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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.

Key words: DNA; Hepatitis B; Viral load

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TO THE EDITOR

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 mm^3 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[9]. 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/mm^3. So, HBV-DNA levels cannot be used alone in co-infected patients with HIV. A CD4 count < 500/mm^3 requires HAART regimen including tenofovir and lamivudine or emtricitabine. A CD4 count ⩾ 500 mm^3 can be treated with entecavir, interferon or adefovir[10].

HBV-DNA load is essential but not sufficient and has few exceptions. Keeffe *et al*[11] showed that complete virologic response (no detectable residual HBV DNA) at 24 wk in patients on anti-viral drugs, and the likelihood of HBeAg sero-conversion 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 $\log_{10}$ IU/mL increase in serum HBV DNA. Virological breakthrough or secondary antiviral treatment failure is usually defined as reappearance or ⩾ 1 $\log_{10}$ IU/mL increase after initial lack of detection or initial ⩾ 1 $\log_{10}$ IU/mL reduction of serum HBV DNA[12]. Virological breakthrough is usually followed by biochemical response[13]. 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[14]. 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[15]. Occult HBV infection has low HBV DNA levels less than 10 000 in the serum and 0.01-0.1 copy per liver cell[16]. 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[17].

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