TELBUVIDINE MONOTHERAPY IN THE TREATMENT OF HBEAG POSITIVE CHRONIC HEPATITIS B INFECTION WITH NORMAL BASELINE ALT LEVELS

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ABSTRACT

Objective: *To study the effect of Telbuvidine (LDT) monotherapy in the treatment of HBeAg positive Chronic Hepatitis B infection (CHB) with normal ALT levels.*

Methodology: *Ninety HBe antigen (HBeAg) positive CHB infection patients were enrolled & followed between June 2008 and June 2011. All of them had ALT levels less than twice the upper normal limit (Mean 36.9 SD 19.9). All patients were HBeAg positive, had serum DNA level $>10^4$ copies/ml and never had previously received anti HBV treatment. All patients were given LDT 600mg daily as initial antiviral treatment for two years.*

Results: *Out of 83 patients who continued the treatment as per protocol, 59 were males and 24 were females between ages of 21 and 50 years. Baseline HBV DNA levels were $7.82x10^7$ copies/ml (Range $4.8x10^4$-$8.3x10^9$copies/ml). By the end of first year (52 weeks) the mean decrease in serum HBV DNA levels was 7.88 log^{10} copies/ml and the proportion of patients having undetectable HBV DNA levels was 73%. At the end of second year of therapy (96 weeks) the percentage of undetectable HBV DNA levels increased to 86%.At the end of 1st (52weeks) and 2nd (96weeks) HBeAg seroconversion rates were 62 % and 86% while HBsAg seroconversion was 8% and 13% respectively.*

Conclusion: *LDT is a reasonable cost effective therapy for HBeAg reactive CHB patients with normal baseline ALT levels resulting in a significant serological and virological response and was well tolerated in our population of Khyber Pukhtunkhwa.*

Key Words: *Hepatitis B virus, Telbuvidine, HBeAg*

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INTRODUCTION

Chronic hepatitis B Virus (HBV) infection is a serious global public health problem[1]. It is estimated that between 235000 and 238000 people die annually due to liver cirrhosis and Hepatocellular carcinoma (HCC) respectively[2]. It is of even more importance to the Asia Pacific region since 75% of those infected with HBV are Asians[4]. Pakistan remains in the intermediate prevalence area for HBV infection with an estimated carrier rate of 2-5%[5]. Weak T cell reactivity to HBV is believed to be the dominant cause for chronic HBV infection[6]. The ultimate goal of therapy for Chronic HBV (CHB) infection is to prevent disease progression and to prolong patient survival[7]. These goals can be achieved as long as HBV replication can be suppressed and sustained. A large prospective cohort study from Taiwan has shown that elevated HBV DNA ($\geqslant 10^4$ Copies/ml) and its persistence significantly increases the risk of cirrhosis, HCC and death regardless of HBe antigen status or the baseline ALT levels[8].

Seven drugs have received approval for the treatment of Chronic HBV infection including interferon alpha, pegylated interferon-alpha and the nucleoside analogues (NUCs) which belong to one of the three structural groups L-Nucleosides (Lamivudine (LMV) and Telbuvidine (LDT)), Alkyl phosphates (Adefovir Dipivoxil (ADF) and

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Tenefovir Dipivoxil Fumarate(TDF) and D-Cyclopentanes (Entecavir (ETV)[9]. Telbuvidine (LDT) is a novel orally administered nucleoside analogue for the use in the treatment of chronic HBV infection. In contrast to the other nucleoside analogues, LDT has not been associated with the inhibition of mammalian DNA polymerase with mitochondrial toxicity. LDT has demonstrated potent activity against HBV with significantly higher rate of response and superior viral suppression compared with Lamivudine. LDT is well tolerated with a low adverse effect profile and no dose limiting toxicity has been observed at its effective dose. LDT is one of the most potent antiviral agents for chronic HBV infection[10] and was approved by Food & Drug Authority (FDA) on 25th Oct, 2006. Therefore we decided conduct this study to find out the efficacy of LDT monotherapy in the treatment of CHB infection in our local population.

METHODOLOGY

This prospective study was approved by the ethics review committee of Khyber Teaching Hospital, Peshawar. Written informed consent before enrolment was taken. All patients were diagnosed as CHB infection based on hepatitis B surface antigen (HBsAg) positivity for more than six months. Ninety HBe antigen (HBeAg) positive CHB infection patients were enrolled and followed between June 2008 and June 2011. Five patients were dropped out because three failed to attend for regular follow-ups, one had massive elevations of creatinine phosphokinase (CPK) requiring stopping therapy and a lady got pregnant. A further two were also dropped because there were concerns regarding compliance with the drug therapy. All the enrolled patients were followed up in three months interval and compliance with the therapy was stressed and ensured. All of them had ALT levels less than twice the upper normal limit (Mean 36.9 SD 19.9). All patients were HBeAg positive, had serum DNA level $>10^4$ copies/ml and never had previously received anti HBV treatment. All patients were given LDT 600mg daily as initial antiviral treatment for two years. Patients were excluded form the study if they were co infected with HIV, HCV or HDV, had evidence of liver cirrhosis on ultrasound or clinical evidence of hepatic decompensation, pancreatitis, HCC, fatty liver, alcoholic hepatitis or pregnancy. Upper GI Endoscopy and ultrasound of abdomen was also performed 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 & HBeAg seroconversion and viral breakthrough.

Viral Breakthrough was defined as persistent (two consecutive determinations) increase in HBV DNA >10,000copies/ml while on treatment.

Analysis of full blood count, liver and renal functions, CPK levels were performed at baseline, after 1st month of stating treatment and then at three monthly intervals using automatic biochemistry analyzer (Hitachi 7600). HBsAg, HBeAg, Anti HBe Antibodies were quantified using radio immunoassay (Abbott Laboratories Ltd). 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 ±SD, categorical data as counts and percentages. HBV DNA levels were presented as log transformation. Data was analyzed using SPSS Version 13.0.

RESULTS

Off the total 83 patients who continued in the study as per protocol, 59 were males and 24 were females between ages of 21 and 50 years. Baseline HBV DNA levels were $7.82x10^7$ copies/ml (Range $4.8x10^4$ copies/ml to $8.3x10^9$ copies/ml). By the end of first year (52 weeks) the mean decrease in serum HBV DNA levels was 7.88 log^{10} copies/ml and the proportion of patients having undetectable HBV DNA levels was 73%. At the end of second year of therapy (96 weeks) the percentage of undetectable HBV DNA levels increased to 86%.

At the end of 1st (52weeks) and 2nd (96weeks) HBeAg seroconversion rates were 62 % and 86% while HBsAg seroconversion was 8% and 13% respectively.

Four patients demonstrated viral breakthrough during the course of treatment, 2 at 62 weeks, one each at 72 weeks and 76 weeks of therapy.

DISCUSSION

Our results are comparatively better at viral clearance as compared to the overseas 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. This needs to be investigated further in the years to come. However there was no data available locally to compare our results. It also further emphasizes the need for more research in to the treatment for HBV in our local population. We consider the only major

problem to be with the reporting of data because patients with HBV infection are being treated successfully across the country and in Khyber Pukhtunkhwa (KPK) with various NUC.

A study by Wursthrn K et al shows that in patients who have effective suppression of viral suppression due to LDT treatment, a rapid decline in serum HBeAg levels during the first year may identify those with a greater likelihood of achieving HBsAg clearance[11]. In the GLOBE Trial, LDT demonstrated superior efficacy to LMV at 2yrs in patients with CHB. Undetectable levels of HBV DNA and HBeAg seroconversion were achieved in 77% and 37% of HBeAg positive patients respectively. Cumulative HBeAg seroconversion rate was 46%[12]. A study by Chan Y 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 Hepatitis B Core antigen (HBcAg) and the induction of cytokines such as interferon gamma (IFN-γ), Tumour Necrosis Factor alpha (TNF-alpha) release at the site of infection compared to non-responsive patients. Enhanced HBV specific T Cell reactivity to LDT therapy, which peaked at treatment week 12 was confined to a subgroup of effective treated patients who achieved greater viral suprssion[6]. Evan et al reported the relatively low expression of programmed death-1 receptor on CD8+ T cells in HBeAg positive CHB patients who received LDT therapy and had HBeAg seroconversion, compared with those counterparts who did not achieve the HBeAg seroconversion[13].

ETV and TDF are potent HBV inhibitors and they have a high barrier to resistance. They widely used as first line monotherapy in developed countries[4]. The NICE Guidelines issued in Aug 2008 as a result of the single technology appraisal process states that ETV is recommended as an option for the treatment of people with chronic HBeAg positive or HBeAg negative CHB in whom antiviral treatment is indicated[14].

The resistance to NUCs is a major issue. But the rate of drug resistance has decreased dramatically with the development of newer generation of NUCs. LMV resistance occurs frequently and is observed in 80% of the patients treated for five years[15]. Among adequately treated patients, the cumulative incidence of resistance over 5years has been reported to be 29% in HBeAg negative patients and 42% in HBeAg positive patients[16]. LDT resistance is slower to emerge however rates are substantial with 25% of HBeAg positive and 11% of HBeAg negative patients experiencing virological breakthrough due to resistance after 2 years of treatment[17].

To further minimize the risk of resistance, unnecessary treatment should be avoided and HBV DNA should be carefully monitored to check for primary non-response (<1 $\log_{10}$ drop in HBV DNA at week 12) as well as partial response (detectable HBV DNA at week 24).

Zeuzam S et al demonstrated that pre-treatment serum HBV DNA $<10^{9}\log_{10}$ copies/ml and ALT levels >2 ULN for the HBeAg positive patients were shown to associated with a high rate of non-detectable HBV DNA, a high rate of HBeAg seroconversion and lower resistance to LDT treatment after 2years[18].

CONCLUSION

This study demonstrated LDT monotherapy to be a reasonable cost effective therapy for HBeAg reactive CHB patients resulting in a significant serological and virological response in our local population of KPK. Because of the absence of the locally available data, we feel there is an increased need for reporting ever increasing data with regard to the effective management of this major public health problem in our society.

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CONTRIBUTORS

MTM conceived the idea, did the data collection and wrote the manuscript. HK did the data collection and analyzed the study. NUI supervised the study. All the authors contributed significantly to the research that resulted in the submitted manuscript.