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Original Article

Clinical and virological outcomes of entecavir therapy in patients with chronic hepatitis B: A real life experience☆

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ABSTRACT

Background: Entecavir (ETV) is a nucleoside analogue (NA) that is effective for treatment of chronic hepatitis B (CHB) due to its low resistance rates and potent antiviral effects. We aimed to evaluate the clinical, biochemical and virological response to ETV in patients without a prior use of nucleos(t)ide (NA-naïve) vs. those who failed prior NA use (NA-experienced) in the treatment of CHB.

Methods: Patients treated between April 2012 and December 2017 were retrospectively studied. A comparison was made between patients treated with ETV in NA-naïve Vs. NA-experienced. Complete virological response (CVR) was defined as achieving undetectable HBV-DNA level, up to 15 IU/ml, partial virological response (PVR) as 15–200 IU/ml and >200 IU/ml for no virological response (NVR) after one year of therapy.

Results: Overall, 148 patients were included (69 NA-naïve and 79 NA-experienced). In NA-naïve group, 51%, 17% and 32% achieved CVR, PVR and NVR vs. 17%, 9% and 75% in NA-experienced group, respectively ($p < 0.001$). HBsAg seroconversion was achieved in 5.8% in NA-naïve group vs. 6.3% in NA-experienced group ($p = 1.00$). HBeAg seroconversion was 17% in NA-naïve group and 25% in NA-experienced group ($p = 0.24$). There was no significant difference in alanine transaminase normalization or in mortality rate between both groups; $p = 0.87$ and $p = 1.00$ respectively.

Conclusion: ETV therapy in CHB results in a better virological response in NA-naïve patients compared to NA-experienced. There were no differences between both groups in regards to the rate of HBsAg or HBeAg seroconversions, biochemical improvements or mortality.

1. Introduction

Chronic hepatitis B (CHB) is a known lethal liver infection due to hepatitis B virus (HBV). Globally, approximately 2 billion people were estimated to be infected with the virus, about 257 million have chronic infection and an anticipated 887,000 people died in 2015 due to acute or chronic complications of hepatitis B [1]. In the late 1980s, studies from Saudi Arabia revealed that 7% of children were positive for HBsAg [2]. This prevalence decreased to less than 0.3% after a universal vaccination policy was implemented in 1989

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[3]. Nonetheless, the burden of HBV infection persists, with a significant burden of chronically active carriers. The objective of CHB treatment is to accomplish complete suppression of HBV replication and hence the improvement of liver disease. The ultimate aim is the prevention of development of cirrhosis, liver failure and hepatocellular carcinoma (HCC). Treatment response is typically evaluated by; alanine transaminase (ALT) normalization, undetectability or substantial reduction in HBV-DNA level, loss of HBeAg and liver histology improvement. Active hepatitis B virus (HBV) replication is the most important risk factor for liver injury and evolution of the disease, hence viral suppression is crucial in the management of CHB infection. The nucleos(t)ide analogues (NA); adefovir dipivoxil, entecavir, telbivudine, and tenofovir are potent inhibitors of HBV replication, however, rarely eradicate the virus [4,5]. Prediction of the probability of long-standing benefit of HBV treatment, was anticipated in the majority of published studies from the early post-treatment improvement of the virological, biochemical and histologic factors. Long-term therapy is indicated to achieve hepatitis B antigen seroconversion, HBV-DNA reduction, ALT normalization and resolution of fibrosis. The long-term therapy is essential to decrease the rate of development of liver cirrhosis, failure and HCC [6].

Entecavir (ETV) is a nucleoside analogue (NA) that is effective first-line treatment option for NA-naïve, CHB patients due to its low resistance rates and potent antiviral effects [7,8]. Studies on treatment of HBV in Saudi Arabia are limited. The objective of this study is to describe the real-life experience of HBV treatment with ETV through studying the clinical, biochemical and virologic response (VR) to ETV therapy in NA-naïve patients versus non-responders to other antiviral therapy (NA-experienced).

2. Patients and methods

2.1. Patients

A retrospective chart review was conducted for all adult patients with CHB who were seen in the hepatology clinic at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, and were treated with antiviral therapy during the period from April 2012 until December 2017. Inclusion criteria were; chronic HBsAg-seropositivity (>6 months), viral load (HBV-DNA) level of more than 2000 IU/ml, ALT more than the upper limit of normal in presence of any stage of fibrosis manifested on histology or fibroscan. We also included patients with cirrhosis who were treated while on the waiting list for liver transplantation. Patients were excluded from the study if they did not fit the above criteria, had a co-infection with hepatitis C or HIV or those with co-existence of any other liver diseases such as autoimmune hepatitis, alcoholic liver disease, drug-induced hepatitis or Wilson's disease. We also excluded patients who had an organ transplant and those who had received HBV therapy as a prophylaxis while they were on immunosuppressive treatment for any reason. Data on baseline demographic and clinical characteristics and on-response to therapy were documented. Laboratory and clinical outcomes were monitored, including viral load (HBV-DNA) levels, HBeAg seroconversion, HBsAg seroconversion, post-treatment ALT, aspartate transaminase (AST) and creatinine levels and post-treatment Model for End-stage Liver Disease (MELD) score were calculated. The measurement of HBV serological markers was performed by the chemiluminescent microparticle immunoassay (CMIA) diagnostic reagent kit (Abbott ARCHITECT, Abbott Laboratories). A comparison was made between patients treated with ETV who were never exposed to nucleos(t)ide analogues previously (NA-naïve group) and those who were treated with ETV in non-responders to prior therapy with nucleos(t)ide analogues (NA-experienced group). In the absence of a universally accepted cut-off point of HBV-DNA level indicating the virological response, we stratified our patients into; complete virological response (CVR) was defined as having HBV-DNA < 15 IU/ml, partial virological response (PVR) as 15–200 IU/ml and >200 IU/ml for no virological response (NVR) after one year of therapy. Patients were also stratified according to their MELD score as Low-risk (good prognosis), with MELD score of ≤15; Moderate-risk (fair prognosis) with MELD score of 15–20; and High-risk (poor prognosis) with MELD of ≥21. For the safety evaluation, we recorded the existence of any of the following: serious adverse events, the need for treatment discontinuations due to adverse events, ALT flares or development of renal dysfunction. Renal dysfunction was defined as abnormal creatinine (>98 μmol/L in females and >110 μmol/L in males). The study was approved by our institutional research committee. To evaluate the course of HBV infection transmission; vertical transmission was proposed when there was a solid history of HBV in the patient's mothers. While horizontal transmission was estimated when there was an unequivocal history of one or more of the following risk factors; surgery, blood transfusion, intravenous drug use, unprotected illegal sexual exposure, invasive dental procedure or tattoo. We compared the duration of the disease from the time of diagnosis until the time of treatment of CHB in the NA-naïve vs. the NA-experienced group. For easy understanding, we divided the duration to short (<10 Years), long (>10 Years), and undetermined duration.

2.2. Statistical analysis

Descriptive statistical analyses were performed for the study sample in terms of demographic and baseline clinical data, overall and by medication groups; NA-naïve and those with NA-experienced. Continuous variables were expressed as mean ± standard deviation (SD). The data was expressed as proportion for categorical variables. Statistical comparisons between the two groups in terms of demographic and baseline clinical data were made using the Chi-square test, Fisher's exact test or the *t*-test, as appropriate. The two groups were also statistically compared in terms of outcomes (HBV-DNA, HBeAg seroconversion (positive to negative), HBsAg seroconversion (positive to negative), the prevalence of normalized ALT and abnormal creatinine post-treatment using the Chi-square test or Fisher's exact test. Statistical significance was considered at $p < 0.05$. All statistical analyses were performed using SPSS 21.0 [Release 21.0.0.0, IBM, USA].

2.3. Ethics statement

This study was approved by King Abdullah International Medical Research Center, Ministry of National Guard Health affairs, Riyadh, Saudi Arabia.

3. Results

Overall, 148 patients were included (69 in NA-naïve group and 79 in NA-experienced group) with a mean age of 52.3 ± 15.2 years, and 79% were males. Among the 79 patients in NA-experienced group, the distribution of previous medications used was as follows: lamivudine in 30 (38%), adefovir in 13 (16.5%) and lamivudine + adefovir combination in 36 (45.5%). The ETV dose in the NA-naïve group was 0.5 mg and 1 mg in 60 and 9 patients respectively. While in the NA-experienced group; 0.5 mg and 1 mg in 9 and 56 patients respectively. In the NA-experienced group, there were 10 patients who had no documented clear dose of ETV. Descriptive statistics for baseline parameters in the two study groups are displayed in Table 1. The two groups were not statistically different in terms of baseline demographic features, comorbidities, risk factors, serology, viral load or clinical presentation ($p > 0.05$). However, there were more patients with abnormal ALT before treatment in NA-experienced

Table 1
Descriptive statistics for demographic and baseline clinical data, overall and by study group. Total number of subjects = 148.

Factor	All patients (N = 148, 100%)	NA-naïve Group (N = 69, 46.6%)	NA-experienced group (N = 79, 53.4%)	p-value[a]
Demographic features				
Age (years) Mean ± SD	52.3 ± 15.2	53.2 ± 14.9	51.5 ± 15.5	0.46
Gender n (%)				
Female	31 (20.9%)	18 (26.1%)	13 (16.5%)	0.15
Male	117 (79.1%)	51 (73.9%)	66 (83.5%)	
Associated comorbidities n (%)				
Diabetes	49 (33.3%)	19 (27.5%)	30 (38.0%)	0.18
Cardiac disease	17 (11.5%)	6 (8.7%)	11 (13.9%)	0.32
Dyslipidemia	33 (22.3%)	14 (20.3%)	19 (24.1%)	0.58
Renal dysfunction	18 (12.2%)	7 (10.1%)	11 (13.9%)	0.48
Risk factors n (%)				
Surgery	18 (12.2%)	8 (11.6%)	10 (12.7%)	0.84
Dental treatment	4 (2.7%)	3 (4.3%)	1 (1.3%)	0.25
Blood transfusion	3 (2.0%)	3 (4.3%)	0 (0.0%)	0.10
Intravenous drug use	2 (1.4%)	0 (0.0%)	2 (2.5%)	0.50
Pre-treatment factors				
ALT Mean ± SD	76.8 ± 123.3	78.5 ± 164.3	75.2 ± 71.5	0.87
Abnormal ALT n (%)	71 (48.0%)	21 (30.4%)	50 (63.3%)	<0.001
AST Mean ± SD	75.5 ± 203.8	96.9 ± 292.0	57.1 ± 62.2	0.28
Abnormal AST n (%)	80 (54.1%)	37 (53.6%)	43 (54.4%)	0.92
HBV-DNA Mean ± SD	$2.6 \times 10^7 \pm 9.5 \times 10^7$	$2.2 \times 10^7 \pm 5.5 \times 10^7$	$3.0 \times 10^7 \pm 1.2 \times 10^8$	0.59
Positive HBeAg n (%)	36 (24.3%)	16 (23.2%)	20 (25.3%)	0.76
Positive HBeAb n (%)	106 (71.6%)	48 (69.6%)	58 (73.4%)	0.60
Clinical decompensation n (%)				
Gastrointestinal bleeding	12 (8.1%)	4 (5.8%)	8 (10.1%)	0.34
Encephalopathy	11 (7.4%)	4 (5.8%)	7 (8.9%)	0.48
Ascites	26 (17.6%)	14 (20.3%)	12 (15.2%)	0.42
SBP	7 (4.7%)	5 (7.2%)	2 (2.5%)	0.25

SD: standard deviation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SBP; Spontaneous bacterial peritonitis.
[a] Based on the *t*-test or the Chi-square test or Fisher's exact test.

group, $p < 0.001$. The comparison of the two groups in terms of clinical outcomes of interest are shown in Table 2. In NA-naïve group, 51%, 17% and 32% achieved CVR, PVR and NVR at 48 weeks of therapy vs. 17%, 9% and 75% in NA-experienced group, respectively ($p < 0.001$). After a median follow-up of 3.7 years, HBsAg seroconversion was achieved in 5.8% in NA-naïve group vs. 6.3% in NA-experienced group ($p = 1.00$). HBeAg seroconversion was 17% in NA-naïve group and 25% in NA-experienced group ($p = 0.24$), while ALT normalization was 76% in NA-naïve group vs. 78% in NA-experienced group ($p = 0.87$). There was no difference in mortality between NA-naïve group (4.3%) and NA-experienced group (3.8%); $p = 1.00$. We performed a sub-group analysis among the NA-experienced group to compare the virological outcome of ETV between the adefovir exposure only group and the lamivudine exposure only group. This revealed that the CVR, PVR and NVR was achieved in 5 (55.6%), 4 (80%) and 21 (72.4%) in the lamivudine group and in 4 (44.4%), 1(20%) and 8 (27.6%) in the adefovir group respectively ($p = 0.55$). Patients who were on combined treatment with lamivudine and adefovir were excluded from this analysis. The small sample size in the adefovir group may have precluded the ability to detect a significant difference in this subgroup of patients.

Analysis of creatinine as a measure of renal dysfunction showed that there were 18 patients with abnormal serum creatinine levels before treatment, 7 in NA-naïve group and 11 in NA-experienced group (Table 1). After treatment, 5 and 9 patients had normalized their creatinine in NA-naïve and NA-experienced groups respectively. There was no significant difference between the two groups in terms of the proportion of patients who had abnormal creatinine levels post-treatment: 29.0% in NA-naïve group and 19.1% in NA-experienced group ($p = 0.18$, Fig. 1). None of our patients developed serious adverse events, treatment discontinuations or ALT flares. Analysis of HBV-DNA by MELD score category at baseline and at follow-up (not shown), revealed no significant association between HBV-DNA and baseline MELD score ($p = 0.21$) and no relationship was also observed between HBV-DNA and MELD score at follow up ($p = 0.81$). In our cohort, 114 (77%) patients were estimated to acquired HBV through a horizontal and 17 (11.5%) through a vertical route ($p < 0.001$). The rout in the remaining patients 17 (11.5%), was undetermined due to unknown precise source. The overall duration of the disease was ranging from 6 months to 30 years. We found that 19%, 13% and 68% and 25%, 29%, 46% had

Table 2
Comparison between the two groups in terms of clinical outcomes. Total number of subjects = 148.

Outcome n (%)	All patients	NA-naïve group	NA-experienced group	p-value[a]
Died	6 (4.1%)	3 (4.3%)	3 (3.8%)	1.00
HBV-DNA				<0.001
Complete virological response	48 (32.4%)	35 (50.7%)	13 (16.5%)	
Partial virological response	19 (12.8%)	12 (17.4%)	7 (8.9%)	
No virological response	81 (54.7%)	22 (31.9%)	59 (74.7%)	
HBeAg Seroconversion	32 (21.6%)	12 (17.4%)	20 (25.3%)	0.24
HBsAg Seroconversion	9 (6.1%)	4 (5.8%)	5 (6.3%)	1.00
Normalized ALT	55 (77.5%)	16 (76.2%)	39 (78.0%)	0.87
Normalized AST	59 (73.8%)	31 (83.8%)	28 (65.1%)	0.058

ALT; alanine transaminase. AST; aspartate aminotransferase.
[a] Based on the chi-square or Fisher's exact test.

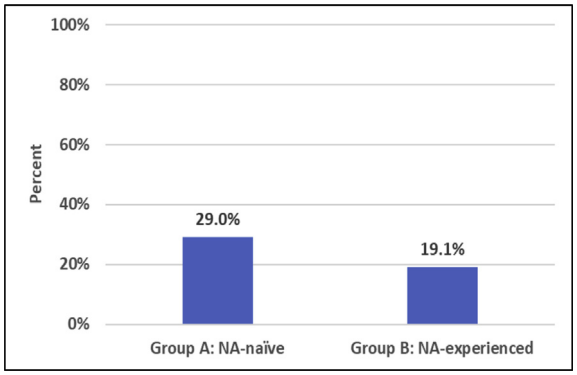

Fig. 1. Percentage of patients with abnormal creatinine post treatment with 95% confidence interval by study group. Total number with no underlying renal disease = 130*. *18 patients with underlying renal disease were excluded.

short, long and undetermined duration in the NA-naïve and NA-experienced group respectively (p = 0.34).

4. Discussion

In this real-life study, we found that treatment with ETV in NA-naïve patients resulted in undetectable HBV-DNA levels in 51% and in only 17% in the NA-experienced patients after 1 year of treatment. In a multicenter European study, 79% of NA-naïve and 54% of NA-experienced patients achieved VR, which is higher than in our cohort [9]. In a recent multicenter study from China, considering VR as HBV DNA <50 IU/mL, VR achieved in 69% of NA-naïve and 53% of NA-experienced patients [10]. In a prospective study from Argentina, 92% of NA-Naïve patients treated for a median of 181 weeks achieved undetectable HBV-DNA [11]. In a study from India, 5-years treatment of NA-Naïve patients revealed undetectable HBV-DNA in 89% and 98% at 1 and 5 years respectively [12]. In a large cohort study, 96 weeks of ETV treatment in HBeAg-positive patients revealed that 30% achieved VR [13]. Unfortunately, local studies on CHB treatment are scarce. Al-Ashgar et al. reported that in a total of 43 patients treated with ETV for 48 weeks, HBV-DNA was undetectable in 58.4% in NA-naïve patients and in 31.6% in NA-refractory patients [14]. The reason for the relatively low rate of response in our cohort is unclear but likely multifactorial. This may include; the strict definition of CVR as HBV-DNA < 15 IU/ml, the existence of more number of HBeAg negative patients and the possible low adherence to medication intake. Further, in the experienced group, it could be due to the development of strong resistant strains caused by previous exposure to NA. HBeAg seroconversion rate in our study, was 17.4% and 25.3% in NA-naïve and NA-experienced patients respectively. HBsAg seroconversion was achieved in 5.8% in NA-naïve vs. 6.3% in NA-experienced after a median follow-up of 3.7 years. Our results of the HBeAg loss are similar to the earlier mentioned study by Reijnders et al. They found 19% of the HBeAg-positive patients lost HBeAg after a median treatment duration of 12 (10–22) months, however, none of the patients lost HBsAg [9]. Hou et al. reported HBeAg loss in 17% of NA-naïve and 15% of NA-experienced patients [10]. HBeAg seroconversion was reported to be 18.2% at 5 years by Ray et al. [12]. In Sherman et al. study, HBeAg seroconversion was achieved in 17% [13]. On the other hand, a higher rate was obtained from the Argentinian trial in which they reported HBeAg clearance in 71% patients after a median of 48 weeks of treatment. In the later study, HBsAg was cleared in 14% patients after a median of 96 weeks of treatment, and 13% patients achieved protective levels of anti-HBs [11]. In the study by Al-Ashgar et al. 11% of patients lost HBeAg at 48 weeks. After extension of treatment for a median of 24 months, 13.3% of HBeAg positive patients converted to HBeAg negative and 2.3% lost HBsAg [14]. In our cohort, ALT normalization was achieved in 76% in NA-naïve vs. 78% in NA-experienced patients (p = 0.87). This is very close to the results from Hou et al. who reported ALT normalization in 87% of NA-naïve and in 83% of NA-experienced patients and Sherman et al. in which 85% had ALT normalization after 69 weeks [10,13]. In Al-Ashgar e al., mean ALT decreased from 88.7 U/L to 37.5 U/L after 48 weeks treatment [14]. Our patient's data were analyzed at week 48 of treatment. Whether an extension of therapy beyond 48 weeks will produce more VR is controversial. In a study by Chang et al., the extension of ETV for up to 5 years in HBeAg positive patients, resulted in VR in 94% and ALT normalization in 80% [15]. In the same study, HBeAg seroconversion was attained in 23% and HBsAg loss in 1.4%. However, this better response may be reflected by the fact that all patients were HBeAg positive, which is known to be good responders compared to HBeAg negative. Al-Ashgar et al. found that treatment extension for a median of 24 months (range 12–60 months), resulted in 67% HBV-DNA undetectability [14]. On the other hand, Chen et al. found no impact of extending therapy of ETV to beyond week 48 on the response in NA-naïve patients who did not achieve a response at week 48 [16]. Other studies have shown that throughout a long-term NA treatment, the loss of HBsAg occurred in limited patients who were HBeAg-positive (10–12% following 5–8 years of treatment), however, it was rather uncommon in patients with HBeAg-negative (0.3–2% following 5–8 years of treatment) [17,18]. Loss of HBsAg was reported in 5% of HBeAg positive patients on ETV for up to 96 weeks [19]. In our cohort, there was no reported serious side effect or ALT flare during the period of therapy and follow up, however non-significant renal dysfunction was recognized among both groups. A strength of this study is that it describes the real-life experience of HBV treatment with ETV through studying the clinical, biochemical and VR to ETV therapy in NA-naïve patients versus non-responders to other antiviral therapy. While numerous international studies have focused on the effect of ETV in patients with CHB, this appears to be the first study that thoroughly assessed the degree of VR to ETV therapy and its safety in the largest cohort of CHB patients in the region. Our study has some limitations. First, the study was conducted in a single-center with a retrospective design with its usual potential for bias because of prescribing and patient selection by physicians. One important drawback is that we did not test for the development of resistant strains in NA-experienced patients. Further, it is possible that some patients were lost to follow-up and thus we were unable to document their outcome. Despite these limitations, our study highlights the efficacy and safety of ETV therapy in the treatment of CHB in adult patients.

5. Conclusions

ETV therapy in chronic HBV results in a high virological response, with concomitant biochemical improvements. Higher rates of HBsAg seroconversions were achieved with ETV therapy in NA-naïve patients as compared to prior NA failures. No significant association was observed between viral load and baseline or follow-up MELD score. We had no serious adverse effect due to the treatment and there was no difference between the 2 groups in terms of renal dysfunction.

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