	—	
Living with donor			0.46			0.07
Yes	43	12/43 (27.9)		43	7/43 (16.3)	
No	58	15/58 (25.9)		57	12/57 (21.1)	
Unknown	39	—		39	—	
Occupational status			0.18			0.34
No	51	14/51 (27.5)		50	8/50 (16.0)	
Part time	14	4/14 (28.6)		14	4/14 (28.6)	
Full time	38	9/38 (23.7)		38	6/38 (15.8)	
Unknown	37	—		37	—	
Donors			0.07			0.07
Parent	6	3/6 (50.0)		6	3/6 (50.0)	
Sibling	29	10/29 (34.5)		29	8/29 (27.6)	
Son/daughter	61	12/61 (19.7)		61	4/61 (6.6)	
Nonrelative	7	1/7 (14.3)		7	1/7 (14.3)	
Spouse	30	4/30 (13.3)		29	3/29 (10.3)	
Nephew	3	1/3 (33.3)		3	1/3 (33.3)	
Cousin	1	0/1 (0.0)		1	0/1 (0.0)	
Brother-in-law	2	1/2 (50.0)		2	1/2 (50.0)	
Nephew-in-law	1	0/1 (0.0)		1	0/1 (0.0)	

*32/140 (22.9%).
†21/139 (15.1%).
One drink = 12 g of ethanol.
‡$P < 0.05$ (chi-square test)

the recidivism group (25.0%; Table 9). Alcoholic damage was found in 3 patients with recidivism.

Information on the presence or absence of acute cellular rejection after discharge was obtained from 130 patients. The incidence of rejection was 6.9% (2/29) for recidivist patients and 5.0% (5/101) for patients who were abstinent.

Patients for Whom Information on Alcohol Relapse Was Not Available

Twenty-nine patients for whom information on alcohol relapse was not available were excluded from the statistical analysis of alcohol relapse. To understand the impact of this exclusion on the results, we analyzed the overall survival and frequency of risks for recidivism for the 29 patients. There was no significant difference in overall survival between abstinent patients, relapsing patients, and patients of an unknown status (data not shown; $P = 0.09$, log-rank test). For abstinent patients, relapsing patients, and patients of an unknown status, the frequency of noncompliance with clinic visits was 3.7%, 12.5%, and 15.4%, respectively ($P = 0.03$); the frequency of smoking after LT was 17.5%, 47.8%, and 100.0%, respectively ($P < 0.001$); the frequency of no marital history was 7.1%, 19.3%,

TABLE 7. Multivariate Analysis of Risk Factors for Recidivism and Harmful Relapse

	Proportional Hazards Analysis		
Risk Factors for Recidivism	Risk Ratio	95% CI	*P* Value
History of treatment for psychiatric diseases other than alcoholism: yes versus no	5.15	1.26-17.78	0.02*
Marital status			
Stable partner	1.00	—	
Widowed/divorced	0.45	0.02-2.46	0.41
No marital history	1.24	0.34-4.99	0.75
Noncompliance with clinic visits: yes versus no	4.36	0.92-15.43	0.06
Posttransplant smoking: yes versus no	2.67	0.97-7.00	0.05

	Logistic Regression Analysis		
Risk Factors for Harmful Relapse	Odds Ratio	95% CI	*P* Value
History of treatment for psychiatric diseases other than alcoholism: yes versus no	5.15	1.26-17.78	0.02*
Marital status			
Stable partner	1.00	—	
Widowed/divorced	0.45	0.02-2.46	0.41
No marital history	1.24	0.34-4.99	0.75
Noncompliance with clinic visits: yes versus no	4.36	0.92-15.43	0.06
Posttransplant smoking: yes versus no	2.67	0.97-7.00	0.05
Pretransplant living: alone versus family	3.21	0.43-23.46	0.25
Pretransplant marital status			
Stable partner	1.00	—	
Widowed/divorced	0.31	0.01-2.32	0.28
No marital history	2.41	0.38-11.76	0.32
Noncompliance with clinic visits: yes versus no	16.32	2.56-149.34	0.004*

*$P < 0.05$.

and 4.2%, respectively ($P = 0.14$); and the frequency of a history of treatment for psychiatric diseases other than alcoholism was 3.9%, 15.6%, and 6.9%, respectively ($P < 0.001$). Although these 29 patients were less compliant with clinic visits than abstinent patients, 21 of the 29 patients visited the clinic regularly, 4 patients fell into noncompliance, 1 patient died, 1 patient changed hospitals, and the data for 2 patients were unknown. However, for 28 of the 29 patients (including 1 deceased patient), data for smoking as well as relapse data were not available.

Interactions Between Recipients Who Returned to Harmful Drinking and Related Donors

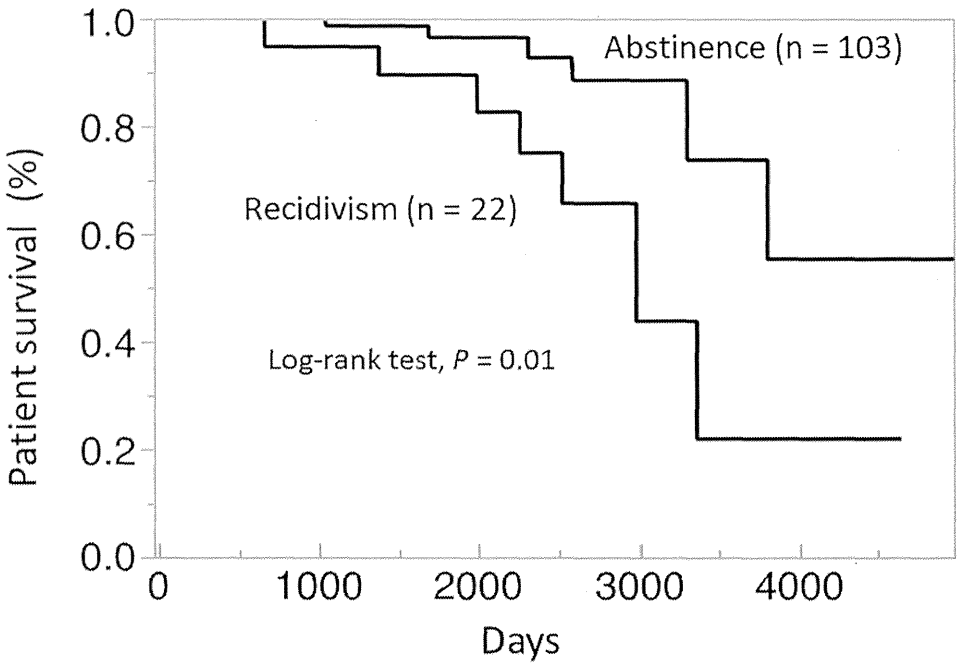
We hypothesized that interactions between a recipient who returns to harmful drinking and the family member who donated the liver might affect outcomes. Although we were not able to examine this directly, we compared the survival rates between recipients living with their donors and recipients who lived separately from their donors. The survival rates were 95.2%, 86.4%, 86.4%, 71.2%, and 63.3% at 1, 3, 5, 7, and 10 years, respectively, for recipients living with donors and 100.0%, 98.2%, 92.0%, 83.5%, and 41.8% at 1, 3, 5, 7, and 10 years, respectively, for recipients living without donors ($P = 0.66$). Although this result does not address the existence or absence of a change in the relationship after the onset of harmful drinking, if such changes do occur, they do not affect survival.

DISCUSSION

Patients undergoing LT for ALC must pledge to remain sober in order to protect the transplanted liver. However, not all recipients are able to maintain sobriety. Alcohol relapse can have a number of negative impacts, including (1) liver dysfunction secondary to alcohol toxicity, (2) noncompliance with medications or clinic visits, (3) rejection secondary to noncompliance, (4) graft failure secondary to rejection or alcohol toxicity, and (5) malignancies and cardiovascular diseases possibly related to smoking (which is highly associated with alcohol relapse). The perception that recipients will relapse may also decrease the willingness of others to donate organs.

Harmful Drinking and Impact

Reports have differed in both the definitions used for harmful drinking and its effects after LT. Schmeding



Numbers at risk	0 years	1 year	3 years	5 years	7 years	10 years
Recidivism	22	22	19	14	7	2
Abstinence	103	103	70	42	25	5

Figure 2. Impact of alcohol relapse on patient survival: comparison of recidivism and abstinence 18 months after transplantation. There was a significant difference in survival between the groups (log-rank test, $P = 0.01$).

TABLE 8. Impact of the Alcohol Consumption Status on Harmful Relapse in 32 Patients With Recidivism

	Patients (n)	Harmful Relapse [n/N (%)]	*P* Value
Recidivism within 6 months			0.91
Yes	12	8/12 (66.7)	
No	16	11/16 (68.8)	
Unknown	4	—	
Frequent use*			0.008†
Yes	9	8/9 (88.9)	
No	14	5/14 (35.7)	
Unknown	9	—	
Binge use‡			0.002†
Yes	6	6/6 (100.0)	
No	8	2/8 (25.0)	
Unknown	18	—	

*Four drinking days per week.
†$P < 0.05$ (chi-square test).
‡Seventy-two grams of ethanol or more for men and 48 g of ethanol or more for women.

et al.[15] found significantly lower 10-year patient survival for patients with alcohol consumption of 80 g/day or more for men or 20 g/day or more for women, and Cuadrado et al.[16] found significantly lower 10-year patient survival for patients with alcohol consumption of 30 g/day or more. In contrast, Tandon et al.[12] defined problem drinking as either any drinking to the point of intoxication or drinking above the

TABLE 9. Histological Changes in Liver Biopsy Samples Throughout the Study

Histological Findings	Recidivism (n = 20)	Abstinence (n = 53)
Minimal or normal changes	2 (10.0)	10 (18.9)
Fatty changes	9 (45.0)	7 (13.2)
Alcoholic damage	3 (15)	0
Cholestatic changes	0	4 (7.5)
Hepatitis	1 (5.0)	6 (11.3)
Rejection	5 (25.0)	21 (39.6)
Fibrosis	0	2 (3.8)
Hepatocellular carcinoma	0	1 (1.9)
Other changes	0	2 (3.8)

NOTE: The data are presented as numbers and percentages. $P = 0.01$ (chi-square test).

toxic threshold (>20 g/day for women and >40 g/day for men) on at least 2 separate occasions, and they found no effect of problem drinking on posttransplant mortality in a North American cohort. Frequent use and binge use contributed to harmful relapse, but early relapse did not. Harmful relapse was significantly related to noncompliance with clinic visits, although our study did not reveal whether noncompliance caused harmful relapse or vice versa because we did not have access to the timing of these elements.

Noncompliance and Rejection

Webb et al.[17] noted that the resumption of problem drinking can lead to noncompliance with the transplant follow-up program, which can, in turn, lead to rejection. In our study, the incidence of noncompliance with clinic visits was significantly greater for patients who had resumed drinking, but the rates of acute cellular rejection confirmed by liver biopsy were similar for the groups. The only patient who died because of chronic rejection was abstinent.

Malignancies and Cardiovascular Diseases

Alcohol use can contribute to the mortality of transplant recipients because of a variety of proximal causes. Burra et al.[18] reported that de novo tumors, cardiovascular events, and social causes (including noncompliance with immunosuppressive therapy, suicide, and trauma) were causes of death or graft failure for a higher percentage of those with alcohol disease in comparison with patients with other etiologies in a large cohort from the European Liver Transplant Registry.[18] Cuadrado et al.[16] reported significantly lower patient survival for patients with alcohol relapse and suggested that alcohol consumption and tobacco use may have contributed to cancer and cardiovascular events, which were frequent causes of death; however, they did not compare the incidences of these diseases between patients who relapsed into alcohol use or smoked and patients who did not. In our study, overexposure to the toxicity of alcohol and nicotine before transplantation might have been a risk factor for postoperative extrahepatic malignancies under immunosuppression therapy. Careful follow-up focusing on malignancies is recommended after LT for ALC whether or not the patient relapses.

Relapse Rates in DDLT and LDLT

In DDLT, organs are considered to be a public resource that should be shared fairly and effectively. Hence, alcohol relapse may result in public opposition to transplantation for ALC. In a study that defined relapse as any alcohol use, the rate of posttransplant alcohol consumption appeared to be quite high: approximately 50% of patients (range = 7%-95%) at a follow-up visit 21 to 83 months after transplantation.[19] We had hypothesized that recidivism might be lower among patients in Japan who had received transplants from family members, but our findings were more complicated. The incidence of recidivism for patients who had received donations from unrelated persons, including brain-dead donors and domino donors, was 14.3%, and the incidence for those who had received donations from spouses was 13.3%, whereas the incidence of recidivism for patients who had received donations from relatives other than spouses was higher (23.3%). The rates of recidivism and harmful relapse were quite high (27.6%-50.0%) when the donors were parents or siblings. Thus, contradicting our hypothesis, the relapse rate is not ubiquitously low for LDLT patients; instead, it is high, especially when a parent is the donor. As for interactions between related donors and relapsing patients, there were no episodes such as divorce or disownment due to recidivism after LT in this cohort as far as personal communications show. The related donors who accepted their own risks before LT might have forgiven the recipients who had relapsed after LT because of their voluntary donation on behalf of love.

We feel that DDLT is suitable for LT for ALC from the point of view of the relapse rate, but efforts are required to decrease the rate even further to ensure that public opinion about organ donation for ALC is favorable.

Limitations

The findings of this retrospective, multicenter study are limited by several factors inherent to this type of study, including variability in documentation, differences in selection criteria and data collection, and missing data. To minimize variability, we sent a standardized collection form containing 150 questions to the transplant centers. The answers either were to be chosen from several options or involved providing a name or a specific value. However, the quality of the pretransplant interviews, from which the baseline data were derived, and the quality of the posttransplant follow-up data across the 36 centers may have varied. The HRAR, CTP, and MELD scores were calculated by H.E. and S.T. The results could have been affected by missing data if the patients who were lost to follow-up were lost because of their drinking, but we cannot know if this is the case. Finally, the element of time should be taken into account in the statistical analyses because the subjects had different lengths of follow-up. Although we had data for the onset of recidivism, we did not have data for the onset of harmful relapse and noncompliance. To solve these limitations, a well-designed prospective study will be necessary.

How Can We Decrease Relapse?

The significantly lower survival rate for relapsing patients shown in this study indicates that preventing relapse is the central strategy for LT for ALC. In order to develop good protocols to decrease relapse, it is important to identify the major (and treatable) risks. Tandon et al.[12] reported that the duration of pretransplant abstinence was a strong predictor of posttransplant problem drinking in a North American cohort of patients undergoing transplantation for alcohol-related liver disease, but they failed to show the optimal period of abstinence. De Gottardi et al.[13] reported the utility of the HRAR score for predicting relapse after transplantation. Gish et al.[20] reported that noncompliance and personality disorders independently predicted recidivism. Kelly et al.[10] identified the following 6 potential predictors of harmful relapse: mental illness, the lack of a stable partner, grams of alcohol consumed per day at the time of assessment, reliance on family or friends for posttransplant support, tobacco consumption at the time of assessment, and lack of insight into alcohol as the cause of the liver disease.[10] Our current study showed that a history of treatment for psychological diseases other than alcoholism before transplantation was a significant indicator of the risk of recidivism, and noncompliance with clinic visits after transplantation and smoking after transplantation were promising (but not statistically significant) indicators. Noncompliance with clinic visits was a significant indicator of the risk of harmful relapse. Notably, we did not find that the HRAR score predicted recidivism or harmful relapse. Because of severe organ shortages, the Japanese Assessment Committee of Indication for Transplantation has used an HRAR score ≤ 2 as a selection criterion for DDLT for ALC in accordance with De Gottardi et al. However, on the basis of our findings, the Japanese Assessment Committee of Indication for Transplantation recently removed the HRAR score restriction.

Although the use of LDLT for ALC is increasing, alcohol relapse after transplantation is not yet widely recognized in Japanese society, and this is the first report on the risk factors for and frequency of relapse in patients undergoing LDLT for ALC in Japan. What Japanese society requests from clinical specialists is not punishment but rescue. To decrease the relapse rate, we have 2 options: we can restrict the patients who receive transplants on the basis of pretransplant indicators, or we can use professional personnel, such as psychiatrists, addiction specialists, and well-trained recipient coordinators, to provide systematic support to high-risk patients. We believe that improving compliance through systematic professional support is necessary for patients undergoing LT for ALC in Japan.

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エクソーム解析に着手し，解析を進めている．しかし，トリオ解析と比較して，大量のシークエンスデータや遺伝子変異情報を適切かつ効率的に処理する必要があり，あらたな計算手法・解析手法の開発が期待される．

一方で，エクソーム解析を利用して，対象とする疾患の原因遺伝子変異が特定されれば，そこからあらたな薬剤や治療法が開発される可能性がある．そればかりか，遺伝的背景に応じて最適な医療を選択する“オーダーメイド医療”の実現へ向けて大きく前進するであろう．

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免疫学

免疫抑制療法の進歩と展開

Current progress in immunosuppression for transplantation

移植医療の歴史は拒絶反応の機序解明と免疫抑制剤による拒絶抑制の歴史ともいえる．免疫抑制剤の進歩は臓器移植の成績に大きく貢献しており，とくに1980年代のカルシニューリン阻害剤（CNIs）の登場は移植成績を大きく向上させ，現在では移植後1年以内の臓器生着率は90％以上である．

本稿では，近年注目されている免疫抑制剤の使用と新しい免疫抑制法について解説する．

免疫抑制法の進歩

臓器移植後の免疫抑制法は作用機序の異なる免疫抑制剤を併用し，それぞれの副作用を軽減する多剤併用療法が一般的になりつつある．細胞の核酸合成を阻害するmycophenolate mofetil（MMF）とCNIsの併用，あるいは抗IL-2レセプター抗体とCNIsの併用，導入療法にalemtuzumab（抗CD52抗体）を用いるなどの工夫により，肝移植においてCNIsが引き起こす腎機能障害を軽減するとされている[1]．近年，mTOR阻害剤が免疫抑制剤として注目されており，腎機能障害を引き起こさないこと，免疫抑制効果に加えて抗腫瘍効果をもち合わせることが特徴である．肝細胞癌に対する脳死肝移植において，mTOR阻害剤は移植後の肝細胞癌再発を抑制することが報告されており，現在国外で臨床試験が行われている[2]．さらに，

表1　免疫抑制剤の種類とその作用機序

	免疫抑制剤	作用
カルシニューリン阻害剤	Cyclosporine A Tacrolimus	IL-2産生抑制/T細胞活性化抑制
M-TOR阻害剤	Sirolimus（Rapamycin）	M-TORを阻害して細胞周期G1期からS期への誘導抑制
	Everolimus	Sirolimusの誘導体
モノクローナル抗体	Alemtuzumab	Anti-CD52/T，B，NK細胞除去
	Basiliximab	Anti-CD25/T細胞活性化抑制
	Belatacept Abatacept	Anti-CD80/86/T細胞のco-stimulation阻害 （CD80.86-CD28 interaction）
	Alefacept	Anti-CD2/T細胞のco-stimulation阻害 （LFA3-CD2 interaction）
	Rituximab	Anti-CD20/B細胞除去
ポリクローナル抗体	Thymoglobulin	種々の細胞表面マーカーに反応/T，B，NK細胞除去
アポトーシス抑制蛋白阻害剤	ABT-737	Bcl-2阻害剤/骨髄移植でドナー反応性リンパ球除去
プロテアソーム阻害薬	Bortezomib	プロテアソーム阻害/形質細胞除去
プリン体合成阻害剤	Mycophenolate mofetil	ミコフェノール酸に加水分解されプリン合成系を選択的に阻害/リンパ球分化抑制
	Azathioprine	チオイノシン酸に変換され，イノシン酸と拮抗して核酸の生合成を阻害/リンパ球分化抑制
ステロイド剤	グルココルチコイド	さまざまな機序による免疫抑制

mTOR阻害剤は移植心冠動脈病変の進行を軽減することから心臓移植の分野で，また腎毒性をもたないことから腎移植においてラ島に対して毒性をもたないことからラ島移植にも有効とされている．1990年代からT細胞活性化における副シグナルの役割の研究が盛んとなった．とくに抗原提示細胞に発現するCD80/86からTリンパ球上のCD28へのシグナル伝達を抑制することにより，抗原特異的に免疫寛容を誘導できることが動物実験で明らかになった．CD28のシグナル伝達を抑制するbelataceptはヒトTリンパ球の活性化を抑制し，腎障害を引き起こすことなく免疫抑制効果を発揮する新しい免疫抑制剤である．海外で2011年6月に腎移植で使用が認可され，アメリカ第Ⅲ相臨床試験では腎移植後1年生存率，臓器生着率はcyclosporine Aと差がなかったものの，移植後3年では腎機能の改善と心血管系のリスク軽減をbelatacept投与群に認めたとしている[3]．副作用としては移植後リンパ増殖症(PTLD)の頻度が有意に高く，とくにEBウイルス未感染の腎移植患者に多くみられたため，現在EBウイルス既感染患者のみへの投与とされている．また，肝移植においてのアメリカ第Ⅱ相臨床試験で術後合併症に伴う死亡例がbelatacept投与群に比較的多く認めたために肝移植まで適応が広げられなかった．Belataceptに関してはさらなるデータの蓄積が必要である[4]．

免疫寛容の誘導

混合キメラの誘導は移植臓器特異的な免疫寛容誘導に重要である．ABT-737はアポトーシス抑制蛋白であるBcl-2の活性阻害剤であり，動物実験でABT-737を骨髄移植後に短期間投与したところ，ABT-737がドナー反応性のリンパ球を除去し，安定した混合キメラが誘導されて，免疫寛容を誘導することができたと報告された[5]．免疫寛容における臨床試験においては国際的な組織であるImmune Tolerance Network(ITN)主導で行われた臨床試験の結果が大きなインパクトを与えた．ハーバード大学ではレシピエントの胸腺への放射線照射，T細胞除去(抗CD2抗体)，rituximab(抗CD20抗体)，cyclophosphamideに加えてドナーの骨髄移植をすることにより10人の腎移植患者のうち7人に免疫寛容を誘導することに成功し，そのうち4人は免疫抑制剤なしに最長11年半の生着を認めている[6]．また，スタンフォード大学では16人の腎不全患者に対して，10回のtotal lymphoid irradiation，腎移植後に5回のthymoglobulin投与，そしてドナーの$CD34^+$細胞と1×10^6個のドナーT細胞を術後11日目に投与したところ，15人の患者でGVHDを起こさずにキメラが確認でき，11例で免疫抑制剤からの離脱に成功している[7]．興味深いことに，レシピエントの血液中においてnatural killer T細胞と$CD4^+CD25^+$制御性T(Treg)細胞の割合が増加しており，それらの細胞がドナー細胞の活性を抑制するとともに，移植された臓器の拒絶を抑制していると考えられている．$CD4^+CD25^+$Treg細胞の発見により自己免疫疾患のメカニズム解明，癌免疫，免疫寛容誘導などのさまざまな分野に新しい道が開かれた[8]．King's College(London, UK)においては肝移植における自己Treg細胞を用いた細胞療法の単独施設臨床研究“ThRIL”が予定されており，その新しい免疫抑制法が注目されている．2005年にはレシピエントの脾細胞をドナー抗原と抗CD80/86抗体とともに培養し，ドナー抗原特異的な免疫不能状態へ誘導した後，その細胞を腎移植後のレシピエントに移入し免疫寛容を誘導するというinfectious toleranceを応用した画期的な方法が考案され，サルを用いた腎移植で成功している[9]．この方法は現在，腎移植，肝移植での臨床試験がはじまっており，その結果が期待されている．

おわりに

iPS細胞やES細胞の発見により近い将来拒絶を起こすことのない細胞や臓器をつくることが現実になりつつある．Treg細胞による細胞療法や免疫寛容の誘導も免疫抑制剤を減量して免疫抑制剤の副作用を軽減しようとする点では同じである．今後，それぞれの患者に合った免疫抑制剤を組み合わせるテーラーメイド免疫抑制が可能となり，さらには免疫寛容へ誘導できるように，この分野におけるさらなる研究が期待されている．

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Switching From Tacrolimus to Cyclosporine A to Prevent Primary Biliary Cirrhosis Recurrence After Living-Donor Liver Transplantation

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Recurrence of primary biliary cirrhosis (PBC) after liver transplantation has been shown to negatively affect graft and patient survival. Recently, protective effects of cyclosporine A against PBC recurrence after liver transplantation have been reported. Participants were 4 patients who underwent living-donor liver transplantation (LDLT) for end-stage liver disease due to PBC. Tacrolimus was used for initial immunosuppression, and this was switched to cyclosporine A at least 3 months after liver transplantation. Targeted trough level of cyclosporine A was 20 times that of tacrolimus. We assessed liver and renal function, as well as antimitochondrial M2 antibody for recipients prior to LDLT, as well as before and after switching immunosuppressive agents. Patients were 1 man and 3 women, and they were ages 45 to 47 years at LDLT. Timing of switching from tacrolimus to cyclosporine A was 13, 3, 7, and 4 months respectively after liver transplantation, and all 4 patients have been on cyclosporine A without adverse effects at 20 to 46 months after transplantation. In 2 of 4 patients who had high titers of antimitochondrial M2 antibody before transplantation, antibody titer did not elevate after LDLT. In the other 2 patients without elevation of antimitochondrial M2 antibody, the titer did not turn positive. Switching from tacrolimus to cyclosporine A was possible without medical problems, and all patients exhibit no recurrence of PBC. Cyclosporine A may be useful for prevention of PBC recurrence after LDLT.

Key Words: Primary biliary cirrhosis – Living-donor liver transplantation – Immunosuppression – Recurrence

Primary biliary cirrhosis (PBC) has been one of the most common indications for liver transplantation in adults. Recurrence of PBC after liver transplantation has been shown to negatively affect graft and patient survival. Recently, protective effects of cyclosporine A (CyA) against PBC recurrence after liver transplantation have been reported.[1,2] Corticosteroids after liver transplantation may

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Table 1 Clinical variables before liver transplantation, and before and after switching from tacrolimus to cyclosporine A

	Patient 1			Patient 2			Patient 3			Patient 4		
	Pre-LT	Before	After	Pre-LT	Before	After	Pre-LT	Before	After	Pre-LT	Before	After
Anti-M2 antibody, U/mL	<5	<5	<5	<5	<5	<5	149	66	66	155	47	94
AST, U/mL	167	15	13	112	15	18	112	103	20	132	19	21
ALT, U/mL	51	9	6	78	9	8	43	163	15	83	22	15
Total bilirubin, mg/dL	12.0	0.8	0.6	2.2	0.4	0.3	19.6	2.1	0.9	19.0	0.6	0.6
Albumin, g/dL	2.8	3.8	4.5	3.0	3.3	3.9	2.7	3.5	4.0	2.3	3.7	4.1
PT-INR	1.2	1.0	1.0	1.2	1.0	1.0	1.2	1.0	1.0	1.2	1.0	1.0
Creatinine, mg/dL	0.4	0.74	0.76	0.48	0.65	0.78	0.5	0.62	1.02	0.68	1.19	1.37

ALT, alanine aminotransferase; AST, aspartate aminotransferase; pre-LT, before liver transplantation; PT-INR, prothrombin time–international normalized ratio.

be important to prevent recurrence of PBC.[3] We retrospectively assessed the outcome of switching from tacrolimus to CyA in patients who underwent living-donor liver transplantation (LDLT) for PBC.

Patients and Methods

Participants were 4 patients who underwent LDLT for end-stage liver disease due to PBC at Jikei University Hospital from 2008 to 2009. Tacrolimus and steroids were used for initial immunosuppression, and these were switched to CyA, steroids, and/or mycophenolate mofetil at least 3 months after liver transplantation. The targeted trough level of CyA was 20 times that of tacrolimus. We assessed liver function, renal function, antimitochondrial M2 antibody, and PBC recurrence among recipients before LDLT, and before and after switching immunosuppressive agents.

Results

Patient 1

The recipient was a woman age 45 years at LDLT who had received a diagnosis of PBC at age 36 years. The donor was the woman's 45-year-old husband. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the recipient's Model for End-Stage Liver Disease (MELD) score was 18, and her Child-Pugh score was 10. Immunosuppressive agent was switched from tacrolimus to CyA at 22 months after LDLT without medical problems or PBC recurrence (Table 1). Antimitochondrial M2 antibody remained negative after LDLT. After LDLT, the patient was treated with insulin for diabetes mellitus due to adverse effects of tacrolimus.

Patient 2

The recipient was a woman age 44 years at LDLT who had received a diagnosis of PBC at age 30 years. The donor was the woman's 48-year-old older brother. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the recipient's MELD score was 11, and her Child-Pugh score was 9. Immunosuppressive agent was switched from tacrolimus to CyA at 3 months after LDLT without medical problems or PBC recurrence (Table 1). Antimitochondrial M2 antibody remained negative after LDLT.

Patient 3

The recipient was a woman age 47 years at LDLT who had received a diagnosis of PBC at age 38 years. The donor was an 18-year-old daughter. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the MELD score was 20, and the Child-Pugh score was 10. Immunosuppressive agent was switched from tacrolimus to CyA at 7 months after LDLT. Recipient had a high titer of antimitochondrial M2 antibody before LDLT; antibody titer did not elevate after LDLT (Table 1). At 20 months after LDLT, liver biopsy was performed for liver dysfunction. Liver biopsy specimen revealed moderate late cellular rejection (isolated central perivenulitis) and mild acute cellular rejection [rejection activity index (RAI) = 2; P1 B1 V0] without PBC recurrence (Fig. 1A).

Patient 4

The recipient was a man age 46 years at LDLT who had received a diagnosis of PBC at age 43 years. The donor was the man's 43-year-old younger sister. ABO blood type–identical LDLT was performed

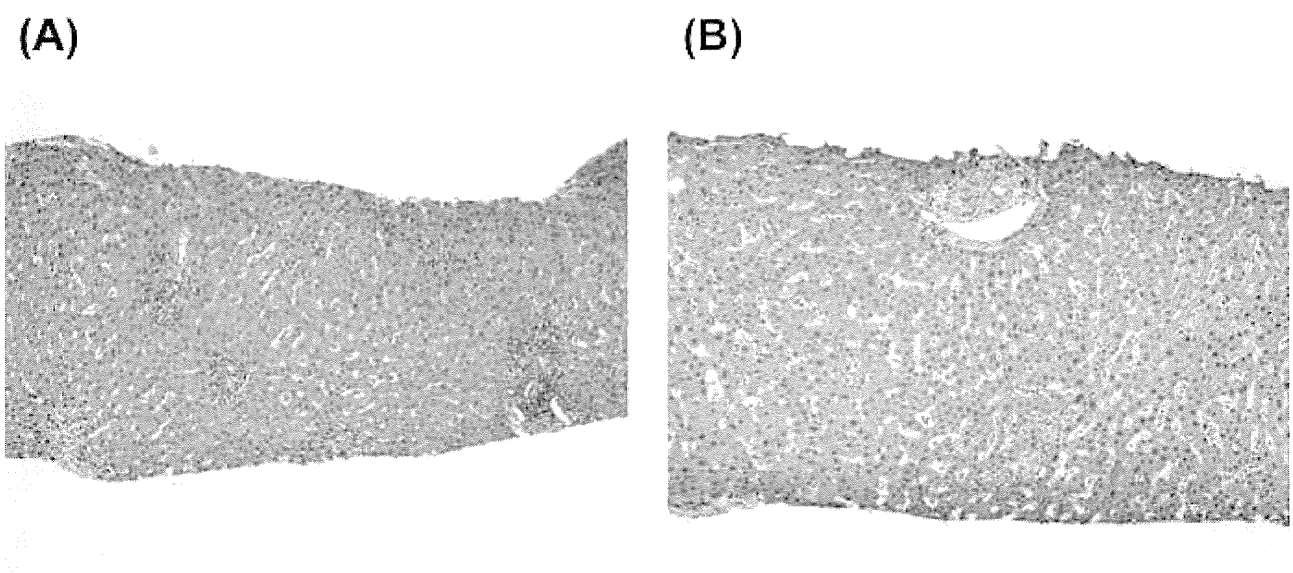

Fig. 1 (A) Liver biopsy specimen for liver dysfunction at 20 months after LDLT for patient 3 revealed moderate late cellular rejection (isolated central perivenulitis) and mild acute cellular rejection (RAI = 2; P1 B1 V0) without PBC recurrence. (B) Liver biopsy specimen for liver dysfunction at 8 months after LDLT for patient 4 revealed moderate acute cellular rejection (RAI = 4; P1 B2 V1) without PBC recurrence.

using the right lobe graft. At LDLT, the recipient's MELD score was 20, and his Child-Pugh score was 12. Immunosuppressive agent was switched from tacrolimus to CyA at 4 months after LDLT. Recipient had a high titer of antimitochondrial M2 antibody before LDLT; antibody titer did not elevate after LDLT (Table 1). At 8 months after LDLT, liver biopsy was performed for liver dysfunction. Liver biopsy specimen revealed moderate acute cellular rejection (RAI = 4; P1 B2 V1) without PBC recurrence (Fig. 1B).

Discussion

With the recent improvements in surgical, anesthetic, and microbiological techniques; the development of immunosuppressive agents; and increasing experience and better patient selection, better outcomes for liver transplantation for end-stage liver disease have been achieved. Liver transplantation is the treatment choice for patients with end-stage liver disease due to PBC; however, the incidence of recurrent PBC increases progressively, and histologic recurrent PBC is reported in approximately one third of patients by 10 years after liver transplantation.[1–6] The pathogenesis of PBC remains uncertain, and the perioperative clinical variables associated with recurrence of PBC after liver transplantation are not completely elucidated.

Despite the era effect of immunosuppressive agents, a major conclusion of most reports in patients who underwent liver transplantation for PBC is that the use of CyA is associated with a lower incidence of PBC recurrence in comparison with tacrolimus.[1–6] However, mechanisms of CyA for prevention of PBC recurrence are unknown. Conversely, tacrolimus is considered as a potent immunosuppressive agent with regard to mortality and graft loss at 1 year, as well as acute rejection.[7] Switching from tacrolimus as the primary immunosuppressive agent for PBC after liver transplantation to CyA as a maintenance immunosuppressive agent may enable safe prevention of PBC recurrence, as well as better outcomes.

Conclusions

Switching from tacrolimus to CyA was possible without sequelae, and all patients exhibit no recurrence of PBC. CyA may be useful for prevention of PBC recurrence after LDLT.

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LETTER TO THE EDITORS

Successful living-donor liver retransplantation by retroperitoneal end-to-end portal vein grafting using recipient's internal jugular vein graft for a patient with portal vein thrombosis

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A 45-year-old male patient, who had undergone living-donor liver transplantation (LDLT) and splenectomy using an extended left lobe graft with hepatico-jejunostomy for end-stage liver disease with portal hyperperfusion caused by primary sclerosing cholangitis (PSC) in October 2009 was admitted to our hospital because of graft failure. At 10-month after LDLT, the patient developed repeated pyrexia caused by cholangitis. Magnetic resonance cholangiopancreatography revealed irregularity and dilatation of intrahepatic bile duct. At percutaneous transhepatic biliary drainage (PTBD), anastomotic stenosis of hepatico-jejunostomy was ruled out. Two months after PTBD, complete portal vein thrombosis (PVT) of the main portal vein developed presumably because of repeated cholangitis and an insertion of the PTBD catheter, for which thrombolytic therapy was attempted, but discontinued because of urinary tract hemorrhage. Doppler ultrasonography and enhanced computed tomography revealed artery-dominant hepatic blood flow, and absence of portal vein flow. Plasma exchange was performed for coagulation disorder and severe hepatic encephalopathy. With a diagnosis of graft failure caused by recurrent PSC with portal thrombosis and the model for end-stage liver disease score of 38, re-LDLT under veno-venous bypass using a right lobe graft was performed at 30-month after the first LDLT. Because the recipient's portal vein could not be used for portal vein reconstruction because of PVT, we performed a grafting using the recipient's left internal jugular vein to restore the portal blood flow. The superior mesenteric vein (SMV) was exposed at the infra-pancreatic portion, and the pancreatic dorsum and the ventral aspect of the portal vein were dissected. The vein graft was anastomosed in an end-to-side fashion with the SMV proximal to the thrombosis, and the free-end of the vein graft was introduced through the pancreatic dorsum to the liver hilum. Then, the vein graft was anastomosed with the donor portal vein in an end-to-end fashion. However, portal inflow was inadequate after the reconstruction, and therefore, an end-to-side proximal anastomosis was switched to end-to-end anastomosis by ligation the inferior mesenteric vein, the inferior pancreaticoduodenal vein, and the splenic vein after hepatic artery reconstruction. Post-transplant enhanced computed

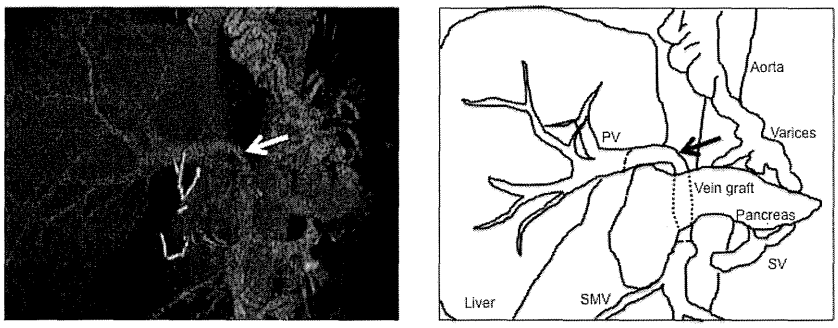

Figure 1 A graft using the recipient's left internal jugular vein was placed in an end-to-end fashion with the superior mesenteric vein proximal to the thrombosis through pancreatic dorsum after ligation the inferior mesenteric vein, the inferior pancreaticoduodenal vein, and the splenic vein. Postre-transplant enhanced computed tomography revealed patency of the vein graft (arrow).

tomography revealed adequate blood flow through the graft (Fig. 1). The patient made a satisfactory recovery, and transferred to an affiliate hospital for rehabilitation at 53 days after re-LDLT, and remains well.

Portal vein thrombosis is a well-recognized complication of end-stage liver disease that ranges from 2% to 26% [1]. The etiology of PVT is often multifactorial, and has not been fully understood. Postnecrotic cirrhosis, hepatitis C virus, cryptogenic cirrhosis, and PSC are associated with a high incidence of PVT [2]. For two decades, PVT was an absolute contraindication to liver transplantation [3]. After publication of a successful liver transplantation in two patients with PVT in 1985 [4], the number of liver transplantation with PVT has increased. PVT is no longer considered as a contraindication for liver transplantation, but adequate method for portal vein reconstruction for patients with PVT remains controversial [5]. PVT is still associated with a considerable peri-operative risk for liver transplantation, because of technical difficulty [6–8]. An adequate portal flow is indispensable to adequate post-transplant graft function. Thrombectomy, jump grafting using recipient's or donor's vessels, and the use of portal vein collaterals have been reported as techniques to restore the portal vein patency at liver transplantation [9]. In grade 1 and 2 cases, thrombectomy is the first choice procedure for portal vein reconstruction [3,8]. In our case, primary recipient's portal vein could not be used for portal reconstruction because of inflammatory and fibrotic changes by complete PVT. Switching from end-to-side to end-to-end fashion of grafting was performed to obtain adequate portal inflow. To the best of our knowledge, our case is the first report of successful re-LDLT by retroperitoneal end-to-end portal vein grafting with the SMV proximal to the thrombosis through pancreatic dorsum using the recipient's internal jugular vein graft for patient with PVT.

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ORIGINAL ARTICLE

Outcomes of living donor liver transplantation for hepatitis C virus-positive recipients in Japan: results of a nationwide survey

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Summary

A nationwide survey of living donor liver transplantation (LDLT) for hepatitis C virus (HCV)-positive recipients was performed in Japan. A total of 514 recipients are reported and included in the study. The cumulative patient survival rate at 5 and 10 years was 72% and 63%, respectively. Of the 514 recipients, 142 patients (28%) died until the end of the observation, among which the leading cause was recurrent hepatitis C (42 cases). According to Cox regression multivariate analysis, donor age (>40), non-right liver graft, acute rejection episode, and absence of a sustained virologic response were independent prognostic factors. Of the 514 recipients, 361 underwent antiviral treatment mainly with pegylated-interferon and ribavirin (preemptive treatment in 150 patients and treatment for confirmed recurrent hepatitis in 211). The dose reduction rate and discontinuation rate were 40% and 42%, respectively, with a sustained virologic response rate of 43%. In conclusion, patient survival of HCV-positive recipients after LDLT was good, with a 10-year survival of 63%. Right liver graft might be preferable for HCV-positive recipients in an LDLT setting.

Introduction

End-stage liver disease caused by chronic hepatitis C virus (HCV) infection is the leading cause of liver transplantation in Western countries [1,2] and Japan [3]. Liver transplantation, including deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT), is an established treatment for these patients, although it unfortunately does not cure HCV-infected recipients. Reinfection by HCV occurs universally and the progression of recurrent hepatitis C in the graft is accelerated compared with chronic hepatitis C infection in the nontransplant population, resulting in the impaired outcome of HCV-positive recipients compared with those with other indications [4–6]. Recently, effective antiviral therapies with new protease inhibitors have been aggressively investigated [7]; however, post-transplant antiviral treatment with pegylated-interferon (PEG-INF) and ribavirin (RBV) has been the main strategy to improve the outcome in both DDLT and LDLT [8] in our study period. While patient survival is significantly improved by achieving a sustained virologic response (SVR) with antiviral treatment among patients with chronic hepatitis C [9], the efficacy of antiviral treatment varies among HCV-positive liver transplant recipients [10].

Here, we conducted a nationwide survey of LDLT for HCV-positive patients and investigated the outcome and prognostic factors for patient survival to further improve the LDLT outcome. We also provide an overview of the antiviral treatment for LDLT recipients in Japan.

Patients and methods

Liver transplantations performed between 1998 and 2012 were collected and reviewed, and the initial LDLT was the subject of this study. The survey was conducted by the Research Group on Hepatitis under the aegis of the Japanese Ministry of Health, Welfare, and Labor. The indication of LDLT for HCV-positive recipients in Japan is similar to that for deceased donor liver transplantation (DDLT) in Western countries [11]. As for cases with hepatocellular carcinoma (HCC), Milan criteria are basically used; however, all institutions apply center-specific extended criteria for those beyond Milan provided that they are without extrahepatic lesions and macroscopic vascular invasions [12]. Data of all consecutive HCV-positive cases were enrolled in the study during this period, completing questionnaire items on computerized database by each institution. A total of 514 HCV-positive recipients from 12 institutions were enrolled in the present retrospective analysis. We first analyzed patient outcome and investigated the factors associated with poor survival among the collected variables. Next, we administered a survey regarding antiviral treatment after LDLT in Japan.

Evaluated variables

The following variables were obtained from the nationwide survey. As for recipient factors, patient age, sex, the existence of pretransplant antiviral treatment, HCV genotype, model for end-stage liver disease (MELD) score, the coexistence of hepatocellular carcinoma, the type of calcineurin inhibitor, use of mycophenolate mofetil (MMF), existence of steroid withdrawal, existence of steroid bolus treatment, splenectomized or not, episodes of acute rejection, existence of the post-transplant antiviral treatment, and achievement of SVR were collected. The diagnosis of acute rejection was based on internationally accepted histologic criteria (Banff guidelines) based on liver biopsies, which was treated with steroid bolus injection initially in the majority of center. The second-line treatments were center dependent, such as 1500–3000 mg of MMF or basiliximab, an interleukin-2 receptor antagonist. Additionally, donor age and the type of partial liver graft were added as variables. The number of LDLT cases per year at each center was also incorporated as a variable, with a cutoff value of 20 cases per year. All these factors were completely fulfilled by each center and assessed for their association with patient outcome. Other incomplete variables which may have a possible association with patient survival, such as IL-28 gene polymorphisms, histological findings, biliary complications, and cytomegalovirus infection, were not incorporated into the analysis.

We then surveyed post-LDLT antiviral treatment. The timing of the antiviral treatment (preemptive or after confirmation of recurrent disease), the antiviral treatment regimen used, time from LDLT to starting antiviral therapy, duration of antiviral therapy, adherence to the treatment, dose reduction rate, and finally the SVR rate were summarized.

Statistical analysis

Continuous variables are reported as medians and ranges, and categorical variables are reported as numbers (proportions). Cumulative survival is presented with Kaplan–Meier curves, and differences in survival between the groups were analyzed with a log-rank test. Factors associated with survival in the log-rank test were then analyzed using a Cox regression analysis. Five patients were lost to follow up during the observation period, and they were censored in the survival analysis. The cutoff value for the continuous variables was basically set according to each mean value, except for the recipient age for which it was set at 60 (mean value of 57) based on literatures. All statistical tests were two-sided, and a P-value of <0.05 was considered significant. The statistical analyses were performed with SPSS statistical software (Chicago, IL, USA) 18.0 for Windows.

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Table 1. Characteristics of living donor liver transplantations for HCV-positive recipients in Japan.

	Total n = 514 (%)
Age (years)	57 (19–73)
Gender: male/female	320 (62)/194 (38)
Body mass index	25 (16–41)
Pretransplant antiviral treatment: yes/no	230 (45)/284 (55)
HCV genotype: 1b/other types	404 (79)/110 (21)
Co-existence of HCC: yes/no	330 (64)/184 (36)
MELD score	15 (4–47)
Transplant at the center with LDLT cases over 20 per year: yes/no	259 (50)/255 (50)
Calcineurin inhibitor: Tac/CsA	324 (63)/198 (37)
Mycophenolate mofetil yes/no	251 (49)/ 263 (51)
Steroid withdrawal: yes/no	144 (28)/370 (72)
Splenectomy: yes/no	284 (55)/230 (45)
Episode of acute rejection: yes/no	127 (25)/387 (75)
Steroid bolus injection: yes/no	414 (81)/100 (19)
Post-transplant antiviral treatment: yes/no	361 (71)/153 (29)
Achievement of SVR: yes/no	154 (30)/360 (70)
Donor age (years)	35 (17–66)
Type of graft: right/non-right	259 (50)/255 (50)

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

Results

Patient characteristics

The characteristics of 514 HCV-positive recipients are summarized in Table 1. There were 320 men and 194 women, with a median age of 57 years (range = 19–73). The median follow-up period was 3.5 years (range = 0.4–13), with a wide spectrum of follow-up duration due to death or shorter observation period from LDLT. The median MELD score was 14.7 (range = 4–47). HCV genotype was 1b in 405 patients (79%). The median age of the living donors was 35 years (range = 17–66), and the graft type was right liver in 259 cases (50%), left liver in 239 cases (46%), and the right lateral sector in 16 cases (4%).

Patient survival

The cumulative patient survival rate at 1, 3, 5, and 10 years was 86%, 76%, 72%, and 63%, respectively (Fig. 1). The causes of patient loss are summarized in Table 2. A total of 142 patients died until the end of the observation. Patient loss due to recurrent hepatitis, which was the leading cause of recipient death in this cohort, occurred in 42 cases, corresponding to 3% of all cases and 30% of lost cases, respectively. Hepatocellular carcinoma recurrence and sepsis were second, with 22 cases each. Additionally, the number of patient death was presented among two groups stratified by the achievement of SVR.

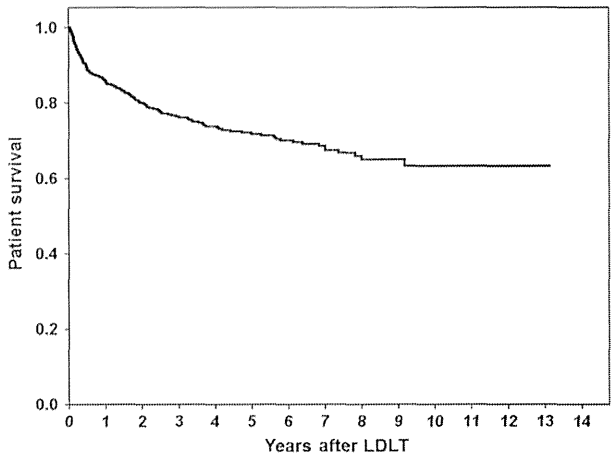

Figure 1 Kaplan–Meier survival curve of the cohort. LDLT, living donor liver transplantation.

Prognostic factors associated with patient survival after LDLT

Recipient and donor factors were analyzed for overall mortality. The results of univariate and multivariate analyses are shown in Table 3. Univariate analysis by the log-rank test revealed that donor age (>40 years; $P < 0.001$), non-right liver graft ($P = 0.036$), an episode of acute rejection ($P < 0.001$), steroid bolus injection ($P < 0.001$), and the absence of SVR ($P < 0.001$) were significant predictors of a poorer outcome of HCV-positive recipients. The Kaplan–Meier survival curves stratified by these factors are presented in Fig. 2. According to Cox regression multivariate analysis, donor age (>40), non-right liver graft, an acute rejection episode, and the absence of SVR were independent prognostic factors (Table 3).

Additionally, we did the same analysis among those achieved SVR after antiviral treatment (n = 154), in which no factor was revealed to be associated with the patient survival (Table 4).

Antiviral treatment after LDLT

Of the 514 recipients, while 153 patients have never undergone antiviral treatment including five patients achieving preoperative SVR, 361 underwent antiviral treatment. Of those, 211 patients (58%) received antiviral treatment after confirmation of recurrent hepatitis C, while the remaining 150 recipients received antiviral treatment preemptively. The summary of the antiviral treatment is shown in Table 5. Time from LDLT to beginning treatment was

Table 2. Causes of patient death.

Patient group	All patients (n = 514) n (%)	With SVR (n = 154) n (%)	Without SVR (n = 360) n (%)
Recurrent HCV	42 (30)	0	42 (37)
Recurrent HCC	22 (15)	8 (30)	14 (12)
Infection	22 (15)	4 (15)	18 (16)
Cerebrovascular diseases	12 (8)	4 (15)	8 (7)
Rejection	8 (6)	0	8 (7)
Graft thrombosis	7 (5)	0	7 (6)
Small for size syndrome	6 (4)	0	6 (5)
Other causes	23 (17)	11 (40)	12 (10)
Total	142	27	115

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

rather short (median: 3 months), whereas the treatment duration was long (median: 17 months), the rate of dose reduction (40%) and discontinuation (42%) were high, and the SVR rate was 43%.

Discussion

This is the largest series of LDLT for HCV-positive recipients reported to date. A total of 514 recipients from 12 Japanese institutions were enrolled and reviewed, with 5- and 10-year cumulative patient survival rates of 72% and 63%, respectively. A recent article from the United Network for Organ Sharing (UNOS) database in the United States of America (USA) reported patient survival rates of 76% and 71% at 5 and 10 years, respectively, among 15 147 HCV-positive DDLT recipients [1]. Similarly, the European Liver Transplant Registry reported 5- and 10-year patient survival rates of 65% and 53%, respectively, among 10 753 HCV-positive DDLT recipients [2]. Based on these reports, the present outcomes of the Japanese nationwide survey of LDLT for HCV-positive recipients are comparable with those of deceased donor whole liver transplantation (DDLT) in both the USA and Europe. However, caution should be paid in comparing the survival results of HCV-positive recipients between LDLT and DDLT. As shown in previous reports [13,14], laboratory MELD score of HCV-positive recipients was higher in DDLT recipients than that in LDLT recipients. Actually, our result, mean MELD score of 15 (median: 14.7, range: 4–47) was lower than that reported in DDLT recipients in Western countries (around 20), which might have a positive impact on patient survival in our study. Another point which should be noted is that the observation period of database of USA and Europe was longer than that of Japan, which might result in the bias of the improvement in techniques and managements in liver transplant.

Table 3. Factors associated with patient survival after living donor liver transplantation for HCV-positive recipients.

Univariate analysis	Hazard ratio (95% confidence interval)	P-value
Recipient age: ≥60 years vs. <60 years	1.322 (0.915–1.876)	0.122
Recipient gender: male versus female	1.072 (0.765–1.432)	0.682
Body mass index: ≥25 vs. <25	0.999 (0.64–1.559)	0.995
Pretransplant antiviral treatment: yes versus no	0.921 (0.721–1.387)	0.912
HCV genotype: 1b versus other types	1.211 (0.781–1.901)	0.723
Co-existence of HCC: yes versus no	0.893 (0.612–1.223)	0.754
MELD score: ≥15 vs. <15	1.125 (0.878–1.389)	0.801
LDLT cases per year: ≥20 vs. <20	1.122 (0.669–1.881)	0.663
Calcineurin inhibitor: Tac versus CyA	0.887 (0.643–1.511)	0.789
Mycophenolate mofetil: yes versus no	0.963 (0.642–1.446)	0.857
Steroid withdrawal: yes versus no	1.003 (0.761–1.621)	0.932
Splenectomy: yes versus no	0.961 (0.623–1.367)	0.889
Episode of acute rejection: yes versus no	3.101 (2.013–5.871)	<0.001
Steroid bolus injection: yes versus no	2.512 (1.541–3.512)	0.003
Achievement of SVR: yes versus no	0.167 (0.121–0.254)	<0.001
Donor age: ≥40 years vs. <40 years	2.231 (1.401–3.331)	<0.001
Type of graft: right liver versus non-right liver	0.422 (0.311–0.711)	0.029
Multivariate analysis		
Episode of acute rejection: yes versus no	3.241 (1.789–5.329)	<0.001
Achievement of SVR: yes versus no	0.181 (0.124–0.301)	<0.001
Donor age: ≥40 years vs. <40 years	2.311 (1.498–3.311)	<0.001
Type of graft: right liver versus non-right liver	0.467 (0.331–0.621)	0.001

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

The present analysis of prognostic factors for impaired patient survival revealed four variables as independent predictors: donor age over 40 years, an acute rejection episode, absence of SVR, and a non-right liver graft. In contrast to the report from USA [13], the center experience did not affect the outcome of patient outcome.

The impact of donor age on outcome has gained increased attention in the DDLT setting due to the

