Original Article

Immune Response Rate after Viral Hepatitis B Immunization in Chronic Liver Disease Patients

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ABSTRACT

Background: Vaccination against hepatitis B infection is recommended for patients with chronic liver disease who are seronegative for hepatitis B infection. However, the response rate is lower, compared with the general population. Currently, there is inconclusive data to establish the best vaccine schedule for this group of patients.

Objectives & Methods: We performed a prospective study in patients with chronic liver disease to evaluate the immune response rate at one month after completion of conventional hepatitis B vaccination (3 doses of recombinant hepatitis B vaccination (20 μg) at 0, 1, 6 months). In patients who could not achieve immune response from conventional regimen was added one additional double-dose. Factors related to immune response were analyzed.

Fifty-five patients were enrolled although 35 patients had completed conventional vaccination. There were 23 males and 12 females, mean age 56.2±10.5 years and 80% were Child Pugh class A. The causes of chronic liver disease were NASH (25.7%), alcoholic hepatitis (17%), chronic hepatitis C (23%), and liver cirrhosis (43%).

Results: A total of 35 vaccinated patients were studied. The 48% and 54% exhibited an immune response after conventional regimen and additional double-dose regimen respectively. The overall immune response increased from 48.6-80%. Higher HBsAb levels were achieved from additional dose of vaccine, the median HBsAb level was 112.4 mIU/mL (range 13.8-833) after the conventional regimen and 639.13 mIU/mL (range 12-833) after the four-dose regimen.

From univariate analysis, the variables associated with a higher immune response for the conventional regimen included non-cirrhosis (p=0.041), albumin > 3.5 g/dL (p=0.002), PT<12 seconds (p=0.027), A/G ratio greater than 1 (p=0.026), MELD < 8 (p=0.029), Child Pugh score ≥ 5 (p=0.015), and platelet >120,000/mL (p=0.049). Patients with Child Pugh score upto 6 and patients with anemia (Hb >11.5) showed an improved response from the additional dose (p=0.041, p=0.04, respectively). However, no significant differences were identified by multivariate analysis.

Conclusions: Patients with chronic liver disease and cirrhosis achieved a lower rate of immune response from conventional regimen of hepatitis B vaccination. However, an additional dose could improve the immune response rate and increase the HBsAb level. The immune response was better in patients at early stages of liver disease.

Key words : hepatitis B vaccination, chronic liver disease, immunization, cirrhosis

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Introduction

Chronic liver disease and liver cirrhosis patients without serological markers of HBV infection are at risk of HBV infection with a potentially worse outcome. Effective vaccination against HBV could reduce HBV infection mortality and is recommended for all patients with chronic liver disease without serologic markers of hepatitis B[1,10].

The standard hepatitis B vaccination schedule consists of 3 doses of recombinant vaccine (20 μg), given at 0, 1, 6 months, which confers immunity in greater than 90% of healthy population[2,3,28]. However, when compared to general population, the response rate to hepatitis B vaccine is lower in immunocompromised patients, AIDS (CD_4 less than 200 cell/mm^3)[11], hemodialysis patients and patients with chronic liver disease. A double-dose regimen (40 μg) has been successfully employed in patients with AIDS or patients on hemodialysis. This regimen has become standard for these patients[5,29]. Other host factors contributing to decrease immunogenicity include[4,6-9] smoking, obesity, advanced age, alcohol ingestion, and immune suppression.

In previous study, patients with liver cirrhosis response poorly to the conventional regimen 28-47%[12-15]. The efficacy of three double-dose hepatitis B virus vaccination at 0, 1 and 6 months in 43 cirrhotic patients waiting for liver transplantation was only 67.5%[17]. Many studies were conducted to find the best regimen for patients with chronic liver disease. However, the response rate increase non-significantly, varying from 37-67.8% in three-double doses vaccine group[13,14,16,18-29] and 40.7-75% in four-double doses of HBV vaccine[19,21]. Currently, there are inconclusive data to establish the best HBV vaccine schedule for chronic liver disease and liver cirrhosis patients.

We conducted a prospective observational trial to evaluate the immune response rate after standard regimen (recombinant hepatitis B vaccine 20 μg intramuscular at 0, 1, 6 month), and the benefit of an additional double dose (40 μg) in the non-response group after receiving the conventional regimen. We also evaluated factors associated with the immune response at the time of vaccination.

Patients & Method

This study was conducted at the Faculty of Medicine, Vajira Hospital, Bangkok, Thailand, between November 2013 and 11 February 2015. Patients with liver cirrhosis or other chronic liver diseases who were seronegative for hepatitis B infection (negative for HBsAg, Anti-HBs, Anti-HBc) were eligible. The inclusion criteria were ages between 18-75 years, liver cirrhosis or chronic liver disease from one of the following causes; chronic hepatitis C with persistent viremia (HCV RNA > 5,000 IU/mL) within 6 months, NASH (pathologically confirmed), alcoholic hepatitis (regular alcohol consumption at least 40 g/day and blood test confirmed). The exclusion criteria included the followings: patient's refusal to provide consent, age <18 or >75 years, malignancy, chronic renal disease (GFR<60 mL/min/1.73 m^2), immunocompromised subjects e.g. HIV co-infection, on immunosuppressive drugs, ongoing Interferon treatment, thrombocytopenia (platelet count<50,000/mm^3) and coagulopathy (INR>1.5). The criteria to terminate the study were severe immunization adverse events and late attendance for scheduled vaccination (more than 2 weeks).

An informed consent was obtained, and all patients were immunized with 3 doses of recombinant vaccine (20 μg) intramuscularly in the deltoid muscle at 0, 1, 6 months. The immune response was evaluated one month after the third dose. A patient was considered a responder, if he/she achieved an anti-HBs level greater than 10 mIU/mL. Those who failed to respond were given one additional double-dose, and the immune response was re-evaluated again one month after the fourth dose.

Before vaccination, details of demographic data (age, gender, BMI, smoking, alcohol drinking, underlying disease and baseline laboratory tests including complete blood count, electrolyte, creatinine, liver function tests, PT (prothrombin time)/INR, and PTT (partial prothrombin time) were obtained.

The followings were analyzed as possible associated factor for vaccine response; age, gender, BMI (body mass index), hemoglobin with blood cells, platelet count, PT, INR, PTT, albumin, Child-Turcotte-Pugh Score, MELD (Model for End Stage Liver Disease) score, metabolic disease, and etiology of chronic liver disease.

Responders were those who archived and immune response (HBsAb level > 10 mIU/mL). HBsAb levels greater than 100 mIU/mL were considered a good immune response, and levels between 10-100 mIU/mL were considered a poor response.

Statistical analysis

Baseline descriptive data were expressed as mean (standard deviations for continuous variables and count (percent of total) for categorical variables. The Chi-square test for numerical data or Fisher's exact test was used for comparison of categorical data. Student t-test was used to compare continuous data and Independent sample Mann-whitney U test in non parametric data. Statistical analysis was performed using SPSS software version 18. A p-value<0.05 was considered to be statistically significant.

Results

Patient characteristics

Fifty-five patients were enrolled in this study. The 35 patients completed 3 doses of vaccine were eligible for analysis (Figure 1). There were 23 (65%) males and 12 (35%) females, age 56.2(10.5 and, BMI 24.8(4 kg/m^2. There were 12 (34%) smokers, 8 (34.3%) active alcoholic hepatitis, 9 (25.7%) diabetics and 10 (28.6%) hypertension. The proportions of Child-Pugh A: B: C were 28 (80%): 6 (17%): 1 (3%), respectively. The average MELD score was 6.93(4.4. Causes of liver disease included NASH (9 patients, 25.7%), alcoholic hepatitis (6 patients, 17%), chronic hepatitis C (8 patients, 23%) and liver cirrhosis from any cause (15 patients, 43%) as shown in Table 1.

Primary Immune response from conventional vaccination and overall response from additional dose regimen

Immune response to the conventional regimen was 48.6% (17/35 patients). The non-responders (18/35 patients) were given an additional double dose, and serum anti-HBs was re-evaluated after one month, only 13 patients were analyzed (5 patients were in process). Seven of 13 (54%) achieved an immune response. The overall response rate increased from 48.6% to 80% (24/30 patients).

The overall median HBsAb level was 465.8 (range 12-833) mIU/mL. The median HBsAb level was 112.4 (range 13.8-833) mIU/mL in the conventional regimen

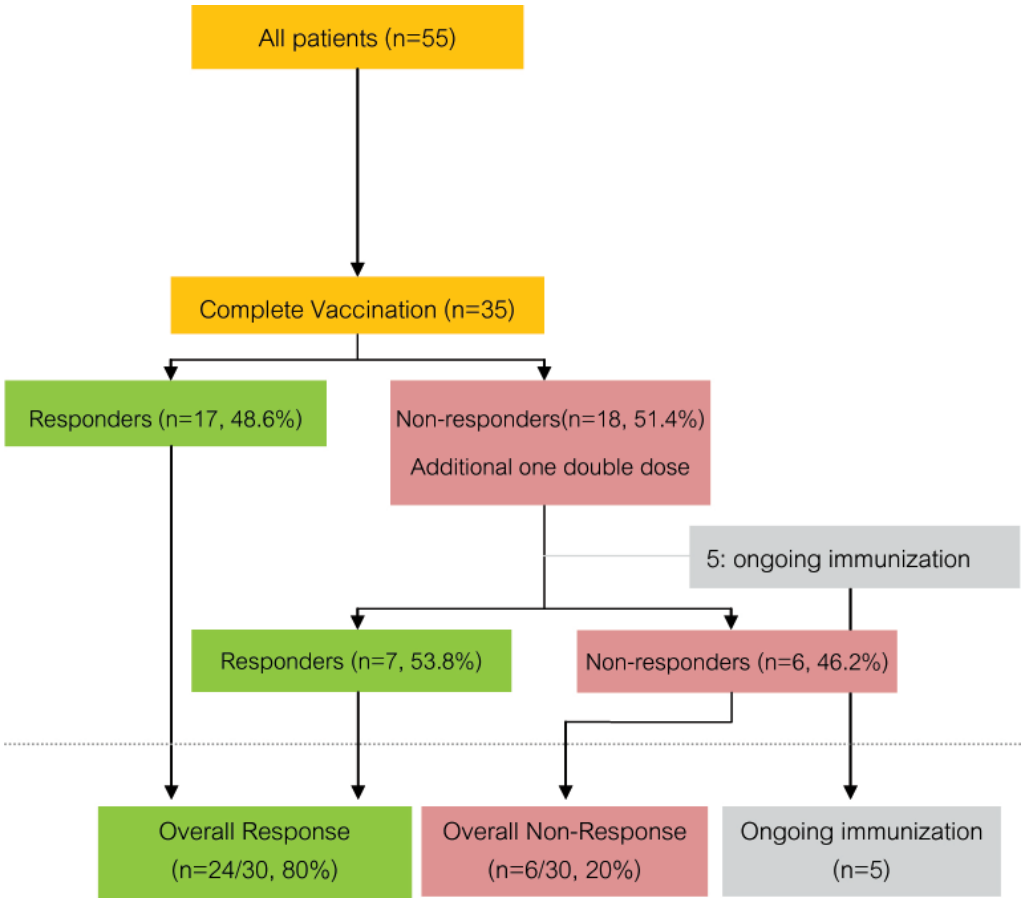

Figure 1. Flow diagram of enrollment and vaccination.

and 639 (range 12-833) mIU/mL after an additional dose (Table 2).

At the end of study, 50% of patients (15/30) were good responders 30%, (9/30) were poor responder, and 20% (6/30) were non-responders.

Table 1. Baseline characteristics of the study patients.

characteristics	N = 35
Age (years) mean (SD)	56.2±10.5
Gender (M:F) (%)	23 (65.7%)/12 (35.5%)
BMI (kg/m^2) mean (SD)	24.8±4
Smoking (%)	12 (34.3%)
Alcohol drinking (%)	8 (23%)
Diabetic mellitus (%)	9 (25.7%)
Hypertension (%)	10 (28.6%)
HCV (%)	8 (23%)
Genotype 1/ 3/NA	6/1/1
Hemoglobin (g/dL)	13.3±3.2
WBC (cells/mL)	7097±2024
Absolute neutrophil count (cells/mL)	3950±1450
Absolute lymphocyte count (cells/mL)	2241±931
Platelet (cells/mL)	158500±66707
ALT (U/L)	57.6±37
Alb (g/dL)	3.96±0.63
Globulin (g/dL)	3.93±0.79
TB	2.4±3
PT	13.4±2.4
Child-Pugh A:B:C (%)	28: 6: 1 (80%:17%:3%)
MELD	6.93±4.4
Diagnosis (%)	
NASH	9 (25.7%)
Alcoholic hepatitis	6 (17.1%)
Chronic hepatitis C	8 (22.9%)
Cirrhosis	15 (42.9%)

Factors associated with immune response in the conventional regimen and the four-dose regimen

In the conventional regimen, 51.4% of patients were non-responders. Non-responders had lower serum albumin (3.66(0.7 vs. 4.28(0.34, p=0.002), more prolonged pro-thrombin time (14.3(2.9 vs. 12.4(1, p=0.015), greater number of liver cirrhosis (11 vs. 4, p=0.041) higher Child-Pugh score (6.4(1.68 vs. 5.2(0.56, p=0.005), and higher MELD score (8.67(4.4 vs. 5.08(3.6, p=0.17) (Table 3).

After an additional dose, the immune response rate was improved, only 20% remaining non-responders. The associated factors for immune response (Table 4) were similar as in the conventional regimen, but patients with more severe liver disease (upto Child Pugh score =6) could achieve a better immune response. Child A patients achieved a more significant immune response rate than Child B and Child A subjects (91.7% vs. 8.3%, p=0.041). When the immune responses across different etiologies analyzed were found no differences (Table 3, 4).

For continuous data, we looked for the cut-off points to predict the outcome of conventional vaccination, and the predictions of those who would benefit from an additional dose. We found that patients with the following factors did not show a favorable outcome from the conventional regimen: platelet ≥ 120,000/mL, Child-Pugh score ≤ 5, serum albumin ≥ 3.5 g/dL, albumin/globulin ratio > 1, PT < 12, MELD ≤ 8,

The Four-dose regimen tended to improve the immune response rate with respect to every variable, especially in patients with hemoglobin >11.5g/dL and Child Pugh score 6 (Table 5).

However, based on multivariate analysis, no significant differences in the associated factors were identified between the responder and the non-responder groups (Table 6).

Adverse Events

Two participants reported minor adverse effects,

Table 2. HBsAb levels in responders.

	HBsAb Level (mIU/mL) of Responders		
	After 3 doses (n=17)	After 4 doses (n=7)	Overall response (n=24)
Mean	316.75 ± 344.77	520.13 ± 357.78	465.75 ± 369.20
Median	112.4 (13.8-833)	639.50 (12-833)	456.8 (12-833)

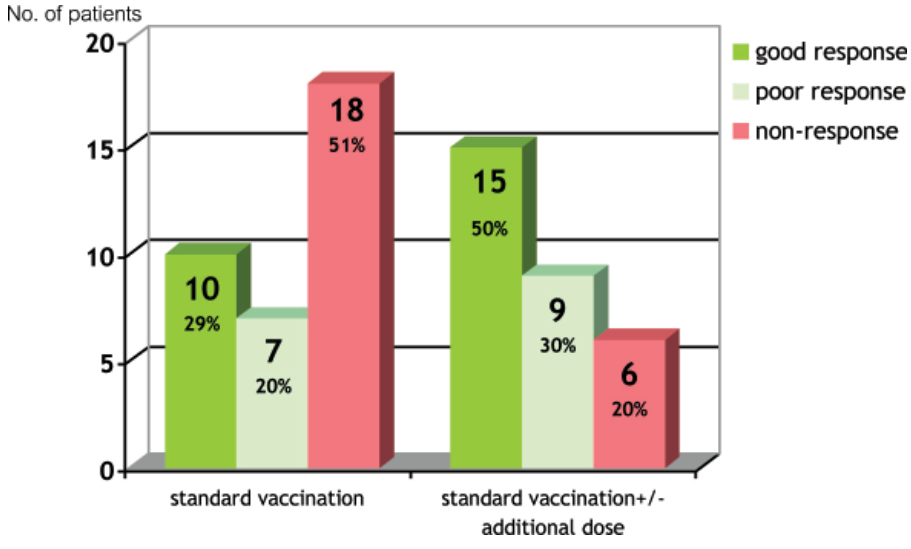

Figure 2. Overall response rates after immunization.

Table 3. Factors associated with the immune response from standard three dose vaccination.

	Non-responders (n=18)	**Responders (n=17)**	***p*-value**
Age (years)	55.37±13	57.1±6.9	0.624
Gender (M:F)	13 (72.2%) / 5 (27.8%)	10 (58.8%) / 7 (41.2%)	0.489
BMI (kg/m^2)	24.9±3.9	24.7±4.2	0.987
Smoking	7 (38.9%)	5 (29.4%)	0.725
Alcohol drinking	6 (33.3%)	2 (11.8%)	0.228
Diabetic mellitus	5 (27.8%)	4 (23.5%)	1
Hypertension	5 (27.8%)	5 (29.4%)	1
Hemoglobin (g/dL)	13.3±4.2	13.4±1.66	0.386
WBC (cells/mL)	6833±1740	7376±2308	0.436
Absolute lymphocyte count	2011±822	2485±1001	0.067
Platelet (cells/mL)	141639±69306	176353±60778	0.062
ALT (U/L)	59.6±44.2	55.5±29.2	0.757
Albumin (g/dL)	3.66±0.7	4.28±0.34	0.002*
Globulin (g/dL)	4.12±0.81	3.7±0.75	0.152
TB	3.12±3.7	1.54±1.8	0.245
PT	14.3±2.9	12.4±1	0.015*
Child-Pugh Score	6.4±1.68	5.2±0.56	0.01*
5	7 (38.9%)	14 (82.4%)	
6	5 (27.8%)	2 (11.8%)	
7	2 (11.1%)	1 (5.9%)	
8-11	4 (22.2%)	0	
Child A	12 (66.7%)	16 (94.1%)	0.88
Child B, C	6 (33.3%)	1 (5.9%)	
MELD	8.67±4.4	5.08±3.6	0.017*
Diagnosis			
NASH	4 (22.2%)	6 (35.3%)	0.471
Alcoholic hepatitis	2 (11.1%)	4 (23.5%)	0.402
Chronic hepatitis C	4 (22.2%)	4 (23.5%)	1
Cirrhosis	11 (61.1%)	4 (23.5%)	0.041*

Table 4. Factors associated with the overall immune response.

	Non-responders (n=6)	Responders (n=24)	*p*-value
Age (years)	56.62±16.85	56.1±8.7	0.947
Gender (M:F)	4 (66.7%) / 2 (33.3%)	15 (62.5%) / 9 (37.5%)	1
BMI (kg/m^2)	26.1±4.5	24.5±4.3	0.438
Smoking	2 (33.3%)	7 (29.2%)	1
Alcohol drinking	1 (16.7%)	4 (16.7%)	1
Diabetic mellitus	2 (33.3%)	5 (20.8%)	0.603
Hypertension	3 (50%)	6 (25%)	0.329
Hemoglobin (g/dL)	11.1±2.7	13.4±1.9	0.021*
WBC (cells/mL)	6367±1547	7304±2181	0.332
Absolute neutrophil count	3782±947	3904±1473	0.849
Absolute lymphocyte count	1758±869	2415±993	0.65
Platelet (cells/mL)	118333±24881	170500±63033	0.021*
ALT (U/L)	41.8±43	64.4±38	0.073
Alb (g/dL)	3.37±0.7	4.1±0.52	0.025*
Globulin (g/dL)	4.2±1.1	3.8±0.7	0.294
TB	2.76±3.3	1.9±2.4	0.347
PT	14.4±1.8	12.8±1.4	0.03*
Child-Pugh Score	7 ± 2.01	5.42±0.77	0.005*
5	1 (16.7%)	18 (72%)	
6	2 (33.3%)	5 (20%)	
7-9	2 (33.3%)	2 (8%)	
11	1 (16.7%)	0 (0%)	
Child A	3 (50%)	22 (91.7%)	0.041*
Child B, C	3 (50%)	2 (8.3%)	
MELD	9.47±3.8	5.7±3.5	0.026*
Diagnosis			
NASH	1 (16.7%)	7 (29.2%)	1
Alcoholic hepatitis	0 (0%)	5 (20.8%)	0.553
Chronic hepatitis C	1 (16.7%)	7 (29.2%)	1
Cirrhosis	5 (83.3%)	8 (33.3%)	0.061

1 patient had low grade fever and pain at the injection site, and another reported mild pain at the injection site. No severe or life threatening complications were reported. The adverse reactions were not associated with vaccination outcome. All adverse reactions were reported after the first dose (20 μg) of vaccine, no adverse events were related to the 40 μg additional dose.

Discussion

The conventional vaccination regimen, three 20 μg doses of recombinant vaccine against hepatitis B virus applied at 0, 1, 6 months resulted in protective immunity in more than 90% of the healthy general population, whereas in chronic liver disease, the figure varies from 18-100% and in liver cirrhosis[12-15]. In our study, in patients with chronic liver disease and those with cirrhosis, the response to conventional regimen was 48%, increased to 80% after the additional double dose. The result was similar to a previous study by Artaza Varasa T[12] showing a 74% overall response rate in chronic liver disease and cirrhosis (57% after 3 doses and a further 17% after an additional double dose). Our overall response rate was not lower than that in the high-dose regimen (40 μg at 0, 1, 2, 6 month) in the study by Rosman AS(17). Employing a double

Table 5. Factors associated with an immune response in the standard and in the 4 dose regimens.

variable	Standard regimen response n=35 (%)			Overall response (standard regimen±additional dose) n=30 (%)		
	Non-responder	Responder	*p*-value	Non-responder	Responder	*p*-value
Hb ≥11.5	11 (31.4%)	14 (40%)	0.264	2 (6.7%)	19 (63.3%)	0.04*
<11.5	7 (20%)	3 (8.6%)	4 (13.3%)	5 (16.7%)		
Plt >120,000	9 (25.7%)	15 (43%)	0.027*	2 (6.7%)	19 (63%)	0.049*
<120,000	9 (25.7%)	2 (5.7%)	4 (13.3%)	5 (16.7%)		
CTP ≤ 5	7 (20%)	14 (40%)	0.015*	1 (3.3%)	17 (56.7%)	0.026*
>5	11 (31.4%)	3 (8.6%)	5 (16.7%)	7 (23.3%)		
CTP ≤ 6	12 (34.3%)	16 (45.7%)	0.088	3 (10%)	22 (73.3%)	0.041*
>6	6 (17.1%)	1 (2.9%)	3 (10%)	2 (6.7%)		
CTP ≤ 7	14 (40%)	17 (49%)	0.104	5 (17%)	23 (77%)	0.366
>7	4 (11%)	0 (0%)	1 (3.3%)	1 (3.3%)		
Alb >3.5	9 (25.7%)	0 (0%)	0.01*	5 (16.7%)	3 (10%)	0.002*
≤ 3.5	9 (25.7%)	17 (48.6%)		1 (3.3%)	21 (70%)	
A/G >1	7 (20%)	14 (40%)	0.015*	1 (3.3%)	17 (56.7%)	0.026*
≤1	11 (31.4%)	3 (8.6%)		5 (17%)	7 (23%)	
PT ≤ 12	2 (5.7%)	8 (23%)	0.027*	0 (0%)	9 (30%)	0.141
>12	16 (45.7%)	9 (25.7%)		6 (20%)	15 (50%)	
MELD ≤ 8	8 (23%)	16 (45.7%)	0.003*	2 (6.7%)	20 (66.7%)	0.029*
>8	10 (28.6%)	3 (3%)		4 (13.3%)	4 (13.3%)	

Table 6. Independent factors associated with the immune response.

Parameter	*p*- value	
	Standard vaccination (n=35)	Overall response after standard vaccination ± additional dose (n=30)
Hb ≥11.5		1
Platelet >120,000	0.652	0.327
CTP ≤ 5	0.999	0.999
CTP≤ 6	0.271	
Albumin >3.5 g/dL	0.998	0.999
A/G >1	0.875	0.999
PT <12	0.600	
MELD ≤ 8	0.999	0.994

dose or giving more doses of vaccine may result in better a response rate. The HBsAb level in our study was higher in patients who were given 4 doses than in those with the conventional dose. Our result confirmed the observation that more frequent vaccine doses or higher doses of vaccine can improve the immune response.

No independent associated factors to predict the immune response were found in our study (based on multivariate analysis). However, patients in an early stage of liver disease achieved a better immune response. For patients with cirrhosis Child A or those with hemoglobin (11.5 g/dL who did not response well to three doses of vaccine better immune response to

additional dose regimen was observed. These observations suggested that in patients with advanced cirrhosis or anemia, it could be better to employ a more frequent or a higher dose regimen. In previous studies, patients with hepatitis C, alcohol ingestion, obesity, advanced age, or smoking had a lower immune response rate. We did not find differences among these parameters, possible owing to small numbers of subjects in our study.

From our results, we recommend the usual conventional regimen of hepatitis B vaccination in patients with chronic liver disease, and the immune response should be tested after a complete vaccination. If the response is inadequate, consider an additional double dose or a different regimen should be considered. In patients with more severe liver disease or in those with of Child Pugh B or MELD > 8 or anemia, we recommend a more frequent dosing or a double dose regimen of vaccination. Because of rather low response rate after vaccination, the anti-HBs titer should be tested in all patients after vaccination.

Conclusion

Patients with chronic liver disease have a lower response to HBV vaccination. Our study showed an immune response rate of 48% after the standard dose regimen, and the overall response rate of 80% after one additional 40 μg dose of HBV vaccine. Larger doses and additional doses could increase the immune response rate to HBV vaccination. Patients with an early stage of chronic liver disease had a better response rate. As the immune response is unpredictable, the anti-HBs titer should be routinely obtained after completion of vaccination.

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