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Outcome of Lamivudine Therapy in Children with Chronic Hepatitis B Virus in Children Welfare Teaching Hospital

Rabab Farhan Thajeel Al-qaysi*, Dhiaa H AL-Baldawi and Ali Kareem Saad

Department of Pediatric Gastroenterology and Liver Diseases, Children Welfare Teaching Hospital, Medical City, University of Baghdad, Iraq

Abstract

Background: Hepatitis B is a major cause of liver disease worldwide, can cause acute and chronic disease, ranking as a substantial cause of cirrhosis and hepatocellular carcinoma. A vaccine against hepatitis B available since 1982, Hepatitis B runs more serious in children due to its chronic behaviour in more than 85%of affected ones.

Patient and method: An observational retrospective cohort study, since 1st August/2015 to 1st February/2016. The patients were gathered from the gastroenterology and liver disease clinic/Child Welfare Teaching Hospital in Baghdad. Among 71 patients with chronic hepatitis B regularly followed up, a total of 32 patients on lamivudine therapy were selected for this study, the patients files were evaluated retrospectively and then followed up during their scheduled visits every 3-6 months. All patients underwent detailed history and physical examination, sent for full blood picture, liver function tests, viral panel and abdominal ultrasound.

Results: Mean ages of patients were 7.8 ± 3.87 years ranging from 2 to 14 years, male were predominating with 71.9:28.1 ratio. The majority of patients with leukemia 31% on chemotherapy and 38% finished chemotherapy, 9% thalassemia, 6% haemophilia and others accident 17%; viral load show significant decrement in Lamivudine receiving patients on chemotherapy with p value <0.001, While in those patients who were not on chemotherapy p value was 0.001. In Lamivudine receiving patients who were on chemotherapy (n=10): 20% and 40% patients with undetectable viral load (HBV DNA –ve) after 6 months and 1 year respectively had significant P value at border line 0.048; and 10%, 30% with seroconversion (HBeAb) after 3 months, 6 months respectively; and 80% normalization of ALT over I year period. While Lamivudine receiving patients with chronic HBV not on chemotherapy (n=22) : had undetectable viral load significant P value 0.026 over I year period; and there are only 9 of 22 had HBeAg +ve, 4 of 9 with seroconversion (HBeAb) after 6 months; while influence on ALT show 81.8% normalization over I year period.

Conclusion: Lamivudine therapy is an effective drug and had a significant effect on children with chronic hepatitis B, This effect was clear on HBV-DNA disappearance, and ALT normalization, HBeAg seroconversion, this was very clear on both groups of children immune compromised and immune competent. It is recommended for all children with chronic hepatitis B who are on chemotherapy to prevent reactivation of the virus.

Keywords: Lamivudine therapy; Hepatitis B; Treatment; Analysis

Introduction

Hepatitis B is a major cause of liver disease worldwide, with a substantial cause of cirrhosis and hepatocellular carcinoma [1]. It is estimated that over 350 million people have chronic infection with HBV [2]. The prevalence of chronic HBV varies widely based on geography. Africa, Asia, and the Pacific disproportionately comprise the largest proportion of individuals with chronic infection, in these endemic areas the rate of HBsAg seropositivity is over 8% [3], non-endemic regions such as North America and Western Europe, the distribution of chronic infection with HBV may reflect geographic immigration patterns of populations [4]. Eight genotypes of HBV have been identified (A through H). The global distribution of genotypes varies by geography; [5,6] risk factors for HBV infection include acquisition by intravenous drugs or blood products. In children, the most important risk factor for acquisition of HBV remains perinatal exposure to an HBsAg-positive mother [7] chronic HBV infection, defined as being positive for HBsAg for longer than 6 months [8]; some individuals fail to mount an adequate immune response, leading to chronic infection [9]. Hepatitis B virus infection becomes chronic in approximately 90 per cent of infants infected at birth, 20 to 50 per cent of children infected from one to five years and one to 10 per cent of individuals infected as older children and adults [10]. Individuals with chronic infection may present in one of four phases of infection: (1) immune tolerant, (2) immune active (hepatitis B early antigen [HBeAg] positive chronic HBV), (3) reactivation (HBeAg negative chronic HBV) or (4) the inactive carrier state treatment usually needed in cases of immune active and reactivation cases [11,12]. Not all patients go through every phase. If chronic infection is established, the spectrum of illness ranges from the healthy carrier state to all of the sequela of chronic hepatitis [11]. Individuals who are immunosuppressed or have an underlying chronic illness are at increased risk of developing chronic infection and reactivation. The serologic markers of hepatitis B are critical regarding the physiology and course of the disease. That include HBsAg and HBeAg are the two antigens and HBsAb, HBcAb, and HBeAb also virus itself can be measured in the serum [13].

Close monitoring is key treatment of chronic infection is in evolution; no one drug currently achieves consistent, complete eradication of the virus [14]. Treatment is geared toward reducing viral load until serum HBV DNA levels become undetectable by a PCR assay, achieving durable HBeAg seroconversion and normalization

***Corresponding author:** Rabab Farhan Thajeel Al-qaysi, Department of Pediatric Gastroenterology and Liver Diseases, Children Welfare Teaching Hospital, Medical City, University of Baghdad, Iraq, Tel: +9647711681191; E-mail: farhan_rabab@yahoo.com

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of ALT level [15]. Interferon alfa exerts an antiviral effect on HBV infection through inhibiting synthesis of viral DNA and exaggerates the cellular immune response against hepatocytes infected with HBV Thus, induces an early reduction of HBV replication [16].

Peginterferon-a2 has largely replaced conventional IFN. PEG-IFN is administered ubcutaneous once weekly, resulting in a relatively continuous drug exposure during the dosing interval [17]. Lamivudine was the first oral antiviral therapy approved for treatment of hepatitis B, it is work into growing DNA chains, causing chain termination [18], also reverse the T cell hypo responsiveness to hepatitis B viral antigens [19,20].

Patient and Method

An observational retrospective cohort study, since 1st August/2015 to 1st February/2016. The patients were gathered from the gastroenterology and liver disease clinic/Children Welfare Teaching Hospital in Baghdad from (2010-2015) where they come for their treatment and follow up.

Among 71 patients with chronic hepatitis B regularly followed up, a total of 32 patients on lamivudine therapy were selected for this study, the rest 39 cases were excluded because they were on another mode of antiviral therapy. All the 32 patients enrolled in this study had chronic hepatitis B infection, was hepatitis B surface antigen (HBsAg) > 6 months.

The patient's files were evaluated retrospectively and then followed up during their scheduled visits every 3-6 months. Most of them were referred from hemato-oncological department where they were treated for their primary illnesses. As they received multiple sessions of blood products transfusions.

Inclusion criteria

Patients had chronic hepatitis B virus, patients on lamivudine therapy.

Patients excluded from this study

Patients with signs of concomitant infection with human immunodeficiency virus or hepatitis C virus, Patients with other causes of liver damage (such as alpha 1-antitrypsin deficiency, Wilson's disease, and autoimmune hepatitis). Patients with chronic hepatitis B who already received any other mode of antiviral therapy previously were excluded. Patients with non-compliance to treatment. Data was gathered by using patient records from the gastroenterology and liver diseases out patients clinic in the children welfare teaching hospital/ Baghdad. Information taken included: Full history and physical examination., Demographic data, by age and gender, Associated disease (leukemia, hemophilia, thalassemia).

Laboratory investigations

Complete blood count, liver function tests, abdominal U/S, (viral panel and viral load were done but not as frequently as needed, this is related to its unavailability in hospital and being very costly in outside labs) and liver biopsy was not done for many reasons mostly due to reluctance of family to any invasive procedures. Venous blood samples were collected from patients and were sent for biochemical analysis (Liver function tests) normal limit for alanine transferase (ALT) 20 IU/ ML, complete blood count. Immune assay by ELISA to detect Viral markers (HBsAg, HBsAb, HBeAg, HBeAb, HBcAb). Real time PCR procedure to detect Viral load of HBV_DNA quantitatively, (>2000 IU/ml detected viral load and <2000 IU/ml undetected viral load.

Statistical Analysis

ANOVA analysis was used to assess differences in the mean of the log of viral load, and Friedman ANOVA used when the data did not meet a normal distribution. Mann Whitney test used to analyze the differences between two groups when the data did not follow the normal distribution. Chi square analysis was used to analyze the association between discrete variables. SPPS 20 software package used to analyzed the data.

Results

Mean age of patients were 7.8 ± 3.87 years ranging from2 to 14 years, male were predominate with 7.2:2.8 ratio. Table 1 shows that the majority of patients were with heamatological diseases, (malignancies, thalassemia and hemophilia), the majority were leukemic patiens 31% on chemotherapy and 38% finished chemotherapy, 9% thalassemia, 6% hemophilia and 17% had unknown causes.

Table 2 shows the Log of viral load in immuncomprised patients with chronic HBV on lamivudine therapy. Viral load show significant decrement in patients on chemotherapy with p value <0.001, While in those patients who were not on chemotherapy p value was 0.001

Table 3 shows Lamivudine receiving patients who were on chemotherapy (n=10); 2/10 (20%) and 4/10 (40%) patients with undetectable viral load (HBV DNA –ve) after 6 months and 1 year respectively had significant P value at border line 0.048; also the table shows 1/10 (10%) and 3/10 (30%) patients with seroconversion achievement (HB eAb) after 3 months, 6 months and 1 year respectively.

Table 4 Shows Lamivudine receiving patients on chemotherapy (n=10) with influence of Lamivudine on ALT over 1 year period: ALT were at baseline ≤2 UNL, 30% and 50%, 70%, 80% at 3 months, 6 months, 1 year respectively with significant P value 0. 033.

Table 5 shows Lamivudine receiving patients with chronic HBV who were not on chemotherapy (n=22); 2/22 (9.11%), 6/22 (27.3%) and 8/22 (36.4%) patients with undetectable viral load (HBV DNA –ve) after 3 months, 6 months and 1 year respectively and had significant P value 0.026; also table show only 9/22 patients (7/22 with/HBeAg negative & 6/22 had no viral panel at baseline due to limitations causes) had HBeAg +ve: 2/9 and 4/9 patients with seroconversion (HBeAb) after 3 months, 6 months and 1 year respectively.

Table 6 shows Lamivudine receiving patients with chronic HBV (n=22); with the influence of Lamivudine on ALT over 1 year period: ALT were at baseline ≤2 UNL (40.9%), 72.7% at 3 months and 81.8% at 6 months, 1 year respectively with significant P value 0.031.

Discussion

This study included 32 pediatric patients with chronic hepatitis B virus, their mean age was 7.8 ± 3.87 years, ranged from 2-14 years; male were predominate with 7.2:2.8 ratio. In comparison with a study that was done in Egypt by El-Sayeda et al. [21], in which 10 children

Variables	No.	Percentage
Leukemia Chemotherapy	10	31%
Finished chemotherapy	12	38%
Thalassemia	3	9%
Hemophillia	2	6%
Unknown	5	17%

Table 1: Demographic characteristics of patient with chronic HBV at baseline.

Log of viral load	Baseline	3 months	6 months	1 year	P value
Hematological malignancy on chemotherapy	6.68 ± 0.94	6.57 ± 0.6	4.67 ± 0.98	3.33 ± 0.99	<0.001
Others without chemotherapy therapy	6.37 ± 1.27	5.32 ± 1.32	4.26 ± 1.39	3.37 ± 0.9	0.001

Table 2: Log of viral load response on patients with malignancies who were on chemotherapy and patients with chronic HBV without chemotherapy, both groups were on lamivudine therapy over 1 year duration.

Variables		Baseline No.%		3 months No.%		6 months No.%		1 year No.%		P Value
HbeAg Status	HBeAg +ve	10	100	9	90	7	70	7	70	0.27
	Seroconversion	0	0	1	10	3	30	3	30	
Virus status	HBV DNA +ve	10	100	10	100	8	80	6	60	0.048
	HBV DNA –ve	0	0	0	0	2	20	4	40	

Table 3: Seroconversion state after using lamevudin (HBeAb), and achieving undetected viral level HBV DNA (-ve) in patients who received Lamivudine while being on chemotherapy (n=10).

Variables		Baseline% No.		3 months% No.		6 months% No.		1 year% No.		P value
ALT	≤2 UNL	3	30	5	50	7	70	8	80	0.033
	≥2 UNL	7	70	5	50	3	30	2	20	

Table 4: Lamivudine receiving patients on chemotherapy (n=10).

Variables		Baseline% No.		3 months% No.		6 months% No.		1 year% No.		P value
HBeAg Status	HBeAg +ve	9	40.9	7	31.8	5	22.7	5	22.7	0.256
	Seroconversion	0	0	2	9.11	4	18.9	4	18.9	
Virus status	HBV DNA +ve	22	100	20	90.9	16	72.7	14	59.1	0.026
	HBV DNA –ve	0	0	2	9.11	6	27.3	8	40.9	

Table 5: Show influence of lamivudine on seroconversion (HBeAb) and undetected HBV DNA (-ve) on patients with chronic HBV, Not on chemotherapy (n=22).

Variables		Baseline No.%		3 months%		6 months%		12 months%		P value
ALT	≤2 UNL	9	40.9	16	72.7	18	81.8	18	81.8	0.031
	≥2 UNL	13	59.1	6	27.3	4	18.2	4	18.2	

Table 6: Shows Lamivudine receiving patients with chronic HBV with influence of Lamivudine over 1 year period from treatment, Patients who were Not on chemotherapy (n=22).

(7:3 M:F; median age: 9.8 years) undergoing chemotherapy for hematological malignancies and suffering from immunosuppressive-induced hepatitis B virus reactivation, were treated concurrently with lamivudine for up to 18 months. In another study done by Stefan et al. [22], in which 16 children were studied, and were treated with lamivudine mean age was 13.6 ranged from 2 to 17.6 years.70% of our patients were males, which agrees with the El-Sayeda et al. [21] study in which 7/3 patients (70%) were males while in the study done by Stefan et al. [22] 9/16 patients (56%) were males.

This study shows 10 patients with hematological malignancies on chemotherapy who had chronic hepatitis B virus, they were on lamivudine therapy, after 6 months 20% (2/10 patients) and after 12 months 40% (4/10 patients) of them had undetectable hepatitis B viral load, these results agree with the study done in Egypt by El-Sayeda et al. [21], in which 10 children undergoing chemotherapy for hematological malignancies, were treated concurrently with lamivudine for up to 18 months period; 8/10 (80%) were HBV-DNA–ve this difference in number of patients with undetected viral load is mostly attributed to the longer duration of treatment and follow up by the mentioned study [21]. In another study which included adult patients, that was done in Greece by Vassiliadis et al. [23], in which Ten hepatitis B virus carriers with hematologic malignancies were included in the study; seven were HBsAg positive, and six had detectable HBV-DNA levels, After a median follow up of 15 months from administration of lamivudine during the course of chemotherapy, no hepatitis B reactivation was observed. HBV-DNA levels were decreased in all 6 patients who had had detectable HBV-DNA at baseline. This study agreed with this study that the viral load decreased over 1 year period from 6.68 ± 0.94 to 3.33±0.99 had significant p value<0.001. Ten patients with HBeAg positive at baseline; at 3 months 1/10 (10%) and at 6 months 3/10 (30%) of patients virological response has become HBeAg negative (i.e. seroconversion), these results agree with the previous study done in Egypt by El-Sayeda et al. [21]; HBeAg+ve seroconversion occurred in 4/9 (44.4%).

In this study the 10 patients showed normalization of serum aminotransferase levels after a period of treatment and this result was compatible with El-Sayeda et al. [21].

The current study shows the 22 patients with chronic hepatitis B virus Without chemotherapy who were on lamivudine therapy, after 3 months 2/22 patients (9.11%) and after 6 months 6/22 patients (27.3%) and after 1 year 8/22 (40.9) of them had undetectable hepatitis virus, all these changes were with significant (p value 0.026); mean viral log decrease by 3 logs after 12 months (6.37 ± 1.27 to 3.37 ± 0.9 mean log10 ± SD), these results agreed with other studies, in multicentre double blinded placebo control trial published in new England journal of medicine done by Jonas et al. [24] they studied 191 children who received lamivudine and 97 patients who received placebo for about 52 weeks, the rate of virologic response at week 52 was higher among children who received lamivudine than among those who received placebo (23 percent vs. 13 percent, P=0.04).

In Korea a study was done by Koh et al. [25] in which 60 children were studied, they were on lamivudine therapy for chronic hepatitis B showed undetected HBV-DNA were 53% after 1 year from treatment.

This study shows that 9 out of the 22 patients with HBeAg positive at base line had HBeAg +ve: 2/9 (22.2%) and 4/9 (44.4%) patients with virological response becoming HBeAg negative (i.e. seroconversion),

these results agreed with Stefan et al. [22], in which 50% of a group of patients responded to lamivudine had HBeAg seroconversion, in the korean study done by Koh et al. [25] seroconversion rates of HBeAg were 42%. While in the previous study, Jonas et al. [24] Lamivudine therapy was well tolerated and was also associated with higher rates of seroconversion from hepatitis B e antigen to hepatitis B e antibody 42/191 patients (26%).

Conclusion

Lamivudine therapy is an effective drug and had a significant effect on children with chronic hepatitis B, This effect was clear on HBV-DNA disappearance, and ALT normalization HBeAg seroconversion, this was very clear on both groups of children immune compromised and immune competent. It is recommended for children with chronic hepatitis B who are on chemotherapy to prevent reactivation of the virus.

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