Adefovir dipivoxil, tenofovir disoproxil fumarate or lamivudine; which is suitable monotherapy medication in the patients with chronic hepatitis B virus infection? one year experience

Abstract

Introduction: The hepatitis B virus infection is responsible for more than one million deaths all over the world. This study design is to compare the efficacy of Lamivudine (LAM), Adefovir Dipivoxil (ADV) or Tenofovir Disoproxil Fumarate (TDF) monotherapy in chronically infected hepatitis B patients.

Methods: We design a prospective cohort study and select patients who were under treatment with TDF (300mg/day), ADV (10mg/day) and LAM (100mg/day). After matching patient’s primary data and on base of our inclusion and exclusion criteria; 19, 20 and 19 patients were enrolled in TDF, LAM and ADV groups, respectively. Then, we evaluated patients at 6 and 12 month after treatment.

Results: Patients primary data was closely matched. After 6 month medication, ALT level in 7 patients (36.8%), 12 patients (60%) and 6 patients (31.6%) of TDF, LAM and ADV groups were back to normal range, respectively (P<0.05). All drugs significantly decrease ALT level after 6 month therapy (P<0.0001). After 12 month, ALT level in 3 patients (37.5%), 14 patients (73.7%) and 6 patients (35.3%) of TDF, LAM and ADV group were comebacks to normal range, respectively. LAM significantly had better effect on ALT level (P<0.05). After 12 month therapy, serocconversion was observed in 40% of ADV group patients (2 of 5 HBeAg positive) and 33.3% of TDF group patients (2 of 6 HBeAg positive) (P>0.05). Finally, response to treatment was observed in 5 patients (45.5%), 7 patients (2 of 5 HBeAg positive) and 33.3% of TDF group patients (2 of 6 HBeAg positive) (P>0.05).

Conclusion: LAM had significantly more potential to normalized ALT level. But, there were no significant differences between TDF, ADV and LAM to reduce the load of virus DNA and serocversion of HBeAg.

Keywords: adefovir dipivoxil, chronic hepatitis b, tenofovir disoproxil fumarate, lamivudine

Abbreviations: LAM, lamivudine; ADV, adefovir dipivoxil; TDF, tenofovir disoproxil fumarate; PT, prothrombin time; ALT, alanine transaminase; HBeAg, HBe antigen.

Introduction

Hepatitis B virus (HBV) is a member of the genus Orthohepadnavirus of Hepadnaviridae family.1 Hepatitis B is one of the most important liver infectious inflammatory disorders which is induced by the HBV and causes inflammation in the hepatic tissues, vomiting, jaundice, etc.2 According to statistical reports, 5 % of world’s population is suffered from chronic (long-term) HBV infection in the worldwide.3 Chronic HBV infection is usually associated with hepato cellular carcinoma as well as hepatic cirrhosis which can lead to death.1 It has been reported that chronic HBV infection is associated with chronic hepatic inflammation (which is called chronic hepatitis) and leads to liver cirrhosis during several years after infection.4 Also, chronic HBV infection increased the rate of incidence of hepatocellular carcinoma in patients.5

According to the statistics, hepatitis B and C induces 50% of hepatocellular carcinomas in European countries.2 Therefore, patients with chronic HBV infection should deprive themselves from consumption of alcohol inasmuch as it increases the risk of hepatic cirrhosis and hepatocellular carcinomas.4

As for the prevalence and complication of this disease, find a well medication is very important. Nevertheless, type of management and indication of antiviral therapy is difference and depended to patients’ condition.9 Seven drugs approve for treatment of chronic HBV infection that included; interferon alfa,10,11 peginterferon alfa-2a,12 Lamivudine (LAM),13 Adefovir Dipivoxil (ADV),14 entecavir,15 Telsivudine16 and Tenofovir Disoproxil Fumarate (TDF).17

Lamivudine is a second-generation nucleoside analogue. This drug inhibits HBV replication and improves liver histology. However, viral gene mutation that laid to Lamivudine resistance is event frequently.18 Recently, Adefovir Dipivoxil, a prodrug of Adefovir, was approved for used in chronic hepatitis B patients.14,19,20 Also, TDF is another most common drug for treatment of chronic hepatitis B virus infection.21 Our cohort study examined comparison of the efficacy of ADV, TDF and LAM in the patients who suffered from chronic hepatitis B virus infection.

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Patients and methods

Patient's selection

We design a prospective cohort study and select patients who were under treatment with ADV, TDF or LAM. For this aim, we collected patient's demographic and past lab test data (before medication) and select patients who had same condition. Our inclusion criteria included all patients with chronic HBV disease who had over 20000 IU/ml HBV DNA and ALT higher than 2 fold of normal range in lab test or had liver positive histological evidence of HBV disease and taking antiviral medication (ADV, TDF or LAM) from a maximum of 4 months ago. Our exclusion criteria included all patients who were under treatment with Interferon, HBC, HBV or HIV infection, decompensated liver disease (serum bil>2/5, PT>3s, history of ascites, abnormal Albumin, hepatic Encephalopathy), other liver disease (autoimmune hepatitis, drug-induced hepatitis), history of any transplantation, liver mass and patients who recently treated with corticosteroid.

Study design and data collection

Before entering patients into the study, their all data including; gender, age, history of disease, history of smoking, prothrombine time (PT), serum creatinine levels, alanine transaminase (ALT), HBe antigen (HBeAg), HBV DNA load were collected. On base of inclusion and exclusion criteria and after matching patients demographic and first lab test (before treatment) data, we selected 19, 20 and 19 patients for ADV, LAM and TDF groups, respectively. Then we follow patients for one year, from their medications were started. Patients in ADV, LAM and TDF groups were under treatment with 10mg/day Adefovir Dipivoxil, 100mg/day Lamivudine and 300mg/day Tenofovir Disoproxil Fumarate, respectively.

Results

Statistical analysis

Statistical data analysis was performed by SPSS version 16. Categorical data were analyzed by two-sided Fisher exact test and chi-square test and Quantitative data were analyzed using student t test. P value under 0.05 considers as a significant level.

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Table 1: Demographic and baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Age</th>
<th>ADV Group</th>
<th>LAM Group</th>
<th>TDF Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>10 (52.6%)</td>
<td>15 (75%)</td>
<td>15 (78.9%)</td>
</tr>
<tr>
<td>history of disease</td>
<td>1 (5.3%)</td>
<td>3 (15%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (21.1%)</td>
<td>4 (20%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>PT time (s)</td>
<td>12.66±0.51</td>
<td>12.63±0.46</td>
<td>12.68±0.61</td>
</tr>
<tr>
<td>Cr level (mg/dl)</td>
<td>0.82±0.11</td>
<td>0.86±0.12</td>
<td>0.83±0.14</td>
</tr>
<tr>
<td>ALT level</td>
<td>167.3±58.23</td>
<td>149.35±48.18</td>
<td>134.52±34.51</td>
</tr>
<tr>
<td>HBeAg (Positive)</td>
<td>5 (26.3%)</td>
<td>3 (15%)</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>HBV DNA level</td>
<td>53683470±27263501</td>
<td>71755908±27059394</td>
<td>63624869±29142710</td>
</tr>
</tbody>
</table>

Biochemical response

The mean of ALT before treatment in ADV, LAM and TDF groups were 34.73±11.42, 39.85±12.33 and 34.63±11.72 years, respectively (P>0.05). After 6 month medication, mean of ALT level in ADV, LAM and TDF groups were 44.37±25.75 U/L, 3 patients were HBeAg positive and mean DNA copy was 885458±213615 (Median=72168).

After 12 month medication, mean ALT level in ADV group was 47.58±23.96 U/L, in LAM group was 43.73±22.93 U/L, in TDF group was 43.78±22.93 U/L and in group C was 38.12±16.29 U/L. There was no significant difference between groups (P>0.05) (Table 2). Also, no significant difference in ALT level were observed between 6 month and 12 month in each groups (P>0.05). But, ALT level in 6 patients (35.3%) of ADV group, 14 patients (73.7%) of LAM group, in 3 patients (37.5%) of TDF group and 4 patients in group C (50%) were back to normal range. This results show Lamivudine can be more effective than Adefovir Dipivoxil (P=0.042) and Tenofovir Disoproxil Fumarate (P=0.028) to normalized serum ALT level after 12 month antiviral therapy.
Virologic and serologic response

Before medication, mean of HBV DNA copy in ADV, LAM and TDF groups were 53683470±2726350IU/ml, 71755908±27059394IU/ml and 63624869±29142710 IU/ml, respectively. There was no significant difference between 3 groups (P>0.05). After 6 month antiviral therapy, mean of HBV DNA was change to 95538688±64670764IU/ml, 94026070±62192807 IU/ml and 451570±320490 IU/ml in ADV, LAM and TDF groups, respectively.

At this stage, there were no significant differences exist between groups (P>0.05). Also, after 12 month medication, mean of HBV DNA copy were 31089155±25085083IU/ml, 627242692±55986449 IU/ml, 4235±3624IU/ml and 2237823±4315734IU/ml in ADV, LAM, TDF and C groups (Table 2). In the end of study, one patient in ADV group, one patient in LAM group and 3 patients in TDF group had undetectable level of HBV DNA. There was no significant difference were observed between groups (P>0.05). Also, in the within each groups was no statistical significant difference Between HBV DNA level before and after treatment (P>0.05) except TDF group. In this group, HBV DNA level after 6 month therapy was significantly lower than that’s primary level (P=0.044).

At the beginning of treatment, 5 patients (26.3%) in ADV group, 3 patients (15%) in LAM group and 6 patients (31.6%) in TDF group had HBeAg positive test (P>0.05) (Table 2). HBeAg in two patients ADV and two patients of TDF group were negative after 12 month medication. There was no significant difference was observed between groups and within each group before and after treatment (P>0.05).

Responses after 12 month treatment

Response to Treatment defined by protocol (HBV DNA level<1000 IU/ml and alanine aminotransferase level less than 1.25 times the upper limit of normal). According to this defined, 2 patient in the Adefovir Dipivoxil group (10.5%), 7 patients in the Lamivudine group (35%), 5 patients in the TDF group (45.5%) and 2 patients in group C (25%) had response to treatment. There was no significant difference between groups (P>0.05).

Discussion

It has been estimated that approximately 350 to 400 million people are chronically infected with hepatitis B in the worldwide.3 Approximately, one third of these people does not control their disease permanently and therefore require treatment to reduce the risk of developing of cirrhosis, fibrosis and hepatocellular carcinoma.22-24 The main goal of treatment for chronic hepatitis B is to achieve sustained suppression of HBV transcription and reduced liver disease to prevent progression of long-term complications of this disease.25 In patients, drug selection is based on the patient's condition, medication effectiveness, and availability of a specific drug or drug resistance to anti-viral medications as well as cost of drugs.26 On the other hand, the response to anti-viral therapy for different drugs are not equal and various factors involved in the outcome of drug therapy such as age, sex, duration of treatment, viral genotype, HBeAg positivity, baseline HBV DNA and baseline ALT.27 The purpose of this study is evaluation of patient’s response to anti-viral drugs therapy (ADV, LAM and TDF) and determines the efficacy of these procedures for finding of suitable therapeutic method.

The gender and mean age of all patients in this study was same to other studies.15,23,28 Same our study, Pradeep et al.,29 in their study expressed that 6 month medication by Adefovir Dipivoxil and Lamivudine can significantly decrease ALT level and viral load in HBV patients. In their study, no significant difference was observed between Adefovir Dipivoxil and Lamivudine to ALT level and HBeAg seroconversion after 6 month therapy,30 but we have a significant decrease ALT level in Lamivudine group after 6 month. Furthermore, in this study after 12 month, Lamivudine significantly better than Adefovir Dipivoxil and Tenofovir Disoproxil Fumarate was able to normalized ALT level. In the other studies shown that ALT normalization by Lamivudine is variable between 41 to 81.8%.10,11,27

We have only one patient in ADV (5.2%), one patient in LAM group (5%) and 3 patients in TDF group (15.7%) that had undetectable HBV DNA level. In the Pradeep et al.,29 study, undetectable HBV DNA level was observed in 4 patients of ADV group (26.7%) and 2 patients in LAM group (13.3%). Also, in consistent with present study Peters MG et al.,31 showed the same undetected level of virus in patients whom received TDF.

Our study revealed that the frequency of loss of HBeAg (seroconversion) for TDF, ADV and LAM was 19.1%, 8.7% and zero, respectively. These results showed that TDF has been associated with higher rates of HBeAg diminishing; however there is not a statistical significant difference between the drugs. Likewise with our research, Marcellin et al.,11 study showed that HBeAg negative amount was 21% for ADV and was 18% for TDF which demonstrated that efficacy of TDF is in accordance to our study. We have not any seroconverted patients in Lamivudine group. Against with our study, other study reported seroconversion by Lamivudine medications between 16 to 22 percent.13,15,29 In other studies by Nelson M et al.,32 Schmutz G et al.,33 Stephan C et al.,34 Jain MK et al.,35 and Benhamou Y et al.,36 have examined the effect of TDF in patients who suffered from both HIV and HBV simultaneously and showed that the frequency of loss of HBeAg effects of TDF can vary between 6 to 40 percent.

Conclusion

Our study results show Lamivudine was superior than Adefovir Dipivoxil and Tenofovir Disoproxil Fumarate to normalization hepatic function. But in other hand, Tenofovir Disoproxil Fumarate better.
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than others are able to reduce viral load and HBeAg seroconversion, but not significantly. However, it seems to reach a more definitive results of clinical trials with larger sample sizes are needed.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

References


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