Tumour markers such as AFP or DCP have been reported to predict the early recurrence of HCC, even in the absence of microvascular invasion in the resected specimen[14,15]. The documentation of microvascular invasion depends on the slice width of the resected specimen and the number of slices investigated. Therefore, early recurrence can occur despite the absence of documented microvascular invasion. However, AFP or DCP levels are raised in nearly 60 per cent of patients with HCC, reflecting the biological behaviour of malignant tumours. The present data indicate that patients with no increase in AFP and DCP levels before surgery have a higher chance of survival without recurrence. In multivariable analysis, both tumour markers were independently associated with death due to recurrence after liver resection with curative intent. Furthermore, patients with a single HCC who had moderately raised AFP and DCP levels still had the prospect of surviving for longer after liver resection than those with high levels of tumour markers.

Considering the number and size of HCCs, a considerable percentage of patients in the 10-year RFS group had a single HCC (91·7 per cent) at the time of liver resection. Even with a raised AFP or DPC level, the risk of early death from recurrent HCC increased when there was more than one lesion. In other words, if a single HCC is found, a patient has an increased chance of surviving for longer after liver resection with curative intent.

Macroscopic HCC appearance was valuable for predicting 10-year RFS after curative liver resection, as shown previously[8]. HCCs of a contiguous multinodular type with clustering of small and contiguous nodules, and simple nodular types with extranodular growth carry a worse prognosis, most likely owing to microvascular invasion. In line with this, patients with these macroscopic types of HCC had a lower chance of long-term survival after liver resection in the present series.

The authors' group previously reported that anatomical resection has therapeutic value for treating patients with HCCs of 2–5 cm in diameter[16]. However, in the present study, this benefit of curative resection was not confirmed, even for HCCs with a diameter of 2–5 cm. This may have been because two extreme patient groups were compared. For example, even for HCC of 2–5 cm in size, the macroscopic appearance, vascular invasion, inflammatory status and fibrosis in the tumour-bearing liver may have been largely different between the two groups.

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ORIGINAL ARTICLE

Lack of Grafted Liver Rejuvenation in Adult-to-Pediatric Liver Transplantation

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Abstract
Background A grafted donor liver should grow and survive under the different conditions presented by a liver transplantation recipient. It has remained unclear, however, whether the age of a grafted liver can be modulated by recipient factors.
Aims This study investigated whether a grafted aged donor liver can be rejuvenated in a pediatric recipient.
Methods Of 119 living donor liver transplants, ten pairs were adult-to-pediatric combinations. Senescence marker protein-30 (SMP-30), which is a protein that is remarkably reduced upon aging, was used as a senescence marker. Immunohistochemical staining for SMP-30 was performed in biopsy specimen after living donor liver transplantation (LDLT). Re-expression of SMP-30 was investigated in a biopsied adult liver ($n = 6$) that had been transplanted in a pediatric recipient.
Results A remarkable expression of SMP-30 was seen in a control pediatric normal liver in comparison with that in an aged adult donor biopsy. Re-expression or an increase in SMP-30 was not observed in the liver of any pediatric recipient who had received an adult liver.
Conclusion An adult grafted liver does not appear to rejuvenate in a pediatric recipient.

Keywords Living donor liver transplantation · Senescence marker protein-30 · Rejuvenation · Pediatric · Graft

Introduction

Many investigators have reported worse outcomes of orthotopic liver transplantation (OLT) with aged donor liver graft [1, 2]. Since living donor liver transplantation (LDLT) is performed with a partial liver graft, lower patient survival has been reported with senile donor grafts than with graft from younger donors [3]. However, if grafted aged liver could adapt to the environment of young or pediatric recipients, resulting in rejuvenation, an aged grafted liver could be regarded as a young graft through the life of the recipient as observed in an in vitro experiment [4]. However, no report of rejuvenation of graft liver in humans has been made thus far.

Senescence marker protein-30 (SMP-30) was found in the liver of rats and is reported to markedly decrease through the senescence process [5, 6]. SMP-30 is associated with Vitamin C synthesis [7], and it has been reported that the senescence process proceeds four times faster in SMP-30 knock-out mouse than in normal mouse [8]. Thus SMP-30 is one of the key elements of senescence. It has also been reported that when SMP-30 decreases, resistance to infectious pathogens would decrease along with organ function, resulting in aging of the organs [9–11].

We therefore used this unique protein expression in the liver to clarify whether a grafted liver can successfully become rejuvenated in adult-to-pediatric LDLT.

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Patients and Methods

Of 119 living donor liver transplants until March 2010, ten pediatric liver transplantations were performed with grafts obtained from parents of the recipients. Eleven biopsies were performed in six patients, when it was clinically indicated. Afterwards, re-expression of SMP-30 was investigated in a biopsied adult liver ($n = 6$) that had been transplanted in a pediatric recipient. Characteristics of recipients and donors are described in Table 1.

Methods of LDLT

LDLT methods have been reported elsewhere [12]. All partial liver grafts were preserved in University of Wisconsin solution and implanted using a piggy-back technique. A dual or triple immunosuppressive regimen was used that included tacrolimus or cyclosporine A, steroid, and mycophenolate mofetil. Biopsy-proven rejections were treated if clinical and laboratory signs mandated steroid bolus treatment.

Immunohistochemical Staining for SMP-30

Four-micrometer liver sections were deparaffinized and rehydrated through 100, 95, and 90% ethanol. In terms of the heat-induced antigen retrieval protocol, a 40-min treatment with Target Retrieval Solution (code S2031, DAKO, Carpinteria, CA) was followed by a 20-min cool-down period at room temperature. The tissue sections were then immunostained using an automated staining system (Autostainer Plus, DAKO, Carpinteria, CA). Slides were incubated with an anti-SMP-30 polyclonal antibody (1:80 dilution, code SML-ROI001, SHIMA Laboratories) for 30 min at room temperature and subsequently with Histofine Simple Stain MAX-PO (MULTI) (Nichirei, Japan). Incubation was performed overnight at 4°C, followed by a wash in three changes of PBS for 5 min. For all staining, the reaction product was developed with the use of 3-diaminobenzidine tetra hydrochloride and H_2O_2. The sections were counterstained with Meyer hematoxylin-eosin. Visualization was labeled polymer (EnVision + system; code K4001, Dako) for 30 min at room temperature, 3,3′-diaminobenzidine as a chromogen for 5 min, and hematoxylin as a counterstain for 5 min.

Among stained hepatocytes, semiquantification was performed based on the comparison with positive controls and negative controls. Positivity of staining was classified as follows: negative −, weak ±, moderate +, strong ++.

Results

Remarkable expression of SMP-30 was seen in a control pediatric liver (10-year-old male, normal liver obtained at liver resection for hepatoblastoma, Fig. 1a, b) and two other pediatric patients (3-year-old patient with neuroblastoma; 1-year-old patient with hepatoblastoma). On the other hand, very limited expression of SMP-30 was

Table 1 Immunohistochemical staining for SMP-30

Donor			Recipient		
Number	Age/relation	SMP-30	Age, primary disease	Liver biopsy (time after LDLT)	SMP-30
1	40/mother	−	6 y, biliary atresia	2 mo	−
				2 y	−
				8 y	−
2	40/mother	+	1 y, biliary atresia	Explant	+
				4 y	+
				5 y	±
3	37/mother	−	5 y, biliary atresia	7 y	−
				8 y	−
4	40/mother	+	11 mo, biliary atresia	Explant	+
				5 y	±
5	37/mother	−	7 mo, fulminant hepatic failure	2 y	−
				3 y	−
6	35/father	−	10 mo, biliary atresia	0.5 y	−

Controls	SMP-30
10 y, hepatoblastoma (normal liver)	++
3 y, neuroblastoma (normal liver)	++
1 y, hepatoblastoma (normal liver)	++

SMP-30 senescence marker protein-30, *LDLT* living donor liver transplantation

Positivity of staining was classified as follows: negative −, weak ±, moderate +, strong ++

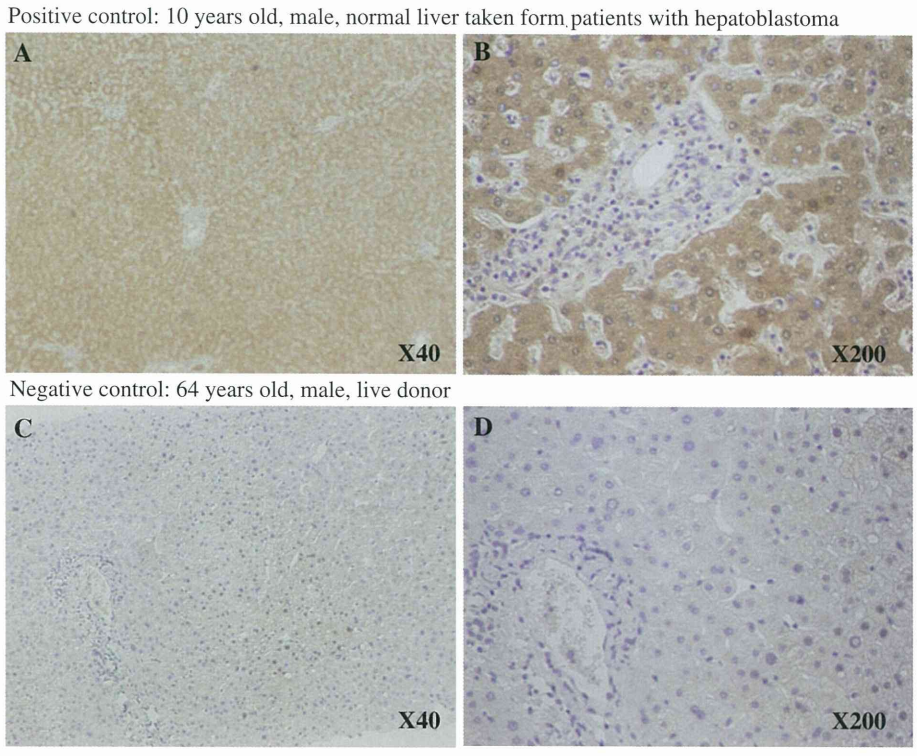

Fig. 1 Immunohistochemical staining for senescence marker protein-30 (SMP-30). **a** Positive control: 10-year-old male, normal liver taken form patients with hepatoblastoma (×40). **b** Same patient as **a** (×200). **c** Negative control: 64-year-old male, live donor (×40). **d** Same patient as **c** (×200)

observed in a case of senile liver (64-year-old male, living donor, Fig. 1c, d), which can be regarded as a negative control.

Figure 2a depicts diseased liver explanted for liver transplantation in a 1-year-old female (case 2). Even in a diseased liver due to biliary atresia, SMP-30 was expressed (Fig. 2a, b). At the time of liver transplantation, the graft liver did not express SMP-30 (37-year-old mother, Fig. 3). After the graft liver was transplanted into the recipient, a series of liver biopsies was performed. Four and 5 years after the LDLT, no increase in SMP-30 in the liver was observed (Fig. 3a–d). Similarly, in the other pediatric recipient for LDLT, SMP-30 was not increased over time (Fig. 4a, b is a 40-year-old living donor; Fig. 4c, d is 5 years after the LDLT, case 4).

The results of the immunohistochemical staining for SMP-30 are summarized in Table 1. No re-expression of SMP-30 was observed in any of the cases.

Discussion

In this study, we clearly demonstrated no re-expression of a senescent marker, SMP-30, in aged liver graft transplanted in pediatric patients. This is the first literature report indicating that no rejuvenation of a graft occurs after liver transplantation based on SMP-30.

With regard to the relationship between aging and liver function, it has been reported that liver function is not altered in the aging process [13], while Hyams has reported a slight derangement of liver function in aged patients [14]. Some investigators have also reported that with aging, drug metabolism of propranolol decreases in hepatocytes of the liver based on an in vitro experiment [15]. On the other hand, a relationship between aging and liver regeneration has been reported in vitro, with DNA synthesis in the hepatocytes of aged rats decreasing but with a preserved repair process as compared with that seen in young rats [16]. Concerning in vivo experiments, there have been some reports indicating a decrease or delay (24 h) in DNA synthesis after partial hepatectomy in elderly rats [17, 18]. Tsukamoto et al. have reported a 24-h delay in liver regeneration with aged, 60-week-old rats compared with 6-week-old rats [19].

In the field of liver transplantation, rejuvenation of the liver has not been fully investigated. Sakai et al. [20] have reported that the survival rate after OLT is similar between aged (28 months old) and young rats (5 months old). However, it has been revealed that fibrosis, bile duct proliferation, and pigment deposition are more observed in aged grafts than in young rats, implying that the liver function of aged liver grafts could be bearable but that aging indeed advances these processes. Recently, Selzner et al. [21] reported that in a rat model with ischemia reperfusion injury, apoptosis induced by TNF-α is increased in aged rats compared with young rats. This mechanism might be one of the causes of poor graft function in an aged liver graft.

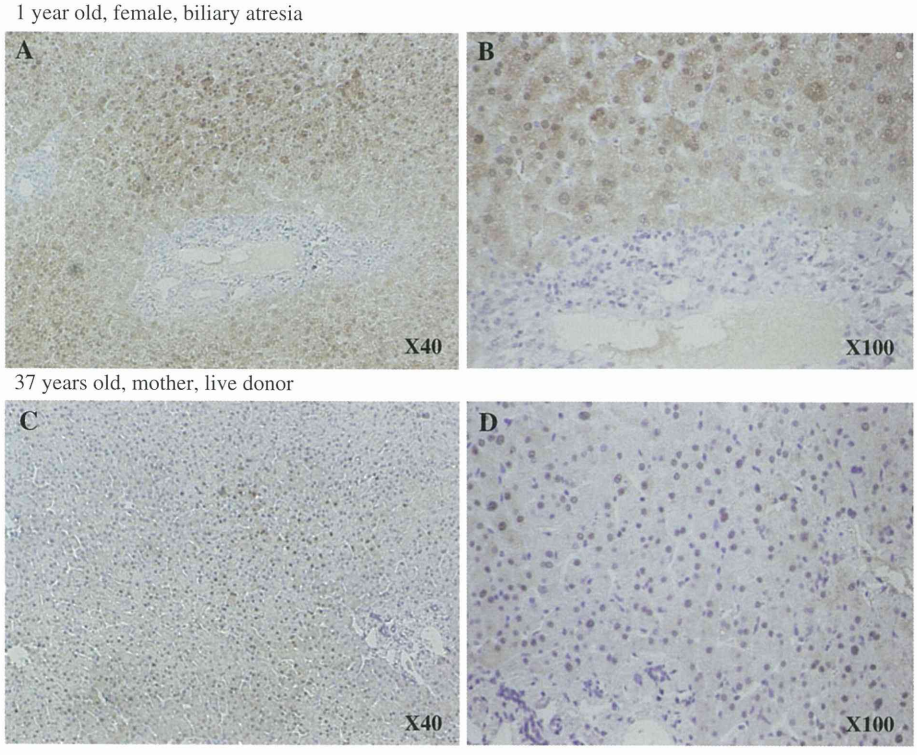

Fig. 2 Immunohistochemical staining for senescence marker protein-30 (SMP-30) (case 2). **a** One-year-old female, biliary atrasia (×40). **b** Same patient as **a** (×100). **c** 37-year-old mother, live donor (×40). **d** Same patient as **c** (×100)

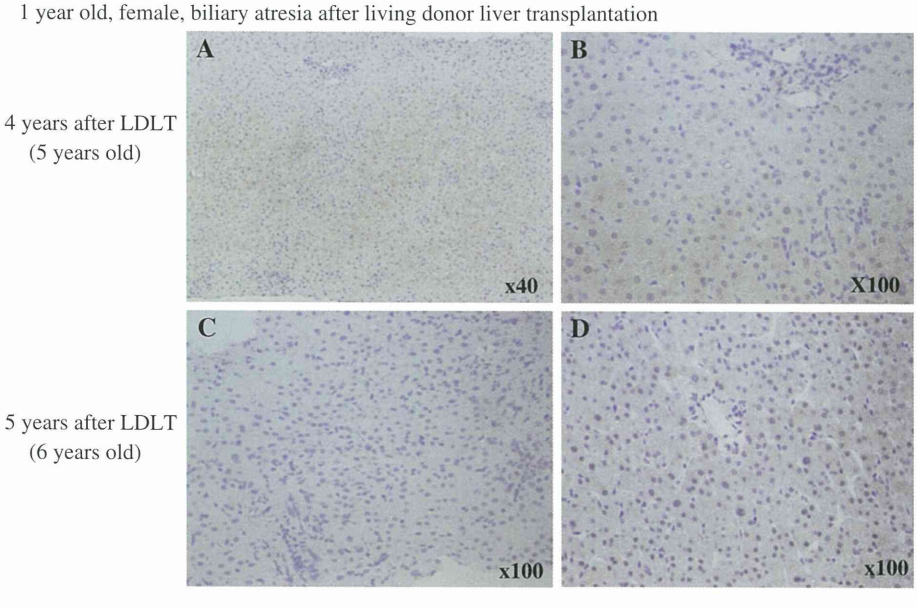

Fig. 3 Immunohistochemical staining for senescence marker protein-30 (SMP-30) (case 2). One-year-old female, biliary atrasia after living donor liver transplantation. **a** Four years after living donor liver transplantation (LDLT) (5 years old) (×40). **b** Same as **a** (×100). **c** Five years after LDLT (6 years old) (×100). **d** Same as **c** (×100)

On the other hand, Conboy et al. [4] reported the rejuvenation of aged progenitor cells in response to exposure to a young systematic environment. In this experiment, it was also reported that old hepatocytes can be rejuvenated in a serum of young rats in terms of DNA synthesis and Ki67 expression, suggesting the possible rejuvenation of hepatocytes.

With regard to hepatocyte proliferation, SMP-30 has a suppressive effect on cell proliferation in the SMP-30 knock-out mouse model [22]. However, many reports have indicated that SMP-30 overexpression can decrease reactive oxygen species and exert a cytoprotective effect [23]. In addition, the possible involvement of apoptosis reduction has been reported [24]. Other than the liver, decreases in SMP-30 are related to organ dysfunction such as that of the brain, ear, and lung [25–28]. If SMP-30 expression is increased in grafted aged liver, the graft survival rate after OLT with aged donor liver could be as good as that with young donor liver.

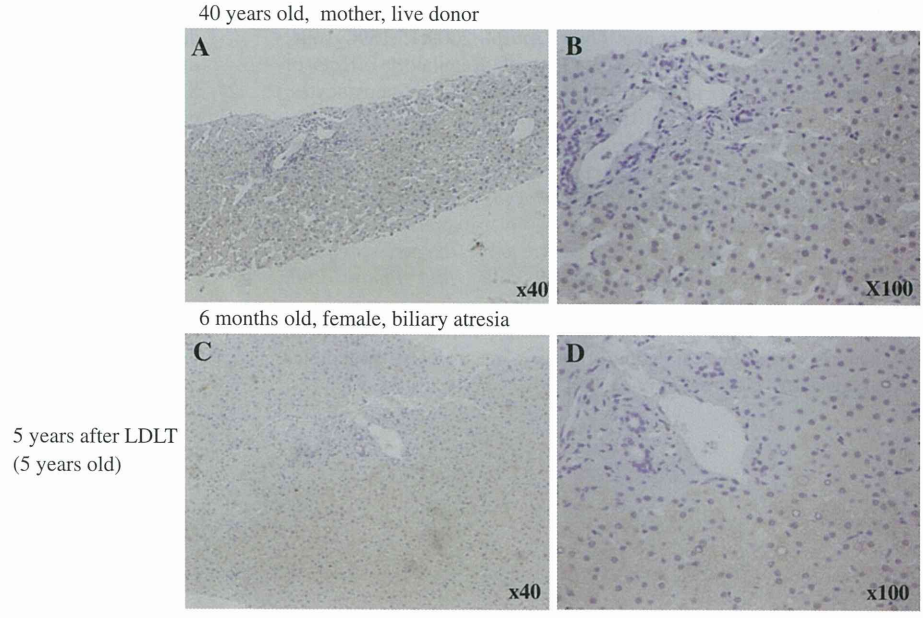

Fig. 4 Immunohistochemical staining for senescence marker protein-30 (SMP-30) (case 4). **a** 40-year-old mother, live donor (×40). **b** Same as **a** (×100). **c** Six-month-old female, biliary atrasia (5 years after living donor liver transplantation [LDLT]) (×40), **d** Same as **c** (×100)

SMP-30 was used as a marker for senescence in this study because it is ubiquitously expressed in pediatric liver and is stable for immunohistochemical investigations of paraffin-fixed samples. Another possible marker of senescence is the telomere length, although a huge number of samples is needed to determine whether there are differences in telomere length, making this method impractical.

In conclusion, it was demonstrated in humans that rejuvenation, as assessed by SMP-30, was not observed in the setting of adult-to-pediatric liver transplantation.

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Surgical Technique

Elective living donor liver transplantation by hybrid hand-assisted laparoscopic surgery and short upper midline laparotomy

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Background. *Although the technique of liver transplantation is well developed, the invasiveness of the operation can be decreased with laparoscopic procedures.*
Methods. *We performed elective living donor liver transplantation (LDLT) through a short midline incision combined with hand-assisted laparoscopic surgery (HALS). Nine selected patients with end stage liver disease underwent the procedure between July, 2010 and February, 2011 (median age 60, median Child-Pugh 9, median MELD score 14). Splenectomy was performed simultaneously in 7 cases. The liver (and spleen) were mobilized by a sealing device under a HALS procedure with an 8-cm upper midline incision, followed by explantation of the diseased liver (and spleen) through the upper midline incision which was extended to 12 to 15 cm. Partial liver grafts were implanted through the upper midline incision.*
Results. *The median duration of the operation was 741 minutes, the median time needed for anastomosis was 48 minutes, the median blood loss was 3,940 g, and the median liver weight was 866 g.*
Eight recipients are alive and have good graft function. A difficult implantation for one patient required an additional right transverse incision. When compared with 13 recent liver recipients who underwent LDLT with a regular Mercedes-Benz-type incision, no clinically relevant drawbacks of the HALS hybrid procedure were observed.
Conclusion. *We have shown the feasibility and safety of LDLT performed through a short midline incision without abdominal muscle disruption with the aid of HALS. (Surgery 2011;150:1002-5.)*

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In an attempt to decrease the morbidity and invasiveness associated with liver surgery, several liver transplant teams have developed laparoscopic approaches to hepatectomy for living donors and patients with hepatic malignancies.[1-5] The surgical procedure performed on liver transplant recipients with portal hypertension is considered one of the most difficult abdominal operations because of the existence of collateral vessels. Nevertheless, selected patients have undergone a less invasive procedure with laparoscopic assistance, including patients with portal hypertension who underwent splenectomy.[6] We postulated that an elective liver transplant recipient procedure could be performed through an upper midline laparotomy after mobilization of the liver and spleen using hand-assisted laparoscopic surgery (HALS). We report a safe method for less invasive liver transplantation via a short midline incision without disruption of the abdominal musculature and nerves.[7]

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MATERIALS AND METHODS

Living donor liver transplantation (LDLT) through a midline incision using a hand-assisted laparoscopic procedure was planned in 9 patients between July 2010 and February 2011. Seven patients had liver cirrhosis due to hepatitis C, in

Table. Comparison of patient demographics and operative results

	HALS + upper midline (n = *9*)	*Mercedes-Benz-type incision* (n = *13*)	P *value*
Age	60 (44–69)	54 (27–72)	NS
Gender (Male:Female)	4:5	8:5	NS
Child-Pugh score	9 (6–14)	10 (5–15)	NS
MELD score	14 (7–43)	15 (7–35)	NS
Graft (RL:ELL)	1:8	6:7	NS
Operation duration (min)	741 (599–839)	812 (654–1,097)	$P < .05$
Anastomosis (min)	48 (37–55)	36 (32–65)	NS
Blood loss (g)	3,940 (1300–18,400)	3,350 (520–5,600)	NS
Explanted liver (g)	866 (596–1,270)	830 (399–1,250)	NS
Outcome	1 death	2 deaths	NS

Values are expressed as median (range).
HALS, Hand-assisted laparoscopic surgery; *MELD,* model for end-stage liver disease; *Anastomosis,* anastomosis for hepatic vein and portal vein reconstruction; *ELL,* extended left lobe graft with middle hepatic vein; *RL,* right lobe graft.

whom splenectomy was performed simultaneously. One patient required LDLT because of hepatitis B cirrhosis, and another for Caroli's disease. The Ethics Committee of Nagasaki University Hospital approved a laparoscopic approach for the living donors as well. After experience with the 3 living donor right hepatectomy procedures, we planned to introduce the procedure in the recipient operation as well. The laparoscopic procedure was described in detail to the recipients and they gave their written consent. Patient demographics are provided in the Table. This combined laparoscopic and upper midline laparotomy procedure was indicated only for elective LDLT without a previous history of upper abdominal surgery. Neither ascites nor the degree of portal hypertension was considered as an exclusion criterion. Splenectomy was performed for preemptive interferon therapy after the liver transplantation.

Operative technique. Patients were placed supine with arms adducted and a urinary catheter, and arterial and central venous lines were inserted. An 8-cm upper midline laparotomy was made followed by a 12-mm infra umbilical incision for the laparoscope. A Gelport (Applied Medical, Rancho Santa Margarita, CA) was used in at the 8-cm incision, and a 5-mm port was placed in the right and left lateral upper abdomen under pneumoperitoneum (CO_2 at 8 mmHg) (Fig, *A*). This configuration enabled the first assistant surgeon, who stood on the left side of the patient, to use the hand port for liver manipulation. The primary operator stood on the right side and used the right lateral 5-mm port for dissection. Using a laparoscopic sealing device (Enseal; Ethicon Endo-Surgery, Cincinnati, OH) and hand assist, the right lobe of the liver was mobilized until the inferior vena cava was exposed (Fig, *B*). For patients who needed splenectomy, the primary operator moved to the left side and used the left lateral 5-mm port to mobilize the spleen from the retroperitoneum, which was handled by the first assistant surgeon through a Gelport from the right side, using a sealing device. After those bilateral mobilizations, the midline incision was extended to 12–15 cm, and a wound protector was applied. The wound was retracted and opened with the Omnitract retractor. Under direct view, the short hepatic veins were divided and the right hepatic vein was encircled through a midline incision as well as by transection of the splenic hilum with an endovascular stapler. After hepatic hilum dissection, explantation of the liver was performed in our regular manner without veno-veno bypass (Fig, *C*).

Implantation of the left hepatic lobe with the middle hepatic vein was performed through the midline under cross-clamping on inferior vena cava using the standard procedure, followed by arterial and biliary reconstruction. Implantation of the right hepatic lobe was performed under partial clamping on inferior vena cava. After the procedure (Fig, *D*), 2 drains were placed through the 5-mm trochers, and the midline wound was closed.

In order to clarify the effect of our HALS hybrid procedure, data from 13 recent cases of the LDLT procedure involving a Mercedes-Benz-type incision after January 2010 were analyzed and compared (Table).

Statistical analysis. Univariate analysis was performed using the chi-square test for categorical factors and the Mann-Whitney test for numerical values. *P* values of less than .05 were considered to be statistically significant.

RESULTS

The Table shows the patient demographics and operation results for our hybrid procedure of LDLT in comparison with LDLT under regular Mercedes-Benz-type incision. Case 2 had massive

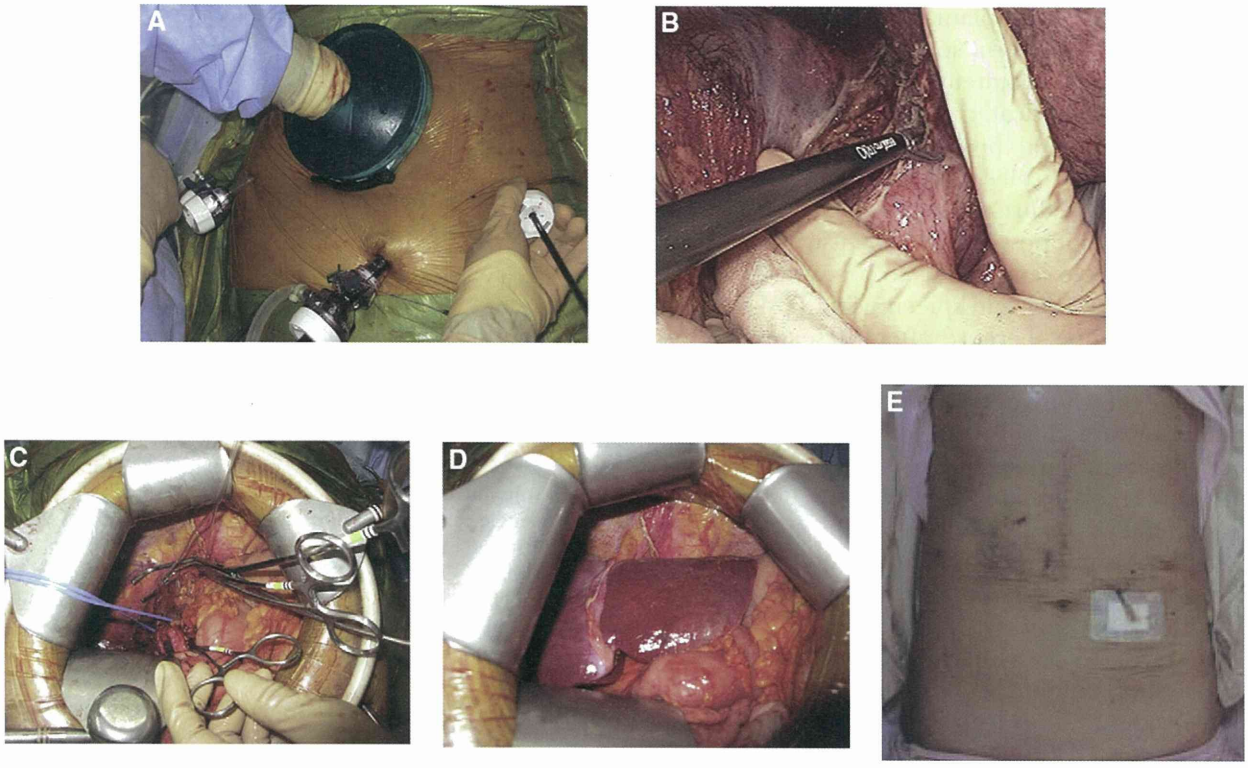

Fig. Case 2, 68 years old, female. (*A*) Hand-assisted port was applied for pneumoperitoneum. (*B*) Laparoscopic mobilization of the diseased liver. (*C*) Anhepatic phase though midline incision. (*D*) Implanted extended left liver lobe graft. (*E*) The abdominal wound 2 months after the operation. A biliary splint and tube jejunostomy was still placed and covered with white gauze.

3.5-L ascites that was evacuated through the laparotomy. A left lobe graft with the middle hepatic vein was implanted through the upper midline incision in 8 patients. The median duration of the operation was 741 minutes (range, 599–839) with a median blood loss of 3,940 ml (range, 1,300–18,400). The hepatic venous and portal venous reconstruction lasted a median of 48 minutes (range, 35–55). In case 2, the caudate lobe vein was also reconstructed. One case (Case 8) required an additional right transverse incision as it involved a difficult implantation. Eight recipients are alive and have excellent graft function. One death (Case 8) occurred due to thrombolytic microangiopathy on day 68. The wound in Case 2 was shown at 2 months after the LDLT (Fig, *E*).

When the results of the HALS hybrid procedure were compared with those of 13 recent LDLT recipients performed using a regular Mercedes-Benz-type incision, no clinically important limitations were observed with the HALS hybrid procedure (Table). In fact, the operative time was less in HALS hybrid cases (HALS: median 741 vs Mercedes-Benz: 812 minutes). Otherwise, there were no important differences between HALS hybrid cases and regular incision cases.

DISCUSSION

We showed the feasibility of LDLT through a midline incision without abdominal muscle disruption as occurs with the usual transverse incision combined with HALS. Because LDLT is performed usually in an elective manner, this procedure could be planned and prepared for.

Before this study, we had performed 130 LDLTs through the usual transverse Mercedes-Benz-type incisions.[8] Based on that experience, we presumed that it would be possible to perform explantation of the liver and spleen followed by implantation of the partial graft liver through a midline incision, because the liver hilum and inferior vena cava are usually located in the center of the upper abdomen. Also, because HALS has been used in the hepatectomy from the living donors, hepatic malignancy, and splenectomy, its use in the recipients seemed logical, because the magnified view under laparoscopy would allow us to obtain hemostasis using sealing devices.[9,10] Because the transverse incision is usually needed only for mobilization of the right liver lobe and spleen, the laparoscopic procedure would allow this mobilization, especially in patients with an increased body mass index.[11,12]

During liver transplantation for patients with hepatitis C, we perform splenectomy for postoperative interferon treatment with ribavirin, which is sometimes complicated by thrombocytepenia.[13] For this combined procedure with mobilization of the liver and spleen, as presented in 7 cases, the HALS procedure showed a marked benefit of visualization not possible with the usual open laparotomy. It made sense for us to perform the mobilization of the liver and spleen using HALS under the laparoscope, because after these procedures the liver transplantation could be performed through the short upper midline incision. Quick celiotomy and closure of the abdomen were also benefits of the upper midline incision.[14] Because no muscle disruption occurred, we believe that postoperative rehabilitation was facilitated. The additional duration of the laparoscopic procedure was offset by the rapid opening and closing of the abdominal incision.

In our series, for the hybrid procedure of HALS and a short midline laparotomy, we selected patients without a history of previous upper abdominal surgery. Although there was still a risk of massive bleeding from collateral vessels, the use of a sealing device with a magnified view allowed us to perform the laparoscopic mobilization. The median blood loss during LDLT was similar to what is reported in large LDLT series.[15] Although we have not had serious complications during the procedure, we would not hesitate to add a wide transverse incision if any difficulty occurred during the procedure, as occurred in our case 8.

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SURGERY TODAY

Review Article

Liver Transplantation for Patients with Human Immunodeficiency Virus and Hepatitis C Virus Coinfection with Special Reference to Hemophiliac Recipients in Japan

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Abstract
Liver transplantation for patients with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) remains challenging. The advent of highly active antiretroviral therapy (HAART) for HIV has reduced mortality from opportunistic infection related to acquired immunodeficiency syndrome dramatically, while about 50% of patients die of end-stage liver cirrhosis resulting from HCV. In Japan, liver cirrhosis frequently develops after HCV–HIV coinfection resulting from previously transfused infected blood products for hemophilia. The problems of liver transplantation for those patients arise from the need to control calcineurin inhibitor with HAART drugs, the difficulty of using interferon after liver transplantation with HAART, and the need to control intraoperative coagulopathy associated with hemophilia. We review published reports of liver transplantation for these patients in the updated world literature.

Key words Liver transplantation · Hepatitis C virus · Human immunodeficiency virus · Coinfection · Highly active antiretroviral therapy

Introduction

According to a report compiled by the Japanese Ministry of Health, Labour and Welfare in October 2006, the number of HIV-infected patients in Japan was 8071 (6275 males and 1796 females), and this number has increased further since.[1] In 2008 there were 1557 new cases reported, including 1126 HIV-positive cases and 431 acquired immunodeficiency syndrome (AIDS) cases.[2] The possible routes of infection include sexual contact, through contaminated or unheated blood products, and mother-to-child transmission. When HIV infection is contracted through blood products, there is often coinfection with HCV.

Since 1995, there has been a major change in the cause of death of HIV-infected patients. It is believed that the major factor contributing to these trends is the improved HIV control achieved in recent years with highly active antiretroviral therapy (HAART).[3] HAART is defined as a combination of drugs from different classes of HIV therapy, comprising nucleoside reverse transcriptase inhibitors (NRTIs), and either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or a protease inhibitor (PI). If the compliance is 95% or more, this therapy is successful in more than 50% of patients.[3–5]

This review focuses on liver transplantation in Japanese patients with HIV and HCV, especially those in whom the disease was caused by receiving contaminated blood products in the past and who may be candidates for liver transplantation.

Epidemiology of HIV–HCV Coinfection in Patients with Hemophilia in Japan

According to a survey by the Ministry of Health, Labour and Welfare in the 2008 fiscal year in Japan, 602 patients with hemophilia A (factor 8 deficiency) and 183 with hemophilia B (factor 9 deficiency) were alive with HIV infection (Table 1).[6] Among these, 524 with hemophilia A (87%) and 162 with hemophilia B (89%) also had HCV infections and liver disease (Table 2). Of the 524 persons with hemophilia A, 33 (6.3%) had cirrhosis, 5 (0.9%) had liver cancer, and 2 (0.4%) had liver failure. Two of these patients underwent a liver transplant procedure. It is highly possible that about 50 of the patients

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Table 1. Coagulation disorders in Japan

	Hemophilia				
	A	B	VWD	VWD-related disease	Total
Total	4211	916	892	452	6471
Male	4185	908	406	246	5745
Female	29	8	486	206	726
HIV negative					
Total	3609	733	885	448	5675
Male	3583	725	404	245	4957
Female	26	8	481	203	718
HIV positive					
Total	602	183	7	4	796
Male	602	183	2	1	788
Female	0	0	5	3	8

Source: Official Report of the National Surveillance on Coagulation Disorders in Japan, 2008
HIV, human immunodeficiency virus; VWD, von Willebrand disease

Table 2. Stage of liver disease in patients with hemophilia and HIV infection (only reported surviving cases with HCV coinfection)

	No hepatitis	Acute hepatitis	Chronic hepatitis	Liver cirrhosis	HCC	Liver failure	Cured with IFN	Spontaneous cure	LT	Total
Hemophilia A	45	2	350	33	5	2	59	26	2	524
Hemophilia B	15	1	100	11	6	0	19	8	2	162
Total	60	3	450	44	11	2	78	34	4	686

Source: Official Report of the National Surveillance on Coagulation Disorders in Japan, 2008
HIV, human immunodeficiency virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LT, liver transplantation; IFN, interferon

with cirrhosis may be candidates for liver transplantation in the future. In fact, this survey revealed that one-third of the deaths of HIV–HCV coinfected patients with blood-borne diseases were caused by liver disease.

A characteristic that should be taken into account when using imported blood products is that the proportion of patients with HCV genotype 1b is low, at 25% vs 70% in general for Japanese, and the proportion of patients with HCV genotype 3a is high, at 23%. Also, one study found that the proportion of patients with HIV–HCV coinfection with an HCV titer below the level of sensitivity of the assay was significantly lower than the proportion of such patients among non-HIV cases of HCV infection, at 44.0% vs 55.4%, respectively.[7] There have been a few reports from other countries on the problems associated with HCV and HIV infections in hemophiliac patients.[8,9]

Liver Transplantations in HIV–HCV Coinfected Patients

Indications for Liver Transplantation in Patients with HIV–HCV Coinfection

Regardless of the presence of hemophilia, the indications for and methods of liver transplantation are the same for patients with HIV–HCV coinfection. Therefore, information on liver transplantation for HIV–HCV coinfected patients without hemophilia is presented in this section. In fact, after successful liver transplantation, hemophilia can normally be cured. In principle, as for a non-HIV-infected patient, liver transplantation is indicated for patients with type C cirrhosis in liver failure and no expectation of a long-term prognosis.[10–14] Liver transplantation is also indicated for patients not yet in liver failure, but with severe liver damage caused by HAART, especially those with chronic hepatitis C, who need to suspend or stop HAART.[15–18] For patients receiving HAART, the indication needs to be considered in terms of both hepatic reserve and status of the HIV infection. Liver transplantation may also be indicated for hepatocellular carcinoma that develops during follow-up.[19] The conditions for liver transplantation are often defined as follows: AIDS symptoms have not surfaced; the CD4+ lymphocyte count is 200–250/μl or above; and as a result of HAART, the amount of HIV in the blood is below the level of sensitivity of the assay. However, there are cases of pancytopenia resulting from portal hypertension and, as such, some institutions believe that the criterion for liver transplantation resolved be a CD4+ lymphocyte count of 100/μl or more.[19–22] Therefore, an issue to be resolved is whether

the indication can be based solely on a CD4+ lymphocyte count. Although a ratio of CD4 to CD8 lymphocyte count of 14% or greater is also considered an indication, individual institutions still refer to their own criteria. A recent study found a significant correlation between the preoperative model for end-stage liver disease (MELD) score and the postoperative survival rates of HIV–HCV coinfected patients: this also warrants investigation.[23]

Results of Liver Transplantation for Patients with HIV–HCV Coinfection

Liver transplantation from deceased donors has been performed in HIV patients since the 1980s in the United States and Europe. Initially the results were poor, with survival rates of only about 47%,[24] but this has improved remarkably since the introduction of HAART (Table 3). According to a review article published in 2004, 51 HIV-positive patients received liver transplantation between 1996 and 2004 worldwide, with liver damage caused by HCV being the indication in 68%. Since 1997, liver transplantation has been performed in 29 HIV patients at the University of Pittsburgh: 26% of these patients were hemophiliac and 89% were HCV-positive.[25] According to a retrospective study by the United Network for Organ Sharing, involving 138 HIV-positive persons and 30520 HIV-negative persons and evaluating liver transplantation, from 1997 when HAART was introduced and thereafter, the prognosis of patients who were only HIV-positive was relatively good.[26] In this study, the prognosis of HIV–HCV coinfected patients was worse than that of patients who were positive only for HIV. A series of reports are listed in Table 3.[13,20,21,25–34] In reality, in addition to those listed there have been many sporadic reports, such as reviews, regarding expectations for liver transplantation, and assessments of indications.

A recent important study in France, on 14 patients, provided details on interferons, HAART therapy, and liver fibrosis.[33] In all patients, the preoperative amount of HIV in the blood was below the level of sensitivity, and the CD4+ T-cell counts ranged from 85 to 1015. As for calcineurin inhibitors, tacrolimus 0.5 mg per week was started in the 2nd week after surgery in principle; however, there were five cases (36%) of an overdose. HAART was recommenced in the 2nd week after surgery, resulting in the long-term administration of steroids. Liver biopsies in the 12th month after liver transplantation revealed one case of fibrosing cholestatic hepatitis (FCH), one case of fibrosis stage F3, two cases of F2, and five cases of F1. The prognosis after transplantation was thought to be encouraging, since there was only one death as a result of FCH in the series.

Living Donor Liver Transplantation for Patients with HIV–HCV Coinfection

The Koike Group of the Ministry of Health, Labour, and Welfare reported seven cases of living donor liver transplantation (LDLT) for HIV–HCV coinfected patients with hemophilia at The University of Tokyo, and one at Hiroshima University.[35,36] The HCV genotypes were 1a and 1b ($n = 1$), 1b and 3a ($n = 1$), 2a ($n = 1$), 2a and 2b ($n = 1$), and 3a and 1b ($n = 1$). The HVC-RNA levels ranged from 2.8 to 1410 kIU/ml, the HIV-RNA levels in two cases were 50 copies/ml or less, being below the sensitivity level, and the CD4+ T-cell counts ranged from 120 to 618/μl and were 250/μl or less in two cases. At the time of the report in 2005, four patients were alive. Small bowel bleeding (suspected cytomegalovirus enteritis) and graft dysfunction were cited as the causes of death of the nonsurviving patients. Interestingly, interferon therapy was given after surgery to the surviving patients, whereas it was suspended in the two patients who died. HAART therapy was not given to one patient on the grounds that the HIV virus disappeared as the interferon treatment progressed. The report stated that the administration of factor 8 products was never required after surgery for patient #1.

Living donor liver transplantation from a hemophilia carrier was reported in 2002,[37] and it seems that LDLT has been performed in up to 10 patients in Japan. As noted in the section on epidemiology, there are some 50 patients coinfected with HIV–HCV from blood products, in whom liver failure has developed. They, like other patients with chronic hepatitis, may be candidates for liver transplantation, so it is necessary to collect sufficient information.

Problems with Liver Transplantation in HIV–HCV Coinfected Patients with Hemophilia

The Blood Concentration of the Calcineurin Inhibitor Used in Combination with HAART Is Increased

The risk of opportunistic infections caused by a delay in starting HAART and the appropriate time to start HAART has not been established. Moreover, early initiation of the therapy is associated with a high risk of drug-induced liver damage.[38,39] A new drug, Ralteglavir, does not interfere with the metabolism of the calcineurin inhibitor, and might reduce the chance of overshooting the trough level of the calcineurin inhibitor.[40]

Progression of HCV Recurrence Is Accelerated in These Patients Compared with Those Who Are Only HIV-Positive[41]

The HIV virus population dynamics manifest via the immune systems, which are targeted by antiviral drugs such as interferon and ribavirin as well as the HAART

Table 3. Reported series of liver transplantation for patients with HIV infection

First author, year, institution (Journal[Ref.])		*n*	Survival	Findings
Ragni, 2003, Pittsburgh (J Infect Dis[27])	HIV only	24	3-Year 72.8%	Risk factor for mortality after LT
	HIV+HCV	15	3-Year 56.9%	CD4+ <200/μl, HAART resume not possible HIV viral load >400 copies/ml
Neff, 2003, Pittsburgh (Liver Transpl[28])	HIV positive	16	14/16	2 HAART discontinued due to liver damage 13/16 HIV negative before LT CD4+ <200/μl (6/16), <100/μl (2/16) ACR (6/16). FK trough level increased (6/16)
Fung, 2004, Review	HIV positive (total)	51	80%	68% HCV coinfection, 26% hemophilia
(Liver Transpl[25])	(Pittsburgh)	29	20/29	
Norris, 2004, London (Liver Transpl[29])	HIV+HCV	7	2/7	4 HCV recurrence, died with sepsis
	HIV only	7	7/7	HBV no recurrence
Moreno, 2005, Madrid (Liver Transpl[30])	HIV+HCV	4	3/4	1 died with FCH 17 months after LT CD4+ <100/μl (2/16) ACR (1/4), no opportunistic infection
Radecke, 2005, Essen (Liver Int[31])	HIV+HCV	5	2/5	2 survived case on HAART
Miró, 2007, Barcelona (J HIV Ther[11])	HIV+HCV	Review ($n > 200$)	1-Year 50%–55% (without LT)	Indication for LT: CD4+ >100/μl, HIV negative SVR rate (post LT) 15%–20%
Schreibman, 2007, Miami (Transplantation[20])	HIV positive	15	3-Year 73.3%	Infectious complication 26.7% vs 8.7% ($P = 0.006$)
	HIV negative	857	3-Year 79.4%	Indication for LT: CD4+ >100/μl, HIV <200 copies/mm^3
Reiberger, 2008, Vienna (Eur J Clin Invest[32])	HIV+HCV (post)	31		HCV viral load increased on immunosuppression
	HIV+HCV (pre)	20		IFN effective if CD4+ preserved
	HCV only (pre)	25		SVR rate: HIV–HCV (post LT) 28%
	HIV+HCV (post LT) 50%, HCV only (post LT) 56%			
Mindikoglu, 2008, UNOS (Transplantation[26])	HIV positive	138	2-Year 70%, 3-year 66%	All after HAART era, HCV+ poor prognostic factor
	HIV+HCV	58	2-Year 52%	
	HIV negative	520	2-Year 81%, 3-year 77%	
Duclos-Vallée, 2008, France (THEVIC study group) (Hepatology[21])	HIV+HCV	35	2-Year 73%, 5-year 51%	Pre LT MELD score most important factor for mortality
	HCV only	44	2-Year 91%, 5-year 81%	HIV coinfection: fibrosis progression (>F2) quicker LT indication: CD4+ > 100/μl, HIV negative
Samri, 2009, France (multicenter) (J Hepatol[33])	HIV+HCV	14	2-Year 93%	LT indication: HIV negative, no AIDS FK and HAART resumed 2 weeks after LT, FK overdose 5/14 (36%) 1 FCH died. 1-year F2 2, F3 1, F4 (FCH) 2
Testillano, 2009, Bilbao (Transplant Proc[34])	HIV+HCV	12	3-Year 62%	Patient survival, HCV recurrence, FCH not different ($P = 0.09$) from LT for patients without HIV
	HCV only	59	3-Year 84%	

.HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; HAART, highly active antiretroviral therapy; FCH, fibrosing cholestatic hepatitis; LT, liver transplantation; ACR, acute cellular rejection; SVR, sustained virological response; IFN, interferon; UNOS, United Network for Organ Sharing; MELD, model for end-stage liver disease; FK, tacrolimus

drugs.[42–45] The best time to start interferon treatment and other post-transplantation measures to prevent HCV, optimal immunosuppressive regimens, and ways of monitoring drug blood levels are being studied, and further reports are expected.[46–51]

According to a review on the effects of interferon treatment after liver transplantation, the SVR rate ranges from 0% to 50%. This article reported that there had been many side effects in HIV-positive patients, especially caused by anemia and a low white blood cell

count, and that the continuation of treatment for such patients had been made possible by administration of the growth factor.[52]

Some Studies Refer to the Correlation Between T-Cell Counts and Acute Rejection

In practice, some studies showed the rate of acute cellular rejection to be similar, regardless of HIV positivity.[11,53] Induction therapy without steroids has also been attempted,[54] and the rate of opportunistic infection is reported to be similar after organ transplantation in HIV-positive patients.[20] Thus, the number of CD4+ lymphocytes present prior to liver transplantation is an important factor.

HAART Drugs Can Cause Hepatic Toxicity[55]

If HAART drugs induce liver failure, the best HAART drug to use after liver transplantation must be selected carefully. HAART drug toxicity can also induce complications with acute cellular rejection or other hepatic problems after liver transplantation. A liver biopsy may be needed to elucidate the real cause. Noncirrhotic portal hypertension has recently been reported in HIV-positive patients. HAART drugs may be related to those unresolved pathogeneses.[56]

The Control of Infection After Liver Transplantation for HIV–HCV Coinfection Is Based on the Count of CD4+ lymphocytes Obtained During the Perioperative Period

Therefore, the timing of recommencement of the HAART drug and the preoperative CD4+ lymphocytes counts are both important factors. According to previous reports, prophylaxis against bacterial and viral infections seems to be the same as for liver transplantation without HIV infection.[20]

The Presence of Hemophilia Makes It Difficult to Manage the Coagulation Time and Control Bleeding During the Intra- and Postoperative Period Before a Transplanted Liver Starts to Function

Moreover, when considering LDLT and when only carrier-donors exist, an assessment of the risks associated with the resection of the carrier-donor's liver would also be a problem.[37]

Conclusions

This review is an overview of liver transplantation performed to date for HIV–HCV coinfected persons. Although there have been no cadaveric liver transplantations for these patients in Japan,[57] conventional knowledge about cadaveric liver transplantation may be applicable in most cases, despite the unresolved problems. In light of the fact that most of these Japanese patients are the victims of contaminated blood products, we believe that the number of liver transplantations will increase, in the context of medical relief.[58]

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Chapter 15: Surgical Management of Pressure Ulcers

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