

## Entecavir for the treatment of real-life chronic hepatitis B patients: a study from Saudi Arabia

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**BACKGROUND AND OBJECTIVES:** Entecavir is a nucleoside analog used in the treatment of chronic hepatitis B. The efficacy of ETV has not been studied in the Saudi population. The objective of the study was to find undetectable HBV DNA after 48 weeks completion of ETV treatment in real-life versus clinical trial patients.

**DESIGN AND SETTING:** A retrospective study in a tertiary care center in Saudi Arabia of patients treated from 2006 January to 2010 June.

**PATIENTS AND METHODS:** Of 43 eligible patients, 24 patients were treatment-naïve and 19 were treatment refractory.

**RESULTS:** Mean HBV DNA viral load was 51 million IU/mL prior to treatment and decreased to 0.16 million IU/mL at 48 weeks. Mean HBV DNA log<sub>10</sub> IU/mL was 6.3 before treatment and decreased to 2.3 log<sub>10</sub> IU/mL ( $P=0.001$ ) at 48 weeks. After 48 weeks treatment, ALT significantly decreased from a mean ALT of 88.7 U/L before treatment to 37.5 U/L ( $P=0.04$ ). After 48 weeks, the HBV DNA was undetectable in 14 (58.4%) in treatment-naïve patients and in 6 (31.6%) treatment-refractory patients. At 48 weeks 17 (60.7%) of HBeAg-negative patients and 3 (20%) HBeAg-positive patients achieved undetectable HBV DNA ( $P=0.003$ ). When the treatment was extended for a median of 24 months (range 12 months to 60 months), 29 (67.4%) achieved undetectable HBV DNA. Among 29 patients who achieved undetectable HBV DNA, the treatment refractory patients reached undetectability within a mean of 32.4 (18.6) months and treatment-naïve patients in a mean of 18.8 (10.5) months ( $P=0.01$ ). Two (13.3%) of HBeAg-reactive patients converted to HBeAg-negative status and one patient (2.3%) lost HBsAg.

**CONCLUSION:** After treatment with entecavir, HBV DNA undetectable at 48 weeks in 58.4% of naïve patients. The response rate was better in HBeAg-negative and treatment-naïve patients compared to HBeAg-positive and treatment-refractory patients.

Approximately 400 million people are chronically infected with hepatitis B virus (HBV).<sup>1</sup> When they are left untreated, the disease progresses to cirrhosis and hepatocellular carcinoma.<sup>2,3</sup> Saudi Arabia is considered endemic for chronic hepatitis B infection.<sup>4,5</sup> Chronic hepatitis B patients in Saudi Arabia are mostly infected with HBV genotype D.<sup>6</sup>

Currently, FDA approved drugs for chronic hepatitis B include standard interferon, pegylated interferon alfa, lamivudine, adefovir, tenofovir, telbivudine and entecavir.<sup>7</sup> Entecavir (ETV) is a nucleoside analog of 2'-deoxyguanosine and inhibits HBV replication at the priming of HBV DNA polymerase and by inhibiting synthesis of both negative-strand and positive-strand

HBV DNA.<sup>8</sup> ETV has been found effective in treating patients who have lamivudine-refractory hepatitis,<sup>9</sup> HBeAg-positive chronic hepatitis B<sup>10</sup> and HBeAg-negative chronic hepatitis B.<sup>11</sup>

In large clinical trials, at the end of 48 weeks, ETV was effective in achieving undetectable HBV DNA in 67% of HBeAg reactive patients and 90% of HBeAg-negative patients.<sup>12</sup> It has been noted that in real-life patients, the treatment responses were different from large phase 3 clinical trials.<sup>13</sup> The response rate of medications in different populations might be different. There are no published studies from Saudi Arabia addressing the efficacy of ETV in the Saudi population. To answer this question a retrospective study was conducted. The

objective of the study was to find the rate of undetectable HBV DNA after 48 weeks of treatment with ETV in a cohort of chronic hepatitis B patients. The secondary objective of the study was to find the predictors of virological response.

## PATIENTS AND METHODS

We conducted a retrospective study of a cohort of chronic hepatitis B patients who were treated with ETV from 2006 January to 2010 June. The inclusion criteria for the study were a diagnosis of chronic hepatitis B in patients treated with ETV for a minimum of 48 weeks with entry level HBV DNA >2000 IU/mL (patients with <2000 IU/mL HBV DNA were receiving ETV treatment because of their cirrhotic status, or they were on prophylaxis to prevent HBV flare up following chemotherapy). Their charts and electronic data were studied and all necessary information was collected in a data collection form. The data was then transferred to SPSS version 16 for analysis.

We identified 70 chronic hepatitis B patients treated with ETV and 43 were eligible for analysis. Twenty-seven were excluded because the HBV DNA level prior to ETV treatment was less than 2000 IU/mL in 21 patients; 3 patients did not complete 48 weeks treatment; HBV DNA of two patients was not available at 48 weeks; and ETV was changed to lamivudine due to drug-induced interstitial nephritis in one patient. Out

of the eligible 43 patients, 26, 10, 6 and 3 patients completed 2 years, 3 years, 4 years and 5 years treatment respectively. Patient statements of compliance with medication, regular clinic visits, regular pharmacy encounters were the source of assessment of compliance with treatment.

Chronic hepatitis B was diagnosed if the patient was HBsAg-positive >6 months, serum HBV DNA >2000 IU/mL, there was persistent or intermittent elevation in ALT/AST levels and or liver biopsy showing chronic hepatitis with moderate or severe necro-inflammation.<sup>8</sup> Naïve patients did not receive any antiviral treatment before starting ETV. Treatment refractory patients were defined as having persistent viremia despite previous treatment with any antiviral agents for a minimum of 6 months before shifting to ETV.

Complete virological response (CVR) was defined as undetectable HBV DNA by real-time PCR assay within 48 weeks of therapy.<sup>12</sup> Partial virological response was defined as a decrease in HBV DNA of more than 1 log<sub>10</sub> IU/mL, but detectable HBV DNA by real-time PCR assay. Primary non-response was defined as less than 1 log<sub>10</sub> IU/mL decrease in HBV DNA level from baseline at 3 months of therapy.<sup>12</sup> Virological breakthrough was defined as a confirmed increase in HBV DNA level therapy.<sup>12</sup> HBV DNA Assay was measured by real-time PCR technology. HBV assay provided a detection limit (analytical measurement range) from 15 to 1 000 000 000 IU/mL. One IU/mL of HBV DNA is equal to 3.41 copies/mL.

The primary outcome of the study was complete viral response (undetectable HBV DNA) at 48 weeks. HBV DNA levels were logarithmically transformed to Log<sub>10</sub> HBV DNA in IU/mL. Descriptive statistics were used to summarize continuous variables. Categorical variables were expressed as proportions while continuous variables were expressed as medians and or means. The Pearson chi-square test was used to compare categorical variables and the t test was used to compare continuous variables. The data was analyzed by statistical software SPSS version 16. A two-tailed *P* value of <.05 was considered statistically significant.

## RESULTS

The baseline characteristics of 43 patients are given in Table 1. The features of cirrhosis seen in 12 (28%) were based on radiological and or histological evidence. Patients who received 0.5 mg ETV were not exposed to lamivudine. The following antiviral agents were used previously in treatment refractory patients: 7 were treated with more than one drug (lamivudine, adefovir, interferon or peginterferon); 4 with lamivudine, 4 with adefovir,

**Table 1.** Baseline characteristics of 43 patients treated with entecavir.

Characteristic	n (%) or mean (SD)
Mean age (SD), years	45.2 (13.5)
Gender male, n (%)	33 (76.7)
Mean BMI (SD)	30.2 (6.6)
Cirrhosis	12 (28)
Treatment-naïve	24 (55.8)
Treatment-refractory	19 (44.2)
YMDD mutation	6
Entecavir 0.5 mg dose	29 (67)
Entecavir 1 mg dose	14 (33)
HBV genotype D	17/20 (85)
HBeAg positive	15 (35)
HBeAg negative	28 (65)
Median duration of treatment (months)	24 (range, 12 to 60)

BMI: body mass index

and 2 with tenofovir. YMDD mutation was detected in 6 patients. Of 11 patients previously treated with lamivudine, 36.4% achieved undetectable HBV DNA at 48 weeks and 63.6% failed to achieve this end point. Of the four patients who were treated previously with adefovir none achieved undetectable HBV DNA at 48 weeks. One of the two patients treated with pegylated interferon alpha 2a achieved undetectable HBV DNA at 48 weeks.

Liver biopsy was done in 14 of 70 patients. Eight patients had moderate degree of necro-inflammatory activity, 5 patients a mild grade of necro-inflammatory activity, and in one patient severe degree of necro-inflammatory activity (as per Metavir scoring system).

Mean HBV DNA viral load of 51 million IU/mL prior to ETV treatment decreased to 0.16 million IU/mL at 48 weeks. Mean  $\log_{10}$  IU/mL HBV DNA was 6.3 before treatment decreased to 2.4  $\log_{10}$  IU/mL HBV DNA after 48 weeks treatment ( $P<.001$ ) (Figure 1). Mean ALT decreased from 88.7 U/L to 37.5 U/L after 48 weeks treatment ( $P<.04$ ). In 24 patients ALT was above 45 U/L before treatment and 14 of them normalized to <45 U/L (Figure 2). Median ALT before treatment was 49 and after 48 weeks treatment it decreased to 31 U/L (normal ALT <45 U/L).

Undetectable HBV DNA (complete virological response) at 48 weeks of treatment was seen in 20 (46.5%), partial-virological response was seen in 20 (46.5%), 2 (4.7%) had no response and 1 (2.3%) had virological breakthrough (Table 2). Among 24 naïve patients, 14 (58.4%) achieved undetectable HBV DNA at 48 weeks and 6/19 (31.6%) treatment refractory patients achieved undetectable HBV DNA ( $P<.07$ ). At 48 weeks, 3/15 (20%) HBeAg-positive patients, and 17 of 28 (60.7%) of HBeAg-negative patients achieved undetectable HBV DNA ( $P<.003$ ) (Figure 2). The binary logistic regression analysis showed HBeAg-negative status a predictor of undetectable HBV DNA at 48 weeks ( $P<.01$ ).

When treatment was extended beyond 48 weeks, with a median of 24 months (range 12 months to 60 months), 75% of naïve patients and 58% of treatment refractory patients achieved undetectable HBV DNA with an overall response of 67.4%. The naïve patients achieved complete virological response in a mean of 18.8 months compared to treatment refractory patients in a mean of 32.4 months ( $P<.018$ ) (Figure 3). One (2.3%) patient lost HBsAg and two patients with HBeAg-positive status converted to HBeAg-negative status within 3 years of ETV treatment.

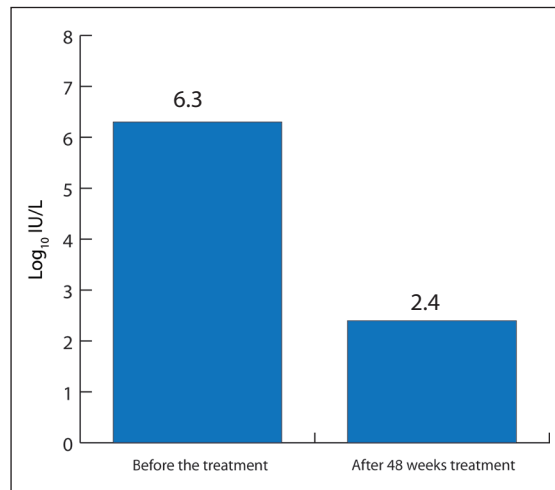
## DISCUSSION

The most important observations we made in this study are that the treatment response at 48 weeks was 60.7% in

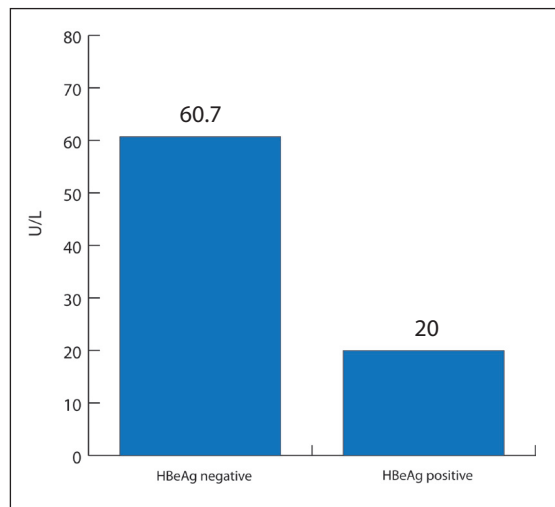
**Table 2.** Treatment response in 43 chronic hepatitis B patients after 48 weeks completion of entecavir therapy.

Treatment response	Whole group	Treatment-Naïve	Treatment Refractory	P
Undetectable HBV DNA	20 (46.5%)	14 (58.4%)	6 (31.6%)	.07
Partial virologic response	20 (46.5%)	8 (33.3%)	12 (63.2)	.43
Viral breakthrough	1/43 (2.3%)	1 (4.16%)	0	-
No response	2/43 (4.7%)	1 (4.16%)	1 (5.26%)	-
Total number of patients	43	24	19	-

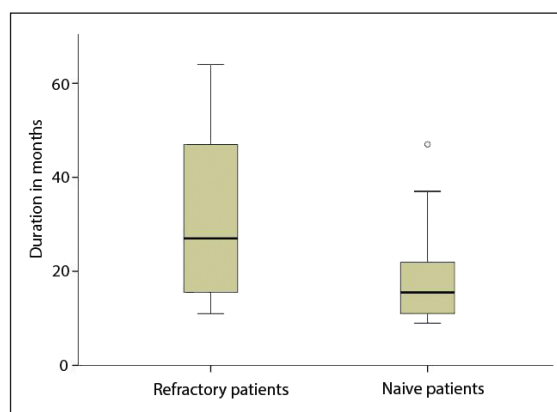
Data are number of patients (%).



**Figure 1.**  $\log_{10}$  HBV DNA decreased significantly after 48 weeks treatment with entecavir ( $P=.001$ ).



**Figure 2.** Undetectable HBV DNA after 48 weeks of entecavir was better in HBeAg-negative than HBeAg-positive patients ( $P=.003$ ).



**Figure 3.** Overall undetectable HBV DNA at the end of follow-up was achieved in 67.4%. Treatment of refractory patients took a mean of 32.4 months compared to 18.8 months in naïve patients.  $P \leq .01$ .

HBeAg-negative patients and 20% in HBeAg-positive patients. The undetectable HBV DNA at 48 weeks in naïve patients was 58.4% and 31.6% in treatment refractory patients. The overall response to ETV at 48 weeks with an undetectable HBV DNA was 46.5%. When the treatment was extended beyond 48 weeks, with a median of 24 months, 75% of naïve patients and 58% of treatment refractory patients achieved undetectable HBV DNA, and the overall response was 67.4%.

In large clinical trials, undetectable HBV DNA after 48 weeks of ETV was seen in 67% of HBeAg-positive patients and in 90% of HBeAg-negative patients.<sup>12</sup> When compared to such results, our patient responses to ETV were modest. At 48 weeks, only 20% of our HBeAg-positive and 60.7% of HBeAg-negative patients had undetectable HBV DNA. The exact reason for the low rate of response in our population is probably multifactorial. This could be due to previous exposure to antiviral agents, a high number of HBeAg-positive patients and probably low compliance in some patients. Similar to our findings, various real-life studies have reported better treatment response in HBeAg-negative chronic HBV patients. A retrospective/prospective, multicenter study conducted at 19 Italian centers with 418 consecutive nucleos(t)ide analogs-naïve chronic hepatitis B patients were treated with ETV. At 48 weeks, 66% of HBeAg-positive patients and 90% of HBeAg-negative patients achieved undetectable HBV DNA (<12 IU/mL). Over all 85% of patients achieved undetectable HBV DNA at first year.<sup>13</sup>

In real-life patients, the undetectable HBV DNA response to ETV at 48 weeks is different from that reported in large clinical trials. A retrospective multicentre study, involving 25 Spanish centers, treated 190 treatment-naïve chronic hepatitis B patients. In that study, undetectable HBV DNA at 48 weeks was 83% (61% HBeAg-positive; 92% HBeAg-negative).<sup>14</sup> A retrospective, multicenter study from five centers in Argentina with 69 treatment-naïve chronic HBV patients were treated with ETV for an average of 110 weeks; the undetectable HBV DNA rate was 77% at 48 weeks in this group. At King's College London, 76% of patients had an HBV DNA <12 IU/mL in a cohort of 154 patients treated with ETV.<sup>13</sup>

In our cohort of 43 patients, 19 (44.2%) were treatment refractory and at 48 weeks the rate of undetectable DNA was 31.6%. Our results are comparable to the experience of others. In one study, 33 patients with chronic hepatitis B refractory to lamivudine were enrolled to receive treatment with entecavir 1.0 mg once daily; HBV DNA became undetectable by PCR assay in 33.3% patients.<sup>15</sup> In another study, 141 HBeAg-positive chronic hepatitis B lamivudine-refractory patients were treated with entecavir 1 mg; at 2 years of treatment, 30% of all entecavir-treated patients achieved HBV DNA of less than 300 copies/mL.<sup>16</sup>

Different studies have reported different rates of HBeAg conversion (from positive to negative status). In one study, HBeAg-positive converted to negative status in 11% of patients ( $n=354$ ).<sup>10</sup> In another study, HBeAg seroconversion was achieved by 17% of all entecavir-treated patients (24 out of 141) versus 6% of all lamivudine-treated patients. In our study, 2 out of 15 (13.3%) HBeAg-positive patients became HBeAg negative after 4 years of treatment. The HBeAg conversion rate in our patients was comparable to other reports.

The limitation of our study is the small number of patients. However, the current study is relevant in the absence of any available data from the region regarding the role of ETV in chronic hepatitis B patients. We often make decisions to choose a particular drug to treat a particular disease based on large phase 3 clinical trials conducted in different populations. The current study emphasizes the relevance of analyzing local data as well as studying real-life patients apart from phase 3 clinical trials. We suggest collecting nationwide data and to come up with comprehensive results so that we know the most appropriate drug to treat our patients.

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