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Original article

Response to Hepatitis B Vaccine in Chronic Hepatitis C Patients Treated with Direct Acting Antivirals

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Abstract

Background and Aims: In Egypt, compulsory vaccination against hepatitis B virus (HBV) infection started in 1992. Patients with chronic hepatitis C (CHC) should be vaccinated against HBV. The aim was to assess the response to HBV vaccine in CHC patients treated with direct acting antivirals (DDAs) in comparison to treatment-naive patients and healthy subjects. **Method:** This retrospective-prospective study was carried out on 360 consecutive adult subjects subdivided into 3 groups. Group I included 150 CHC patients who vaccinated after getting sustained virologic response (SVR) following treatment with DAAs. Group II comprised 110 CHC treatment- naive patients while the control group comprised 100 healthy subjects. Three intramuscular 20 µg doses (at 0, 1 & 6 months) of HBV-vaccine (rDNA) were administered; HBs Ab titres were evaluated 6 – 8 weeks after the 3rd dose. **Results:** CHC patients (treated or treatment-naïve) had highly significant lower mean HBs Ab titre than controls. Twelve patients in group I (8%) had no response to HBV vaccine in comparison to 4.5% in group II and 1% controls. About 83.3%in group I compared to 85.5% in group II and 98% controls had a good response. In CHC treated patients, HBsAb titre was negatively associated with FIB-4 score, fibrosis stage and ALT levels while positively associated with platelet count. The fibrosis stage was the most significant predictor of weak response. **Conclusion:** CHC Patients demonstrate a significantly weak response to HBV vaccine. Concomitant DAAs treatment does not influence response.

Key words: Hepatitis B virus , Hepatitis C virus, Hepatitis B vaccine.

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the most common causes of chronic liver disease leading to cirrhosis and hepatocellular carcinoma worldwide. The world health organization estimates that in 2015, 257 million people were living with chronic HBV infection, and 71 million were living with chronic HCV [1]

Co-infection with HBV and HCV is not infrequent because both viruses have some common modes of transmission and risk factors [2]. Co-infections with HCV and HBV increase the risk of cirrhosis. So vaccination against HBV should be required for all HCV patients [3].

With Direct acting antivirals (DAAs), HCV infection became treatable by realistic chance of eliminating the virus [4]. It is estimated that more than 80% of HCV-infected individuals in all genotypes attain SVR [4, 5]. On the other hand, many HCV patients have a lifelong risk of re-infection [4].

The World Health Organization (WHO) advises that all Egyptians get vaccinated against Hepatitis B (HBV), which was included in the Egyptian EPI in 1992 [6,7].

There has been a significant decrease in HBV infection rates in the United States as a result of the vaccination program, which has been available for over 40 years [8, 9].

Aim of the study

To assess the response to HBV- vaccine in successfully treated CHC patients with direct acting antivirals (DDAs) compared to treatment naïve CHC patients and healthy subjects.

Patients And Methods

This study was a retrospective- prospective clinical cohort study carried out on 360 individuals attended the department of Hepatology, Gastroenterology and Infectious Diseases, Benha University Hospital and its outpatient clinics, during the period between December 2019 & September 2021. The study protocol was approved by the Ethics Committee of Benha Faculty of Medicine. The enrolled individuals were subdivided into ٣groups:

- **Group I:** included consecutive 150 adult CHC patients after compeletion of 12 weeks of DAAs therapy and SVR achievement.
- **Group II**: included consecutive 110 adult treatment-naive CHC patients.

- **Group III (control group)**: included consecutive 100 apparently healthy subjects with negative HCV Ab and HBs Ag. All patients gave written informed consent before enrollment in the study.

The inclusion criteria were: age older than 18 years, and CHC (in the cases group) that was diagnosed by both HCV- Ab (by 4th generation ELISA test) and HCV- RNA-PCR positivity for ≥6 months for GII before inclusion in the study. We excluded patients (or controls) who were positive for HBs Ag or HBcAb (total); underwent previous HBV-vaccination; pregnant, diabetic; underwent haemodialysis, organ transplantation, or immunosuppressive therapy; or who demonstrated malignancy and/or decompensated cirrhosis with ascites and/or HCC. Non-HCV healthy controls were recruited from subjects who came for vaccination for pre-employment and pre-marital purposes or contacting HbsAg-positive patients.

Demographic data for patients and controls including age, gender and body mass index (BMI) were collected. Laboratory data, including haemoglobin level, white blood cell count, platelet count, liver function profile (ALT, AST, total bilirubin, prothrombin concentration and serum albumin) and HCV-viral load, were collected for all cases. FIB-4 score was calculated for all cases according to the standard formula [10, 11] . Abdominal ultrasonography was performed to exclude the presence of ascites and/or hepatic focal lesions, and fibroscan were done for treated CHC and untreated CHC patients.

Vaccination of all the studied subjects was accomplished by administering 3 doses of Hepatitis B vaccine (rDNA), each dose containing 20 µg of the active ingredient, purified HbsAg in a 1-mL volume; the vaccine was intramuscularly injected into the deltoid muscle at 0, 1, and 6 months. The response to the vaccine was measured by quantitatively assessing HBsAb titres (by ELISA test, according to the manufacturer's instructions), 6 - 8 weeks after the 3rd vaccination dose. Non-responders are defined as subjects who had a HBs-Ab titre of less than 10 mIU/mL, poor responders are subjects with a HBs-Ab titre between 10 and 100 mIU/mL, and good (robust) responders are those who had HBs-Ab titre of more than 100 mIU/mL.

Viral and clinical case definitions:

- A positive HBsAb test was defined as having a titre of 10 mIU/ml or above.

- Staging of liver fibrosis was based on FIB-4 index and radiographic morphology of the liver on ultrasound [5].
- Definition of a case of cirrhosis was based on clinical , biochemical (INR level >1.2, persistent high levels of total bilirubin (>1.2 mg/dl) or low platelet count ($<150 \times 10^9$) and ultrasound imaging data [12,13].

Statistical Methods:

SPSS (version 21) was used for statistical analysis. Comparison of patients and control groups was performed by using a two tailed "t" test for continuous variables and a Chi square test for categorical or dichotomous variables. Non-parametric tests were used when indicated. Univariate regression analysis was performed to assess the association between continuous variables and HBsAb titre within CHC patients. Independent samples two-tailed "t" test was performed to assess the association between categorical or dichotomous variables and HBsAb titre. Significant variables associated with HBsAb titre in all univariate analyses were included in a multivariate regression analysis to identify independent predictors of the response. Pearson correlation test was performed to test the correlation between age and HBsAb titre. For all tests, 0.05 was set as the level of significance.

Results

This study included 150 CHC patients treated with DAAs (GI), 110 treatment naive(GII) and 100 healthy controls(GIII), (the age range was 19-60 years), the mean age of group I, II and controls was (50.8, 45.1 and 30.8 years) respectively and females were predominant in the studied groups which was (80%, 72.7% and 63%) respectively with mean BMI (30.4, 31.3 and 30.8 Kg/m2) respectively in group I, II and controls.

Tables (1) and (2) show descriptive demographic and laboratory data for the studied groups. Regarding the laboratory data in GI, GII and GIII, the mean value of hemoglobin level was (13, 13.1 and 13.5 gm/dl) respectively, the mean value of WBCs count was (6.7, 6.2 and 7.2 $X10^3$) respectively, the mean value of platelets count was (215.2, 198.1 and 258.6 $X10^3$) respectively. Regarding the mean value of ALT (31, 48.6 and 32.6 U/L) and AST was (28.6, 45.5 and 32.1 U/L) in GI, GII and GIII respectively. Regarding the mean value of PC was (93.2%, 89.8 and 94.6%) in GI, GII and GIII respectively. The mean value

of AFP was (4.9 and 10.1 ng/ml) in GI and GII respectively.

Regarding the response to hepatitis B vaccine, we found that CHC patients (either treated or naïve) had significantly lower HBsAb titres than healthy controls and significantly more number of non-responders (Table 3, Figure 1 and 2). Concomitant therapy with DAAs had no positive effect on the antibody response to HBV vaccination in CHC treated patients.

In CHC patients treated with DAAs, HBsAb titre was negatively associated with age (P<0.001), ALT (P=0.03), fibrosis stage (P=0.001) and FIB-4 score (P<0.001) and positively associated with platelet count (P<0.001) (Table 4).

The present study found that advancement of liver fibrosis affects the HBV vaccine response as out of the assessed 94 patients in CHC patients treated with DAAs, the number of patients with F0 were 38, 32/38 represent 84% gave good response, the number of patients with F1 were 30, 28/30 represent 93.3% gave good response, the number of patients with F2 were 10, 10/10 represent 100% gave good response, the number of patients with F3 were 8, 4/8 represent 50% gave good response while the number of patients with F4 were 8, 6/8 represent 75% gave good response (Table 5). The fibrosis stage was the most significant predictor for HBV vaccine response with negative relationship (Table 6).

In treatment naïve patients, HBsAb titre was negatively associated with ALT (P=0.001), AST (P=0.03), FIB-4 score (P=0.011) and positively associated with platelet count (P=0.001) (Table 4).

Table (1): Demographic features of the studied groups:

	GI **(Treated CHC)** **n=150**	**GII** **(Untreated CHC)** **n=110**	**GIII** **(Control)** **n=100**
Sex N(%)			
Male	30 (20%)	30 (27.3%)	37 (37%)
Female	120 (80%)	80 (72.7%)	63 (63%)
Age (Y) (Mean± SD)	50.8 ± 11.61	45.1 ± 10.43a	36.7 ± 9.19ab
BMI (Mean± SD)	30.4 ± 6.67	31.3 ± 5.45	30.8 ± 5.69

Table (2): Laboratory data of the studied groups:

Mean ±SD	**GI (Treated CHC) n=149**	**GII (Untreated CHC) n=110**	**GIII n=100**
Hb (gm/dl)	13 ± 1.36	13.1 ± 1.32	13.5 ± 1.42ab
WBCs (/mm3)	6.7 ± 1.62	6.2 ± 1.59a	7.2 ± 1.92ab
Platelet (×1000)	215.2 ± 55.79	198.1 ± 65.47a	258.6 ±55.17ab
AST (U/L)	28.6 ± 14.47	45.5 ± 25.97a	32.1 ± 18.47b
ALT (U/L)	31 ± 15.42	48.6 ± 32.53a	32.6 ± 20.14
PC (%)	93.2 ± 7.96	89.8 ± 7.92a	94.6 ± 4.38b
S.Albumin(gm/dL)	4.1 ± 0.37	4 ± 0.29a	4.2 ± 0.32b
S. creat(mg/dL)	0.87 ± 0.20	0.82 ± 0.14a	0.89 ± 0.21b
N	69	14	
AFP(ng/ml)	4.9 ± 3.70	10.1 ± 10.98a	

Table (3): HBV vaccine response and HBs Ab titre after 6-8weeks of full doses of HBV vaccination of the studied groups:

	G I n=150	**G II n=110**	**G III n=100**	**P1 value**	**P2 value**	**P3 value**	**P value**
HBsAb titre(IU/L) (Mean± SD)	846.42 ± 525.79	739.77 ± 531.88	1088.31 ± 479.52ab	0.11	**<0.001****	**<0.001****	**<0.001****
Response N(%)							**<0.001****
Non-responder	12 (8%)	5 (4.5%)	1 (1%)	0.52	**0.001****	**0.003****	
Poor responder	13 (8.7%)	11 (10%)	1 (1%)				
Good responder	125 (83.3)	94 (85.5%)	98 (98%)				

***Significant difference (P value <0.05). **Highly significant (P value <0.01)**
P1 value: P value of group I and II P2 value: P value of group I and III
P3 value: P value of group II and III P value: P value of all group.

Table (4): Correlation between HBs Ab and (Age, BMI, laboratory investigations, fibroscan, FIB4 and Anti-bilharzial Ab) in each group:

	G I (150)		**G II (110)**		**G III (100)**	
HBs Ab	R1	P1 value	R2	P2 value	R3	P3 value
Age	-0.47	**<0.001****	-0.15	0.12	-0.11	0.28
BMI	-0.10	0.23	-0.02	0.84	0.18	0.08
Hb	0.03	0.73	-0.03	0.73	-0.03	0.77
Platelet	0.32	**<0.001****	0.30	**0.001****	-0.12	0.23
AST	-0.15	0.07	-0.21	**0.03***	0.09	0.40
ALT	-0.18	**0.03***	-0.31	**0.001****	-0.03	0.78
FIB4	-0.41	**<0.001****	-0.24	**0.011***	-0.008	0.94
S. creat	-0.08	0.31	-0.08	0.42	0.024	0.82
AFP pre-treatment	-0.186	0.13	-0.08	0.77		
AFP post-treatment	-0.26	0.051				
F KPa	-0.34	**0.001****	0.014	0.90	0.56	**<0.001****
CAP(db)	0.123	0.255	0.004	0.97	0.45	**0.006****

***Significant difference (P value <0.05). **Highly significant (P value <0.01)**

P1 value: P value of group I and II P2 value: P value of group I and III
P3 value: P value of group II and III P value: P value of all group.

Table (5): Fibroscan in [Non-, poor-, and good] responders in GI:

Response G I (94)	Non responder N=8	Poor responder N=6	Good responder N=80	Statistical test	P value
Stage N(%)					
F0 (38)	4 (10.52%)	2 (5.26%)	32 (84.2%)	FET= 13.72	**0.03***
F1 (30)	0 (0%)	2 (6.67%)	28 (93.3%)		
F2 (10)	0 (0%)	0 (0%)	10 (100%)		
F3 (8)	2 (25%)	2 (25%)	4 (50%)		
F4 (8)	2 (25%)	0 (0%)	6 (75%)		
KPa (Mean ±SD)	22.38 ± 30.32	8.03 ± 4.17	6.83 ± 3.66	F= 10.55	**<0.001****
CAP N(%)					
S0 (34)	6 (17.64%)	2 (5.88%)	26 (76.47%)	FET= 8.62	0.12
S1 (28)	0 (0%)	2 (7.14%)	26 (92.86%)		
S2 (18)	2 (11.1%)	2 (11.1%)	14 (77.78%)		
S3 (14)	0 (0%)	0 (0%)	14 (100%)		
CAP (dB/m) (Mean ±SD)	214.0 ± 61.61	240.33 ± 40.99	253.0 ± 51.51	F= 2.13	0.13

***Significant difference (P value <0.05)** ****Highly significant (P value <0.01).**
P value: P value of non , poor and good responders in GI.

Table (6) Multi-linear regression of HBV vaccine response among group GI:

GI	Beta	P value	95% C.I. Lower	Upper
Fibrosis stage	-.758-	.028	-587.378-	-37.299-
CAPs	.512	.288	-229.970-	728.240
dB	-.434-	.334	-13.096-	4.703
AFP	-.124-	.624	-74.039-	45.708
FIB4	.410	.257	-114.304-	399.933
F test	2.69			
P value	0.051			
r^2	0.487			
Adjusted r^2	0.306			

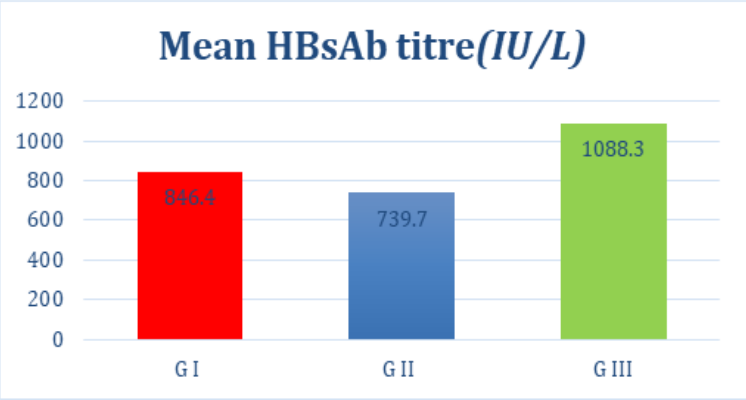

Figure (1): Mean of HBs Abtitre among the studied groups

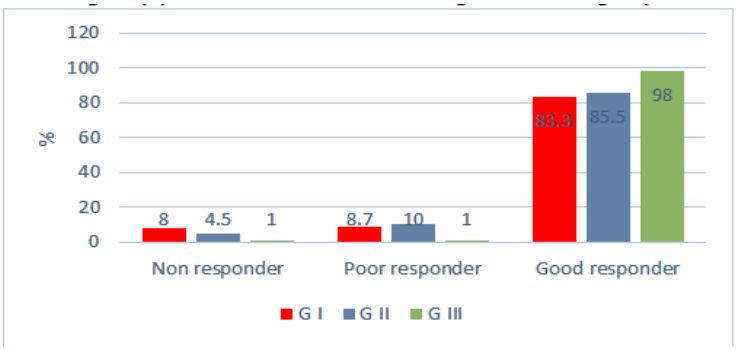

Figure (2): [Non-, poor-, and good] responders among the studied groups

Discussion

Co-infection with HBV or HCV has been linked to an increased risk of cirrhosis and a worsening of liver disease [(14)]. In light of this, the necessity of HBV prevention in HCV patients is underscored [(3)].

In the present study, the mean value of HBsAb in treated, untreated CHC patients and controls was (846.4, 739.7 and 1088.3 IU/L respectively) with the highest level in controls. Twelve out of 150 treated CHC patients (8%) gave no response to HBV-vaccine in comparison to five out of 110 (4.5%) untreated CHC patients and one out of 100 (1%) healthy controls with a statistically highly significant difference between treated CHC patients and controls and between untreated CHC patients and controls. A poor response (HBsAb 10-100 mIU/ mL) was achieved in 13/150 (8.7%) treated CHC patients compared to 11/110 (10%) untreated CHC patients and 1/100 (1%) controls. A good (robust) response (HBsAb >100 mIU/ mL) was achieved in 125/150 (83.3%) treated CHC patients compared to 89/110 (85.5%) untreated CHC patients and 98/100 (98%) controls. So, there was a significantly lower level of HBsAb titre and higher number of non and poor responders to HBV vaccination in CHC patients (either treated with DAAs or naïve) when compared with control group.

This result comes in accordance with a previous study that found that 4/32 patients with CHC (12.5%) did not respond to HBV vaccination in comparison to complete response (100%) of healthy controls [(15)]. This finding is explained by the evidence that HCV infects immune cells, such as macrophages, B cells, and T cells, with many reports suggesting that the HCV- core, the first protein expressed during the early phase of viral infection, moderates immunomodulatory functions to suppress host immune responses. This altered

function of immune cells caused by HCV infection may explain the ineffective immune response to HCV [16,17] and may subsequently affect the response to vaccination.

Also this result is in agreement with a previous study that found untreated HCV-infected patients had a lower response rate to HBV vaccination, with a response rate of 50% when they get 3 or more vaccine doses, compared to the general population's response rate of 90% to 98% [18]. In addition, another study reported that 4.5% of untreated patients did not respond to HBV vaccine in comparison to 1.9% of healthy controls. A good (robust) response (HBsAb >100 mIU/ mL) was achieved in 87/112 (77.6%) cases compared to 51/54 (94.4%) controls [19]

Another study reported that the vaccination-induced seroprotection rates were significantly higher in the control group than in untreated HCV patients (P = 0.04) as 58 of 70 of untreated patients (82.85%) and 112 of 121 healthy subjects (92.56%) had been seroconverted (HBsAb ≥ 10 mIU/mL) within three months following the third dose of the vaccine [20].

Concomitant therapy with DAAs had no positive effect on the antibody response to HBV vaccination in chronically infected individuals, according to our study results. As there is a statistically no significant difference between treated and untreated patients. There was agreement with another study which found that hyporesponsiveness to the HBV vaccination is common in chronic HCV patients even after achieving SVR following DAAs as they found 57.1% of patients were responders and 42.9% of non-responders to the HBV vaccine. A higher rate in the non-responder group than our study (8%) may be due to the presence of isolated HBcAb which is often regarded as one of the important reasons for diminished response to HBV vaccine [21].

In patients treated with DAAs, fibrosis stage was shown to be the most important predictor of HBV vaccination response (P=0.028). This result is in agreement with a previous study which reported that HCV infection seems to impair HBV vaccine response and liver cirrhosis was being the only identifiable risk factor for hypo-responsiveness among studied patients [18].

There is significant negative correlation between HBsAb and FIB4 in treated and untreated patients. The parameters that indicate advanced fibrosis inform of high AST levels, thrombocytopenia and increased FIB4 scores, were associated with decreased HBsAb titres. Also, this result was observed

in another study which reported that there was an association between a higher FIB-4 score and mean HBsAb response level (P=0.008) as patients with more advanced CLD demonstrate lower response to HBV vaccine [(19)]. In contrast, another study did not find a statistically significant difference when the vaccination response was evaluated in relation to the histological findings [(22)]. Another research compared the vaccination response in 65 CHC patients with 20 compensated cirrhotic individuals and found no differences [(23)].

Conclusions

The present study confirms that patients with CHC (either treated with DAAs or treatment naïve), demonstrate a lower response to HBV vaccination. The fibrosis stage was the most significant predictor for HBV vaccine response with negative relationship. Clearance of HCV infection did not ameliorate the response to HBV vaccine.

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