LETTERS TO THE EDITOR

DNA-guided hepatitis B treatment: Viral load is insufficient with few exceptions

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Abstract
In DNA-guided hepatitis B treatment, viral load is insufficient, and requires other viral markers for treatment of hepatitis B patients as in patients with acute exacerbation of chronic hepatitis B, end-stage renal disease on dialysis, human immunodeficiency virus co-infected patients. There are exceptions to this rule: a residual level hepatitis B virus (HBV) DNA at 24 wk predicts beneficial outcome and reduced resistance at 1 year. The genotypic viral resistance to antiviral agents and occult HBV infection can be determined by HBV-DNA levels.

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Key words: DNA; Hepatitis B; Viral load

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We read with interest the article “DNA-guided hepatitis B treatment: viral load is essential, but not sufficient” by Barcena Marugan et al[1]. We agree that viral load is essential but requires other viral marker for treatment of hepatitis B patient.

Patients with exacerbation of chronic hepatitis B, requiring treatment, can be differentiated from acute hepatitis B based on hepatitis B virus (HBV) DNA[2], but the sensitivity and specificity increase with addition of IgM anti-HBc. Low or undetectable DNA levels were seen in acute hepatitis[3], whereas HBV DNA levels became detectable during reactivation of chronic hepatitis[4]. Kumar et al[5] in their study showed a low level of HBV DNA (< 0.5 pg/mL) in about 96% of patients with acute infection, as opposed to 13% in those with exacerbation of chronic hepatitis. The sensitivity and specificity of low levels of HBV DNA for identifying an acute infection are 96% and 86.6%, respectively, which increase to 100% and 97.9% respectively with high titers of IgM anti-HBc.

Tong et al[6] applied the four criteria (European Association for the Study of the Liver, a treatment algorithm by an independent panel of hepatologists in the United States, an Asian-Pacific consensus statement and the practice guidelines from the American Association for the study of liver disease) to treat 369 HBsAg-positive patients with antiviral therapy. Using these criteria for antiviral therapy as stated by the guidelines, only 20%-60% of hepatocellular carcinoma (HCC) patients and 27%-70% of patients who died of non-HCC were identified for antiviral therapy. If the criteria were broadened with baseline serum albumin ≥ 3.5 gm/dL or less or platelet counts of ≤ 130 000/mm³ or less, 89%-100% of deaths from non-HCC liver-related complications and 96%-100% HCC patients would be identified for antiviral therapy.

In patients with end-stage renal disease on dialysis with HBV infection, it remains very difficult to predict the severity and outcome of liver disease based on the HBV-DNA level per se[7]. Liver biopsy appears to be the only definitive and reliable means to establish the activity of liver disease in patients on dialysis. It is recommended before starting antiviral therapy and undergoing kidney transplantation. Weisberg et al[8] have shown that the estimated 5-year survival rates in patients with end stage renal disease, chronic persistent hepatitis, chronic active hepatitis and chronic active hepatitis with cirrhosis due to hepatitis B are 97%, 86% and 55%, respectively.

In human immunodeficiency virus (HIV) infected patients with HBV, there is an increased risk of cirrhosis,
end-stage liver disease and death from liver disease, especially in patients with a low CD4 cell count or concomitant alcohol use. The treatment of HBV patients co-infected with HIV depends on HBV-DNA levels, histological evidence of active and/or advanced disease (Metavir > A2 and/or ≥ F2) and CD4 counts whether < or ≥ 500/mm³. So, HBV-DNA levels cannot be used alone in co-infected patients with HIV. A CD4 count < 500/mm³ requires HAART regimen including tenofovir and lamivudine or emtricitabine. A CD4 count ≥ 500 mm³ can be treated with entecavir, interferon or adefovir.

HBV-DNA load is essential but not sufficient and has few exceptions. Keeffe et al. showed that complete virologic response (no detectable residual HBV DNA) at 24 wk in patients on anti-viral drugs, and the likelihood of HBeAg seroconversion and maintenance of an undetectable level of HBV DNA are high, and resistance unlikely occurs. So the residual level HBV DNA at 24 wk can be used as a predictor of beneficial outcome and reduced resistance at 1 year.

The genotypic viral resistance to antiviral agents can be determined by ≥ 1 log₁₀ IU/mL increase in serum HBV DNA. Virological breakthrough or secondary antiviral treatment failure is usually defined as reappearance or ≥ 1 log₁₀ IU/mL increase after initial lack of detection or initial ≥ 1 log₁₀ IU/mL reduction of serum HBV DNA. Virological breakthrough is usually followed by biochemical response. So, a change of serum HBV DNA can be an earliest predictor of viral resistance to antiviral agents. All patients commencing antiviral therapy should have quantitative HBV DNA measurements at baseline and three months after starting therapy. It helps identify response and primary treatment failure in patients on lamivudine.

Occult HBV infection is defined as the detection of HBV-DNA in the serum or liver tissue of patients with negative hepatitis surface antigen. Occult HBV infection has low HBV DNA levels less than 10000 in the serum and 0.01-0.1 copy per liver cell. The likelihood of antiviral therapy benefit is low as most patients with occult HBV infection have very low levels of HBV DNA. Serum HBV DNA levels fluctuate in cryptic HBV carriers, repeating the HBV test over time is a useful tool in identifying the occult HBV status.

REFERENCES

1 Barcena Marugan R, Garcia Garzon S. DNA-guided hepatitis B treatment, viral load is essential, but not sufficient. World J Gastroenterol 2009; 15: 423-430
2 Orenbuch-Harroch E, Levy L, Ben-Chetrit E. Acute hepatitis B or exacerbation of chronic hepatitis B-that is the question. World J Gastroenterol 2008; 14: 7133-7137
3 Webster GJ, Reinaud S, Maini MK, Whalley SA, Ogg GS, King A, Brown D, Amlot PL, Williams R, Vergani D, Dusheiko GM, Bertoletti A. Incubation phase of acute hepatitis B in man: dynamic of cellular immune mechanisms. Hepatology 2000; 32: 1117-1124
4 Gayno S, Marcellin P, Loriot MA, Martinot-Peignoux M, Levy P, Erlinger S, Benhamou JP. Detection of serum HBV-DNA by polymerase chain reaction (PCR) in patients before reactivation of chronic hepatitis B. J Hepatol 1992; 14: 357-360
5 Kumar M, Jain S, Sharma BC, Sarin SK. Differentiating acute hepatitis B from the first episode of symptomatic exacerbation of chronic hepatitis B. Dig Dis Sci 2006; 51: 594-599
6 Tong MJ, Hsien C, Hsu L, Sun HE, Blatt LM. Treatment recommendations for chronic hepatitis B: an evaluation of current guidelines based on a natural history study in the United States. Hepatology 2008; 48: 1070-1078
7 Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2001; 34: 1225-1241
8 Weissberg JI, Andres LL, Smith CI, Weick S, Nichols JE, Garcia G, Robinson WS, Merigan TC, Gregory PB. Survival in chronic hepatitis B. An analysis of 379 patients. Ann Intern Med 1984; 101: 613-616
9 Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Muñoz A, Thomas DL. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002; 360: 1921-1926
10 Koziel MJ, Peters MG. Viral hepatitis in HIV infection. N Engl J Med 2007; 356: 1445-1454
11 Keeffe EB, Zeuzem S, Koff RS, Dieterich DT, Esteban-Mur R, Gane EJ, Jacobson IM, Lim SG, Naoumov N, Marcellin P, Piravatsith T, Zoulil F. Report of an international workshop: Roadmap for management of patients receiving oral therapy for chronic hepatitis B. Clin Gastroenterol Hepatol 2007; 5: 890-897
12 Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007; 45: 507-559
13 Papatheodoridis GV, Dimou E, Lazaris A, Papadimitriou V, Hadziyannis JS. Course of virologic breakthroughs under long-term lamivudine in HBeAg-negative precore mutant HBV liver disease. Hepatology 2002; 36: 219-226
14 Locarnini S, Hatzakis A, Heathcot J, Keeffe EB, Liang TJ, Mutimer D, Pawlotsky JM, Zoulil F. Management of antiviral resistance in patients with chronic hepatitis B. Antivir Ther 2004; 9: 679-693
15 Conjevaram HS, Lok AS. Occult hepatitis B virus infection: a hidden menace? Hepatology 2001; 34: 204-206
16 Cacciola I, Pollicino T, Squadrario G, Carenzio G, Villari D, de Franchis R, Santantonio T, Brancatelli S, Colucci G, Raimondo G. Quantification of intrahepatic hepatitis B virus (HBV) DNA in patients with chronic HBV infection. Hepatology 2000; 31: 507-512
17 Chen CJ. Time-dependent events in natural history of occult hepatitis B virus infection: the importance of population-based long-term follow-up study with repeated measurements. J Hepatol 2005; 42: 438-440

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