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Prevention of Hepatocellular Carcinoma Resulting From Hepatitis B: Are We There Yet?

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The article by Gordon et al[1] in this issue of *Clinical Gastroenterology* and *Hepatology* provides an intriguing insight into the possibilities for prevention of hepatocellular carcinoma (HCC) among patients with chronic hepatitis B viral (HBV) infection. These authors found, in a US-based study, a 60% decrease in occurrence of HCC among patients who received antiviral therapy for hepatitis B compared with those who did not.

Worldwide it has been estimated that 350 million persons are chronically infected with hepatitis B and that up to 620,000 die annually from HBV-related liver disease.[2] Similarly, it has been estimated that there are approximately 625,000 new cases of HCC each year, approximately half of which are associated with HBV.[3] In a large cohort of hepatitis B surface antigen–positive individuals from Taiwan, death from liver cancer occurred approximately twice as frequently as death from chronic liver disease and cirrhosis.[4] It is now well established that vaccination against hepatitis B is very effective in preventing HBV infection. Data from Taiwan have shown convincingly that rates of childhood HCC have decreased significantly since the implementation of universal infant vaccination in that country in 1984.[5] As vaccination programs have proliferated and coverage extended, it is reasonable to expect that rates of HBV-related HCC in this and future generations will be decreased. Unfortunately, this is of no benefit to those individuals who already are chronically infected with HBV, hence raising the question of whether treatment of already established chronic hepatitis B might have a role in reducing the risk of cancer.

The study was performed in a well-characterized population from the Chronic Hepatitis Cohort Study receiving their health care from 1 of 4 health care systems in Hawaii, the Pacific Northwest, Michigan, and Pennsylvania. The electronic health records of these systems were queried to identify patients with chronic hepatitis B and then cross-referenced with those who received treatment with one or another of the forms of antiviral treatments directed against hepatitis B. Investigators additionally were able to glean demographic information regarding these subjects, together with parameters that they used to estimate the presence and severity of liver disease. These data were used to help conclude that the beneficial effect noted with antiviral therapy occurred independently of liver disease severity.

The authors themselves noted some inherent weaknesses in their study. One of these was that they were unable to assess the duration of antiviral treatment—it is not unreasonable to surmise that the beneficial effects of therapy may be related to the duration of viral suppression on antiviral treatment. The antiviral agents included in their analysis have varying degrees of efficacy as well. Thus, entecavir and tenofovir have now become the

standard treatments whereas lamivudine and adefovir largely have been discarded because of high rates of viral resistance and lower potency, respectively. Relatively few patients (49 of 820) received interferon (either standard or pegylated) as their antiviral treatment and yet interferon is used only for a relatively short period of time (4–12 mo) and is associated with dichotomous antiviral outcomes: either it works or it does not. It may perhaps have been simpler to have excluded patients receiving interferon from this study.

The authors dealt extensively with the underlying severity of liver disease as a confounding factor for risk of HCC (ie, the more severe the liver disease, the higher the risk of HCC). Information on liver biopsy was not available for the large majority of patients and the authors used various surrogates to estimate the severity of underlying liver disease. Thus, they used commonly performed laboratory tests to estimate the degree of hepatic fibrosis using 2 standard algorithms: the FIB4 and AST to Platelet Ratio Index (APRI). With these parameters, they estimated that the beneficial effects of antiviral therapy occurred across a wide spectrum of FIB4 scores.

The issue of HCC prevention with antiviral treatment has come up relative to hepatitis C and there is growing evidence that eradication of hepatitis C viral (HCV) infection results in a reduced incidence of HCC. Thus, several cohort studies have now shown that achieving a sustained virologic response is associated with lower rates of liver disease progression and lower rates of HCC development.[6,7] Interestingly, it has been noted that HCC still occurs after HCV eradication in patients with underlying cirrhosis owing to treated chronic hepatitis C, but the rate appears to be substantially lower than among those patients with cirrhosis who are still viremic. It has been more difficult to show a similar effect with treatment of hepatitis B. One possible explanation is that HBV rarely is eliminated, but instead more often is suppressed by treatment. An early study using interferon suggested that therapy could decrease the rate of HCC in HCV infection but not HBV, but this has not been confirmed in subsequent studies. Retrospective studies of HCC incidence with long-term treatment with lamivudine also have had variable findings. Thus, studies from Korea and Japan[8,9] showed a decrease in HCC with use of lamivudine, whereas an analysis of the Greece Cohort Study Group found that lamivudine monotherapy did not eliminate HCC risk in patients with hepatitis B e antigen–negative chronic hepatitis B.[10] The risk of HCC was noted to be particularly high in patients with cirrhosis. A more recent study[11] found that patients treated with entecavir had lower rates of HCC than either those on lamivudine or those who were in an untreated control group.

A 5-year study of entecavir in “field-practice” patients in Italy showed no apparent suppression of HCC despite excellent viral suppression and safety.[12] Finally, Kim et al[13] used a novel approach in a recent study looking at cases of HCC occurring in long-term registration trials of tenofovir. They compared the actual incidence with that predicted by the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) score that had been developed in Taiwan based on a long-term follow-up cohort study of untreated patients. Interestingly, this study showed ongoing cases of HCC even among noncirrhotic patients and it was this latter group in which the effect of treatment appeared to be the most obvious.

Implications of the Present Study

The present analysis is an important finding in furthering our quest to prevent HBV-related HCC. Ultimately, the best evidence would be positive results from a prospective randomized controlled trial. However, this would be very difficult to do given the large number of subjects that would need to be enrolled and the prolonged duration of antiviral therapy needed to see an effect. The study published by Liaw et al[14] was indeed a prospective randomized controlled trial, but it included all clinical outcomes as an end point; thus, cirrhosis and liver failure, as well as HCC. Although this study was stopped early by a data safety monitoring board because of obvious clinical benefit, only a small number of subjects had developed HCC by that time. There is a tantalizing hint that the rate of HCC was indeed lower in the group treated with lamivudine compared with those on placebo.

The present study by Gordon et al[1] indicates that antiviral treatment is effective in preventing HCC, and furthermore it is effective across a spectrum of baseline characteristics including degrees of fibrosis and viral loads. However, at present there are insufficient data to really indicate to us who might benefit most from treatment. Thus, current practice guidelines are focused on maximizing the benefit of antiviral treatment in preventing progression of liver disease to cirrhosis or hepatic decompensation.[15] Therefore, patients with active liver disease at baseline are recommended for treatment in this context. However, those who are inactive carriers of hepatitis B are not currently treated. Perhaps more important is the large proportion who are classified as having immune-tolerant HBV infection based on having very high levels of viral replication with normal serum aminotransferase levels. These patients are often younger and currently it is recommended that they be observed but not treated, but if the findings by Gordon et al[1] are valid, these patients may well be suitable targets for antiviral treatment too, aimed at reducing the incidence of HCC.

As is often the case, the present study identifies the need for more research in this area. Ideally, we need large-scale, prospective, randomized controlled trials of therapy using modern, potent anti-HBV agents to see if this therapy reduces the risk of HCC. Such studies would have to examine the feasibility and safety of very prolonged treatment with nucleoside or nucleotide analogues to assess the risk benefit ratio of this approach. Nonetheless, it appears we may be making inroads into the disease burden of hepatitis B, with timely screening, diagnosis, and effective antiviral treatment.

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