

A Randomized Comparative Study of Efficacy of Lamivudine and Adefovir Combination versus Tenofovir versus Entecavir in Decompensated Cirrhotic Patients of Hepatitis B

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Submission: September 07, 2015; Published: September 21, 2015

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Abstract

Decompensation is a frequent presentation of Hepatitis B related liver disease. In India transplantation is not easily available. Hence antiviral drugs form the backbone of management. Lamivudine and Adefovir, either as alone or as combination has been useful, Entecavir and tenofovir have good efficacy. These drugs have different side effect, resistance and cost profile which is important considering long term treatment

Aim: To compare the efficacy of lamivudine and adefovir (L+A) combination, tenofovir and entecavir for treatment of decompensated chronic Hepatitis B.

Methods: Chronic Hepatitis B patients with decompensated (either ascites, GI bleeding or encephalopathy at presentation) were randomized in to three groups. Lamivudine and adefovir combination, tenofovir and entecavir (18 patients in each group). All three groups were comparable in terms of their age, sex, baseline CTP score, baseline MELD score, median HBV DNA log, HBeAg positivity. Clinical, biochemical and virological parameters like CTP score (mean reduction), MELD score (mean reduction), HBV DNA log reduction (mean log reduction & % of undetectable HBV DNA), HBeAg loss, HBeAg seroconversion were studied at baseline, at 24 weeks and at 48 weeks of treatment. Alcoholic patients were advised to strictly abstain. Statistical analysis was done using t test, Chi-square test and ANOVA with SPSS16 software.

Results: Out of 54 patients, 2 patients were lost follow up & 1 patient developed HCC. These were excluded from study. Four patients died due to liver disease (2 in lamivudine and adefovir combination group and 1 each in tenofovir and entecavir group). There was no incidence of altered renal function or lactic acidosis due to any study drug. Analysis of clinical biochemical and virological parameters were carried out. Mean CTP reduction (24, 48 weeks) for lamivudine and adefovir combination (L+A) was (0.69, 1.33), tenofovir (1.50, 1.94) and entecavir (1.56, 2) with p value (0.18, 0.13). CTP \geq 2 detection was found as L+A (20%, 50%), tenofovir (38%, 48%) and entecavir (44%, 64%). Decrease in MELD score (24, 48 weeks) was L+A (1.4, 1.7), tenofovir (2, 2.4) and entecavir (2.4, 2.7) with p value (0.09, 0.46). HBV DNA mean log reduction (24, 48 weeks) was L+A (2.6, 3.73), tenofovir (3.06, 3.94) and entecavir (2.69, 3.31) with p value (0.8, 0.58). The values for undetectable HBV DNA (24, 48 weeks) were L+A (48%, 67%), tenofovir (50%, 60%) and entecavir (60%, 75%) with p value (0.71, 0.81). At 48 weeks, HBeAg loss was seen in L+A (n=4, 50%), tenofovir (n=4, 50%), entecavir (n=2, 66%) with p value=0.88. HBeAg seroconversion was not seen in any patient. None of the above results were statistically significant.

Conclusion: The efficacy of lamivudine and adefovir, tenofovir and entecavir was comparable. Tenofovir reduced HBV DNA more than others and entecavir has more CTP score & MELD score reduction, though differences were not statistically significant. Longer follow up and larger sample size may lead to definitive conclusions.

Keywords: Hepatitis B; HBeAg; Hepatocellular carcinoma; MELD

Abbreviations: L+A: lamivudine and adefovir; CHB: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; HBeAg: Hepatitis B e Antigen

Introduction

About 400 million people are infected with chronic hepatitis B (CHB) infection worldwide, causing significant morbidity and mortality [1]. Complications like cirrhosis, liver failure, and/or hepatocellular carcinoma (HCC) are expected to develop in

15%-40% of patients with CHB leading to estimated 1 million deaths worldwide [2]. The development of jaundice, ascites, hepatic encephalopathy or variceal bleeding indicates liver decompensation. In cirrhotic patients the 5-year probability of decompensation is 15%-20%, with higher risk associated with viral replication. Annual progression rate of progression from

compensated cirrhosis to decompensated cirrhosis is around 4.6% [3]. Decompensated cirrhosis has 5 year survival of 14% compared with 84% in patients with compensated cirrhosis [4]. The 5 year mortality rate from decompensated cirrhosis ranged from 41 to 67% [5].

The only definitive treatment for end stage liver disease is liver transplantation. In developing countries most patients with advanced hepatitis B do not have access to transplant services [6]. Safe oral antiviral drugs have dramatically changed the management of chronic HBV infection. These drugs improve or stabilize liver disease in patients who are not transplant candidates or are on waiting list or do not have access to liver transplantation.

Current clinical practice guidelines advocate sustained HBV DNA suppression to reduce sequelae [7-9]. Various drug options tested in decompensated hepatitis B presently available are lamivudine, adefovir (mono, de novo or add on combination with lamivudine) entecavir, tenofovir. Lamivudine [10-12] and Adefovir [13,14] have demonstrated improved clinical outcomes (decreased mortality and improved liver function) in decompensated CHB patients, but the clinical benefit of lamivudine is limited by the emergence of resistant mutant strains [15,16] Adefovir was found to be less efficacious than tenofovir or entecavir. Several studies showed that combination therapy with lamivudine and adefovir is better than ADV monotherapy in LAM-resistant patients infected with HBV [17,18].

Recommended oral first-line therapies for chronic hepatitis B are tenofovir and entecavir. Comparing entecavir Vs lamivudine, entecavir (0.5 mg dose) is superior to lamivudine in treatment naïve hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients [19,20] and entecavir resistance is extremely low [21] However, entecavir is less efficacious in lamivudine-refractory patients even at 1.0 mg daily, with the reported resistance rate at 5 years of 51%.

Tenofovir is superior to adefovir in HBeAg-negative and HBeAg-positive treatment-naïve patients [22]. Additionally, tenofovir demonstrated potent antiviral activity in a subset of lamivudine-experienced HBeAg-positive patients [23] and in patients with suboptimal response to adefovir [24]. There has been no development of resistance to tenofovir through 144 weeks of therapy but there are concerns regarding the long-term safety of tenofovir in some HBV patients including nephrotoxicity and metabolic bone disease [25]. Patients with decompensated cirrhosis are frequently malnourished and may have low vitamin D levels [26].

Though Entecavir and tenofovir are better therapeutic options at present, they have few limitations and long term data is awaited. Lamivudine and adefovir combination has been tested in lamivudine resistance patients as de novo or add on therapy with good results.

The present study tried to compare the efficacy of these drugs in Indian population. Importance of drug efficacy, safety, cost profile is underscored by the fact that majority of Indian patients depend on them on long term due to scarcity of liver transplantation units. There is scant data about efficacy, side effects of these drugs in Indian population, and cost of these

drugs substantially differs. The cost of entecavir and tenofovir is higher than lamivudine and adefovir combination especially as patients need lifelong therapy. Hence lamivudine and adefovir combination arm was included in this study.

Patients and Methods

Study patients

Adult patients with chronic hepatitis B who had decompensated cirrhosis and were enrolled in the study from 2010 to 2012 in a large tertiary care public hospital in Mumbai, India. The diagnosis of cirrhosis was based on clinical, laboratory, histological and imaging studies with at least one sign of liver decompensation (ascites, variceal bleeding, hepatic encephalopathy, non-obstructive jaundice). Patients co-infected with hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, or human immunodeficiency virus and with autoimmune hepatitis, hepatorenal syndrome, HCC or severe heart, brain, renal diseases were not included in study. Patients who had received any antiviral therapy for hepatitis B in past were excluded. The patients with history of alcohol ingestion were advised to strictly abstain.

Study objective

The primary objective was to compare efficacy of lamivudine and adefovir combination, tenofovir and entecavir in treatment of decompensated chronic hepatitis B patients. It was also aimed to assess safety of these drugs.

Study design

This was single centre, randomized controlled study. Eligible patients were randomized into one of the treatment arm of lamivudine (100mg) + adefovir (10mg) or tenofovir (300mg) or entecavir (0.5mg). At Baseline all patients were assessed clinically in detail. Biochemical evaluation CBC, LFT, RFT, Creatinine clearance, PT, INR was done. Virological assessment included HBV-DNA, HBeAg, Anti HBeAg, Anti-HBs. Other tests like Anti-HCV, ELISA for HIV and autoimmune markers were also done. Drug doses were adjusted according to creatinine clearance. Patients baseline CTP and MELD score were calculated. Patients informed consent was taken.

Efficacy assessment

Efficacy of these drugs were assessed either clinical & biochemical (Change in CTP score or MELD score). Virological improvement was assessed with change in HBV-DNA (measured in log) and HBeAg loss or seroconversion.

Follow up

Patients were evaluated at monthly interval for serum creatinine, creatinine clearance and drug dosages adjusted accordingly. Then patients were evaluated at 24 weeks & at 48 weeks with biochemical and virological parameters as mentioned above. Any patient clinically suspected of side effects was evaluated.

Statistical methods

Data was expressed as mean \pm S.D., median (range) or frequency or percentage when appropriate. Student t test,

Chi-square test and ANOVA were used to compare whenever appropriate. P value less than 0.05 was considered significant.

Results

Study patients

A total of 54 patients (41 males and 13 females) with mean age of 47 years were enrolled in the study. The baseline CTP and MELD score in each group were 8 and 13 respectively and were comparable in all groups. Virological studies show baseline HBV DNA as log and in each group was comparable median log₁₀⁵. Decompensating events were as follows ascites (78%), variceal bleeding (47%). In 45% patients there was more than one decompensatory event at presentation. HBeAg positivity in our study was 20%. There were no statistically significant differences between groups in any of clinical or virological parameters (Table 1).

Clinical and biochemical responses

Clinical and biochemical evaluation for efficacy was done at 24 weeks and 48 weeks in the form of change in CTP and MELD score. The results are shown in (Table 2). Mean CTP reduction at 24 weeks was 0.69, 1.50, 1.56 for L+A, tenofovir and entecavir (p value=0.11) while at 48 weeks they were 1.33, 1, 94, 2 respectively (p value=0.32). Thus for improvement in CTP score entecavir was better than L+A and tenofovir, though it was not statistically significant.

Decrease in MELD score at 24 weeks was 1.4, 2, 2.4 for L+A, tenofovir and entecavir (p value=0.62) while at 48 weeks they were 1.7, 2.4, 2.7 respectively (p value=0.61). Thus for MELD score was better with entecavir than L+A and tenofovir, though it was not statistically significant.

Virological response

Mean log reduction in HBV DNA at 24 weeks 2.6, 3.06, 2.69 for L+A, tenofovir and entecavir (p value=0.67) while at 48 weeks it was 3.73, 3.94, 3.31 respectively (p value=0.58). Thus HBV DNA load is reduced more with tenofovir, than by L+A and then by entecavir.

The percentage of patients with undetectable DNA at 24 weeks

was 48%, 48%, 60% for L+A, tenofovir, entecavir (p value=0.71) while at 48 weeks it was 67%, 58%, 75% (p value=0.81).

Serological response

HBeAg status of the patients was also assessed. At baseline 10/54 patients were positive. At 48 weeks, HBeAg loss was seen in L+A (n=4, 50%), Tenofovir (n=4, 50%), Entecavir (n=2, 66%). p value=0.88. HBeAg seroconversion was not seen in any patient.

Safety

Study patients were observed for any drug related side effects. Drugs were tolerated well. Two patients at baseline have higher serum creatinine one due to renal calculus disease (tenofovir group) and other due to diabetic nephropathy (entecavir group) both was given drugs according to creatinine clearance. No change in creatinine clearance was noted during study period. No incidence of lactic acidosis was found.

Out of 54 patients enrolled, 1 patient (L+A) developed HCC and one patient in each group tenofovir and entecavir lost follow up, so all 3 were excluded from study. Four patients died due to liver disease (2 in L+A group and 1 each in tenofovir and entecavir group).

Discussion

In this study, we compared combination of lamivudine and adefovir, tenofovir and entecavir in patients of decompensated chronic hepatitis B patients prospectively over a period of 1 year.

Decompensation was the first event in all patients leading to disease recognition. This indicates lack of awareness and deficient screening of hepatitis B in India. Epidemiology of study population reflects Indian hepatitis B profile. Male propensity (78%), age distribution (mean age 47 years) is similar to comparative studies. In one Indian study mean age of decompensated hepatitis B patients was 43 years, and incidence of ascites was 70%, variceal bleeding was 28% and HBeAg positivity 28% [27]. Other global studies [5,27-30] also show comparable values as follows, age (46, 54 years), ascites (30, 49, 62, 63, 70%), GI bleeding (8-30%), hepatic encephalopathy (5-19%) and more than one feature (29-75%). Our study shows similar pattern. In our study, parameters were as follows mean age 47 years, ascites (78%), Variceal bleeding (47%). As isolated decompensatory event ascites (44%), variceal bleeding (11%) and rest 45% has more than one decompensatory event at presentation. HBeAg positivity in our study was 20%, while rest of the studies show 24-28% positivity.

Due to its simplicity and practice, CTP score has been widely applied as the prognostic marker in patients with decompensated cirrhosis [31,32] CTP score is one of the risk factors for assessing patients with decompensated cirrhosis [33], Change in CTP score in various studies is as follows, CTP score mean reduction ≥ 2 was found in lamivudine 39%, adefovir 27%, entecavir (35-49%) tenofovir 26% [34-38]. Lamivudine and adefovir combination has been tried mostly in lamivudine resistant patients as add on therapy. But one study showed that de novo combination of lamivudine and adefovir in decompensated patients cause more significant reduction of CTP score as compared to add on therapy [34].

Table 1: Baseline demographic and disease characteristics of each group are shown in Table 1.

Baseline parameters	L+A n=18	T n=18	E n=18	P
Age (Median)	50	43	47	0.13
Sex (Male)	14	14	13	0.88
Baseline CTP	8	8	8	0.21
Baseline MELD	12	14	13	0.36
HBV DNA (log value)	5	6	5	0.80
HBeAg (pos)	4	4	3	0.89
H/O Alcohol ingestion	7	10	9	0.57
Ascites	15	13	14	0.66
GI Bleed	7	7	11	0.28
Encephalopathy	0	2	2	0.33

Table 2: Clinical and Biochemical Results.

Results Parameters	L+A(n=16 wk 24 ,n=15 wk 48)	T(n=16)	E(n=16)	P value
1. C T P score ≥ 2 decrease				
At week 24	3(20%)s	6(37.5%)	7(43.8%)	0.181
At week 48	6(40%)	7(43.8%)	10(62.5%)	0.133
2. CTP score- change in CTP				
At week 24	0.69 \pm 0.94	1.50 \pm 1.673	1.56 \pm 1.153	0.116
At week 48	1.33 \pm 1.05	1.94 \pm 1.57	2.00 \pm 1.37	0.326
3. Decrease in MELD score				
At week 24	1.4 \pm 3.36	2.0 \pm 3.25	2.4 \pm 1.82	0.620
At week 48	1.7 \pm 2.36	2.4 \pm 3.89	2.7 \pm 1.87	0.611
1. Change in serum HBV DNA (median log decrease)				
At week 24	2.60 \pm 1.35	3.06 \pm 1.88	2.69 \pm 1.35	0.674
At week 48	3.73 \pm 1.39	3.94 \pm 1.88	3.31 \pm 1.82	0.577
2. HBV DNA undetectable (%)				
At week 24	8(48%)	8 (50%)	10(60%)	0.717
At week 48	10 (67%)	10(62%)	12(75%)	0.815
Serological Response				
1. HBeAg loss				
At week 48	2(50%)(n=4)	2(50%)(n=4)	2((66%)(n=3)	0.885

In our study CTP ≥ 2 reduction was found as follows lamivudine+adeфовir (27%), tenofovир (43.8%) and entecavir (62%) Mean CTP score reduction was 1.3, 1.9, 2 for respective groups. Thus CTP score response was better as compared to other studies for tenofovир as well as entecavir. Better responses can be explained by the high percentage of lamivudine resistance (14, 33, to 100%) in other studies while our study does not have such data, all patients were treatment naïve.

MELD score has emerged as a better objective measure of prognosis in end stage liver disease patients. Decrease in MELD score is a good prognostic marker. Efficacy in reducing MELD score of various drugs is as follows lamivudine (-2), adefovir (-2) entecavir (-1.7 to -2.6) tenofovир (-2) [14,35-38] while in our study MELD reduction were as follows, Lamivudine +Adefovir (-1.7) tenofovир (-2.4), entecavir (-2.7).

Virological improvement was assessed using HBV-DNA levels as log values. Undetectable HBV-DNA at 1 year in various drug therapies are as follows lamivudine (60-80%), adefovir (20-59%), entecavir (73-89%) tenofovир (71%) and lamivudine and adefovir combination-de novo (90%) and add on (40%) [34-38]. Our study showed similar trends with lamivudine and adefovir combination (67%), tenofovир (58%) and entecavir (75%). Mean log decrease in HBV-DNA was 3.73, 3.94 and 3.31 for L+A, tenofovир and entecavir. All Results in all these groups were not statistically significant.

One year survival in L+A (88%), tenofovир (94%) and entecavir (94%), was good and was comparable to other studies lamivudine (84, 88%), adefovir (67, 87%) entecavir (77, 91%), tenofovир (96%)

HBeAg loss occurred in 50%, 66%, 50% in L+A, Entecavir and Tenofovир group, comparable to other studies [34]. Study drugs did not lead to alteration of renal function in any patient and there was no incidence of lactic acidosis suggesting the safety of these drugs in our population. However our study has few limitations. The sample size was small and the follow up was only 1 year. The study highlights comparability in terms of efficacy and safety of three drug regimens in decompensated chronic hepatitis B in India.

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