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EDITORIAL

Is low central venous pressure effective for postoperative care after liver transplantation?

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The central venous pressure (CVP) has been regarded as an important factor for reducing blood loss and the blood transfusion rate during major hepatectomy, and can be controlled by positive end-expiratory pressure (PEEP) or certain drugs and the optimal positioning of the patient [1–4].

In this issue of *Surgery Today*, Wang et al. [5] describe the beneficial effects of lowering the CVP for achieving a better postoperative outcome compared with conventional fluid management in deceased donor liver transplantation based on a prospective randomized controlled study. They report that the low CVP group showed (1) less intraoperative blood loss, (2) a decreased need for intraoperative blood transfusion, (3) fewer lung-related complications at 1 month postoperatively, (4) a shorter intubation period and (5) equal patient survival at 1 year after liver transplantation. A previous retrospective study showed intraoperative blood transfusion to be a risk factor for postoperative lung complications [6]. The present study was done in a prospective, randomized manner, which yielded the same results as those seen in the previous retrospective study. The methods used to reduce the CVP in the present study were the use of the Fowler position, fluid restriction and drugs (e.g., nitroglycerin, furosemide and somatostatin). These methods have also been used in previous studies to reduce the intraoperative CVP, and therefore they appear to be valid for this kind of study [2].

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Although the results provided in the article were of high importance, lowering the CVP during liver transplantation might still be controversial and may have ambivalent aspects with regard to the lack of a relationship between the early complication rates, including renal, hepatic and pulmonary complications, and the CVP following liver transplantation [7–10]. For example, apart from the reduced pulmonary complication rate, and the lower blood loss and blood transfusion rate, what would be the influence of lowering the CVP on the postoperative care following liver transplantation? If blood product administration during the intensive care period is increased, then the policy to limit CVP during surgery would be in vain. Therefore, the readers will also want to know: How would the perfusion in the organ be affected? How would the lactate level in the blood after LT be affected, not only at the end of surgery but also during the postoperative period? How would the post-transplant blood product requirements be affected?

In fact, the period in which the CVP is lowered may be of importance. For example, Feng et al. [7] reported that a low CVP during the pre-anhepatic phase reduced the intraoperative blood loss, protected the liver function and it also had no detrimental effects on the renal function after LT. On the other hand, Cywinski et al. reported that a low CVP during the post-anhepatic phase was not associated with any benefit in terms of immediate postoperative allograft function, graft survival or patient survival [10]. In addition, the cut-off value for CVP monitoring in previous studies varied between 5 and 10 mmHg.

We therefore await further reports from other investigators before drawing any definitive conclusions about the above-mentioned issues, since liver transplant surgery, especially partial liver transplantation, is often affected by multiple factors [11].

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Hepatology Research

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Original Article

Disease recurrence plays a minor role as a cause for retransplantation after living-donor liver transplantation for primary biliary cirrhosis: A multicenter study in Japan

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Aim: To clarify the role of disease recurrence as a cause of graft loss after living-donor liver transplantation (LDLT) for primary biliary cirrhosis (PBC), we investigated explant grafts, as well as the native liver and liver biopsy specimens, of patients who underwent retransplantation.

Methods: Of 516 patients who underwent LDLT for PBC and were registered in the Japanese Liver Transplant Registry, nine patients (1.7%) underwent retransplantation.

Results: Seven patients undergoing retransplantation later than 6 months after primary liver transplantation (LT) were enrolled. All seven patients were female, with ages ranging from 34–57 years, and Model for End-Stage Liver Disease scores ranging 10–28. The right lobe was used as graft in one and the left lobe in six. The initial immunosuppression regimen was tacrolimus in six and cyclosporin in one. The period between the primary LT and retransplantation ranged 11–120 months, with a median of 36 months. Three patients survived and four patients died due to poor graft functions or complications after retransplantation. The primary causes of primary graft loss revealed by histological examination of the explant livers were chronic rejection in three, portal thrombus and/or steatohepatitis in three and outflow block in one. PBC recurrence was observed in 3 and the stage was mild in all.

Conclusion: PBC recurrence has a small impact as a cause of graft loss after LDLT.

Key words: histology, living-donor liver transplantation, primary biliary cirrhosis, recurrence, retransplantation

INTRODUCTION

PRIMARY BILIARY CIRRHOSIS (PBC) is a major indication for liver transplantation (LT). Because autoimmune mechanisms possibly contribute to the etiology of PBC, the possibility of recurrence after transplantation and the impact on the clinical course have been reason for considerable concern. Rates of recurrence have been reported to range 9–35% in deceased-donor LT in Western countries.[1] In living-donor liver transplantation (LDLT) in Japan, the rates have been reported to range 1–40% on the basis of histological evidence.[2–6] However, this range is not reliable because routine liver biopsy is not standard. Furthermore, the impact of recurrence on the clinical course is unclear. The proportion of grafts lost due to disease recurrence was reported to be 2% 10 years after transplantation by Rowe *et al.*[7] On the other hand, Charatcharoenwitthaya *et al.* reported that recurrent PBC was not associated

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with death or retransplantation.[8] There have been no reports of graft failure secondary to recurrent PBC in Japan, either.[2–6]

The difficulty of performing histological diagnosis of recurrent PBC using needle biopsy specimens is a barrier for studying the impact of recurrent PBC, although histological examination is the gold standard.[6,9,10] Heterogeneity of histological changes is a major hurdle for diagnosis on the basis of needle biopsy specimens. To overcome this problem, we conducted a multicenter study using whole hepatic grafts explanted during retransplantation for PBC.

METHODS

OF 516 PATIENTS who underwent LDLT for PBC and who were registered in the Japanese Liver Transplant Registry, nine patients (1.7%) underwent retransplantation. The demographic data of the recipients and primary donors and information on the clinical courses were obtained.

A current author (Y. N.) performed histological investigation of the native liver, the liver biopsy specimens if present, and the explant grafts. The diagnosis of acute cellular rejection (ACR) and chronic rejection was made according to the Banff criteria.[11,12] Staging of PBC was based on the Nakanuma staging system.[13]

This study was approved by the Ethical Committee of Tokyo Women's Medical University as the central office of the multicenter study, or at each institution if necessary, and it conforms to the provisions of the Declaration of Helsinki (as revised in Seoul, Korea, October 2008).

RESULTS

OF THE NINE patients who underwent retransplantation, two died within 6 months after retransplantation. One died due to graft failure secondary to severe acute rejection and another due to small-for-size syndrome. In both cases, we examined the clinical courses and explanted livers, and confirmed the diagnoses. We enrolled the remaining seven patients in this study.

The demographic and operative data of the recipients and primary donors and the clinical courses are shown in Table 1. All patients were female and had histories of pregnancies. Human leukocyte antigen DR8 was detected in all recipients except no. 5 and in the donors of recipients no. 3, 6 and 7. The donor was the patient's husband in two cases, son in three, sister in one and mother in one.

Primary immunosuppression was performed with a triple regimen consisting of calcineurin inhibitor, steroids and antimetabolites (azathioprine, mizoribine) in three patients, and calcineurin inhibitor and steroids in four patients. The calcineurin inhibitor was tacrolimus in all patients except no. 6 in which cyclosporin was converted to tacrolimus 1 year after transplantation.

All patients were treated with ursodeoxycholic acid (UDCA) and no. 1 and 7 with bezafibrate prior to primary transplantation. All patients were given UDCA after transplantation and only no. 3 was given bezafibrate transiently.

Patients 1, 4, 6 and 7 continued to complain of fatigue even after transplantation. Postoperative complications are shown in Table 1. The period between the primary transplantation and retransplantation ranged 11–120 months, with a median of 36 months. Three patients survived and four patients died due to poor graft functions or complications after retransplantation.

Histological findings of the native liver, the liver biopsy specimens and the explant grafts are summarized in Table 2. The stage of PBC of the native liver was 4 in all patients except no. 7. The primary causes of primary graft loss were chronic rejection in three (no. 2, 3 and 6), portal thrombus in one (no. 7), nonalcoholic steatohepatitis (NASH) in one (no. 4), portal thrombus and NASH in one (no. 5), and outflow block in one (no. 1). Briefly, submassive necrosis from ischemic etiology and liver cirrhosis of chronic congestive etiology were observed in no. 1. Foamy cell arteriopathy, duct loss with degenerative epithelial damage with severe cholestasis, and centrilobular and C-C and P-C bridging fibrosis were observed in no. 2. In both patients 4 and 5 with NASH, the stage had progressed from stage 2 in the biopsy specimens to stage 3 in the explanted livers.[14] Portal vein thromboembolism and altered intrahepatic circulation was also observed in no. 5. Marked centrilobular necrosis and hemorrhage with mild inflammation and fibrosis and portal venopathy with repeated thromboemboli were observed in no. 7.

Recurrence of PBC was observed in no. 2, 6 and 7 in the specimens of on-demand needle or wedge biopsies and confirmed in the explanted livers (Figs 1–3). Histological progression of PBC was very mild or mild and the recurrence was not the main cause of graft failure. We evaluated: (i) mononuclear inflammatory infiltrates; (ii) formation of lymphoid aggregates; (iii)

Table 1 Demographic data, operative data and clinical courses

Patient no.	1	2	3	4	5	6	7
Age (years)	52	40	34	37	47	47	57
Time from diagnosis to LT (months)	22	3	60	55	65	132	99
AMA	>320	80	40	80	NA	Negative	160
Anti-M2 (mg/dL)	1859	1550	NA	NA	NA	NA	152
IgM (mg/dL)	1037.8	172.8	426	115	340	NA	524
IgG (mg/dl)	1945.7	884.2	1774	1373	2921	NA	180
ANA	640	±	Negative	±	Negative	320	NA
Child–Pugh score	7	8	11	12	12	14	10
MELD score	10	11	17	24	22	28	11
Primary donor							
Relation	Husband	Mother	Husband	Sister	Son	Son	Son
Age (years)	50	60	34	47	19	20	23
Sex	Male	Female	Male	Female	Male	Male	Male
Operative variables							
Blood type combination	Compatible	Identical	Identical	Compatible	Compatible	Compatible	Identical
GRWR	1.00	0.95	0.88	0.77	1.07	0.58	0.90
Graft type	Left	Right	Left	Left	Left	Left	Left
Operation time (min)	751	550	665	615	730	680	870
Cold ischemic time (min)	82	38	56	53	111	95	131
Warm ischemic time (min)	53	44	33	40	38	45	41
Blood loss (g)	2400	2470	850	10 320	6190	8005	4500
Postoperative complications	Hemoperitoneum, biliary stenosis, ACR, hepatic vein stenosis	Biliary stenosis, ACR, EBV infection	Chronic rejection	ACR	ACR Artery-portal shunt	Biliary leakage and stenosis	Portal vein thrombosis
Time of retransplantation (months)	39	24	36	88	120	20	11
Outcome of retransplantation	Dead (49 days)	Alive	Dead (59 days)	Alive	Alive	Dead (15 days)	Dead (284 days)
Causes of death	Lung bleeding		Graft failure			Graft failure	Graft failure

ACR, acute cellular rejection; AMA, antimitochondrial antibody; ANA, antinuclear antibody; EBV, Epstein–Barr virus; GRWR, graft recipient weight ratio; Ig, immunoglobulin; LT, liver transplantation; MELD, Model of End-stage Liver Disease; NA, not applicable.

Table 2 Histological findings of the native liver, biopsy specimens and explanted liver

Patient no.	1	2	3	4	5	6	7
PBC staging of native livers							
Stage	4	4	4	4	4	4	2
Bile duct loss	3	3	3	3	3	2	1
Fibrosis	3	2	3	3	3	3	1
Orcein deposition	3	2	3	3	3	2	1
Hepatitis activities	1	1	1	0	0	1	1
Cholangitis activities	0	0	0	0	0	0	0
Needle biopsies	Congestion at 6 months	Suspected rPBC (duct loss and hepatitis) at 20 months	No biopsy	rPBC (cholangitis) and NASH at 71 months	rPBC (cholangitis and granuloma) and NASH at 90 months	No biopsy	ACR at 9 months
Main diagnosis	Outflow block	Chronic rejection	Chronic rejection	NASH	PVT and NASH	Chronic rejection	PVT
PBC recurrence	No	Mild (mild chronic cholangitis)	No	Mild (focal duct damage and portal fibrosis)	Mild (focal duct loss and portal inflammation)	No	No

ACR, acute cellular rejection; NASH, non-alcoholic steatohepatitis; PVT, portal vein thrombosis; rPBC, recurrence of PBC.

epithelioid granuloma; and (iv) bile duct damage according to Neuberger's criteria for the diagnosis of recurrent PBC based on liver histology.[15] In patient no. 2, biopsy showed (i) and (iv) (probable recurrence) and the explanted liver showed (i), (ii) and (iv) (definite recurrence); in no. 6, biopsy showed (i), (ii) and (iv) (definite recurrence), and the explanted liver showed (i), (ii) and (iv) (definite recurrence); and in no. 7, biopsy showed (i), (iii) and (iv) (definite recurrence), and the explanted liver showed (i), (ii) and (iv) (definite recurrence).

Case report of three patients with histological diagnoses of recurrent PBC

Patient no. 2 had refractory ACR requiring steroid pulse therapy on postoperative day (POD) 12, 36, 43, 97, 103, 420 and OKT3 monoclonal antibody on POD 434. Liver dysfunction associated with biliary dilatation developed 20 months after LDLT and we performed hepaticojejunostomy and wedge liver biopsy, which revealed suspected recurrence of PBC. Immunosuppression consisted of tacrolimus (3.0 mg/day), steroid (5 mg) and mizoribine (50 mg). Immunoglobulin M was 136, antimitochondrial antibody (AMA) 80 and anti-M2 152 mg/dL. Aggressive liver failure developed despite increased immunosuppression thereafter. She underwent retransplantation 24 months after LDLT.

In patient no. 4, alkaline phosphatase (ALP) began to increase 65 months after LDLT and liver dysfunction developed thereafter. Liver biopsy was performed 71 months after LDLT. Immunosuppression consisted of tacrolimus (2.0 mg/day) and steroid (5 mg). Aspartate aminotransferase (AST) was 44, ALP 432, γ-glutamyltransferase (γ-GT) 17, total bilirubin 1.7 mg/dL, AMA 80 and AMA-M2 155 mg/dL. Tacrolimus was changed to Neoral (Cyclosporine; Novartis, Basel, Switzerland), and mycophenolate mofetil (MMF) (2000 mg/day) was added. Ascites developed 1 year after and liver failure developed. She underwent retransplantation 88 months after LDLT.

In patient no. 5, liver dysfunction developed (AST, 82 IU/L; ALP, 685 IU/L) 50 months after LDLT and was successfully treated with steroid pulse therapy. Liver dysfunction developed and liver biopsy was performed 90 months after LDLT. Total bilirubin was 1.2 mg/dL, AST 57 IU/L, ALP 585 IU/L and γ-GT 48 IU/L. AMA and M2 were not measured. Immunosuppression consisted of tacrolimus only (4.0 mg/day), and MMF (2000 mg) was added thereafter. Portal hypertension started to develop. Radiological examinations yielded a diagnosis of artery-portal shunt of segment 3 of the graft. Shunt

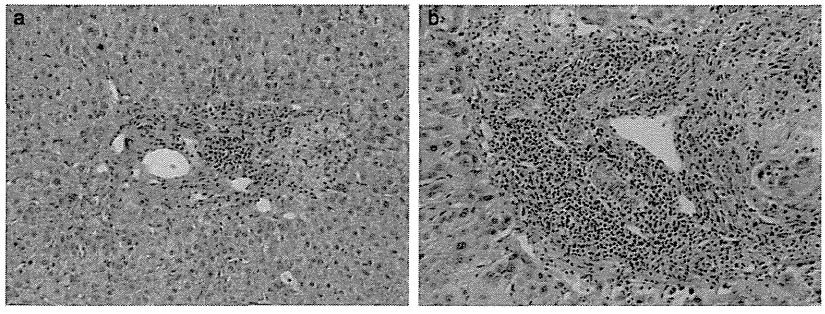

Figure 1 Histological findings of patient no. 2. (a) Wedge liver biopsy at postoperative month 20. Suspected recurrence of primary biliary cirrhosis (PBC) with bile duct loss and mild lobular and portal hepatitis. (b) Second explant liver (allograft). Suspected recurrence of PBC with moderate portal hepatitis and minimal bile duct damage (hematoxylin–eosin, original magnification ×200).

occlusion using metallic coils failed and led to liver failure. She underwent retransplantation 120 months after LDLT.

DISCUSSION

HISTOLOGICAL EXAMINATION IS the gold standard for recurrent PBC. Hubscher *et al.* reported the histological features to be mononuclear portal inflammation, portal lymphoid aggregate, portal granulomas and bile duct damage.[9] These findings are observed also in complications other than recurrent PBC. Lymphoid aggregate can be observed in chronic hepatitis, and bile duct damage and/or vanishing bile duct can be observed in chronic rejection or in the end stage of chronic cholangitis. Foamy cell arteriopathy, which is another specific feature of chronic rejection, is seldom observed on needle biopsy. Duct loss without portal granuloma suggests chronic rejection. The current study focusing on explanted allografts was conducted to avoid these uncertain factors.

Recently, late cellular rejection, chronic hepatitis, and de novo autoimmune hepatitis were discussed as causes of late liver allograft dysfunction.[16] Haga *et al.* reported perivenular lymphoplasmacytic infiltration in a case of their series, which simulated autoimmune hepatitis rather than typical PBC. In our series, ANA was strongly positive prior to primary transplantation in two patients but there were no such findings.

The incidence of recurrent PBC increased along with long-term follow up. Montano-Loza *et al.* studied the cumulative probability of PBC recurrence after LT.[17] Their histological study was not based on protocol biopsy. The overall 5- and 10-year probability of recurrence was 13% and 29%, respectively, in their series. They analyzed risk factors for recurrence and the clinical impacts. Although PBC transplant recipients receiving cyclosporin have a lower risk of disease recurrence, the development of recurrent PBC had no impact on long-term patient survival during 10 years of follow up. The incidence in LDLT based on protocol biopsy was 40% during 10 years of follow up.[3] Besides the increasing incidence, progression of recurrent PBC is still a concern, although progression of recurrent PBC was slow within 10 years of follow up in our series. In Japanese registries of LT, some cases of mortality after 10 years have been reported but information about their causes is not available.[18] A precise study of these cases is required to reveal the risks including recurrence in long-term follow-up.

Protocol biopsies for early diagnosis of recurrent PBC may not be essential to improve clinical courses of

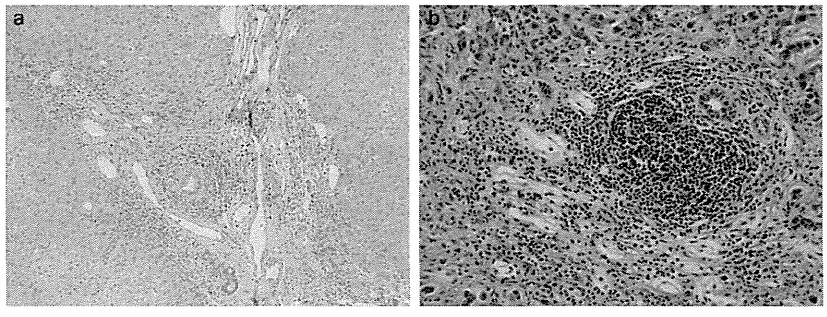

Figure 2 Histological findings of patient no. 4. (a) Needle liver biopsy at postoperative month 71. Recurrence of primary biliary cirrhosis (PBC) with non-suppurative cholangitis and moderate portal hepatitis and fibrosis. (b) Second explant liver (allograft). Suspected recurrence of PBC with focal duct damage and portal inflammation (hematoxylin–eosin, original magnifications: [a] ×150; [b] ×200).

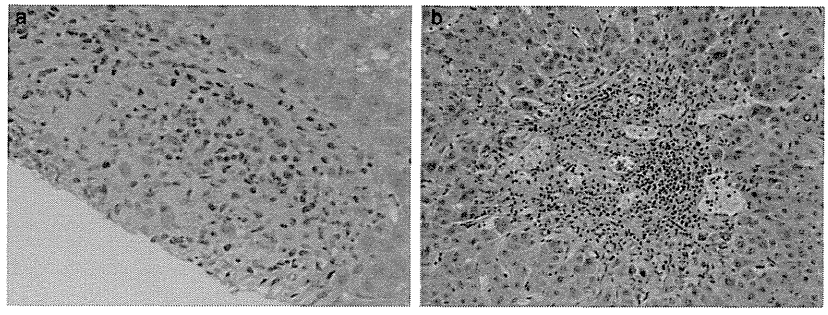

Figure 3 Histological findings of patient no. 5. (a) Needle liver biopsy at postoperative month 90. Recurrence of primary biliary cirrhosis (PBC) with focal cholangitis and epithelioid granuloma. (b) Second explant liver (allograft). Suspected recurrence of PBC with bile duct loss and portal inflammation (hematoxylin–eosin, original magnifications: [a] ×250; [b] ×200).

patients after LT for PBC. Timely biopsies and suitable radiological examinations, when hepatic chemistries deteriorate, are important to improve the clinical course within 10 years after transplantation.

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Evaluation of immune function under conversion from Prograf to Advagraf in living donor liver transplantation

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Although some reports have shown the safety and efficacy of conversion from Prograf to Advagraf in liver transplantation, there have been no reports showing the change of immune function after conversion. The aim of this study is not only to analyze the safety and efficacy of conversion from Prograf to Advagraf, but also to evaluate the immune function using the ImmuKnow assay.

Material/Methods: Of the 168 living donor liver transplantation (LDLT) patients, 21 recipients whose liver function was stable after discharge in outpatient clinic and who agreed to conversion from Prograf to Advagraf were enrolled in this study. Liver, renal, and immune functions were retrospectively reviewed.

Results: There were no significant differences in liver and renal function after conversion from Prograf to Advagraf. The intracellular adenosine triphosphate levels before and after conversion were 263±157 and 256±133 ng/ml, respectively, and there was also no significant difference in immune function. None of the recipients showed adverse effects, rejection, or severe infection during the study. It should be further noted that none of the recipients had to increase the dose of Advagraf, while five of 21 recipients (24%) were able to reduce the dose of Advagraf during this study.

Conclusions: Conversion from Prograf to Advagraf in LDLT can be performed safely and effectively without affecting liver, renal, and immune function.

Key words: Advagraf • tacrolimus • ImmuKnow • LDLT

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BACKGROUND

Immunosuppressive therapy is essential to preserve graft function in solid organ transplant recipients [1]. Prograf (Astellas Pharma, Inc.), which is a calcineurin inhibitor developed as an oral twice-daily medicine containing tacrolimus, has been the standard therapeutic regimen all over the world [2]. However, the oral twice-daily regimen has led to non-compliance, and non-compliance causes life-threatening rejection and late graft dysfunction [3,4]. To prevent this, Advagraf (Astellas Pharma, Inc.), a modified tacrolimus formation, was developed as an oral once-daily medicine. At present, conversion to Advagraf therapy has been accepted in various stable organ transplant recipients [5–11].

However, there have been no reports that show the actual changes of immune function after conversion. The ImmuKnow assay (Cylex™ ImmuKnow®-the Cylex Immune Cell Function Assay, Cylex, Inc., USA), which was approved by the Food and Drug Administration in 2002, has been shown to be capable of directly measuring the global immune response, especially T-cell-mediated immunity in transplant recipients. This assay has been shown to reliably distinguish between immune profiles of overimmunosuppression and underimmunosuppression and has been reported to be a convenient, non-invasive, *in vitro* assay, and to be effective as an immune monitoring tool for organ transplant recipients [12,13]. The aim of this study is to analyze the safety and efficacy of conversion from Prograf to Advagraf using not only liver and renal function but also immune function using the ImmuKnow assay.

MATERIAL AND METHODS

Patients

A total of 168 recipients underwent living donor liver transplantation (LDLT) from August 1997 to September 2011 at Nagasaki University Hospital. Of these recipients, 21 who underwent conversion from Prograf to Advagraf were enrolled in this study. They included 13 men and 8 women, with a median age at transplantation of 59 (range, 2–73). Original diagnoses included 3 hepatitis C virus (HCV) cirrhosis, 7 hepatitis B virus (HBV) cirrhosis, 5 alcoholic liver cirrhosis, and 6 others. Of these patients, 8 had hepatocellular carcinoma. The characteristics of the patients are shown in Table 1.

Table 1. The characteristic of the recipients.

Variable	Recipients (n=21)
Gender (male: female)	13: 8
Age	59 (2–73)
Original diagnosis*	HBV-LC: 2 HBV-LC/ HCC: 5 HCV-LC/ HCC: 3 Alcoholic LC: 5 BA: 4 FHF: 2
Duration between LDLT and conversion (months)	33 (7–171)
Duration after conversion (months)	8 (3–29)
Dose of Advagraf at conversion (mg/day)	2 (1–4)

* HBV – hepatitis B virus; HCV – hepatitis C virus; LC – liver cirrhosis; HCC – hepatocellular carcinoma; BA – biliary atresia; FHF – fulminant hepatic failure.

Protocol of immunosuppressant

The baseline protocol of immunosuppressants consisted of Prograf and steroids. The steroids were discontinued three to six months after staged reduction, as long as the liver function was stable without rejection. Prograf was initiated at the dose of 1 mg twice a day after transplantation, and regulated to adjust the desired tacrolimus trough level, 10–15 ng/ml within one month after transplantation and 5–10 ng/ml thereafter. In the outpatient clinic, Prograf was gradually reduced as long as the liver function was stable, and maintained at a minimal dose to prevent both adverse effects and rejection. The indications of the conversion were that liver functions had been stable for at least the three previous months in the outpatient clinic before conversion and that the recipient's fully informed consent to conversion was given. The initial dose after conversion to Advagraf started with the dose equivalent to the dose of Prograf at conversion.

Laboratory evaluation

Tacrolimus trough (Tac), total bilirubin (T-Bil), alanine aminotransferase (ALT), estimated Glomerular Filtration Rate (eGFR), serum creatinine (Cr), and fasting blood sugar (FBS) levels were recorded just before conversion and at the last follow-up and evaluated retrospectively.

The ImmuKnow assay

The immune function was evaluated using Cylex™ ImmuKnow®-the Cylex Immune Cell Function Assay (Cylex, Inc. USA). This assay

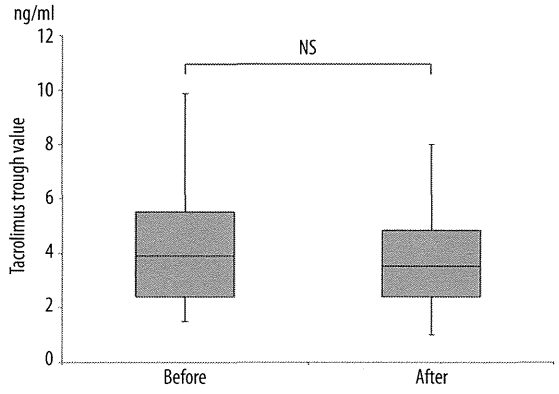

Figure 1. The change of the tacrolimus trough level before and after conversion. Tac levels before and after conversion were 3.9±2.4 and 3.5±2.1 ng/ml, respectively and there was no significant difference in Tac.

was performed according to the manufacturer's protocol [14]. A whole blood sample was collected from each recipient just before conversion and at the last follow-up. The blood sample was collected into an 8-ml sodium heparin vascutainer tube and tested within 10 hours. The whole blood was diluted with a sample diluent, added to a microtiter plate well, and incubated with phytohemagglutinin for 15 to 18 hours in a 37°C, 5% CO_2 incubator. The following day, CD4+ cells were positively selected within the microwells with magnetic particles coated with anti-human CD4 monoclonal antibody (Dynabeads, Dynal, Oslo, Norway) and a strong magnet (model 1050 magnet tray, Cylex, Inc., Columbia, MD) and washed to remove residual cells. A lysing reagent was added to release intracellular adenosine triphosphate (ATP). A luciferin/luciferase mixture was then added to the cell lysate. Within 10 minutes after the addition of the enzyme, released ATP was measured with a GloRunner™ Microplate Luminometer (Turner Biosystems CA).

Statistical analysis

Results for continuous variables were expressed as the median (range). Data for continuous variables were compared using the Mann-Whitney U test. We set statistical significance at $p<.05$.

Results

Change in Tac level and liver functions after conversion.

As shown in Figure 1, the Tac levels before and after conversion were 3.9±2.4 and 3.5±2.1 ng/ml, respectively, and there was no significant difference in Tac. Figure 2 shows liver function. The serum ALT levels before and after conversion were 25±13 and 25±19 IU/l, respectively, and the serum T-Bil levels were 0.9±0.5 and 30.9±0.5 mg/dl, respectively. There was no significant difference in liver function.

Change in renal functions and FBS levels after conversion

Figure 3 shows renal function and FBS level. The serum eGFR levels before and after conversion were 66.8±29.0 and 64.1±27.8 ml/min/1.73 m^2, the serum Cr levels were 0.87±0.23 and 0.82±0.27 mg/dl, and the serum FBS levels were 92±32 and 93±35 mg/dl, respectively. There was no significant difference in renal function or FBS level.

Change in ATP levels after conversion

Figure 4 shows the immune function. The ATP levels before and after conversion were 263±157 and 256±133 ng/ml, respectively. There was also no significant difference in immune function. In addition to these results, none of the recipients showed adverse effects, rejection, or severe

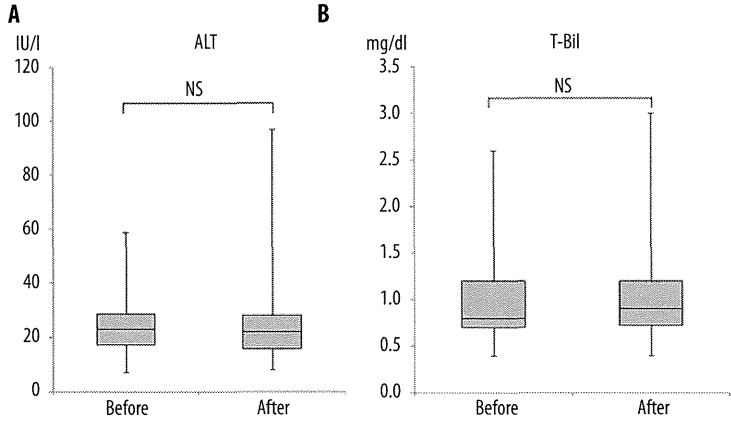

Figure 2. The change of liver functions before and after conversion. (**A**) Serum ALT levels before and after conversion were 25±13 and 25±19 IU/l, respectively. (**B**) Serum T-Bil levels were 0.9±0.5 and 30.9±0.5 mg/dl, respectively. There was no significant difference in liver function.

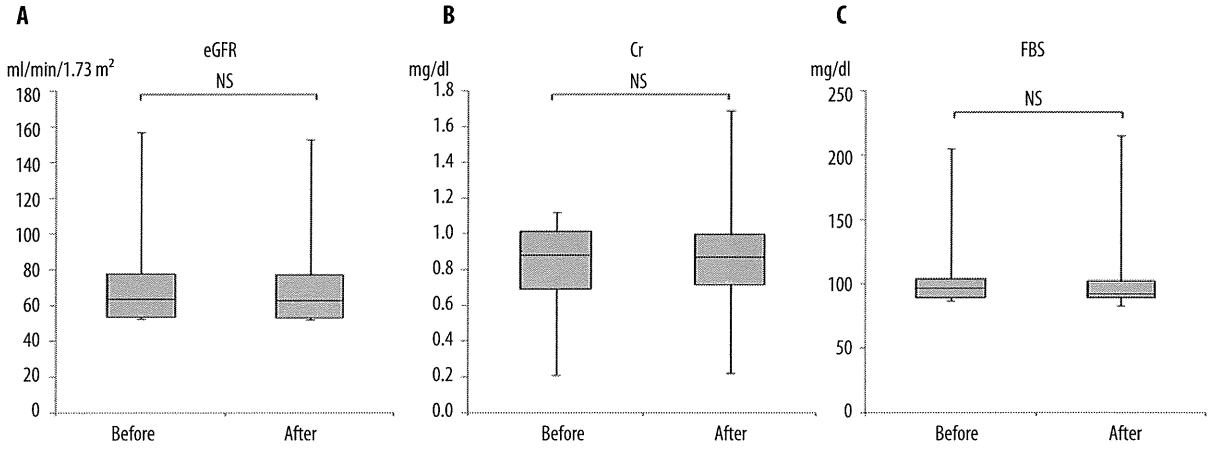

Figure 3. The change of renal functions and FBS before and after conversion. (**A**) Serum eGFR levels before and after conversion were 66.8±29.0 and 64.1±27.8 ml/min/1.73 m², respectively. (**B**) Serum Cr levels were 0.87±0.23 and 0.82±0.27 mg/dl, respectively. (**C**) Serum FBS levels were 92±32 and 93±35 mg/dl, respectively. There was no significant difference in renal functions or FBS level.

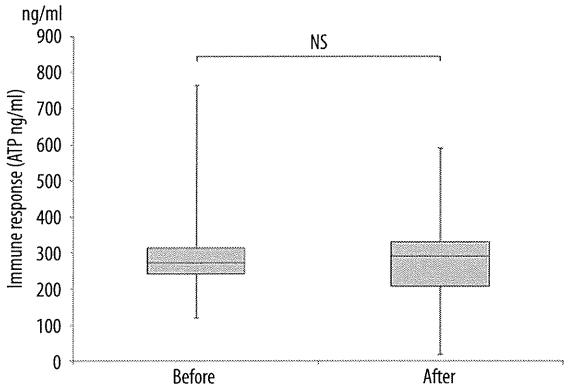

Figure 4. The change of immune function before and after conversion. ATP levels before and after conversion were 263±157 and 256±133 ng/ml, respectively. There was also no significant difference in immune function.

infection during the study. It should also be noted that none of the recipients had to increase the dose of Advagraf, and five of the recipients (24%) could reduce the dose of Advagraf without rejection during this study.

Discussion

Although some reports have shown the safety and efficacy of conversion from Prograf to Advagraf with regard to liver and renal function [8–11], the actual immune function has not yet been clarified. Liver transplantation has been the standard therapeutic option for end-stage liver diseases and reduces the mortality and morbidity of end-stage liver diseases as reflected in the 1- and 5-year survival rates [15–17]. This is mainly the result of improved immunosuppression due to the introduction of a calcineurin inhibitor. Prograf was the immediate-release form of tacrolimus and the oral twice-daily medicine used to prevent various complications in solid organ transplantations and has been accepted as the standard therapeutic regimen all over the world [2,18,19]. However, the estimated rates of nonadherence to immunosuppressive regimens in solid organ transplant recipients range from 15 to 55% [15–17]. Nonadherence has been identified as a leading cause of preventable graft loss [3,4]. It has been proposed that simpler dosing regimens, such as an oral once-daily regimen, may help to improve adherence in transplant recipients [20]. In fact, the prolonged-release form of tacrolimus (Advagraf) was developed as an oral once-daily medicine, and some data have shown that an oral once-daily regimen was associated with an increased likelihood of patient adherence compared with an oral twice-daily regimen [21]. Some reports have evaluated liver and renal function before and after conversion and have shown that the conversion can be applied to liver transplant recipients [8–11]. This study was also able to suggest that conversion does not affect liver and renal function, which is consistent with previous reports.

Additionally, we adapted the ImmuKnow assay to evaluate of the actual immune function. This assay was approved by the US Food and Drug Administration in 2002 for measuring CD4+ T cell immunity [5]. A meta-analysis by Kowaski et al. reported that this assay was useful in monitoring the immune response and assessing the relative risk of infection and rejection [6]. However, no reports have evaluated the safety and efficacy of conversion from Prograf to Advagraf with regard to immune function using this assay. As a result, there

was no significant difference in immune function before and after conversion; this result suggested that conversion also did not affect immune function. In addition, it was important that none of the recipients showed adverse effects, rejection, or severe infection and none had to increase the dose of Advagraf, while five of 21 recipients (24%) were even able to reduce the dose of Advagraf during this study. In our policy of immunosuppression, especially in long-term cases, we reduce and maintain the dose of immunosuppressant as long as possible, keeping the lowest level of tacrolimus needed to prevent rejection. According to the results of this study, Advagraf might be a feasible treatment for avoiding an overdose of tacrolimus.

Conclusions

This study suggested that the conversion of Advagraf can be safely and effectively applied to stable LDLT recipients without affecting liver, renal, and immune function.

Disclosure

The authors have no conflicts of interest or funding to disclose.

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REVIEW ARTICLE

Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus co-infection: update in 2013

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Abstract Because of the progress of anti-retroviral therapy (ART) for human immunodeficiency virus (HIV), mortality due to opportunistic infection resulting in AIDS has been remarkably reduced. However, meanwhile, half of those patients have died of end-stage liver cirrhosis due to hepatitis C virus (HCV) with liver cirrhosis and early occurrence of hepatocellular carcinoma. Recently, in 2013, non-cirrhotic portal hypertension due to ART drugs or still unknown mechanisms have become problematic with early progression of the disease in this patient population. Liver transplantation (LT) could be one treatment of choice in such cases, but the indications for LT perioperative management, including both HIV and HCV treatments and immunosuppression, are still challenging. In this review, we update the literature on HIV/HCV co-infection and LT as well as recent effort for modifying allocation system for those patients.

Keywords Co-infection · Hepatitis C virus · HIV · Human immunodeficiency virus · Liver transplantation

Introduction

The causes of death of human immunodeficiency virus (HIV) infected patients have dramatically changed since 1995. A major background factor behind these trends is the improved HIV control achieved with anti-retroviral therapy (ART) [1]. Despite dramatic reduction of death due to acquired immunodeficiency syndrome (AIDS), co-infected hepatitis C virus (HCV)-related death due to liver failure or hepatocellular carcinoma (HCC) became a serious problem, not only in Japan but all over the world, including England [2]. In Japan, in the late 1980s, contaminated blood products for hemophilia caused co-infection by HIV and HCV. In such cases, liver transplantation (LT) is the only possible treatment option to achieve long-term survival, but several modifications of perioperative management are required recently for better outcome.

In this review, the outcome and the points of management of LT for HIV/HCV co-infected patients were reviewed to save relatively young patients with HIV/HCV co-infection bearing HCC [3, 4], non-cirrhotic portal hypertension (NCPH) [5–7], and decompensated liver cirrhosis [8, 9]. An updated critical review of the literature in 2013 was performed, and new information on problems and results for LT for HIV/HCV co-infection were included.

Upcoming topics regarding LT indications for HIV/HCV co-infection in 2013

Non-cirrhotic portal hypertension

In HIV/HCV coinfected patients, liver failure due to HCV hepatitis was enhanced by ART-related hepatotoxicity, especially manifesting as non-cirrhotic portal hypertension [5–7]. One of the ART drugs, Didanosin (DDI), has been suspected for serious morbidity. Thus, not only in cases with deteriorated liver function, such as in Child–Pugh B or C cases, but also even in Class A cases, patients' liver function can easily deteriorate abruptly [10, 11]. The actual natural course of pure NCPH is unknown, because it can be modulated with HCV or other causes and reported as only case series. However, an important study regarding "Non-cirrhotic portal hypertension in HIV mono-infected patients without HCV" was published in 2012 [12]. All five patients had portal hypertensive symptoms such as ascites or variceal bleeding after ART medication. We need to await their prognostic information, since it can be extrapolated into HIV/HCV co-infected patients after successful HCV eradication.

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Therefore, all HIV/HCV co-infected patients should be carefully followed up so as not to miss the opportunity for LT. Recently, in Japan, a scoring system was created for listing a deceased donor LT for those patients with HIV/HCV co-infection due to previous contaminated blood products.

Hepatocellular carcinoma

Recently it became evident that HCC in HIV/HCV co-infected patients develop HCC at a very early stage of life, such as in the 30s and 40s [3, 4]. The molecular mechanism of its development still remains unclear, but surveillance in those patients should be considered for HCC strictly. In Japan, HIV/HCV co-infected hemophilic patients have been undergoing periodic examination for liver-related disease on a research basis. Early detection could contribute to treatment choices such as liver resection or liver transplantation. Regardless of the infectious status of HIV, treatment strategy for HCC in HIV/HCV infected patients should be the same in HCV mono-infected patients. Namely, whether liver resection could be performed or not should be based on the liver functional reserve. Also radio frequency ablation and transarterial chemoembolization can be selected according to the location, size and number of HCC.

Current results of LT for HIV/HCV co-infected patients in 2013

Indications for LT

As HCV mono-infected patients, LT should be considered when patients develop deteriorated liver function as indicated by a Child–Pugh score of class B or C in co-infected patients. Recently, Murillas et al. reported that the Model for End-stage Liver Disease (MELD) score is the best prognostic factor in HIV-infected patients [13]. HIV/HCV co-infected patients might be considered for LT before their MELD score increases to achieve comparable results with HCV mono-infected patients. Several studies showed that aggressive fibrosis in HIV/HCV co-infected patients compared with HCV mono-infected patients [14, 15], but the mechanism of this aggressive fibrosis remains unclear. Recently, transient elastography or acoustic radiation force impulse (ARFI) imaging to check for liver stiffness has been introduced as an effective and noninvasive modality to determine patients' candidacy for LT [16, 17].

Regardless of the presence of hemophilia, the indications and methods for performing liver transplantation remains unchanged for patients with HIV/HCV co-infection. In fact, after a successful liver transplantation, hemophilia can normally be cured. Usually, the conditions for liver transplantation are as follows: (1) AIDS symptoms have not surfaced; (2) CD4+ T lymphocyte count is 150–200/μl or above; and (3) as a result of ART, the amount of HIV RNA in the blood by PCR method is below the level of sensitivity of the assay.

In HIV/HCV co-infected patients, current studies show that a count of more than 100/μl CD4+ T lymphocytes is acceptable [18, 19], because patients generally have portal hypertension, which can cause leukocytopenia. In such patients, the ratio of CD4/CD8 is reported to be a realistic marker to predict postoperative complications including opportunistic infections. When the ratio is less than 0.15, the incidence of infectious complications is significantly higher [20].

In 2013, based on the evidence of rapid progression of the liver cirrhosis and portal hypertension in patients with HIV/HCV co-infection, a ranking system for waiting list of deceased donor LT has been set up in Japan. Even HIV/HCV co-infected liver cirrhotic patients with Child–Pugh class A can be listed for LT as "point 3" because of NCPH nature. Also co-infected patients with Child–Pugh class B and C can be listed as "point 6" and "point 8" based on the data from our HIV/AIDS project team of the Ministry of Health, Labor, and Welfare of Japan, and world literatures [21–23]. It is basically considered for previous victims of contaminated blood products for hemophilia.

Results of LT for patients with HIV/HCV co-infection

In the United States and Europe, liver transplantation from deceased donors has been performed in HIV patients since the 1980s. At that time, the outcomes of LT were very poor [11]. Recent series of reports are listed in Table 1 [24–31]. The reality is that, in addition to those listed therein, there have been many sporadic reports, such as reviews, expectations for liver transplantation, and assessment of indications.

In general, most reports concluded that the results were 10% worse than in the cases with HCV mono-infection, with a 3-year survival of around 60–70%. Recently, a 5-year patient survival of around 50% was reported, and there is debate whether these results can be accepted for patients of a younger age and were co-infected through previous use of a contaminated blood product. In Japan, the Tokyo group reported six cases of living donor liver transplantation (LDLT) between 2001 and 2004 [32]. Terrault et al. reported that older donor age, combined kidney-liver transplantation, an anti-HCV positive donor, and a body mass index <21 kg/m^2 were independent predictors of graft loss [33]. After LT, several studies showed that acute cellular rejection was more frequent and more severe in HIV/HCV co-infected patients than in HCV mono-infected patients, possibly due to difficulties in achieving optimal immunosuppression because of interactions between antiretroviral agents and immunosuppression.

Table 1 Updated outcome of liver transplantation for HIV positive recipients

Authors	Year	Country	*n*	Patient survival (%)			
				1 year	3 years	5 years	
Duclos-Vallee et al. [25]	2008	France	35	–	73	51	
Tsukada et al. [32]	2011	Japan	6	66	66	50	Only LDLT, only hemophilia
Terrault et al. [33]	2012	US	89	76	60	–	
Miro et al. [26]	2012	Spain	84	88	62	54	
Anadol et al. [27]	2012	Germany	32	90	65	60	
Harbell et al. [28]	2012	USA	125	91	67	–	
Baccarani et al. [31]	2012	Italy	32	–	79	69	
Di Benedetto et al. [46]	2012	Italy	30	75	65	50	with HCC
Ragni et al. [29]	2013	USA	15	71	38	–	only hemophilia

HCC hepatocellular carcinoma, *LDLT* living donor liver transplantation

Lowered outcome can be presumed from previous reports. Final mortality (graft loss) after LT was usually due to infection and multiorgan failure. As in Miro's report the causes due to the higher proportion of organs from donation after cardiac death (DCD) donors, higher rate of combined liver-kidney transplantation, increased rate of acute cellular rejection, HBV co-infection and infection. However, it was of note that there was no death due to infections related to HIV.

Preoperative management of HIV/HCV in liver transplantation

The number of HIV-RNA copies before LT is suggested as an independent risk factor of postoperative mortality, so that HIV should be controlled sufficiently before LT [30]. Accordingly, in patients who are under consideration to receive LT, ART can be safely stopped before LT, because HIV is generally well controlled for a long period by ART. Also ART can be toxic for the virgin graft, which underwent ischemia/reperfusion injury and liver resection in a donor. Once it is settled down after liver transplant, especially in LDLT cases, ART can be resumed with meticulous adjustment with calcineurin inhibitors.

Actually, after LT, ART should be restarted as soon as possible, because HIV-RNA appears at 3 to 30 days after ART is stopped [34], but the timing of restart of ART depends on the patient's condition, including liver function [35]. As long as the liver function has not fully recovered, or partial liver graft such as in LDLT has not yet sufficiently regenerated, ART cannot be started. Castells et al. reported in their case-control study that ART was started at a median of 8 days after LT (range 4–28 days) [36]. ART administered after LT should be the same as the preLT regimen, but the majority of ART drugs, including protease inhibitors and non-nucleoside reverse transcriptase inhibitors, have interactions with calcineurin inhibitors (CNI) or mammalian target-of-rapamycin (mTOR) [37], so that the monitoring of blood levels of immunosuppression is extremely important to avoid infectious complications or rejection. It can easily overshoot beyond the therapeutic level. Currently, a novel HIV-1 integrase inhibitor, raltegravir, is expected to be a feasible drug because it has no interactions with CNI, unlike other drugs [38, 39]. Therefore, the current recommended strategy in the light of LT could be to try raltegravir as ART before LT and see if HIV can be controlled with raltegravir. If it is the case, CNI could be used as usual after LT. However, if raltegravir cannot control HIV or cannot be applied due to other reasons, meticulous management of CNI (e.g. once a week administration with frequent trough monitoring) or Mycophenolate mofetil protocol should be considered. In fact, the novel protease inhibitor anti-HCV drug, telapreir, has the same character as ART drugs for HIV, and transplants team learn to overcome such drug interactions when post-LT HCV mono-infected patients are treated with telaprevir.

The treatment strategy for HCV in HIV/HCV co-infected patients is the same as in HCV mono-infected patients. Combination therapy of pegylated interferon (Peg-IFN) and ribavirin is the standard treatment both before and after LT in 2013. The treatment should be started as soon as possible, because in HIV/HCV co-infected patients, HCV recurrence may be accelerated in an immunocompromised state [40, 41]. As mentioned above, the novel protease inhibitor telaprevir is currently being introduced as an effective drug to achieve sustained viral response (SVR) of 70%, even in genotype 1b, with Peg-IFN/ribavirin in a non-transplant setting [42], but this drug is metabolized via cytochrome P450, as are CNI and various protease inhibitors of ART for HIV. Close monitoring of the CNI trough level should be performed, and although triple therapy with telaprevir/Peg-IFN/ribavirin or even without Peg-IFN is currently reported to be effective to prevent HCV recurrence after LT in HCV mono-infected cases, special attention should be paid when

this regimen is adapted for HIV/HCV co-infected patients. Additionally, mutational status of the IL28 B genotype should be investigated before interferon therapy for both donor and recipient.

Immunosuppression

Several reports have demonstrated both the in vitro and in vivo effectiveness of rapamycin in reducing HIV replication [43–45]. Di Benedetto et al. found that rapamycin monotherapy was significantly beneficial in long-term immunosuppression maintenance and HIV control after LT [46]. Mycophenolate mofetil is expected to be an effective immunosuppressive drug because of its efficacy in reducing HIV infection by both virological and immunological mechanisms. Mycophenolic acid, a selective inhibitor of the de novo synthesis of guanosine nucleotides in T and B lymphocytes, has been proposed to inhibit HIV replication in vitro by depleting the substrate (guanosine nucleotides) for reverse transcriptase. Using these drugs, a more effective regimen of immunosuppression with ART may be established. However, more information needs to be obtained to establish concrete immunosuppressive protocol.

As to steroids, several studies proposed that a steroid-free regimen can be safely applied and effective in LT for HCV cirrhosis. In HIV/HCV co-infected patients, a steroid-free protocol may play a beneficial role in preventing both HIV and HCV recurrence after LT [47, 48].

Hepatocellular carcinoma

Liver transplantation has been performed also for indication of HCC. The most updated study indicated that the existence of HCC did not change the outcome of LT provided that HCC was downstaged preoperatively for UCSF criteria [49]. Also for these cases sirolimus tended to be used as primary immunosuppressive agents. This encouraging result awaits further reports [50].

Conclusions

The above is an overview of liver transplantation performed to date in HIV/HCV- co-infected patients. Although, the results are 10% lower in patient survival after LT than those for HCV mono-infected patients, LT could be feasible in selected cases with HIV/HCV co-infection after careful evaluation within suitable stages of the disease. In light of the fact that most HIV/HCV co-infected patients in Japan are the victims of contaminated blood products, it is believed that the importance of liver transplantation will increase in the future in the context of medical relief as well. Our investigating team under the Ministry of Health, Labor, and Welfare of Japan has made all possible efforts to clarify the appropriate timing to put HIV/HCV co-infected patients on a waiting list for LT.

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Conflict of interest None declared.

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