ORIGINAL RESEARCH PAPER

Biological Science

A STUDY TO DETERMINE FOLLOW-UP STRATEGY FOR DIFFERENTIATING A TRUE INACTIVE CARRIERS FROM CHRONIC HEPATITIS PATIENTS WITH HBEAG NEGATIVE BY THE HBV DNA CUTOFF VALUE

KEY WORDS:

Subhash Kumar Saw* Department of Biotechnology, Magadh University, Bodh Gaya, India. *Corresponding Author

MD. Mohammad Sohail Department of Biotechnology, Magadh University, Bodh Gaya, India.

Jainendra Kumar Department of Biotechnology, Magadh University, Bodh Gaya, India.

ABSTRACT

Background & Objective: As compare to true inactive carrier a significantly different prognosis generally observed in Patients with HBeAg-negative chronic hepatitis B (CHB). To differentiate this two condition accurately there are no reliable strategy. To determine follow-up strategy for differentiating a true inactive carriers from chronic hepatitis patients with HBeAg negative by the HBV DNA cutoff value.

Materials And Methods: We had enrolled potential inactive carriers who were consecutive untreated patients. This inactive carriers defined as HBV DNA < 2000 IU/mL, normal ALT levels, anti-HBe-positive and definitely HBeAg-negative. HBV DNA level to ≥ 2000 IU/mL was defined as the HBV reactivation. Patients whose HBV DNA levels remained at < 2000 IU/mL were classified as true inactive carriers and patients whose HBV DNA level to ≥ 2000 were classified as false inactive carriers during the first year.

Results: Among 112 inactive carrier (age, 48.3 ± 13.1 years) who were initially selected, 75 were males. As identified, 23.2 ± 7.9 IU/L and 359 ± 478 IU/mL were serum ALT and HBV DNA levels, respectively. In 24 patients there were a significant drop in HBV reactivation during the first year. Between true and false inactive carriers there were a significantly different ALT and HBV DNA levels. In patients, whose baseline HBV DNA level was ≥ 200 IU/mL as compare to patients whose baseline HBV DNA level was < 200 IU/mL, HBV reactivation developed more often during a follow-up of 354 ± 175 days.

Conclusion: From true inactive carriers to differentiate patients with HBeAg-negative CHB, HBV DNA level was useful tool. As per HBV DNA level of inactive carriers applied follow-up strategies need to vary.

INTRODUCTION:

In current senerio hepatitis B virus infection is considered as one of the biggest health care challenge across the globe specially in developing country like India [1]. For the diagnosis of acute or chronic HBV infection as an established serological marker HBV surface antigen (HBeAg) is the established serological marker used routinely and even this will play an important role for the surveillance of persons and screening of blood or organ donors [2]. By neutralizing antibodies a strong immunogenic response can induced by HBeAg. Within the major hydrophilic loop of HBeAg, between amino acids 124 and 147, main antigenic determinant ("a" determinant) is located [3]. A conformational changes in HBeAg was induced by mutations and natural variations.

Suppression of HBV replication and remission of hepatitis is indicated by loss of HBeAg in hepatitis B virus (HBV) [4,5]. Even in an HBeAg-negative patient, HBV could continuously or intermittently replicate as found during detecting HBV in the serum by the application of sensitive methods [6,7]. Homogeneous can not be termed for HBeAg-negative HBV carriers as this groups includes a wide range of patients which includes from inactive carrier to cirrhosis or aggressive HBeAg-negative hepatitis patients [8,9].

In HBV carriers with an HBV DNA level of ≥ 2000 IU/mL significantly higher risk are associated with both hepatocellular carcinoma and cirrhosis, as suggested by the recent trials [10-13]. for inactive carriers 2000 IU/mL is considered as HBV DNA cutoff leve as guided by the recent guidelines [14,15].

As compare to true inactive carrier a significantly different prognosis generally observed in Patients with HBeAg-negative chronic hepatitis B (CHB). To differentiate this two condition accurately there are no reliable strategy. To determine follow-up strategy for differentiating a true inactive carriers from chronic hepatitis patients with HBeAg negative by the HBV DNA cutoff value.

MATERIALS AND METHODS:

We had enrolled potential inactive carriers who were consecutive untreated patients. This inactive carriers defined as HBV DNA < 2000 IU/mL, normal ALT levels, anti-HBe-positive and definitely HBeAg-negative. HBV DNA level to ≥ 2000 IU/mL was defined as the HBV reactivation. Patients whose HBV DNA levels remained at < 2000 IU/mL were classified as true inactive carriers and patients whose HBV DNA level to ≥ 2000 were classified as false inactive carriers during the first year.

Inactive carrier state was determined by appearance of any clinical indications over three month for one year. At each visit HBV DNA levels were checked along with albumin, bilirubin and serum ALT.

Statistical softwere SPSS ver 13.0 (SPSS Inc., Chicago, IL, USA) were used to calculate statistical mesurements. Values were considered statistically significant when p value < 0.05.

RESULTS:

Among 112 inactive carrier (age, 48.3 ± 13.1 years) who were initially selected, 75 were males. Baseline characteristics was demonstrated in table 1.

Table 1: Baseline Characteristics Of HBV Carriers According To The Development Of Abnormal ALT Levels Or HBV Reactivation Within One Year

Parameters	All patients (No. = 112)	Normal ALT a group (No. = 102)	Abnormal ALTa group (No. = 10)	p value	True inactive carriers (No. = 89)	False inactive carriers (No. = 23)	p value
Age (years)	48.3 ± 13.1	49.2 ±13.1	43.6 ±10.3	0.121	49.1 ±10.1	45.9 ±10.5	0.316
Male (N%)	75 (67%)	68 (66.6%)	7 (70)	0.714	60 (67.4%)	15 (65.2%)	0.628

Diabetes (N%)	10 (8.9%)	9 (8.8%)	1 (10%)	0.944	9 (10.1%)	1 (4.3%)	0.295
BMI (Kh/m2)	23.2 ± 3.1	24.1 ± 3.1	25.3 ± 2.9	0.294	23.1 ± 2.9	22.9 ± 3.3	0.916
ALT (IU/L)	23.4 ± 9.1	23.4 ± 8.7	32.4 ± 8.1	<0.001	22.7 ± 9.3	26.1 ± 8.2	0.027
Bilirubin (mg/dl)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4	0.659	0.8 ± 0.4	0.8 ± 0.4	0.894
Albumin (g/dl)	4.3 ± 0.2	4.3 ± 0.2	4.3 ± 0.3	0.921	4.7 ± 0.4	4.7 ± 0.4	0.351
HBV DNA (IU/ml)	358 ± 459	339 ± 468	479 ± 528	0.714	261 ± 319	826 ± 561	<0.001

As identified, 23.4 ± 9.1 IU/L and 358 ± 459 IU/mL were serum ALT and HBV DNA levels, respectively (table 1). It had been observed that ALT level were normal in 102 patients where as in 10 patients it was became abnormal (table 1). In 23 patients who were false inactive carriers within one year HBV reactivation developed.

In 23 patients there were a significant drop in HBV reactivation during the first year. Between true and false inactive carriers there were a significantly different ALT and HBV DNA levels. In patients, whose baseline HBV DNA level was ≥ 200 IU/mL as compare to patients whose baseline HBV DNA level was < 200 IU/mL, HBV reactivation developed more often during a follow-up of 354 ± 175 days.

DISCUSSION:

Several studies had already confirmed that with the risk of disease progression in HBV carriers is directly correlated with HBV DNA level [16-18]. Even few studies had confirmed that independent of the ALT level and HBeAg status a prominent risk for developing iver cirrhosis and HCC was HBV DNA level [19,20]. Therefore, with an HBV DNA level < 2000 IU/mL in HBV carriers the probability of HBV reactivation chedule and to estimate prognosis.

In present studies Between true and false inactive carriers there were a significantly different ALT and HBV DNA levels. In patients, whose baseline HBV DNA level was ≥ 200 IU/mL as compare to patients whose baseline HBV DNA level was < 200 IU/mL, HBV reactivation developed more often during a follow-up of 354 ± 175 days. Inactive carrier state was determined by appearance of any clinical indications over three month for one year. At each visit HBV DNA levels were checked along with albumin, bilirubin and serum ALT.

There were several studies which confirms that AlT level can not be a accurate one to indicate the actual status of inactiveness. Thus from HBeAg-negative CHB patients who are on inactive HBV replication state is difficult to differentiating HBV carriers by the only ALT level measurement. We are not able to correlate the association of BMi as even in any previous trial such correlation is not observed. Short duration of follow up is the main limitation of this study. Different trials has already established that in hepatic steatosis in CHB patients, BMI and elevated TG levels were associated among themselves [21-23]. But it has been noticed that with even this short duration of study distinctive result was observed and can be considered as a distinctive direction towards clinical dissuasion based on the values observed in this trial. However in future further more detailed study with long duration is in need.

CONCLUSION:

From true inactive carriers to differentiate patients with HBeAg-negative CHB, HBV DNA level was useful tool. As per HBV DNA level of inactive carriers applied follow-up strategies need to vary.

REFERENCE :

1. Kane, M. 1995. Global programme for control of hepatitis B infection. Vaccine 13(Suppl. 1):S47–S49.
2. Banerjee, K., R. C. Guptan, R. Bisht, S. K. Sarin, and P. Khandekar. 1999. Identification of a novel surface mutant of hepatitis B virus in a seronegative chronic liver disease patient. Virus Res. 65:103–119.
3. Howard, C. R., and L. M. Allison. 1995. Hepatitis B surface antigen variation and protective immunity. Intervirology 38:35–40.
4. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, Tobias H, Wright TL. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. Clin Gastroenterol Hepatol. 2006;4(8):936–62.
5. Chu CM, Liaw YF. Natural history of chronic hepatitis B virus infection: an immunopathological study. J Gastroenterol Hepatol. 1997;12(9-10):S218–22.
6. Brechot C, Hadchouel M, Scotto J, Degos F, Charnay P, Trepo C, Tiollais P. Detection of hepatitis B virus DNA in liver and serum: a direct appraisal of the chronic carrier state. Lancet. 1981;2(8250):765–8.
7. Bonino F, Hoyer B, Nelson J, Engle R, Verme G, Gerin J. Hepatitis B virus DNA in the sera of HBsAg carriers: a marker of active hepatitis B virus replication in the liver. Hepatology. 1981;1(5):386–91.
8. Bonino F, Brunetto MR. Chronic hepatitis B e antigen (HBeAg) negative, anti-HBe positive hepatitis B: an overview. J Hepatol. 2002;39(suppl 1):S160–3.
9. Lin CL, Liao LY, Liu CJ, Yu MW, Chen PJ, Lai MY, Chen DS, Kao JH. Hepatitis B viral factors in HBeAg-negative carriers with persistently normal serum alanine aminotransferase levels. Hepatology. 2007;45(5):1193–8.
10. Zacharakis G, Koskinas J, Kotsiou S, Tzara F, Vafeiadis N, Papoutselis M, Maltezos E, Sivridis E, Papoutselis K. The role of serial measurement of serum HBV DNA levels in patients with chronic HBeAg(-) hepatitis B infection: association with liver disease progression. A prospective cohort study. J Hepatol. 2008;49(6):884–91.
11. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol. 2008;48(2):335–52.
12. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295(1):65–73.
13. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130(3):678–86.
14. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol. 2009;50(2):227–42.
15. Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, Kern ER, McHugh JA, Petersen GM, Rein MF, Strader DB, Trotter HT. National Institutes of Health consensus development conference statement: management of hepatitis B. Hepatology. 2009;49(5 Supple):S4–S12.
16. Chan HL, Tsang SW, Liew CT, Tse CH, Wong ML, Ching JY, Leung NW, Tam JS, Sung JJ. Viral genotype and hepatitis B virus DNA levels are correlated with histological liver damage in HBeAg-negative chronic hepatitis B virus infection. Am J Gastroenterol. 2002;97(2):406–12.
17. Manno M, Cammà C, Schepis F, Bassi F, Gelmini R, Giannini F, Miselli F, Grottola A, Ferretti I, Vecchi C, De Palma M, Villa E. Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. Gastroenterology. 2004;127(3):756–63.
18. Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, Kern ER, McHugh JA, Petersen GM, Rein MF, Strader DB, Trotter HT. National Institutes of Health consensus development conference statement: management of hepatitis B. Hepatology. 2009;49(5 Supple):S4–S12.
19. Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology. 2002;35(6):1522–7.
20. Papatheodoridis GV, Hadziyannis SJ. Diagnosis and management of pre-core mutant chronic hepatitis B. J Viral Hepat. 2001;8(5):311–21.
21. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346(16):1221-31.
22. Bondini S, Kallman J, Wheeler A, Prakash S, Gramlich T, Jondle DM, Younossi ZM. Impact of non-alcoholic fatty liver disease on chronic hepatitis B. Liver Int. 2007;27(5):607–11.
23. Peng D, Han Y, Ding H, Wei L. Hepatic steatosis in chronic hepatitis B patients is associated with metabolic factors more than viral factors. J Gastroenterol Hepatol. 2008;23(7 Pt 1):1082–8.