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Elsewhere Reviews

THERAPY OF ACUTE HEPATITIS C WITH INTERFERON: HOW GOOD IS IT REALLY?

Omata M, Yokosuka O, Takano S, Kato N, Hosoda K, Imazeki F, Tada M, et al. Resolution of acute hepatitis C after therapy with natural beta interferon. Lancet 1991;338:914-915.

ABSTRACT

To test whether interferon can prevent acute non-A, non-B hepatitis from becoming chronic, a prospective controlled trial was conducted in 25 patients; 11 were treated for an average of 30 days with a mean of 52 megaunits of interferon and 14 acted as controls. 4 patients in the treatment group who continued to have raised serum aminotransferase concentrations after a year's follow-up were given a second course of interferon. Follow-up at 3 years has revealed that all but 1 of those treated showed normal serum aminotransferase, whereas only 3 controls showed such change ($p < 0.02$). Serum hepatitis C virus RNA became undetectable in 10 of 11 treated and in only 1 of 12 control patients, which suggests that interferon prevents the progression of acute non-A, non-B hepatitis to chronicity by eradicating HCV.

COMMENTS

This is an intriguing publication that raises the possibility of preventing the development of chronic hepatitis C by treating patients with interferon during the acute phase of their disease. Although the difference between the response rate in the treated group vs. the control group, defined either by normalization of serum ALT or serum HCV RNA negativity, was statistically significant, several issues need to be resolved before the interferon treatment of acute hepatitis can become accepted.

Interferon-β treatment was able to clear serum HCV RNA and normalize serum aminotransferases in 10 of 11 treated patients (91%) by the second and third year of observation. This is in contrast with results obtained among patients with chronic hepatitis C in whom the long-term sustained response rate is about 25% (1, 2). However, several prospective studies of the natural history of non-A, non-B hepatitis have shown that about 50% of the patients will spontaneously normalize serum aminotransferases and probably with disease resolution (3). The higher prevalence of chronic viral infection and ALT elevation observed in their control group (8 of 9 and 8 of 11, respectively) is at variance with the expected rate of chronicity (about 50%). Therefore their results might be less spectacular than they seem. We lack a readily available test for the diagnosis of acute hepatitis C. The direct detection of serum HCV RNA by reverse transcription/polymerase chain reaction is not amenable for implementation as a routine assay, and current immunoassays do not allow the diagnosis of the acute phase of HCV infection (4). Therefore this potential treatment would have to be implemented with the presumptive diagnosis of acute hepatitis C; however, this is plagued with inaccuracies, and the danger will be to treat patients with other causes and subject them to potentially serious side effects, particularly if their condition is an autoimmune liver disease (5, 6).

The authors have put together patients with a history of blood transfusion and others with sporadic type who may have a more benign outcome (2). They have not provided much information on the underlying conditions that led to blood transfusions and the degree of certainty regarding the diagnosis of "acute" hepatitis C in each patient.

It is unclear to us why the authors chose interferon-β, which needs to be administered intravenously, and not interferon-α, which can be given subcutaneously and has been better studied regarding its efficacy and safety (1, 2). These results will need to be confirmed with interferon-α and in a larger group of patients.

The mechanisms of chronicity in HCV infection remain undefined. In contrast to chronic hepatitis B (7), no evidence exists for HCV integration in the host genome. Also, HCV does not seem to modify the host immune response. Therefore it is unclear how interferon therapy would be more efficacious in the earlier stages of HCV infection as proposed by Omata et al. If these observations are confirmed in a larger group of patients, the definition of the mechanisms for a more effective therapeutic action of interferon in the acute phase may give us some insight into what determines chronicity in HCV infection.

The authors were cautious in not recommending the use of interferon-β for acute hepatitis C and we share that caution.

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THE IMMUNE RESPONSE IN CHRONIC HEPATITIS B VIRUS INFECTION: THE "CORE" OF THE PROBLEM?

Ehata T, Omata M, Yokosuka O, Hosoda K, Ohto M. Variations in Codons 84-101 in the Core Nucleotide Sequence Correlate with Hepatocellular Injury in Chronic Hepatitis B Virus Infection. J Clin Invest 1992;89:332-338.

ABSTRACT

Individuals with chronic hepatitis B virus (HBV) infection are generally divided into asymptomatic healthy carriers and patients with chronic liver disease. Several studies have suggested that the hepatitis B core antigen could be an immunological target of cytotoxic T lymphocytes (CTL). To investigate the possible pressure site from CTL, the entire core region of HBV DNA was sequenced in 30 subjects (10 asymptomatic healthy carriers and 20 patients with chronic liver disease). No significant changes in the nucleotide sequence and deduced amino acid residue were noted in the 10 healthy carriers. In contrast, a cluster of changes in a small segment of 18 amino acids (codons 84-101 from the start of the core gene) was found in 15 of the 20 chronic liver disease patients. All these 15 patients had advanced liver diseases (chronic active hepatitis and cirrhosis), whereas only mild liver disease (chronic persistent hepatitis) was found in the five patients without mutations. These data suggest that the region with mutation clustering is the major target of CTL, and that the mutations evolve under the pressure of immune selection.

COMMENTS

Of the many patients infected with HBV, only approximately 10% progress to have chronic liver disease (1). Although the clinical and pathological stages in this progression are well documented, the mechanisms underlying the hepatocellular damage remain an enigma. These patients have evidence of chronic viral replication, as manifested by the presence of HBV DNA and HBeAg. However, the hepatic injury is not thought to be related to direct viral damage because HBV has not been demonstrated to be cytopathic. Instead, most attempts to explain the pathogenesis of the chronic liver disease have focused on host-related factors.

The immune response to HBV infection is often implicated in the development of liver disease, and the hepatic injury is thought to result from the cellular immune response to infected hepatocytes (2). To understand the basis of this hypothesis, one must understand the mechanisms of immune recognition involved in cellular cytotoxicity. In response to viral infections, the immune system generates viral antigen-specific cytotoxic T cells (3). The antigen receptor complex on these CD8 lymphocytes recognizes viral antigens as peptides bound to class I histocompatibility antigens on the surface of infected cells. The peptides are generated by digestion of viral antigens and can be as short as 12 to 14 amino acids in length. Once the antigen receptors identify the peptide/class I complex, the T cells bind to the virus-infected cells. This binding is stabilized through the interaction of adhesion molecules. The T cells then lyse the virus-infected target cell (4). This action is essential in clearing a viral infection because of the need of destroying the intracellular source of viral replication. Released virus particles can then be neutralized and cleared by the circulating antibody. Thus hepatocytes are sacrificed by the immune system to control HBV.

Several types of data support the central role that antiviral cytotoxic immune responses play in the normal immune clearance of HBV infection. Cellular immunity to HBcAg is seen in patients who clear the viral infection and become antigen negative (5). In contrast, the reactivation of viral replication is often seen in patients who are immunosuppressed or given immunosuppressive medications (1). Evolution of chronic hepatitis B viremia to a nonreplicative, asymptomatic carrier state is often accompanied by the development of immunity to HBeAg (5). Importantly, whereas therapy with interferon may be effective in inhibiting HBV replication, it also augments antiviral cytotoxic immune responses in several ways (6). This latter activity may be most important to interferon's effectiveness in inducing viral clearance because agents that simply inhibit viral replication are rarely effective (7).

If immunity is of benefit in resolving acute hepatitis B infection, how might it be deleterious in patients with chronic hepatitis B infection? A scenario can be envisioned where ongoing viral replication exists that for some reason cannot be controlled or eliminated. Cellular immune reactions continue to destroy infected cells; however, because the virus is not eliminated, this leads to progressive hepatic destruction. Such a scenario would require a paradoxical immune response: effective cytotoxic activity that can lyse infected hepatocytes, but the overall immune response that is, for some reason, unable to clear the infection. Although virulence characteristics of a particular strain of hepatitis B could be