

EFFICACY OF TELBIVUDINE IN THE TREATMENT OF HBeAg NEGATIVE CHRONIC HEPATITIS B WITH NORMAL BASELINE ALT LEVELS

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ABSTRACT

Background: Pakistan remains in intermediate prevalence area for hepatitis B with an estimated carrier rate of 2.5%. Over last 10 years, treatment for HBV has improved, improving the prognosis and long term outcome. We conducted this trial to study the efficacy of Telbivudine (LdT) monotherapy in the treatment of HBeAg negative chronic hepatitis B infection with normal ALT levels. **Methods:** Ninety-six adults of both sexes suffering from HBeAg negative chronic hepatitis B who previously never had any antiviral treatment were recruited in this study between June 2008 and June 2011. LdT 600 mg daily was given to all the patients for two years. **Results:** Among 85 patients who successfully completed two years of LdT treatment, 54 were males and 31 females between 18 and 62 years of age. All had HBV DNA levels between 2.8 to 13.1 log 10 copies/ml. At the end of one year treatment, the proportion of the patients with serum HBV DNA levels undetectable by PCR was 85% which increased to 94% by the end of second year of treatment. HBsAg seroconversion rate was 2% at end of 1st year and 4.9% at the end of 2nd year. No patient was found to be exhibiting viral breakthrough during the treatment. **Conclusion:** Telbivudine therapy is an effective option for the treatment of adult HBeAg negative CHB patients in our population.

KEY WORDS: Chronic Hepatitis B, Telbivudine, HBeAg.

INTRODUCTION

More than two billion people worldwide are known to be infected with Hepatitis B virus (HBV) and about 350 million are known to be chronically infected, while alarmingly more than 500,000 people die annually of diseases related to HBV infection.¹ Individuals with chronic hepatitis B (CHB) have increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC).^{1,2} In CHB carriers, the risk of progression to cirrhosis and HCC have been linked to high levels of HBV DNA.^{3,4} Pakistan remains in the intermediate prevalence area for hepatitis B with an estimated carrier rate of 2.5%.⁵

Over last 10 years, treatment for HBV has improved, improving the prognosis and long term outcome.⁶

Knowing the high prevalence of HBV infection in Pakistan and the data being reported regarding treatment in local population of Khyber Pukhtunkhwa province with Nucleoside analogue (NUC), telbivudine (LdT), we decided to conduct this study to find out the efficacy of LdT therapy in patients suffering from HBeAg negative chronic HBV infection.

MATERIAL AND METHODS

Ninety-six adults of both sexes between 18 and 62 years of age suffering from HBeAg nega-

tive CHB who previously never had any antiviral treatment were recruited in this study, between June 2008 and June 2011, at Khyber Teaching Hospital, Peshawar. Approval from ethics review committee was taken and written informed consent from all the patients was obtained. LdT 600 mg daily was given to all the patients.

CHB was defined as detectable HBsAg for the last six months and serum HBV DNA levels greater than 6 log 10 copies/ml. Exclusion criteria included co-infection with HCV, HIV, HDV, evidence of hepatic decompensation, pancreatitis, alcoholic hepatitis, fatty infiltration, HCC, creatinine more than 1.5 mg/dl, bilirubin more than 2 mg/dl, albumin less than 3.3 g/dl, prolonged prothrombin time and pregnancy. Upper GI endoscopy and ultrasound of abdomen was performed during initial enrolment on all patients before starting treatment to rule out any stigmata of chronic liver disease (CLD).

The study focussed on the main therapeutic endpoints at the end of first and second years of therapy including proportion of patients with non detectable serum HBV DNA levels, HBsAg seroconversion and viral breakthrough. Viral breakthrough was defined as persistent (two consecutive determinations) increase in HBV DNA >10,000 copies/ml while on treatment.

Analysis of full blood count, liver and renal functions, and creatinine phosphokinase (CPK) levels were performed at baseline, after 1st month of starting treatment and then at three monthly intervals. HBsAg, HBeAg, Anti HBe antibodies were quantified using radio immunoassay. HBV DNA Quantification was done using Ampiclor HBV test (Roche Diagnostics, Basel, Switzerland) with a detection limit of 300 copies/ml. Quantitative data was presented as mean \pm SD and categorical data as counts and percentages. Data was analyzed using SPSS version 13.0.

RESULTS

Out of the 96 patients initially enrolled, 9 failed to attend for regular follow up while due to concerns regarding drug compliance 4 further patients were excluded from the study. Alanine Transaminase (ALT) levels were either within the normal range or less than twice the upper normal limit in all patients.

Among 85 patients who successfully completed two years of LdT treatment, 54 were males and 31 females, between 18 and 62 years of age (Mean 43). All had HBV DNA levels between 2.8 to 13.1 log₁₀ copies/ml (Median 10^{7.7} copies/ml). At the end of one year (week 52) treatment, the proportion of the patients with serum HBV DNA levels being undetectable by PCR (less than 300 copies/ml) was 85% which increased to 94% by the end of second year (96 weeks) of treatment. HBsAg seroconversion rate was 2% at end of 1st year and 4.9% at the end of 2nd year. No patient was found to be exhibiting viral breakthrough during the treatment.

DISCUSSION

The goal in HBV treatment is to improve quality of life and survival by preventing progression to cirrhosis, HCC and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner, which is shown to decrease the histological activity in liver and less risk of progression.^{6,7}

Two types of antiviral medications can be used in the treatment of CHB: Interferon and the nucleoside analogues.⁸ Among the nucleoside analogues Lamivudine, Adefovir dipivoxil, Entecavir (ETV) and LdT have been approved by the United States FDA for the treatment of HBV.⁹ A major concern for this class of drugs is mitochondrial toxicity which is manifested as hepatic failure, nephrotoxicity, pancreatitis, neuropathy, myopathy and lactic acidosis.¹⁰ Furthermore emergence of drug resistance in patients on long term maintenance therapy with these drugs can result in diminished drug efficacy.¹¹

LdT is an orally bio-available L-nucleoside with potent and specific anti HBV activity. Absorption is not affected by food intake so it can be taken with or without food. Half life of the activated drug is long (>14 hours) allowing once daily administration. It has selective and specific antiviral activity against HBV and other hepadna viruses. It impairs HBV DNA replication by chain termination.

LMV and LdT are still widely used in the treatment of CHB patients who have not previously received treatment.¹² The efficacy and safety of LdT treatment for CHB has been proved in many studies previously.^{11,13}

In our study, LdT treatment provided rapid and profound HBV suppression with respect to the primary efficacy end point (mean HBV DNA reduction from baseline). Our results are comparatively better at viral clearance as compared to the data reported in the past. This may well be because of different demographic characteristics of our patients or due to different genotypes of HBV prevalent in our population. However there is no local data available to compare our results.

A randomized control trial by Chan et al compared one year treatment with ADV and LdT in 135 patients. They found greater HBV reduction with LdT at week 24 (39% vs. 12%) and at week 52 (60% vs. 40%) of treatment.¹⁴ In a study by Leung et al, two years treatment with LdT was found to be significantly superior to LMV in both HBeAg positive and HBeAg negative CHB patients for all the direct measures of the antiviral effect including the reduction in HBV DNA levels from baseline (-5.7 vs. -4.4 in HBeAg positive and -5.0 vs. -4.2 in HBeAg negative), PCR negativity 56% vs. 39% and 82% vs. 57% in HBeAg positive or negative patients respectively.¹⁵

In GLOBE trial, HBV DNA reduction with LdT was compared with LMV. It was evident by week 12 (-4.36 log vs. -4.08 log respectively in HBeAg negative CHB). The HBV DNA reduction persisted through week 52 of treatment with greater histological response and larger proportion of patients with undetectable HBV DNA (88.3% vs. 71.4% respectively in HBe Ag negative patients).^{13,16}

A study by Chan et al revealed that effectively treated patients showed increased frequency of peripheral blood CD4(+) T Lymphocytes, an augmented proliferative response of HBV specific T-cells to the Hepatitis B Core antigen (HBcAg), and the induction of cytokines such as gamma interferon (IFN- α), tumour necrosis factor alpha (TNF α) release at the site of infection compared to non responsive patients.¹⁷

ETV and TDF are potent HBV inhibitors and because of having high barrier to resistance they

are preferred first line monotherapy in developed countries.¹⁸

The NICE Guidelines issued in Aug 2008 also recommend use of ETV for the treatment of people with chronic HBeAg positive or HBeAg negative CHB in whom antiviral treatment is indicated.¹⁹

The resistance to NUCs remains a major issue. However the rate of drug resistance has decreased dramatically with the development of newer generation of NUCs. LMV resistance is observed in 80% of the patients treated for five years. Among adequately treated patients, the cumulative incidence of resistance over 5 years has been reported to be 29% in HBeAg negative patients and 42% in HBeAg positive patients.²⁰ LdT resistance is slower to emerge but substantial with 25% of HBeAg positive and 11% of HBeAg negative patients experiencing virological breakthrough due to resistance after 2 years of treatment.²¹ To reduce the risk of resistance, unnecessary treatment should be avoided and HBV DNA should be carefully monitored to check for primary non-response (<1 log₁₀ drop in HBV DNA at week 12) as well as partial response (detectable HBV DNA at week 24).

CONCLUSION

Telbivudine therapy is an effective option for the treatment of adult HBeAg negative CHB patients in our population.

More research is required to determine the most effective management of this major public health problem in our society.

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