Acta Med. Okayama, 2019
Vol. 73, No. 1, pp. 41–50

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Predictive Factors for Successful Vaccination Against Hepatitis B Surface Antigen in Patients Who Have Undergone Orthotopic Liver Transplantation

Ailee Ikeda[a], Akinobu Takaki[a]*, Tetsuya Yasunaka[a], Atsushi Oyama[a], Takuya Adachi[a], Nozomu Wada[a], Hideki Onishi[a], Fusao Ikeda[a], Hidenori Shiraha[a], Kazuhiro Yoshida[b], Takashi Kuise[b], Daisuke Nobuoka[b], Ryuichi Yoshida[b], Yuzo Umeda[b], Takahito Yagi[b], Toshiyoshi Fujiwara[b], and Hiroyuki Okada[a]

Departments of [a]Gastroenterology and Hepatology, and [b]Gastroenterological Surgery, Transplant and Surgical Oncology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

Post-orthotopic liver transplantation (OLT) hepatitis B recurrence is well-controlled with a nucleos(t)ide analogue and hepatitis B immunoglobulin (HBIG) combination, but the high cost and the potential risk of unknown infection associated with HBIG remain unresolved issues. Low-cost recombinant hepatitis B virus (HBV) vaccine administration is a potential solution to these problems. We retrospectively analyzed the rate and predictive factors of HBV vaccine success in 49 post-OLT patients: liver cirrhosis-type B (LC-B), n = 28 patients; acute liver failure-type B (ALF-B), n = 8; and non-HBV-related end-stage liver disease (non-B ESLD) who received a liver from anti-hepatitis B core antibody-positive donors, n = 13. A positive anti-hepatitis B surface antibody response was achieved in 29% (8/28) of the LC-B group, 88% (7/8) of the ALF-B group, and 44% (4/9) of the adult non-B ESLD group. All four non-B ESLD infants showed vaccine success. The predictive factors for a good response in LC-B were young age, marital donor, and high donor age. ALF-B and non-B ESLD infants are thus good vaccination candidates. LC-B patients with marital donors are also good candidates, perhaps because the donated liver maintains an efficient immune memory to HBV, as the donors had already been infected in adulthood and showed adequate anti-HBV immune responses.

Key words: acute liver failure, hepatitis B, hepatitis B vaccine, liver cirrhosis, liver transplantation

Controlling hepatitis B virus (HBV) activation after orthotopic liver transplantation (OLT) has been acknowledged to be easier than before, as the administration of a nucleos(t)ide analogue in combination with hepatitis B immunoglobulin (HBIG) is a promising protocol [1, 2]. However, because HBIG is a product of human donated blood, it carries a risk of being infected with unknown pathogens. In addition, HBIG is extremely expensive, costing approximately $600 USD every 3 months in Japan [3]. Newer-generation nucleos(t)ide analogues such as entecavir or tenofovir have a very strong HBV-DNA reduction power with few adverse effects (AEs), but the life-long administration of these drugs is also expensive and carries the risk of unknown occult AEs, as these agents are nucleos(t)ide analogues that bind DNA. Therefore, the active immunization of recipients with an HBV vaccine is a candidate approach to reducing the required amounts of HBIG and nucleos(t)ide analogue for treat-

Received July 4, 2018; accepted October 30, 2018.
*Corresponding author. Phone: +81-86-235-7218; Fax: +81-86-225-5991
E-mail: akitaka@md.okayama-u.ac.jp (A. Takaki)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

ment [4]. Vaccines containing hepatitis B surface antigen (HBsAg) are widely administered to healthcare workers and students, with an estimated efficacy of ≥90%, and they are considered reasonably safe [5].

Several research groups have investigated the vaccine response in post-OLT patients with liver cirrhosis type B (LC-B) and acute liver failure type B (ALF-B). The vaccine effects were not sufficient for LC-B, whereas some success was noted for ALF-B. Even a double-dose vaccine trial resulted in only 2 of 24 patient (8.3%) responders among those receiving deceased-donor OLT (DDLT) [6]. A prospective study with mainly LC-B patients in DDLT revealed success in 9 of 27 patients (33%) [7], with the lymphocyte-to-eosinophil ratio being the only marker predicting vaccine responders.

Most of the relevant studies have been conducted in post-DDLT patients, and the details of the donors have not been analyzed. In Japan, the brain-dead donor pool is very small, and living donor liver transplantation (LDLT) is widely performed [8]. This situation should be improved, as LDLT carries substantial risks to the living donors. In this environment, the health of the donors can also be investigated.

Evidence regarding the effects of HBV vaccine on post-LDLT patients is lacking. We reported that 9 of 22 (41%) post-OLT LC-B patients responded well to vaccines [9]. To identify good candidates for vaccine administration, we herein report a summary of our substantial experience with patients, including those with non-HBV-related end-stage liver disease (non-B ESLD) who received a liver from an anti-hepatitis B core antibody (HBcAb)-positive donor, with a focus on the HBV vaccine effects.

Patients and Methods

Study design and patients. We conducted a retrospective analysis of the medical records of 49 post-OLT patients who received an HBV vaccination. These 49 patients were 28 with LC-B, 8 with ALF-B, and 13 with other non-B ESLD, including 4 infants with non-B ESLD. The patients were diagnosed and treated at Okayama University Hospital between August 1998 and May 2017.

This study design was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital (No. Rin1192), and it adhered to the Declaration of Helsinki. All patients provided their written informed consent for their cases to be used in the present retrospective analyses.

Treatment protocol. OLT was performed at the Department of Gastroenterological Surgery Transplant and Surgical Oncology, Okayama University Hospital. The HBV vaccination was started ≥1 year after the OLT in each patient's case. The vaccine consisted of recombinant purified HBsAg (Bimmugen®; Kaketsuken, Kumamoto, Japan; or Heptavax®-II; MSD, Tokyo). A 10-μg pro dose was injected subcutaneously twice at 4-week intervals, and then once after 10-12 weeks. The patients who showed anti-HBsAb titers >100 mIU/mL without HBIG for a minimum of 6 months were defined as good responders.

Clinical assessments and statistical analyses. All clinical assessments performed in this study involved the collection of the patients' medical history and laboratory examination findings. Every datum presented in these analyses is the median value with the range. A univariate analysis was performed to examine the correlation between the HBV vaccine response and the clinical characteristics of the patients with different liver disease backgrounds (LC-B, ALF-B, and non-B ESLD). We performed a multivariate logistic regression analysis to examine the correlation between the HBV vaccine response and the clinical parameters in LC-B. In the univariate and multivariate analyses, a p-value <0.05 was defined as significant. All statistical analyses were performed using the JMP® software program, ver. 13 (SAS, Cary, NC, USA).

Results

Patient backgrounds. The demographic and other baseline characteristics for all of the patients as well as the donor-related factors are summarized in Table 1. Some of the missing data and DDLT related donor data were not obtained. The parameters of these data are specified. The HBV vaccination started at 55 (range 49-59) years of age in the LC-B group, 40 (33-55) years in the ALF-B group, 51 (21-71) years in the adult non-B ESLD group, and 4 (1-8) years in the infant non-B ESLD group. The numbers (percentages) of HBsAg-positive patients at OLT were 28 (100%) in the LC-B group, 2 (33%) in the ALF-B group, 0 (0%) in the adult non-B ESLD group, and 0 (0%) in the infant

non-B ESLD group.

The numbers (percentages) of hepatitis B surface antibody (HBsAb)-positive patients at OLT were 2 (7.1%) in the LC-B group, 4 (67%) in the ALF-B group, 1 (11%) in the adult non-B ESLD group, and 0 (0%) in the infant non-B ESLD group. The positive rate of HBV DNA copies in LC-B was 30%. HCC was detected at the OLT in 15 patients (54%) in the LC-B group and 2 patients (22%) in the adult non-B ESLD group.

Regarding the donor-related factors, OLT was performed at the median donor age (range) of 45 (30-49) years in the LC-B group, 36 (29-48) years in the ALF-B group, 41 (32-65) years in the adult non-B ESLD group, and 60 (58-64) years in the infant non-B ESLD group. A blood relationship (percentage) between donors and recipients was found in 17 pairs (61%) of the LC-B group, 8 pairs (100%) in the ALF-B group, 5 pairs (56%) in the adult non-B ESLD group, and 4 pairs (100%) in the infant non-B ESLD group. The numbers (percentages) of donors with high levels of anti-HBsAb (>100 mIU/mL) were 10 (38%) in the LC-B group, 1 (14%) in the ALF-B group, 4 (50%) in the adult non-B ESLD group, and 4 (100%) in the infant non-B ESLD group.

Response rate in vaccination. Good vaccine responses were achieved in 8 patients (29%) with LC-B, 7 patients (88%) with ALF-B, 4 patients (44%) with non-B ESLD (adults), and all 4 patients (100%) with non-B ESLD (infants) (Fig. 1). The overall success rate was 42% (19/45) in the adults and 100% (4/4) in the infants.

HBV vaccination for LC-B. The correlation between the HBV vaccine response and the clinical characteristics of the LC-B patients is shown in Table 2. A good vaccine response in blood-relation donors was noted in only 1 of 17 cases (5.9%), although a good vaccine response was noted in unrelated donors in 7 of 11 cases (64%) ($p=0.0007$). Regarding blood relationships (or lack thereof), a non-consanguineous marital relationship (7 of 9 cases, 78%) was significantly associated with vaccine success compared with sibling (1 of 5 cases, 20%), offspring (0 of 10 cases, 0%), and parental relationships (0 of 2 cases, 0%) as well as DDLT (0 of 2 cases, 0%) ($p=0.0008$).

Older female donors were also associated with a good response. ABO blood type compatibility between donors and recipients (6 of 12 cases, 50%) was associated with a good response compared to identical blood types between donors and recipients (2 of 16 cases, 13%) ($p=0.028$). In addition, anti-hepatitis B e antibody (HBeAb)-positive donors and anti-HBsAb-positive recipients at OLT were significantly correlated with a good response. The multivariate analysis showed that donor non-relation (mostly marital donors), a

Table 1 Demographic and other baseline characteristics of recipient- and donor-related factors

	LC-B	ALF-B	non-B ESLD (adult)	non-B ESLD (infant)
N	28	8	9	4
Recipient-related factors				
Age at OLT	52 (44–56)	36 (28–53)	47 (20–65)	1 (1–6)
Age at start of vaccine	55 (49–59)	40 (33–55)	51 (21–71)	4 (1–8)
Sex (M)	25 (89%)	2 (25%)	3 (33%)	4 (100%)
HBsAg positive at OLT	28 (100%)	2/6 (33%)	0 (0%)	0 (0%)
HBsAb positive at OLT	2 (7.1%)	4/6 (67%)	1 (11%)	0 (0%)
HBV DNA at OLT (≥3.7 log IU/mL)	8/27 (30%)	0 (0%)	0 (0%)	Not done
MELD at OLT	15 (10–18)	23 (16–38)	19 (15–25)	Not done
HCC at OLT	15 (54%)	0 (0%)	2 (22%)	0 (0%)
Donor-related factors				
Age at OLT	45 (30–49)	36 (29–48)	41 (32–65)	60 (58–64)
Sex (M)	12 (43%)	5 (63%)	5 (56%)	2 (50%)
ABO (identical)	16 (57%)	7 (88%)	6 (67%)	4 (100%)
Blood relation (yes)	17 (61%)	8 (100%)	5 (56%)	4 (100%)
Donor HBsAb (>100 mIU/mL)	10/26 (38%)	1/7 (14%)	4/8 (50%)	4 (100%)
Donor HBcAb (+)	12/26 (46%)	2/6 (33%)	8/8 (100%)	4 (100%)

ALF-B, acute liver failure type B; HBcAb, anti-hepatitis B core antibody; HBsAb, anti-hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LC-B, liver cirrhosis type B; MELD, Model for End-Stage Liver Disease criteria; non-B ESLD, non-HBV-related end stage liver diseases; OLT, orthotopic liver transplantation.

higher donor age, and a younger recipient age at vaccine start were significant factors influencing a good response.

HBV vaccination for ALF-B. The HBV vaccination for ALF-B was successful (88%), as previously reported [9]. No marked differences in patient background were observed between the HBV vaccine responders and non-responders, as most achieved suc-

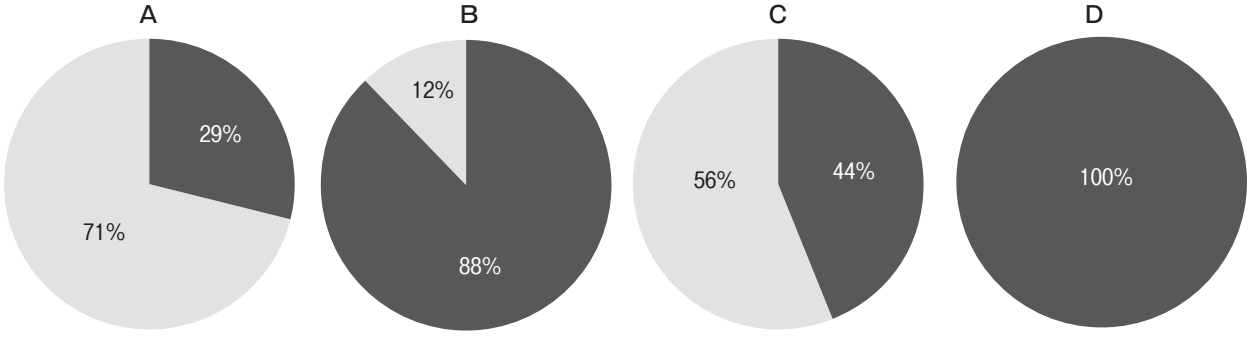

Fig. 1 The good responder rate for HBV vaccination in post-OLT recipients. HBV vaccination succeeded in 8 (29%) of 28 patients with HBV-related cirrhosis (LC-B, **A**), 7 (88%) of 8 patients with acute HBV liver failure (ALF-B, **B**), 4 (44%) of 9 patients with adult non-HBV-related end-stage liver diseases (adult non-B ESLD, **C**), and all 4 patients (100%) with infant non-B ESLD (infant non-B ESLD, **D**). *Dark-gray* filled areas indicate success and *light-gray* filled areas indicate failure of HBV vaccination.

Table 2 The correlation between HBV vaccine response and clinical characteristics in LC-B

(**A**) Recipient-related factors

		Vaccine success number (%)	Univariate analysis, *p*-value	Multivariate analysis, *p*-value
Age at OLT	≥52	3/15 (20)	0.280	
	<52	5/13 (38)		
Age at start of vaccine	≥55	3/14 (21)	0.401	0.0166**
	<55	5/14 (36)		
Sex	M	7/25 (28)	0.849	
	F	1/3 (33)		
HBsAg at OLT	+	8/28 (29)	—	
	−	0/0		
HBsAb at OLT	+	2/2 (100)	0.020*	0.090
	−	6/26 (23)		
HBcAb at OLT	+	8/28 (29)	—	
	−	0/0		
HBeAg at OLT	+	5/11 (45)	0.114	
	−	3/17 (18)		
HBeAb at OLT	+	4/16 (25)	0.630	
	−	4/12 (33)		
HBV-DNA at OLT (>3.7 log IU/mL)	+	3/8 (38)	0.566	
	−	5/19 (26)		
MELD at OLT	≥15	5/16 (31)	0.824	
	<15	3/11 (27)		
HCC	+	5/15 (33)	0.547	
	−	3/13 (23)		
NA	+	8/27 (30)	0.407	
	−	0/1 (0)		
INR	≥1.58	5/14 (36)	0.401	
	<1.58	3/14 (21)		

Table 2
(B) Donor-related factors

		Vaccine success number (%)	Univariate analysis, *p*-value	Multivariate analysis, *p*-value
Age at OLT†	≥45	7/13 (54)	0.008*	0.0016**
	<45	1/13 (7.7)		
Sex	M	1/12 (8.3)	0.034*	0.090
	F	7/16 (44)		
ABO	compatible	6/12 (50)	0.028*	0.050
	identical	2/16 (13)		
	incompatible	0/0		
Blood relation	related	1/17 (5.9)	0.0007*	0.0009**
	unrelated	7/11 (64)		
Relation	spouse	7/9 (78)	0.0008*	
	brother	1/5 (20)		
	offspring	0/10 (0)		
	parent	0/2 (0)		
	brain-dead patient	0/2 (0)		
HBsAb	+	5/11 (45)	0.165	
	−	3/15 (20)		
HBsAb	≥100	5/10 (50)	0.095	
	<100	3/16 (19)		
HBcAb	+	5/12 (42)	0.264	
	−	3/14 (21)		
HBeAb	+	4/5 (80)	0.010*	0.080
	−	4/21 (19)		

HBcAb, anti-hepatitis B core antibody; HBeAb, anti-hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, anti-hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio for prothrombin time; LC-B, liver cirrhosis type B; MELD, Model for End-Stage Liver Disease criteria; NA, nucleoside/nucleotide analogs; OLT, orthotopic liver transplantation.
*p-value for statistical significance is defined as $p<0.05$ in univariate analysis. **p-value for statistical significance is defined as $p<0.05$ in multivariate analysis. †Because the 26 OLT includes 2 cases of deceased donor OLT, the ages of the donors cannot be determined in the 2 cases.

cess (Table 3).

HBV vaccination for adult non-B ESLD. The vaccine response was not sufficiently good in our adult non-B ESLD patients, although we expected a good response. The vaccine responders in the adult non-B ESLD group showed a severe pre-OLT condition, indicated by higher Model for End-Stage Liver Disease criteria (MELD) scores as shown in Table 4. One of the possible vaccine success-related factors found in the LC-B analysis, donor non-relation, tended to result in a good response compared to donor relation (75% vs. 20%) ($p=0.090$).

HBV vaccination for infant non-B ESLD. The HBV vaccination was completely successful in the infant non-B ESLD group, although the number of patients in this group was small (n=4).

Discussion

Post-OLT HBV vaccinations were administered to LC-B, ALF-B, and non-B ESLD patients with HBV-infected donor livers. The good responder rate was highest in the infants with non-B ESLD, high in ALF-B, and low in the LC-B group and the adults with non-B ESLD. The good responders in the LC-B group consisted mainly of young patients, as expected, whereas liver transplantation from older donors and marital donors showed unexpectedly significant immune induction.

OLT is usually the only curative therapeutic option for patients with acute and chronic liver failure [10], HCC [11], or primarily genetic metabolic defects of the liver [12]. LC-B and ALF-B have been major indications for OLT. The use of nucleos(t)ide analogues in

Table 3 The correlation between HBV vaccine response and clinical characteristics in ALF-B

(A) Recipient-related factors

		Vaccine success number (%)	Univariate analysis, *p*-value
Age at OLT	≥36	4/5 (80)	0.312
	<36	3/3 (100)	
Age at vaccine start	≥40	3/4 (75)	0.216
	<40	4/4 (100)	
Sex	M	2/2 (100)	0.431
	F	5/6 (83)	
HBsAg at OLT	+	1/2 (50)	0.105
	−	4/4 (100)	
HBsAb at OLT	+	4/4 (100)	0.105
	−	1/2 (50)	
HBcAb at OLT	+	5/6 (83)	−
	−	0/0	
HBeAg at OLT	+	0/0	−
	−	5/6 (83)	
HBeAb at OLT	+	5/6 (83)	−
	−	0/0	
HBV-DNA at OLT (>3.7 log IU/mL)	+	0/0	−
	−	7/8 (88)	
MELD at OLT	≥23	4/4 (100)	0.216
	<23	3/4 (75)	
HCC	+	0/0	−
	−	7/8 (88)	
NA	+	4/5 (80)	0.312
	−	3/3 (100)	
INR	≥2.05	5/5 (100)	0.137
	<2.05	2/3 (67)	

combination with HBIG has been accepted as the best way to control the recurrence of HBV DNA [4]. However, given that HBIG is made from donated human blood, it is very expensive to procure and carries a risk of harboring unknown infectants or pathogens. Historically, many HBIG reduction protocols have been introduced with some degree of success [4]. Strong and safe new nucleos(t)ide analogues such as entecavir or tenofovir alafenamide, have recently been used as a monotherapy [13]. However, remaining HBsAg-free with an anti-HBs-positive status is still deemed important. Active immunization with recombinant HBsAg is a promising approach for achieving an anti-HBs response at low-cost using safe methods.

We conducted a recombinant HBsAg vaccination protocol for post-OLT patients to prevent the reactivation of HBV. The HBV vaccination succeeded in 8 patients (29%) with LC-B, 7 (88%) with ALF-B, and 4 (44%) with adult non-B ESLD. Although the success rate in the LC-B group was not as high in the present study as in previous reports, we identified several factors that predict a good response. A non-blood relationship between the donor and recipient—observed mainly in transplants between married partners—was a significant predictive factor of a good response, as the 2 patients with DDLT showed no response.

Our previous investigation in a relatively small number of patients (22 LC-B patients and 5 ALF-B patients) revealed that higher donor age, marital transplant, and high-titer anti-HBsAb in the donor were predictive of a good response to HBV vaccination [9]. We observed a good response with marital donors and older donors in the present study as well. The marital status means that the donors were infected with HBV in adulthood, and an immune tolerance could not be achieved; therefore, a strong immune response had been established after marriage. Although we did not include the anti-HBsAb titer in the present multivariate analysis, the univariate analysis indicated that a higher anti-HBsAb titer was correlated with vaccine success. Marital donors usually have an immune response against the HBV of the recipient that should be polar-

Table 3

(B) Donor-related factors

		Vaccine success number (%)	Univariate analysis, *p*-value
Age at OLT	≥36	3/4 (75)	0.216
	<36	4/4 (100)	
Sex	M	5/5 (100)	0.137
	F	2/3 (67)	
ABO	compatible	1/1 (100)	0.592
	identical	6/7 (86)	
	incompatible	0/0	
Blood relation	related	7/8 (88)	–
	unrelated	0/0	
Relation	spouse	0/0	0.465
	brother	3/4 (75)	
	offspring	2/2 (100)	
	parent	2/2 (100)	
	brain-dead patient	0/0	
HBsAb	+	2/2 (100)	0.390
	–	4/5 (80)	
HBsAb	≥100	1/1 (100)	0.563
	<100	5/6 (83)	
HBcAb	+	2/2 (100)	–
	–	4/4 (100)	
HBeAb	+	1/1 (100)	–
	–	5/5 (100)	

ALF-B, acute liver failure type B; HBcAb, anti-hepatitis B core antibody; HBeAb, anti-hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, anti-hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio for prothrombin time; MELD, Model for End-Stage Liver Disease criteria; NA, nucleoside/nucleotide analogs; OLT, orthotopic liver transplantation.

ized to the same sequence.

In one previous study, HBV vaccination in LDLT donors was reported to have the capacity to transfer an anti-HBV immune response to the recipient [14]. Of note, however, the adoptive transfer of the HBV-specific immune response was established in recipients only when the anti-HBsAb titers were very high. Our present analyses demonstrated that high anti-HBsAb was a predictive factor only in the univariate analysis. This might be because of the relatively small number of patients.

Since almost all of the present post-OLT ALF-B patients responded well to the vaccine, we were unable to determine any vaccine response-predictive factors. Such a high response rate to HBV vaccination was also shown previously [9]. It is widely accepted that ALF-B patients already have a very strong HBV-specific immune response causing fatally severe inflammation.

Contrary to our expectations, the success rate in the post-OLT adult non-B ESLD patients was not very high in the present study. Although the recipient immune system failed to tolerate HBV and was believed to easily induce an anti-HBsAb response, the frequency of a vaccine response among the recipients was low. This phenomenon is a new finding that should be kept in mind for the management of patients who have undergone OLT, as a vaccination can be expected to be ineffective in some patients. We found that a high pre-OLT MELD score was related to vaccination success in this group. The MELD score is calculated based on the serum bilirubin level, the international normalized ratio for prothrombin time (INR), and the serum creatinine level. A high MELD score was reported to be positively correlated with the serum interleukin (IL)-21 level in HBV-related acute-on-chronic liver failure [15]. IL-21 has been shown to accelerate the HBsAg clearance and promote anti-HBsAb production [16]. Such phenomena might suggest that a high MELD score reflects a good immune response against HBV vaccine; however, our post-OLT patients would not have been experiencing a cytokine storm, and the number of patients in this group may have been too small to draw definitive

Table 4 The correlation between HBV vaccine response and clinical characteristics in adult non-B ESLD

(A) Recipient-related factors

		Vaccine success number (%)	Univariate analysis, *p*-value
Age at OLT	≥47	2/5 (40)	0.764
	<47	2/4 (50)	
Age at vaccine start	≥51	2/5 (40)	0.764
	<51	2/4 (50)	
Sex	M	2/3 (67)	0.340
	F	2/6 (33)	
HBsAg at OLT	+	0/0	−
	−	4/9 (44)	
HBsAb at OLT	+	1/1 (100)	0.182
	−	3/8 (38)	
HBcAb at OLT	+	0/0	−
	−	4/9 (44)	
HBeAg at OLT	+	0/0	−
	−	4/9 (44)	
HBeAb at OLT	+	0/0	−
	−	4/9 (44)	
HBV-DNA at OLT (>3.7 log IU/mL)	+	0/0	−
	−	2/5 (40)	
MELD at OLT	≥19	4/6 (67)	0.0297*
	<19	0/3 (0)	
HCC	+	0/2 (0)	0.094
	−	4/7 (57)	
NA	+	0/0	−
	−	4/9 (44)	
INR	≥1.65	3/5 (60)	0.286
	<1.65	1/4 (25)	

mechanistic conclusions.

Soejima *et al*. [17] reported that HBV vaccination was successful in 6 of 11 patients (55%) who underwent an LDLT for ALF-B (3 patients) and non-B ESLD (8 patients). Their findings differed from ours in that the average age of the 6 responders was significantly younger than that of the non-responders. One reason for this discrepancy may be that their participants included 3 non-adults, as our infants responded very well. Although the number of patients was relatively small, we should pay attention to the low vaccine response in the present adult non-B ESLD group, as it is likely that patients in this group are not good candidates for post-OLT HBV vaccination.

We noted that all 4 pediatric cases of non-B ESLD successfully achieved anti-HBV immunity after HBV vaccination. Similar observations of a high frequency of immune induction in infants have been described by other investigators: 17 of 19 patients (89%) [18], 33 of 37 patients (89%) [19], 41 of 49 patients (84%) [20], 47 of 60 patients (78%) [21], and 36 of 67 patients (54%) [22]. In the present study, however, among adult OLT patients who did not have ALF-B, there was no significant difference in the age of recipients at OLT. The immune response induced by an HBV vaccine has been shown to be higher in newborns than in adults because of the higher antibody and memory Th2 responses with lower primary IFN-γ responses in newborns [23]. These findings may explain the success rate discrepancy between the infants and adults in the present study.

Pathophysiologically, memory B lymphocytes specific for HBsAg seem to play an important role in the induction of anti-HBV immunity. HBsAg-specific memory B lymphocytes were detected in HBs-vaccinated subjects and continuously produced anti-HBsAb [24]. In contrast, the induction of HBsAg-specific regulatory T cells was demonstrated in OLT patients with HBV-related liver disease immunized by an HBV vaccine, resulting in a poor response of OLT recipients to conventional vaccines [25]. Differences in

Table 4

(B) Donor-related factors

		Vaccine success number (%)	Univariate analysis, *p*-value
Age at OLT	≥41	3/5 (60)	0.286
	<41	1/4 (25)	
Sex	M	2/5 (40)	0.764
	F	2/4 (50)	
ABO	compatible	0/1 (0)	0.094
	identical	2/6 (33)	
	incompatible	2/2 (100)	
Blood relation	related	1/5 (20)	0.090
	unrelated	3/4 (75)	
Relation	spouse	3/4 (75)	0.165
	brother	1/2 (50)	
	offspring	0/2 (0)	
	parent	0/1 (0)	
	brain-dead patient	0/0	
HBsAb	+	3/7 (43)	0.216
	−	1/1 (100)	
HBsAb	≥100	1/4 (25)	0.148
	<100	3/4 (75)	
HBcAb	+	4/8 (50)	−
	−	0/0	
HBeAb	+	1/4 (25)	0.148
	−	3/4 (75)	

HBcAb, anti-hepatitis B core antibody; HBeAb, anti-hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, anti-hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio for prothrombin time; MELD, Model for End-Stage Liver Disease criteria; NA, nucleoside/nucleotide analogs; non-B ESLD, non-HBV-related end stage liver diseases; OLT, orthotopic liver transplantation.
*p-value for statistical significance is defined as $p<0.05$ in univariate analysis.

the balance between memory B cells and regulatory T cells may determine the outcome of HBV vaccination.

Toward the goal of boosting the immunization effects, double-dose immunization, elongation of vaccine protocols, and adjuvant usage have been tested. A Japanese study showed that a double-dose vaccine resulted in 18 of 40 HBV-related liver disease patients (45%) responding to an HBV vaccine [22]. A relatively large number of vaccinations was shown to result in the induction of HBV immunity: 19 times (range 11.5-30 times) in LC-B and 4 times (range 2.5-5 times) in ALF-B before ceasing HBIG treatment [9]. The use of several adjuvant vaccines has also been reported, although the efficacy of this approach was not very high at 44% [26,27]. Careful monitoring should be continued after vaccine success, as even when immunization with HBV has been achieved, the gradual loss of anti-HBsAb (−46% at 1 year, −57% at 2 years, and −82% at ≥3 years) has been reported to occur in post-OLT patients despite high levels of anti-HBsAb prior to OLT [28].

In conclusion, a prophylactic HBV vaccination for OLT patients succeeded in 29% of LC-B patients, 88% of ALF-B patients, 44% of adult non-B ESLD patients, and 100% of infant non-B ESLD patients. The predictive factors for a good response in LC-B were marital transplant, higher donor age, and younger age at the vaccine start. The present adult non-B ESLD patients were not good responders, whereas infant non-B ESLD patients appear to be good responders who should receive an HBV vaccination because of the strong immune response against HBV. In order to take advantage of the HBV vaccine in OLT for HBV-related liver diseases, further investigations into the use of HBV vaccines should be performed, including evaluations of the nature and dose of the vaccine itself, the timing, interval, and frequency of administration, and the use of adjuvants and combinations with other therapeutic modalities.

References

1. Ishigami M, Ogura Y, Hirooka Y and Goto H: Change of strategies and future perspectives against hepatitis B virus recurrence after liver transplantation. World J Gastroenterol (2015) 21: 10290–10298.
2. Kennedy M and Alexopoulos SP: Hepatitis B virus infection and liver transplantation. Curr Opin Organ Transplant (2010) 15: 310–315.
3. Takaki A, Yagi T, Iwasaki Y, Sadamori H, Matsukawa H, Matsuda H, Shinoura S, Umeda Y, Miyake Y, Terada R, Kobashi H, Sakaguchi K, Tanaka N and Shiratori Y: Short-term high-dose followed by long-term low-dose hepatitis B immunoglobulin and lamivudine therapy prevented recurrent hepatitis B after liver transplantation. Transplantation (2007) 83: 231–233.
4. Takaki A, Yagi T and Yamamoto K: Safe and cost-effective control of post-transplantation recurrence of hepatitis B. Hepatol Res (2015) 45: 38–47.
5. Holmberg SD, Suryaprasad A and Ward W: Updated CDC recommendations for the management of hepatitis B virus-infected health-care providers and students. MMWR Recomm Rep (2012) 61: 1–12.
6. Rosenau J, Hooman N, Hadem J, Rifai K, Bahr MJ, Philipp G, Tillmann HL, Klempnauer J, Strassburg CP and Manns MP: Failure of hepatitis B vaccination with conventional HBsAg vaccine in patients with continuous HBIG prophylaxis after liver transplantation. Liver Transpl (2007) 13: 367–373.
7. Yang A, Guo Z, Ren Q, Wu L, Ma Y, Hu A, Wang D, Ye H, Zhu X, Ju W and He X: Active immunization in patients transplanted for hepatitis B virus related liver diseases: A prospective study. PLoS One (2017) 12: e0188190.
8. Egawa H, Tanabe K, Fukushima N, Date H, Sugitani A and Haga H: Current status of organ transplantation in Japan. Am J Transplant (2012) 12: 523–530.
9. Takaki A, Yagi T, Yasunaka T, Sadamori H, Shinoura S, Umeda Y, Yoshida R, Sato D, Nobuoka D, Utsumi M, Yasuda Y, Nakayama E, Miyake Y, Ikeda F, Shiraha H, Nouso K, Fujiwara T and Yamamoto K: Which patients respond best to hepatitis B vaccination after a hepatitis B virus-related liver transplantation? J Gastroenterol (2013) 48: 1373–1383.
10. Mochida S: Indication criteria for liver transplantation for acute liver failure in Japan. Hepatol Res (2008) 38 Suppl 1: S52–55.
11. Furukawa H, Shimamura T, Suzuki T, Taniguchi M, Nakanishi K, Yamashita K, Kamiyama T, Matsushita M and Todo S: Liver transplantation for hepatocellular carcinoma: the Japanese experience. J Hepatobiliary Pancreat Sci (2010) 17: 533–538.
12. Kasahara M, Sakamoto S, Horikawa R, Koji U, Mizuta K, Shinkai M, Takahito Y, Taguchi T, Inomata Y, Uemoto S, Tatsuo K and Kato S: Living donor liver transplantation for pediatric patients with metabolic disorders: the Japanese multicenter registry. Pediatr Transplant (2014) 18: 6–15.
13. Manini MA, Whitehouse G, Bruce M, Passerini M, Lim TY, Carey I, Considine A, Lampertico P, Suddle A, Heaton N, Heneghan M and Agarwal K: Entecavir or tenofovir monotherapy prevents HBV recurrence in liver transplant recipients: A 5-year follow-up study after hepatitis B immunoglobulin withdrawal. Dig Liver Dis (2018) 50: 944–953.
14. Schumann A, Lindemann M, Valentin-Gamazo C, Lu M, Elmaagacli A, Dahmen U, Knop D, Broelsch CE, Grosse-Wilde H, Roggendorf M and Fiedler M: Adoptive immune transfer of hepatitis B virus specific immunity from immunized living liver donors to liver recipients. Transplantation (2009) 87: 103–111.
15. Hu X, Ma S, Huang X, Jiang X, Zhu X, Gao H, Xu M, Sun J, Abbott WG and Hou J: Interleukin-21 is upregulated in hepatitis B-related acute-on-chronic liver failure and associated with severity of liver disease. J Viral Hepat (2011) 18: 458–467.
16. Li Y, Tang L and Hou J: Role of interleukin-21 in HBV infection: friend or foe? Cell Mol Immunol (2015) 12: 303–308.
17. Soejima Y, Ikegami T, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, Yamashita Y and Maehara Y: Hepatitis B vaccination after living donor liver transplantation. Liver Int (2007) 27: 977–982.
18. Chang SH, Suh KS, Yi NJ, Choi SH, Lee HJ, Seo JK and Lee KU: Active immunization against de novo hepatitis B virus infection in pediatric patients after liver transplantation. Hepatology (2003) 37: 1329–1334.
19. Kwon CH, Suh KS, Yi NJ, Chang SH, Cho YB, Cho JY, Lee HJ, Seo JK and Lee KU: Long-term protection against hepatitis B in pediatric liver recipients can be achieved effectively with vaccination after transplantation. Pediatr Transplant (2006) 10: 479–486.
20. Lee S, Kim JM, Choi GS, Park JB, Kwon CH, Choe YH, Joh JW and Lee SK: De novo hepatitis b prophylaxis with hepatitis B virus vaccine and hepatitis B immunoglobulin in pediatric recipients of core antibody-positive livers. Liver Transpl (2016) 22: 247–251.
21. Lin CC, Chen CL, Concejero A, Wang CC, Wang SH, Liu YW, Yang CH, Yong CC, Lin TS, Jawan B, Cheng YF and Eng HL: Active immunization to prevent de novo hepatitis B virus infection in pediatric live donor liver recipients. Am J Transplant (2007) 7: 195–200.
22. Yoshizawa A, Yamashiki N, Ueda Y, Kaido T, Okajima H, Marusawa H, Chiba T and Uemoto S: Long-term efficacy of hepatitis B vaccination as post-transplant prophylaxis in hepatitis B surface antigen (HBsAg) positive recipients and HBsAg negative recipients of anti-hepatitis B core positive grafts. Hepatol Res (2016) 46: 541–551.
23. Ota MO, Vekemans J, Schlegel-Haueter SE, Fielding K, Whittle H, Lambert PH, McAdam KP, Siegrist CA and Marchant A: Hepatitis B immunisation induces higher antibody and memory Th2 responses in new-borns than in adults. Vaccine (2004) 22: 511–519.
24. Tuaillon E, Tabaa YA, Petitjean G, Huguet MF, Pajeaux G, Fondere JM, Ponseille B, Ducos J, Blanc P and Vendrell JP: Detection of memory B lymphocytes specific to hepatitis B virus (HBV) surface antigen (HBsAg) from HBsAg-vaccinated or HBV-immunized subjects by ELISPOT assay. J Immunol Methods (2006) 315: 144–152.
25. Bauer T, Gunther M, Bienzle U, Neuhaus R and Jilg W: Vaccination against hepatitis B in liver transplant recipients: pilot analysis of cellular immune response shows evidence of HBsAg-specific regulatory T cells. Liver Transpl (2007) 13: 434–442.
26. Rosenau J, Hooman N, Rifai K, Solga T, Tillmann HL, Grzegowski E, Nashan B, Klempnauer J, Strassburg CP, Wedemeyer H and Manns MP: Hepatitis B virus immunization with an adjuvant containing vaccine after liver transplantation for hepatitis B-related disease: failure of humoral and cellular immune response. Transpl Int (2006) 19: 828–833.
27. Di Paolo D, Lenci I, Cerocchi C, Tariciotti L, Monaco A, Brega A, Lotti L, Tisone G and Angelico M: One-year vaccination against hepatitis B virus with a MPL-vaccine in liver transplant patients for HBV-related cirrhosis. Transpl Int (2010) 23: 1105–1112.
28. Sintusek P, Posuwan N, Wanawongsawad P, Jitraruch S, Poovorawan Y and Chongsrisawat V: High prevalence of hepatitis B-antibody loss and a case report of de novo hepatitis B virus infection in a child after living-donor liver transplantation. World J Gastroenterol (2018) 24: 752–762.