Rapid Communication

Serum soluble interleukin-2 receptor levels in patients with chronic hepatitis B virus infection and its relation with anti-HBc

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Abstract

AIM: To investigate the relationship between serum soluble interleukin-2 receptor (sIL-2R) level and anti-HBc in patients with chronic hepatitis B virus (HBV) infection.

METHODS: Sera from 100 patients with chronic HBV infection and 30 healthy controls were included in this study. The patients were divided into group A [HBsAg (+), HBeAg (+) and anti-HBc (+), n = 50] and group B [HBsAg (+), HBeAg (+) and anti-HBc (--), n = 50]. sIL-2R levels were determined using ELISA. HBV DNA and alanine aminotransferase (ALT) were also detected.

RESULTS: Serum sIL-2R levels were significantly higher in patients with chronic HBV infection than in healthy controls. Moreover, serum sIL-2R levels were significantly higher in patients with HBsAg (+), HBeAg (+) and anti-HBc (+) (976.56±213.51×10^3 U/L) than in patients with HBsAg (+), HBeAg (+) and anti-HBc (--) (393.41±189.54×10^3 U/L, P<0.01). A significant relationship was found between serum sIL-2R and ALT levels (P<0.01) in patients with chronic HBV infection, but there was no correlation between sIL-2R and HBV DNA levels. The anti-HBc status was significantly related to the age of patients (P<0.01).

CONCLUSION: The high sIL-2R level is related to positive anti-HBc in chronic hepatitis B patients. Positive anti-HBc may be related to T-lymphocyte activation and negative anti-HBc may imply immune tolerance in these patients.

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Key words: Chronic hepatitis B; Hepatitis B virus; Anti-HBc; Soluble interleukin-2 receptor; Immune tolerance

INTRODUCTION

About 350 million persons are chronically infected with hepatitis B virus (HBV) in the world[1]. Carriers of HBV are at an increased risk of developing cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC)[2]. China has the greatest burden of hepatitis B and liver cancer in the world. A third of all chronic HBV carriers live in China. Each year, about half a million Chinese die of liver cancer or liver failure due to hepatitis B. However, HBV has no cytopathic effect on hepatocytes. Some liver damages caused by HBV are attributed to immune clearance of virus-infected cells and associated immune reactions. While antibody response in patients with HBV infection plays a critical role in viral clearance through the formation of complexes with viral particles and their removal from the circulation[3], specific cellular immune response plays a main role in hepatic necrosis due to HBV infection and in the persistence of viral infection[4].

IL-2R system plays an important role in the activation and proliferation of lymphocytes[5]. IL-2R is expressed on the cell membrane of lymphocytes and contains at least three different chains. Serum sIL-2R is predominantly released from activated T lymphocytes and can serve as an index of activation of T lymphocytes[6]. Serum sIL-2R levels are significantly higher in patients with chronic HBV infection than in healthy controls[7]. The serum sIL-2R level one year after interferon administration may be a useful marker of interferon's therapeutic effectiveness[8].

In the present study, we determined the serum levels of sIL-2R in chronic hepatitis B patients with positive or negative anti-HBc to analyze the elevated patterns of sIL-2R in patients with different anti-HBc status.

MATERIALS AND METHODS

Patients

Serum samples were obtained from 100 Chinese patients...
## DISCUSSION

HBV infection is a major health problem. About 350 million persons are chronically infected with HBV in the world. HBV itself is non-cytopathic and it is widely accepted that the mechanism of hepatocellular injury is the host anti-viral immune response\[9\]. A human leukocyte antigen (HLA) class I-restricted cytotoxic T-lymphocyte (CTL) response to one or more HBV-encoded antigens on the hepatocyte membrane is a major mechanism of hepatocellular injury and clearance of infected cells\[10\]. Serum sIL-2R is predominantly released from activated T lymphocytes\[11\]. It was reported that serum sIL-2R levels reflect cellular IL-2 receptor expression\[12\]. Hence, levels of serum sIL-2R are useful in monitoring T-lymphocyte activity and serial measurement aids in assessing the progression of the disease\[13\].

High levels of serum sIL-2R have been observed in patients with chronic HBV infection\[7,8,12-14\] and hepatitis C virus (HCV) infection\[15\]. Serum sIL-2R levels indicate the degree of liver damage in patients with chronic HBV infection\[8\]. Our results showed that serum sIL-2R levels were significantly higher in patients with chronic HBV infection than in healthy controls. The serum sIL-2R levels were significantly related to the serum ALT levels, but did not correlate with serum HBV DNA levels in patients with chronic HBV infection. These results are consistent with previous findings of Sawayama et al\[8\].

Anti-HBc is detected in virtually all patients exposed to HBV, and its presence is one of the markers of past or present infection. The levels of anti-HBc can vary and are not always indicative of disease activity. It is important to note that while anti-HBc is a significant marker, it is not a definitive indicator of chronic hepatitis B infection, as some patients may have low or undetectable levels of anti-HBc despite having active infection.

## Statistical analysis

The significance of difference between the two groups was determined with Student’s t test and Wilcoxon's rank-sum test. P<0.05 was considered significant.
to HBV[15] and typically persists for life[17]. However, many patients with chronic HBV infection are negative for anti-HBc in China probably due to the fact that Chinese people acquire the infection at birth or during the early postnatal period[18,19]. These patients may have an immune tolerance to the virus for several decades of life[20,21]. We found that serum sIL-2R levels were significantly higher in patients with HBsAg (+), HBeAg (+) and anti-HBc (+) than in patients with HBsAg (+), HBeAg (+) and anti-HBc (-). Furthermore, patients with anti-HBc (+) were older than those with anti-HBc (-). Transfer of hepatitis C core antigen-reactive T cells is associated with the resolution of chronic HBV infection[23]. Based on these results, it seems that patients with chronic HBV infection who are negative for anti-HBc may be in a status of immune tolerance to the virus. Serum sIL-2R levels and anti-HBc may be useful indicators of immune status in patients with chronic HBV infection. Serum sIL-2R levels reflect the activation of T lymphocytes[24]. Hence, positive anti-HBc may be related to the activation of T lymphocytes.

Though interferon alpha to some extent hastens the loss of HBsAg in Chinese patients, the treatment is generally less effective than in white patients. This is probably due to the fact that the majority of Chinese people have a long period of immune tolerance to the virus[23]. Several studies have revealed that serum sIL-2R levels can serve as an index of the activation of T lymphocytes[24,25]. The serum sIL-2R level one year after interferon administration may be a useful marker of its therapeutic effectiveness[26]. Our results showed that elevated serum sIL-2R and positive anti-HBc were related to the high levels of serum ALT in patients with chronic HBV infection. Low serum ALT levels are associated with the poor response to interferon alpha treatment in patients with chronic HBV infection[23]. Hence, we can deduce that elevated serum sIL-2R levels, positive anti-HBc and high ALT concentrations may serve as indicators for interferon alpha treatment in Chinese patients with chronic HBV infection. However, further exploration is needed.

In conclusion, serum sIL-2R levels are related to anti-HBc and serum ALT concentrations, but not related to HBV DNA levels in patients with chronic HBV infection. Positive anti-HBc may be related to T-lymphocyte activation and negative anti-HBc may imply immune tolerance in these patients.

REFERENCES

1 Lee WM. Hepatitis B virus infection. N Engl J Med 1997; 337: 1733-1745
2 Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 1988; 61: 1942-1956
3 Böcher WO, Galun E, Marcus H, Daudi N, Terkelbaum D, Shouval D, Löhrl HF, Reisner Y. Reduced hepatitis B virus surface antigen-specific T helper cell frequency of chronic HBV carriers is associated with a failure to produce antigen-specific antibodies in the trimera mouse. Hepatology 2000; 31: 480-487
4 Monsalve-De Castillo F, Romero TA, Estévez J, Costa LL, Atencio P, Porto L, Callejas D. Concentrations of cytokines, soluble interleukin-2 receptor, and soluble CD30 in sera of patients with hepatitis B virus infection during acute and convalescent phases. Clin Diag Lab Immunol 2002; 9: 1372-1375
5 Lai KN, Leung JC, Tam JS, Leung NW. T lymphocyte activation in chronic hepatitis B infection: interleukin 2 release and its receptor expression. Am J Gastroenterol 1989; 84: 1532-1537
6 Rubin LA, Nelson DL. The soluble interleukin-2 receptor: biology, function, and clinical application. Ann Intern Med 1990; 113: 619-627
7 Müller C, Knoflach P, Zielinski CC. Soluble interleukin 2 receptor in acute viral hepatitis and chronic liver disease. Hepatology 1989; 10: 928-932
8 Sawayaama Y, Hayashi J, Kawakami Y, Furusyo N, Ariyama I, Kishihara Y, Ueno K, Kashiwagi S. Serum soluble interleukin-2 receptor levels before and during interferon treatment in patients with chronic hepatitis B virus infection. Dig Dis Sci 1994; 49: 163-169
9 Ifan Y. Immune downregulation leads to upregulation of an antiviral response: a lesson from the hepatitis B virus. Microbes Infect 2002; 4: 1317-1326
10 Franzese O, Kennedy PT, Gehring AJ, Gatto J, Williams R, Maini MK, Bertolletti A. Modulation of the CD8+ T-cell response by CD4+ CD25+ regulatory T cells in patients with hepatitis B virus infection. J Virol 2005; 79: 3322-3328
11 Rubin LA, Galli F, Greene WC, Nelson DL, Jay G. The molecular basis for the generation of the soluble interleukin 2 receptor. Cytokine 1990; 2: 330-336
12 Leung NW, Leung JC, Tam JS, Lau JT, Lai KN. Effects of alpha-interferon and prednisone on serum-soluble interleukin-2 receptor (sIL-2R) in chronic hepatitis B infection. Am J Gastroenterol 1992; 87: 113-117
13 Alberti A, Chemello L, Fattovich G, Pontisso P, Semenzato G, Colletta C, Vinante F, Pizzolo G. Serum levels of soluble interleukin-2 receptors in acute and chronic viral hepatitis. Dig Dis Sci 1989; 34: 1559-1563
14 Casafont F, Echevarria S, Pons Romero F. Interleukin-2 activity and serum levels of soluble interleukin-2 receptors in chronic active hepatitis B. Dig Dis Sci 1990; 35: 1045
15 Hayashi J, Kishihara Y, Yamaki K, Yoshihura E, Ohmiya M, Tani Y, Ikematsu H, Kashiwagi S. Serum levels of soluble interleukin-2 receptors and effects of interferon-alpha for patients with chronic hepatitis C virus. Dig Dis Sci 1995; 40: 1837-1841
16 Jung MC, Pape GR. Immunology of hepatitis B infection. Lancet Infect Dis 2002; 2: 43-50
17 Seeff LB, Beebe GW, Hoofnagle JH, Norman JE, Buskell-Bales Z, Waggonier JG, Kaplowitz N, Koff RS, Petrini JL, Schiff ER. A serologic follow-up of the 1942 epidemic of post-vaccination hepatitis in the United States Army. N Engl J Med 1987; 316: 965-970
18 Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: The effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. Hepatology 2001; 34: 139-145
19 Lai CL, Lin HJ, Lau JN, Flok AS, Wu PC, Chung HT, Wong LK, Leung MP, Yeung CY. Effect of recombinant alpha 2 interferon with or without prednisone in Chinese HBsAg carrier children. Q J Med 1991; 78: 155-163
20 Lok AS, Lai CL, Wu PC, Lau JY, Leung EK, Wong LS, Fung YL. Alpha-interferon treatment in Chinese patients with chronic hepatitis B infection: The effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. Hepatology 2001; 34: 139-145
21 Lai CL, Lin HJ, Lau JN, Flok AS, Wu PC, Chung HT, Wong LK, Leung MP, Yeung CY. Effect of recombinant alpha 2 interferon with or without prednisone in Chinese HBsAg carrier children. Q J Med 1991; 78: 155-163
22 Lok AS, Lai CL, Wu PC, Lau JY, Leung EK, Wong LS, Fung YL. Alpha-interferon treatment in Chinese patients with chronic hepatitis B infection: The effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. Hepatology 2001; 34: 139-145
23 Yuen MF, Lai CL. Treatment of chronic hepatitis B. Lancet Infect Dis 2001; 1: 252-261