Trial of lamivudine in hepatitis B surface antigen carriers with persistent hepatitis B core IgM antibody

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ABSTRACT

Objective: The persistence of hepatitis B core immunoglobulin M (HBc IgM) antibody in hepatitis B surface antigen (HBsAg) carriers is a risk factor with hidden dangers and forecasts the existence of liver damage. A trial of lamivudine in such subset of carriers was carried out for the first time in this study.

Methods: A total of 62 HBsAg with hepatitis e antibody individuals (age range, 25-45 years) with persistent HBc IgM antibody were randomized to receive either 100 mg lamivudine (32/62) or placebo (30/62) daily for 6 months. The study was performed from June 2000 to October 2002. The carriers were regular attendees of the Virology Center in Mosul, North Iraq for follow up. Enzyme-linked immunosorbent assay technique was performed to detect the different hepatitis B virus markers.

Results: Among the lamivudine group, HBc IgM antibody seroclearance achievement rate was 81.3% and HBsAg seroconversion rate was 9.4% compared to 6.3% and 3.3% in the placebo group. Number of adverse clinical events were observed, but were of mild nature and tolerable by the participants who completed the study.

Conclusion: The trial of lamivudine in this subset of HBsAg carriers proved to be safe and efficacious. More studies are needed prior to recommending the drug for routine use on selected HBV carriers.

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Entering the new millennium, hepatitis B virus (HBV) infection continues to be a considerable health problem and chronic hepatitis B infection is a documented cause of serious liver diseases.[1] Chronic infection is divided into 2 phases based on the relative level of HBV replication. First, the high replicative phase that is characterized by the presence in the serum of hepatitis B e antigen (HBeAg) and HBV-DNA with high infectivity. Second, the relatively low replicative phase, which is characterized by the presence of hepatitis B e antibody (anti-HBe) and HBV-DNA in the liver but integrated into the host genome.[1,2] Those in the high replicative phase usually tend to have severe and aggressive chronic hepatitis, while those in the low replicative phase tend to have minimal or chronic hepatic changes.[1,2] Therefore, the first group of patients has received precedent attention and are the main candidates for different antiviral therapies. Meanwhile, the second group of patients is neglected to face their ambiguous fate. Chronic hepatitis B carriers are subjected to varying degrees of progressive liver damage exacerbation[3,4] mediated by T-cells with appearance of hepatitis B core immunoglobulin M antibody (anti-HBc IgM) marker,[5,6] which is a sensitive indicator of viral replication and disappears within 4-8 months after the acute stage.[7,8] Moreover, with the use of highly sensitive

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and specific serological assay methods, persistence and variations in the kinetics of this antibody is bewildering and frequently observed during different chronic hepatitis B infection states.[8,9] Therefore, all chronic forms of hepatitis B infection including the carrier states are potentially important clinically since they can develop or have liver damage with progression to serious consequences later in life.[10-13] Lamivudine (3TC), is the first orally administered nucleoside analogue antiviral agent that inhibits HBV replication. It is approved as a monotherapy or in combination with other antiviral agents for the treatment of chronic hepatitis B with HbeAg.[14,15] Lamivudine is preferred to interferon for the initial treatment of patients with chronic hepatitis B and for individuals with cirrhosis and high levels of viral replication.[16] Lamivudine seems to be safe and the suppression of viral replication achieved may be associated with substantial clinical improvement.[17,18] Emergence of a lamivudine resistance virus can develop during prolonged treatment.[15,19]

The main goal of treating chronic hepatitis B cases is to arrest the disease progression before irreversible damage to the liver is established. The use of this antiviral in chronic HBsAg/anti-HBe carrier forms is lacking and needs now to receive more spacious attention specially circulating virions with viral activity in these carriers are documented with the advent and development of the new DNA technologies.[10,11] In reality, a significant number of asymptomatic HBsAg/anti-HBe carriers with persistent anti-HBc IgM in this country were found to have different stages of liver damage documented by liver biopsy.[20] Therefore, a trial of lamivudine, for the first time, was carried out amongst such carriers with serological (anti-HBc IgM positive) and histological evidence of viral activity in Mosul, North Iraq.

Methods. A total of 62 HBsAg/anti-HBe individuals with persistent anti-HBc IgM (age range, 25-45 years) were randomized to receive either lamivudine (32/62) or placebo (30/62) for 6 months. The study was performed from June 2000 to October 2002. The carriers were regular attendees of Public Health Laboratory, Virology Center in Mosul, North Iraq for follow up. All participants were asymptomatic and gave verbal or written consent before screening and enrolling into the study. Both groups were reassured that they are taking the appropriate therapy and were followed up for one year. Each patient was evaluated and monitored for the efficacy and safety measures of the drug every 2 months individually. The main efficacy measurement proposed for the drug intake was anti-HBc IgM seroclearance and the therapy period was extended for up to 6 months in cases that showed disappearance of this marker before this period, aiming to declare the effect on HBsAg status after that. The lamivudine was discontinued in cases that showed seroclearance of both markers before 6 months. Patients compliance and well tolerability of the drug were also monitored during therapy intake and after its discontinuation. The clinical adverse events and abnormal biochemical laboratory data at each visit was registered. Hepatic assessment was performed through monitoring alanine aminotransferase (ALT) and bilirubin levels and clinically for jaundice as a signal of infection flare up or recurrence of hepatitis. Renal function was assessed by blood urea and creatinine clearance estimation. The participants were asymptomatic with normal liver biochemical tests. Enzyme-linked immunosorbent assay test was performed to detect different HBV markers. The study was utilized by using Biotest Kits (Germany) for HBsAg and anti-HBs and Hepanostika Kits (Organon Teknika, Netherlands) for HBeAg, anti-HBe, anti-HBc IgM and total anti-HBc. Coinfection with HCV or HIV were excluded by appropriate serologic tests.

Results. Initially 74 patients were enrolled in the study. Of 38 individuals labeled to receive lamivudine,

Table 1 - Efficacy measurements in lamivudine intake group compared to placebo intake group in chronic HBsAg/anti-HBe carriers with persistence anti-HBc IgM marker.

Parameters	**Lamivudine group (N = 32)**								**Placebo group (N = 30)**							
								Total								**Total**
Efficacy measurements	0	2	4	6	8	10	12*	**n (%)**	0	2	4	6	8	10	12*	**n (%)**
Anti-HBc IgM seroclearance	0	0	4	8	10	4	0	**26 (81.3)**	0	0	0	0	1	0	1	**2 (6.3)†**
HBsAg seroclearance	0	0	0	0	1	1	1	**3 (9.4)**	0	0	0	0	1	1	1	**1 (3.3)‡**
HBeAg reversion	0	0	0	0	0	0	0	**0 0**	0	0	0	0	0	0	0	**0 0**

*bimonthly follow-up, †p<0.001, ‡p=not specified.
HBc IgM - hepatitis B core immunoglobulin M, HBsAg - hepatitis B surface antigen, HBeAg - hepatitis B e antigen, anti-HBe - hepatitis B e antibody

32 patients succeeded to complete the study and 6 were withdrawn; 3 being intolerable to the adverse events, 2 due to lack of communication (travel outside the city), and one refused repeated blood sampling. Of 36 individuals labeled to receive placebo, 30 only succeeded to complete the study and 6 were withdrawn; 2 being intolerable to repeated blood sampling, and 4 due to lack of communication. The efficacy parameters of lamivudine trial in the studied population are shown in **Table 1**. After one year, the registered seroclearance rate of anti-HBc IgM in the lamivudine group was significant (81.3%, 26/32) compared to the rate observed in placebo group (6.6%, 2/30) and differ statistically ($p<0.001$). Meanwhile, the registered seroclearance rate of HBsAg in the therapy group (9.4%, 3/32) was notable but statistically insignificant compared to rate observed in the placebo group (3.3%, 1/30). In the lamivudine group, anti-HBc IgM disappeared in 4 cases in the 4th month, 8 in the 6th month, 10 in the 8th month, and 4 in the 10th month compared to 2 cases in the 8th and 12th months in the placebo group. Hepatitis B surface antigen seroconversion was detected in lamivudine group in 3 cases in the 8th, 10th, and 12th months compared to 2 cases in the 10th and 12th in placebo group. The seroclearance rates of both anti-HBc IgM and HBsAg markers were sustained during the study. Anti-HBe seropositivity was persisted in all carrier cases and reversion to HBeAg was not encountered. Anti-HBs marker was detected in 3 patients who developed HBsAg seroclearance in the lamivudine group and in the orphan case that showed disappearance of this antigen in the placebo group. The main adverse clinical events encountered in cases that completed the study in the lamivudine intake group are shown in **Table 2**. Dizziness (9.4%), headache (12.5%) generalized muscular aches (12.5%), and throat and nasal discomfort (15.6%) were the most distressing events but were tolerable by the participants. Jaundice was not observed among cases undergoing this study. Renal function tests were maintained within normal limits in all cases through out the study.

Table 2 - The adverse clinical events reported in lamivudine intake chronic HBsAg/anti-HBe carriers with persistence anti-HBc IgM marker.

Adverse events*	**n†**	**(%)**
Dizziness	2	(6.3)
Nausea and vomiting	3	(9.4)
Abdominal pain	3	(9.4)
Headache	4	(12.5)
Cough and chest discomfort	3	(9.4)
Throat and nasal discomfort	5	(15.6)
Generalized muscular aches	4	(12.5)

*these adverse events were mild and did not necessitate drug withdrawal.
†more than one adverse event was encountered in most patients.
HBsAg - hepatitis B surface antigen, anti-HBe - hepatitis B e antibody, HBc IgM - hepatitis B core immunoglobulin M

Discussion. The HBsAg carrier rate among adult normal Iraqi population was estimated to be 4% and the frequency of HBeAg and anti-HBe (among these group) was 20% and 65% in Baghdad City.[21] On the other hand, in Mosul City all tested blood donor carriers were found to be anti-HBe positive[22,23] and a significant number of them are persistently positive for anti-HBc IgM.[8,20] Furthermore, abnormal liver histology with ongoing hepatic damage was encountered in significant number of such carriers who underwent liver biopsy.[20] Thereby, the detection of this antibody is distressing and indicates hidden dangers and forecasts the existence of viral activity with ongoing liver damage either due to continual viral activity from acute stage or reactivation of their existing carrier stage.[5,6,20]

In this study, the detected seroclearance rates of anti-HBc IgM and HBsAg markers with sustained normalization of ALT levels among patients treated with lamivudine are interesting and notable compared to placebo group (**Table 1**). These parameters indicate good drug efficacy in this subset of chronic hepatitis B carrier forms. Albeit a number of adverse events were observed in treated patients who completed the study, but were of mild intensity and does not necessitate withdrawal from the study indicating good patient compliance and tolerability. Throat and nasal discomfort, headache, and generalized muscular aches were the prevailing adverse events registered (**Table 2**). Moreover, reversion to HBeAg status was conspicuously absent and no clinical or serological evidence of mutant strains emergence were observed. A handful of studies were performed in Eastern Asia and North America to study the efficacy of lamivudine as a monotherapy for treating a selected cases of chronic hepatitis B with HBeAg.[14,15,19] The drug was approved to be safe and efficacious with suppression of HBV replication, improved hepatic damage, and prevented progression of fibrosis. The antiviral response was defined as HBeAg seroconversion, decrease or undetectable serum HBV-DNA, and histologic improvement (as a decrease in necroinflammatory score).[14,15,19] Loss of HBsAg was detected in 2% of cases treated with lamivudine in the United States of America[15] and no cases in Asian patients.[14,19] The seroclearance rate of anti-HBc IgM as a risky marker and the HBsAg seroconverted rate in the treated patients in this study are encouraging compared to aforementioned studies. Since some cases showed early disappearance of this antibody, before 6 months, the manipulation in the timing and the dose may be needed in future studies. This study can open the door for the first time to use antiviral agents in subsets of

chronic HBsAg carriers, with serologic or histologic evidence of viral activity, in different countries where HBV infection is endemic and the burden of liver diseases is high.

In conclusion, a trial of lamivudine in this subset of HBsAg carriers proven to be safe and efficacious. More studies are need prior to recommending the drug for routine use on selected HBV carriers.

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