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# Efficacy of Telbivudine in the Treatment of Chronic Hepatitis B Infection in Population of Peshawar, Pakistan

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## ABSTRACT

**Objectives:** To study the efficacy of telbivudine in 2 years treatment of chronic hepatitis B infection in local population of Peshawar.

**Study Design:**

**Place and Duration of Study:** This study was conducted in Khyber Teaching Hospital, Peshawar from June 2007 to June 2012.

**Patients and Methods:** 83 patients, 56 males and 27 females of chronic hepatitis B with no other liver problem like hepatitis C and D, alcoholic hepatitis, fatty liver, hepatocellular carcinoma etc were included in the study. HIV, pancreatitis and pregnancy was also ruled out before study was undertaken. Base line investigations of CBC, Liver and kidney profile, CPK, HBsAg, HBeAg, HBe antibody, HBV DNA, Ultra sound abdomen and upper GI endoscopy were conducted in the subjects. Each patient was given oral telbivudine 600mg/d for 2 years. Biochemical, serological, virological and clinical follow ups were conducted after one month of starting treatment and then every 3 months. Biochemical, serological and virological end points were observed beside adverse effects of telbivudine. Data was analyzed using SPSS version 15.0.

**Results:** Mean serum ALT was reduced from 36.9 iu/ml from first visit to 21.0 iu/ml (p value=0.001) after 24 months of treatment. The serum viral load decreased from 165277.82iu/ml to 3.80 iu/ml from initial to final visit after 2 years of treatment. No viral breakthrough was reported during 24 months of treatment with telbivudine. The drug was well tolerated without any significant adverse effects.

**Conclusion:** Treatment of chronic hepatitis B patients with telbivudine shows statistically significant reduction in viral load and serum ALT with no significant adverse effects

**Key Words:** Hepatocellular Carcinoma, Telbivudine, Ampiclor

## INTRODUCTION

Chronic hepatitis B virus (HBV) infection remains an important public health problem, infecting 350 million people world wide.[1]The disease is prevalent in all parts of the world but especially endemic in Asia, the south pacific region, Sub Saharan Africa and other regions.[2] It is estimated that 500,000 people die annually of HBV related complications.[3] Hepatitis B carrier rate in Pakistan is 2.5% which reflects an intermediate prevalence area.[4] There is increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC) among individuals with chronic hepatitis B (CHB)[5-6], though this process takes decades to evolve.[7] The end point complications of CHB are directly proportional to serum HBV DNA concentration, a measure of viral load.[8-9] Rapid and sustain suppression of HBV replication is the goal for the treatment of CHB.[10-13]

The incidence of the complications of chronic HBV infection has declined with the advent of oral nucleos(t)ide analogues.[14-15] Recent literature suggest, that therapeutic efficacy and the emergence of resistance are related to degree of viral suppression achieved early in the course of treatment.[16-18] It means, during a prolonged treatment, the more the viral load decline in the initial stage, the better the outcome will be.[19]

Telbivudine, a potent oral nucleos(t)ide analogue induces rapid and profound inhibition of HBV DNA replication. The drug may modulate the immune system through a similar pathway with IFN, inhibiting viral replication directly.[20] Telbivudine does not inhibit mammalian DNA polymerase with mitochondrial toxicity as associated with other nucleos(t)ide analogues. Considering high prevalence of CHB in Pakistan, present study was conducted with an aim to determine the efficacy of telbivudine monotherapy in the treatment of chronic hepatitis B infection.

## PATIENTS AND METHOD

This study was conducted from June 2007 to June 2012 at Khyber Teaching Hospital, Peshawar. Approval was granted by ethical review committee, Khyber Teaching Hospital to conduct this study. A detail of procedure

was explained to all patients and written consent was obtained from all subjects before inclusion in the study. Eighty six patients were enrolled in the study who were diagnosed as CHB infection having HBsAg positive for more than six months, none received HBV treatment. All subjects excluded from the study who were simultaneously infected with HCV, HDV, HIV, have evidence of liver cirrhosis on sonography or clinical evidence of liver decompensation, alcoholic hepatitis, pancreatitis, fatty liver, hepatocellular carcinoma or pregnancy. Chronic liver disease (CLD) was ruled out from all subjects by performing ultrasound abdomen and upper GI endoscopy. All subjects were given tablet telbivudine 600 mg/d orally for two years. Subjects were investigated for CBC, liver and renal function, CPK levels at baseline, after first month of starting treatment and then every three months using automatic biochemistry analyzer (Hitachi 7600), HBsAg, HbeAg, Anti HBe antibodies were quantified using radio immunoassay (Abbot Laboratories). HBV DNA quantification was done using Ampiclor HBV Test (Roche Diagnostics, Basel, Switzerland) having a detection limit of 300 copies/ml. Data was analyzed using SPSS version 15.0. Main therapeutic end points were observed at the end of first and second years of therapy including proportion of patients with non detectable serum HBV DNA levels, HBsAg and HbeAg seroconversion and viral breakthrough. Viral breakthrough is defined as persistent (two consecutive determinations) increase in HBV DNA > 10,000 copies/ml while still on treatment.

# RESULTS

Among eighty six patients enrolled, three patients were dropped from the study as they failed to attend regular follow ups. Eighty three subjects completed 2 years study protocol. Among these eighty three patients, 56 (67.5%) were males and 27 (32.5%) were females between the ages of 18 and 65 years with mean age 28 ±11.68 years. The follow up period was approximately 24 months for each patient. HBsAg, HbsAb was positive in 83 (100%) patients. The mean serum ALT was reduced from 36.9 iu/ml from first visit to 21.0 in the last visit, after 2 years (p value = 0.001). The serum viral load decreased from 165277.82 iu/ml to 3.80 iu/ml from initial visit to the last visit at 24 months. Sero conversion rate at month 06 and 09 months was 46/83 (55.42%) and 47/83 (56.62%) respectively. No viral breakthrough was reported.

There were no significant side effects reported among subjects during study period of two years. Two patients complained of mild myelgia that subsided spontaneously. In another two subjects, there was slight elevation of serum creatine phospho kinase values (< 2ULN), but there was no indication of with drawl of treatment and all subjects continued treatment as per schedule with remission of complaints.

**Table No.1: Changes in Serum ALT (iu/ml) in different visits, n = 83**

| Statistics | Serum ALT V1 | Serum ALT V2 | Serum ALT V3 | Serum ALT V4 | Serum ALT V5 | Serum ALT V6 | Serum ALT V7 | Serum ALT V8 | Serum ALT V9 | Serum ALT V10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Mean | 36.95 | 33.88 | 33.83 | 37.62 | 30.66 | 30.12 | 29.59 | 26.40 | 28.71 | 21.50 |
| Median | 32.00 | 32.00 | 24.50 | 29.00 | 24.00 | 30.00 | 24.00 | 23.00 | 30.00 | 31.50 |
| SD | 19.93 | 25.51 | 27.10 | 25.51 | 20.08 | 12.84 | 13.24 | 12.56 | 8.09 | .58 |
| Minimum | 14.00 | 16.00 | 14.00 | 16.00 | 14.00 | 16.00 | 16.00 | 17.00 | 21.00 | 16.00 |
| Maximum | 114.00 | 226.00 | 168.00 | 126.00 | 115.00 | 65.00 | 65.00 | 58.00 | 39.00 | 32.00 |

**Table No.2: Changes in Serum Viral Load (iu/ml) in different visits.**

| Statistics | V 1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Mean | 165277.82 | 52844.07 | 26539.25 | 12407.46 | 6261.74 | 2760.54 | 1751.24 | 451.19 | 3.80 | 3.80 |
| Median | 80998.00 | 9623.00 | 321.00 | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 |
| SD | 217905.24 | 90281.31 | 50974.34 | 22993.38 | 15899.17 | 7654.35 | 4304.81 | 1303 | .00 | .00 |
| Minimum | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 | 3.80 |
| Maximum | 1180418.00 | 417532.0 | 197460.00 | 92179.0 | 56989.00 | 25336.00 | 15920.0 | 3926 | 3.80 | 3.80 |

# DISCUSSION

Clinical trials designed to demonstrate a benefit on clinical outcome of chronic hepatitis B infection would need to enroll hundreds and thousands of patients at risk of developing cirrhosis, hepatocellular carcinoma and liver failure.[5-6] Since these end point events may follow years or decade to occur during course of the disease, therefore, clinical trials of hepatitis B treatment have relied on intermediate end points that reflect viral replication and liver disease activity as surrogates for clinical benefit.[7] These intermediate end point include Biochemical ( serum ALT, a cheap and reliable marker of liver inflammation ), Virological (suppression of HBV replication with undetectable serum HBV DNA ), Serological (loss of HBeAg with or without sero conversion anti Hbe ) and Histological (decrease in necrosis and inflammation score by ≥ 2 points with no worsening of fibrosis ).[7]

In our study there is marked improvement of serum ALT, decrease of viral load and sero conversion of HBeAg during 2 years treatment with telbivudine.[21-23] A study comparing telbivudine with another nucleoside analogue lamivudine reports that at 52 weeks of treatment, telbivudine resulted in significantly higher rates of undetectable serum HBV DNA (46 %) compared to lamivudine 31 % (p=0.005).[22] Same study also reveals that proportion of patients with ALT normalization was higher with telbivudine (60 %) compared to lamivudine (51 %). Similar results of superior efficacy of telbivudine over lamivudine were shown in GLOBE trial.[24-25]

Present study does not find any serious side effects among subjects after two years of treatment with telbivudine. Mild myalgia reported in two patients was spontaneously subsided. Other studies have reported myalgia and myositis to occur with use of nucleos(t)ide analogues. [22,23] In this study there were two subjects who showed mild elevation of CPK. This same effect has also been reported by other studies.[22, 26]

# CONCLUSION

The findings from our study indicated that based on treatment response, HBV DNA has shown a statistically significant improvement. Reduction in serum ALT is also statistically significant. Telbivudine is effective in treating HBV infection. It is well tolerated and safe with no adverse effects.

# REFERENCES


1. Liaw YF. HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. Hepatol Int 2009;3:425-33.
2. Lok ASF, McMahon BJ. Chronic Hepatitis. Hepatol 2001;34(6):1225-41.
3. Gaeta GO, Stornaiuolo G. Therapy of chronic hepatitis B: focus on telbivudine. Dig Liver Dis 2007; 39: 372-8.
4. Abbas Z, Jafri W, Hamid S. management of Hepatitis B: Pakistan society for the study of liver diseases (PSSLD) practice guidelines. J coll physicians surg Pak 2010; 20: 198-201.
5. Elgouhari HM, Abu-Rajab Tamimi TI, Charey WD, Hepatitis B virus infection: understanding its epidemiology, course and diagnosis. Clev Clin J Med 2008;75:881-9.
6. Maryugan RB, Garzons G, DNA guided hepatitis treatment, viral load is essential, but not sufficient. World J Gastroentrol 2009; 15:423-30.
7. Chotiyaputta W, Lok ASF, Endpoints of hepatitis B treatment. J Viral Hepat 2010; 17: 675-84.
8. Chen J, Yang HI, Su J. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006; 295: 65-73.
9. Iloej UH, Yang HI, Su J. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroentrol 2006;130:678-86.
10. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int 2008; 2:263-83.
11. Keefe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. Clin Gastroentrol Hepatol 2008;6:1315-41.
12. Lok ASF, McMahon BJ. Chronic hepatitis B. Hepatol 2007;45:507-39.
13. European Association for the study of the liver. East clinical practice guidelines; management of hepatitis B. J Hepatol 2009; 50:227-42.
14. Liaw YF, Sung JJ, Chow WC. Lamivudine for patients with chronic hepatitis and advanced liver disease. N Engl J Med 2004; 351:1521-31.
15. Yuen MF, Seto WK, Cow DH. Long term lamivudine therapy reduces the risk of long term complications of chronic hepatitis B infection even in patients without advanced disease. Antivir Ther 2007;12:1295-1303.
16. Zollner B, Schafer P, Feucht HH, Schroter M, Petersen J, Laufs R. Correlation of hepatitis B virus load with loss of e antigen and emerging drug resistant variants during lamivudine therapy. J Med Virol 2001; 65: 659-65.
17. Locarnini S, Qi X, Arterburn S, Snow A, Brasgart C, Currie G, et al. Incidence and predictors of emergence of adefovir resistant HBV during four years of adefovir dipivoxil (ADV) therapy for patients with chronic hepatitis B (CHB) [Abstract] Hepatol 2005; 42: 17.
18. Di Bisceglie AM, Lai CL, Gane E, Chen YC, Thongsawat S, Wang Y, et al. Telbivudine GLOBE trial: maximal early HBV suppression is predictive of optimal two year efficacy in nucleoside treated hepatitis B patients [Abstract]. Hepatol 2006;44: 230A.
19. Nguyan MH, Keefe EB, Chronic hepatitis B: Early viral suppression and long term outcomes of therapy with oral nucleos(t)ides. J Viral Hepat 2009;16:149-55.
20. Cai W, Xie Q, An B, Wang h, Zhou X, Zhao G, et al. On-treatment serum HBsAg level is predictive of sustained off-treatment virologic response to telbivdine in HbeAg positive chronic hepatitis B patients. J Clin Virol 2010; 48: 22-26.
21. worsthorn K, Jung M, Riva A, Goodman ZD, Lopez P, Bao W, et al. Kinetics of hepatitis B

surface antigen decline during 3 years of telbivudine treatment in hepatitis B e antigen positive patients. Hepatol 2010; 52: 1611-20.

22. Safadi R, Xie Q, Chen Y, Yin YK, Wei L, Gyu S, et al. Efficacy of switching to telbivudine in chronc hepatitis B patients previously treated with lamivudine. Liver Int 2011; 31:667-75.
23. Chan HLY, Heathcoate EJ, Marcellin P, Lai CL, Cho M, Moon YM, et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir. Ann Intern Med 2007; 147:745-54.
24. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2 year GLOBE trial results: Telbivudine is superior to lamivudine in patients with chronic hepatitis B. Gastroenterol 2009;136: 486-95.
25. Lai CL, Gane E, Chao WH. Two years results from the GLOBE trial in patients with chronic hepatitis B: greater clinical and antiviral efficacy for telbivudine (LdT) vs lamivudine. Hepatology 2006; 44: 222A.
26. Zheng MH, Shi KQ, Dai ZJ, Ye C, Chen YP. A 24 week, parallel group, open label, randomized clinical trial comparing the early anti viral efficacy of telbivudine and entecavir in the treatment of hepatitis B e antigen positive chronic hepatitis B virus infection in adult Chineese patients. Clin Therapeutics 2010; 32: 649-58.

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