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ORIGINAL ARTICLE

The Effect of Lamivudine Oral Therapy in the Treatment of Hbeag Positive Patients

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ABSTRACT

AIM: Lamivudine treatment achieves good virological and biochemical responses in chronic hepatitis B (CHB) patients, this study aimed to determine the effect of lamivudine oral therapy 100mg/day, in HBeAg positive Egyptian patients after 6 months of treatment.

METHODS: This study included 40 CHB Egyptian patients (33 males and 7 females) whom HBeAg was positive. Investigations included: Pre-treatment liver profile, hepatitis B serology, HCV antibodies by ELISA and HBV-DNA-PCR levels .After six months of lamuvudine therapy(100mg/d), liver profile, HBeAg status and PCR levels were measured..

RESULTS: HBV-DNA-PCR became undetectable in 21 patients (52.5%), reduced in 16 patients (40%) and increased viremiawas detected in 3 patients (7.5%). Seroconversion occurred in 11 patients (27.5%) and rest of patients who were 29 (72%) remained positive and significant decrease and normalization of transaminases was achieved in all patients .

CONCLUSION: Lamivudine therapy achieved good results related to PCR levels, normalization of transaminases as well as its tolerability and absence of undesirable effects.

Key words: Chronic Hepatitis B; HBeAg positive; Lamivudine – Egypt-PCR

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INTRODUCTION

Approximately one third of the world's population has serological evidence of past or present infection with HBV[1]. Studies in the Middle East show the prevalence of HBsAg to range from 3% to 11% in Egypt[2]. HBV-related end stage liver disease or HCC are responsible for over 1 million deaths per year and currently represent 5–10% of cases of liver transplantation[3]. The aim of treatment of chronic hepatitis B is to achieve sustained suppression of HBV replication and remission of liver disease. Approved Antiviral Therapies for CHB patients include Standard IFN, Peg IFN & Nucleoside/ Nucleotide analogues (NUCs) including Lamivudine, Adefovirdipivoxil, Tenofovir, Entecavir&Telbivudine[3]. Lamivudine is the most widely used drug in treatment of hepatitis B due to its availability and cheap price in addition to less side effects[4]. This study aims at assessmentof the effect of Lamivudine oral therapy in HBeAg – positive chronic hepatitis B Egyptian patients after 6 months of treatment.

METHODS

This is a retrospective study done on 40 chronic HBV patients in the National Hepatology& Tropical Medicine Research Institute in Egypt.

Patients were (HBeAg +ve) and received Lamivudine oral therapy

(100 mg/day) for 6 months (from March till August 2011) to assess the virological (undetectable HBV-DNA by real-time PCR assay within 48 weeks of therapy) and biochemical (Normalization of the serum ALT level) responses[5].

Table 1 Patients received treatment according to followinginclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Males and females patients ⩾ 18 years old	Age < 18 or > 60 years
Positive HBV viremia by PCR	Negative HBV viremia
Positive serology for HBsAg for more than 6 months	Positive serology for HCV.
Compensated chronic HBV liver disease	Patients having stigmata of liver cell failure as in such population, Entecavir or tenofovir are much safer and more effective[6].
HBeAg positive patients	Patients who have received prior anti-viral therapy for HBV. Exclusion of steroids and/or immunosuppressive drugs administration. Patients with organ transplants.

All patients were subjected to:

- Through history taking and clinical assessment for manifestation of liver cell failure.
- History of drug intake (with special reference to parenteral anti-Schistosomaltreatment), surgical operations, blood transfusion, dental procedures, cigarette smoking and alcohol consumption.
- Full laboratory evaluation to assess the patient's condition before starting treatment, including:
- Liver biochemicalprofile :

ALT(alanine aminotransferese), AST (aspartate aminotransferese), Bilirubin level (total, direct and indirect), Serum albumin, PT, PC% (prothrombin time and concentration),and INR (international normalized ratio).

• Kidney function tests :Serum urea and creatinine.

• HBV Profile:

- HBsAg and HBeAg (detected by ELISA).
- HBV-DNA-PCR (quantitative), following the World Health Organization international standard for HBV DNA nucleic acid amplification techniques.

• HCV antibody (by ELISA).

• Alpha feto-protein.

- Abdominal Ultrasound: to evaluate liver echopattern, presence of ascites, hepatic focal lesions or portal vein thrombosis.

Assessment after 6 months of treatment included:

- Liver biochemical profile: (ALT, AST, Serum albumin, and Bilirubin level).
- Kidney function tests (serum urea and serum creatinine).
- HBV-DNA-PCR (quantitative).
- HBeAg .
- Abdominal ultrasonography.

Statistical analysis

Patient's quantitative data were expressed by mean and standard deviation (SD). They were compared by paired and unpaired t-student test. Non parametric correlation was done to correlate non parametric quantitative data. Qualitative data were expressed by number and percent. They were compared by Chi-square test and Wilcoxon signed rank test. In all test, p-value was considered significant if less than 0.05.

RESULTS

The present study is a retrospective study done on 40 chronic HBV patients (HBeAg +ve) in the National Hepatology& Tropical Medicine Research Institute in Egypt, who were recruited from March 2011 till August 2011.

They were 33 males (82.5%) and 7 females (17.5%), and their mean of age was 31± 8.08 years.

The mean of ALT, AST, and HBV-DNA-PCR before treatment, was 57.83 ±34.6 (U/L), 50.48 ±25.2 (U/L), and 50778340 ±113256132(IU/ml) respectively.

After analyzing the entire patients' data, with regular oral intake of lamivudine 100mg once daily for 6 months, the statistical analysis revealed that lamivudine was well tolerated among all patients, and that 11(27.5%) patients had seroconversion (shifted from HBeAg positive to HBeAg negative after 6 months treatment), while 29 (72.5%) patients remained HBeAg positive.

Table 2 shows the levels of the starting ALT, AST and PCR in relation to final results of seroconversion.All the results were of non statistical significance.

Also there was no statistical significance as regards age and seroconversion, the mean age of HBeAg negative patients was 33 ±8.56 years old, while that of patients who remained HBeAg positive was of 30±7.82 years.

Table 3 shows the levels of ALT, AST and PCR post treatment in relation to final results of seroconversion. There was a decrease in their values in comparison to those before treatment; However, All the results were of non statistical significance as p values were 0.199, 0.305, and 0.244 respectively.

PCR levels obtained after 6 months of treatment showed that 21 patients (52%) achieved virological response, 16 patients (40%) showed reduced level of PCR, while 3 patients had increased HBV-DNA-PCR level (7.5%) that may be attributed to primary drug resistance however this was not assessed in our study.

Among those (21 patients) who showed virological response, 6 patients (28.57%) showed seroconversion, while 15 (71.42%) remained unchanged.

The changes in the PCR levels, ALT and AST pre and post treatment were statistically significant, with p values of (P=0.02, 0.0001, and <0.01 respectively), which proves the general improvement in the patients PCR results and liver biochemical profile post treatment with lamivudine, as shown in table 4.

Table 2 Comparison between the starting ALT, AST and PCR levels in relation to final results of seroconversion.

	HBeAg	Mean ±SD
ALT/40 U/L	Negative	57.73 ±39.85
	Positive	57.86±33.23
AST/40U/L	Negative	49.55±30.13
	Positive	49.55±30.13
PCR I.U	Negative	15310563±18606880
	Positive	6423163513±0617026

Table 3 AST, ALT and PCR results after 6 months of treatment in relation to seroconversion.

	HBeAg	No. of Patients	Mean ±SD
ALT/40 U/L	Negative	11	41.55±19.577
	Positive	29	34.07±14.731
AST/40U/L	Negative	11	34.64 ±12.714
	Positive	29	29.90 ±12.940
PCR I.U/mL	Negative	11	3778132±5203285
	Positive	29	595562±1115587

Table 4 Comparisonbetween PCR, ALT and AST levels before and after 6 months treatment among studied group.

	Before (Mean±S.D)	After (Mean±S.D)
PCR	92017299±153508	1433081±2998074
ALT	57.83±34.639	36.13±16.294
AST	50.47±25.199	31.20±12.894

DISCUSSION

The present study was conducted to describe the effect of lamivudine oral therapy 100 mg daily, as an antiviral treatment in HBeAg positive patients after 6 months of therapy.

In our study, Lamivudine showed good clinical tolerability in the studied patients as well as good antiviral efficacy, this was in accordance with the study done by Allam *et al*[7] in 2012, and by Chan in 2007[8], who stated that lamivudine therapy is of potent efficacy.

As regards the epidemiological features of our patients, there was male sex predominance in the studied population as they were 33 males compared to 7 female patients. This came close to what was mentioned by El-Zayadi in 2007[9], who reported the high prevalence of chronic hepatitis B among males with a male: female ratio of (9: 1) and also, came closer to the study conducted by Osman in 2011[10], where there was male sex predominance.

In our study, the mean age of the studied population was 31±8 years, withno significant difference regarding the age and the post treatment responses.This was in disagreement with Bonino et al. (2007)[11],who investigated the effect of pre-treatment factors on post-treatment responses on 518 patients treated with Peg Interferon alpha-2a and/or lamivudine and revealed that younger age, female gender were defined as significant predictors of initial biochemical and virological response at 24 weeks of treatment. On the other hand, a study that was done by Nakamuta *et al*[12] In 2005, agreed with us, as they evaluated 249 patients with chronic hepatitis B and they found that the age was an independent factor for the virologicalresponse.

Regarding the seroconversion, we found that 11(27.5%) patients had seroconversion, while 29 (72.5%) patients remained unchanged with non significant value.Our result was in agreement with Allam *et al*[7], 2012, who mentioned that 25% of the HBeAg positive patients showed seroconversion on lamivudine oral treatment, but they differ from us in the duration of treatment which remained for 1 year.

Also our work went with Robert and his colleagues, in 2006[13], who determined that seroconversion occurred in only 20% of the studied group of patients, but they differ from us in number of the studied patients which was 715 patients and their treatment lasted for 52 weeks.

Our findings were not agreeing with Dienstag and co-workers, 2003[14], who had reported that lamuvudine inducedseroconversion ranged from 70-90% in western countries. The study included 401 HBeAg positive patients with LAM 100mg/day for at least 24 weeks. Also they mentioned that as long as the duration of treatment lasted, the seroconversion rates increase.

IIn our study we were mainly minded with the quantitative HBV-DNA-PCR test results of our patients prior to treatment and after 6 months of continuous therapy with lamuvudine 100mg/day to detect the effect of therapy on the virological response. Prior to lamivudine therapy the DNA-PCR level was 92017299±153508 IU/mL and 1433081 ± 2998074 post treatment, with a significant results indicating general improvement in the patients HBV-DNA-PCR levels post treatment for 6 months.

Our results went with the data of Chang *et al*[15] in 2006, who declared that lamivudine suppresses serum HBV-DNA-PCR to undetectable levels in almost all patients with a median of treatment up to 48 weeks of continuous treatment, reaching about 36% with a significant *p*-value (<0.001), but they differs with us in the duration of treatment.

After 6 months of treatment with lamivudine, we had a significant reduction in ALT and AST with *p* value (<0.001), with mean of ALT and AST levels equal to 41.55±19.577, 34.64±12.714 respectively in patients who had seroconversion.This reflected that significant biochemical response had occurred as a result of Lamivudine therapy. This went hand in hand with the study of Osman in 2011[10], who reported that transaminases was normalized in 71% of the patients with pretreatment elevation and, also, went in agreement with Papatheodoridis *et al*[16] in 2005, who reported that biochemical remission with Lamivudine therapy reached 84% at 12 months.

These results matched also with Jules *et al*[17] in 1999, who declared that serum aminotransferase levels returned to normal and remained so in his study after 52 weeks of treatment.

Also, this went with the study done by Robert *et al*[18] in 2006, who proved lamuvudine effect in ALT normalization in about 60% of patients with a highly significant value (*P*=0.02).

On the other hand, we didn't match the opinion of George *et al* (2005), who declared that there is ALT increase after lamivudine monotherapy, and this might be attributed to the development of resistance and there was also a difference between us in the duration of therapy that was 72 weeks of continuous treatment.

In conclusion, we can say that Lamivudine therapy is effective in HBeAg positive CHB Egyptian patients and can improve the patient's outcome related to PCR levels and liver enzymes.

CONFLICT OF INTERESTS

The Authors state that they have no conflict of interest (COI).

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