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Original Research Article

An Assessment of Efficacy and Viral Resistance Rate of Entecavir

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Abstract

Aim: The aim of the present study was to investigate the long-term efficacy and viral resistance rate of entecavir and explore the factors associated with virologic response, including quantitative hepatitis B surface antigen (qHBsAg) levels.

Methods: The present study was conducted in the Department of Gastroenterology, Mediversal hospital, Patna and 200 consecutive treatment-naïve HBV-infected patients, whose treatment was initiated with 0.5 mg of daily entecavir were enrolled.

Results: The majority of patients were male (65%) and the median patient age was 49 years old (range, 18 to 80). The patients were followed up for a median of 29.0 months (range, 6.0 to 77.4). 110 (55%) patients were HBeAg-positive and 90 patients (45%) were HBeAg-negative. The mean baseline HBV DNA load was 6.47 ± 1.40 log10 IU/mL and 36% of the patients had liver cirrhosis at initiation of entecavir treatment. Univariate analysis revealed that older age, presence of liver cirrhosis, lower HBV DNA load, HBeAg negativity, lower platelet count, and prolonged PT were statistically significant factors associated with virologic response. In multivariate analysis, only HBeAg-negativity and lower HBV DNA load were independently associated with virologic response.

Conclusion: In conclusion, continuous treatment with entecavir for treatment-naïve, genotype-C, CHB patients showed an excellent virologic response rate and a low rate of resistance, which is comparable to results from registration trials. Baseline HBV DNA loads, qHB-sAg levels, and HBeAg status were predictors of virologic response during entecavir treatment.

Keywords: Hepatitis B virus; Entecavir; Quantitative hepatitis B surface antigens; Virologic response

Introduction

Hepatitis B virus (HBV) infection is a major health problem. [1] Globally, 257 million people are chronically infected with the virus (estimated prevalence: 3.7%). [2] However, the epidemiological scenario varies greatly across different geographic regions, mainly due to different socioeconomic conditions and an uneven vaccination coverage. [3,4] It has then remained stable due to the input of new infections brought by HBV-infected immigrants. [5,6] To date, the clinical presentation of CHB shifted toward older ages and more severe diseases. [7]

Chronic hepatitis B (CHB) is a major global health problem and a leading cause of liver-related complications, including cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. The goal of nucleoside/nucleotide analog (NA) therapy for CHB is to suppress the replication of hepatitis B virus (HBV) in a sustained manner, and prevent disease progression to decompensated cirrhosis and HCC. [8-10] However, the durability of off-treatment virological responses has not been fully estimated in patients in whom complete virological suppression is achieved with NA therapy, and relapse rates after stopping NA treatment have not been well established.

According to the recommendations of the Asian Pacific Association for the Study of the Liver (APASL), [11] NA therapy should be stopped in hepatitis B e antigen (HBeAg)- positive CHB patients after HBeAg seroconversion has persisted for more than 12 months. However, some patients develop hepatitis relapse after stopping NA therapy, even when the above recommendation has been followed. [12,13] Therefore, indexes to monitor relapse rates after the cessation of NA treatment are urgently required.

ETV is a potent inhibitor of HBV replication, which is commercially available since 2005. In phase III randomized clinical trials (RCT) entecavir at a dose of 0.5 mg/day in treatment-naïve patients suppressed HBV DNA to undetectable levels by year one in 67% of HBeAg-positive and in 90% of HBeAg negative patients. [14,15] Recent reports showed that when administered for 2 to 5 years, resulted in a better HBV DNA suppression and higher rates of HBeAg seroconversion. [16,17] It has a high genetic barrier to resistance and a strong resistance profile in treatment naïve patients, but genotypic resistance is higher in patients previously treated with lamivudine. Recently reported results of more than 6 years of therapy showed that in nucleos(t)ide-naïve patients, the cumulative probability of genotypic resistance to ETV was 1.2%. [18] Also, ETV treatment have shown that it can improve fibrosis of the liver and can cause fibrosis and cirrhosis regression. [19]

The aim of the present study was to investigate the long-term efficacy and viral resistance rate of entecavir and explore the factors associated with virologic response, including quantitative hepatitis B surface antigen (qHBsAg) levels.

Materials and Methods

The present study was conducted in the Department of Gastroenterology and Hepatology , Mediversal Hospital, Patna, Bihar, India for two years and 200 consecutive treatment-naïve HBV-infected patients, whose treatment was initiated with 0.5 mg of daily entecavir were enrolled. All patients were chronically infected with HBV and were confirmed as HBsAg-positive for at least 6 months. Exclusion criteria consisted of coinfection with hepatitis C virus or hu- man immunodeficiency virus, prior treatment history with NUCs or interferon, entecavir treatment less than 24 weeks, prior diagnosis of hepatocellular carcinoma, being younger than 18 years old, and insufficient clinical data. The indication for antiviral therapy followed those of the Korean Association for the Study of the Liver guidelines [20] and included: HBeAg-positive CHB patients with HBV DNA loads of ≥ 20,000 IU/mL and alanine transaminase (ALT) levels of ≥ 2 × the upper normal limit (UNL), HBeAg-negative CHB patients with HBV DNA loads ≥ 2,000 IU/mL and an ALT level of ≥ 2 × the UNL, compensated cirrhotics with HBV DNA loads ≥ 2,000 IU/mL regardless of the ALT level, and decompensated cirrhotics with any detectable HBV DNA loads.

Assessment

All patients underwent complete blood counts, liver function tests, HBV virologic markers, HBV DNA load counts, and imaging studies (abdominal sonography, computed tomography, or magnetic resonance imaging); these assessments were completed at baseline and were repeated at 3- to 6-month intervals. HBsAg, anti-HBs antibody, HBeAg, and anti-HBe antibody levels were examined by enzyme immunoassay. HBsAg levels were quantified by automated chemiluminescent microparticle immunoassay (Architect HBsAg, Abbott, IL, USA). HBV DNA loads were measured using the COBAS TaqMan HBV quantitative test (Roche Molecular Systems Inc., Branchburg, NJ, USA), with a lower detection limit of < 9 IU/mL. Viral mutational analysis was per- formed by direct sequencing of the reverse transcriptase (RT) domain of the HBV polymerase gene. Virologic responses were defined as a reduction in HBV DNA loads to < 60 IU/mL. Biochemical response was defined as ALT < 40 U/L. Virologic breakthroughs were defined as an increase in serum HBV DNA loads by > 1 log10 above the nadir after achieving a virologic response during continued treatment. Liver cirrhosis was determined by liver biopsy or an imaging modality combined with two positive laboratory findings (e.g., platelet levels < 100,000/μL, albumin levels < 3.5 g/dL, or prothrombin time [PT, international normalized ratio] > 1.3).

Statistical Analyses

Baseline characteristics were summarized with descriptive statistics and are presented as a mean ± standard deviation or as percentages. In all study subjects, continuous variables were compared parametrically us- ing the Student t test or non-parametrically using the Mann-Whitney U test. Categorical variables were com- pared using the chi-square test or the Fisher exact test as appropriate. Cumulative rates of virologic and biochemical responses were analyzed using the Kaplan-Meier method. Independent risk factors predicting achievement of virologic response and viral resistance were analyzed with the stepwise Cox regression analysis. A two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM Co., Armonk, NY, USA).

Results

Table 1: Baseline characteristics

Variable	Value
Male sex	130 (65)
Age, yr	49 (18–80)
Duration of follow-up, mon	29.0 (6.0–77.4)
Duration of ETV administration, mon	26.5 (6.0–77.4)
HBeAg (+):HBeAg (–) patients	110 (55):90(45)
HBV DNA, log_{10} IU/mL	6.47 ± 1.40
Liver cirrhosis	72 (36)
qHBsAg, log_{10} IU/mL[a]	3.59 ± 0.69
WBC, × 10^3/μL	5.08 ± 1.61
Hemoglobin, g/dL	14.3 ± 1.8
Platelet, × 10^3/μL	152.2 ± 62.4
AST, U/L	112.8 ± 183.9
ALT, U/L	154.7 ± 292.3
Total bilirubin, mg/dL	1.27 ± 1.93
Albumin, g/dL	3.9 ± 0.5
Prothrombin time, INR	1.13 ± 0.19

The majority of patients were male (65%) and the median patient age was 49 years old (range, 18 to 80). The patients were followed up for a median of 29.0 months (range, 6.0 to 77.4). 110 (55%) patients were HBeAg-positive and 90 patients (45%) were HBeAg-negative. The mean baseline HBV DNA load was 6.47 ± 1.40 log10 IU/mL and 36% of the patients had liver cirrhosis at initiation of entecavir treatment.

Table 2: Univariate and multivariate analysis of factors associated with virologic response in entecavir-treated chronic hepatitis B patients

	Univariate		Multivariate	
Variable	HR (95% CI)	*p* value	HR(95% CI)	*p* value
Age, yr	1.015 (1.009–1.022)	< 0.001		
Male sex	1.008 (0.883–1.152)	0.904		
Liver cirrhosis	1.472 (1.288–1.682)	< 0.001		
HBV DNA, log_{10} IU/mL	0.615 (0.587–0.644)	< 0.001	0.671 (0.635–0.709)	< 0.001
HBeAg (–)	0.347 (0.303–0.397)	< 0.001	0.607 (0.521 0.708)	< 0.001
WBC, × 10^3/μL	0.949 (0.910–0.988)	0.012		
Hemoglobin, g/dL	0.967 (0.934–1.002)	0.061		
Platelet, × 10^3/μL	0.997 (0.996–0.998)	< 0.001		
AST, U/L	1.000 (1.000–1.000)	0.588		
ALT, U/L	1.000 (1.000–1.000)	0.438		
Total bilirubin, mg/dL	1.032 (1.001–1.064)	0.045		
Albumin, g/dL	1.096 (0.957–1.255)	0.187		
Prothrombin time, INR	2.177 (1.621–2.922)	< 0.001		

Univariate analysis revealed that older age, presence of liver cirrhosis, lower HBV DNA load, HBeAg negativity, lower platelet count, and prolonged PT were statistically significant factors associated with virologic response. In multivariate analysis, only HBeAg-negativity and lower HBV DNA load were independently associated with virologic response.

Discussion

Hepatitis B virus (HBV) is estimated to have infected more than 2 billion people worldwide, of whom 350 to 400 million people are chronically infected. [21] Chronic hepatitis B (CHB) patients are at an increased risk for liver-related complications, including cirrhosis, liver failure, hepatocellular carcinoma, and death. [22] The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) study demonstrated that progression to liver cirrhosis and hepatocellular carcinoma are strongly correlated with HBV DNA loads. [23,24]

The majority of patients were male (65%) and the median patient age was 49 years old (range, 18 to 80). The patients were followed up for a median of 29.0 months (range, 6.0 to 77.4). 110 (55%) patients

were HBeAg-positive and 90 patients (45%) were HBeAg-negative. HBV DNA is a critical goal in treating CHB patients. [25,26] Genotype C is associated with a high likelihood of a longer period of persistent hepatitis, which increases the risk of liver cirrhosis and hepatocellular carcinoma. [27,28]

The mean baseline HBV DNA load was 6.47 ± 1.40 log10 IU/mL and 36% of the patients had liver cirrhosis at initiation of entecavir treatment. Univariate analysis revealed that older age, presence of liver cirrhosis, lower HBV DNA load, HBeAg negativity, lower platelet count, and prolonged PT were statistically significant factors associated with virologic response. In multivariate analysis, only HBeAg-negativity and lower HBV DNA load were independently associated with virologic response. Yang et al [29] found a reduced risk of liver related events and HCC in entecavir-treated patients who experienced virologic response. A previous study also found increased HCC risk in patients with incomplete virologic response to treatment. [30] The patients with lower HBV DNA loads and baseline HBeAg-negativity had a significantly greater probability of achieving virologic response ($p < 0.001$). Thus, the two independent factors found to be predictive of virologic response in our study, baseline HBV DNA loads and HBeAg status, are comparable to previous viral efficacy studies of both lamivudine-treated and entecavir-treated patients. [31.32]

Conclusion

In conclusion, continuous treatment with entecavir for treatment-naïve, genotype-C, CHB patients showed an excellent virologic response rate and a low rate of resistance, which is comparable to results from registration trials. Baseline HBV DNA loads, qHB-sAg levels, and HBeAg status were predictors of virologic response during entecavir treatment.

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