

# Does Hepatitis B Treatment Reduce the Incidence of Hepatocellular Carcinoma?

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It has been difficult to prove that hepatitis B virus (HBV) treatment reduces the incidence of hepatocellular carcinoma (HCC). Most previous studies have been retrospective without adequate controls. In this issue of HEPATOLOGY Hosaka et al. present data on a large cohort, propensity matched for HCC risk with historical controls, demonstrating that HCC incidence is reduced with entecavir therapy.

The advent of potent oral antivirals for the treatment of chronic HBV has had a major impact on our ability to treat this disease. Entecavir and tenofovir are both highly effective, very well tolerated, and there is very little to no resistance. The fall in viral load on treatment is dramatic. The effect on inflammation as measured by alanine aminotransferase (ALT) or on biopsy is equally impressive. Yet the effect of these agents on long-term outcomes such as the development of cirrhosis and HCC remains in question. Hepatologists and others have embraced the use of potent antivirals as effective methods to reduce the incidence of these outcomes, but the evidence supporting this action has been remarkably difficult to come by. In part this is because it takes many years for these outcomes, HCC in particular, to present themselves, much longer than pharmaceutical companies are prepared to wait for licensing, and longer than the duration of most investigator-initiated follow-up studies. The other reason is that it is no longer possible to undertake a randomized controlled trial with an untreated control group, so strong is the belief that these agents are effective. It is considered unethical to leave patients untreated for the duration required to assess changes in incidence of cirrhosis and HCC.

There has been a single randomized controlled trial using oral agents in which patients with HBV cirrhosis were treated with lamivudine or nothing.<sup>1</sup> This study showed that there was a reduction in “outcomes” in the treated group. However, it was not clear that there was a reduction in the incidence of HCC. Once those who developed HCC early after recruitment, and who presumably had undiagnosed HCC prior to enrollment, were excluded, the improvement in HCC incidence was no longer significant. A number of studies have attempted to address this question, the results of which were summarized in a review earlier this year. Lai and Yuen<sup>2</sup> found that the results from interferon studies are inconsistent, but the vast majority of studies of oral antiviral agents demonstrated a decrease in HCC incidence. Only one study was randomized (referred to above).<sup>1</sup> The agents used included only lamivudine and adefovir. The studies included more than 2,000 subjects, cirrhosis and noncirrhosis patients, and demonstrate a reduction in HCC incidence in both groups. A prior meta-analysis<sup>3</sup> and a systematic review<sup>4</sup> came to the same conclusion. Nonetheless, with the one exception these were all retrospective data, with all the caveats that come with such studies. Implicit in the discussion of these studies is that even in the absence of additional randomized controlled data the evidence is sufficiently strong to support that antiviral therapy does reduce HCC incidence.

In addition to these analyses there is a considerable amount of indirect evidence that adequate suppression of viral replication, however achieved, leads to improved outcomes. Entecavir has been shown to reverse fibrosis and even cirrhosis.<sup>5</sup> We also know that the risk of HCC is related to the viral load,<sup>6</sup> so that presumably reduction of viral load with therapy will reduce the incidence of HCC. Virological response to entecavir has been shown to be associated with better outcomes than in those who did not achieve a sufficient response (and therefore, presumably better outcomes than those who have not been treated).<sup>7</sup> However, this would not be considered high-level evidence, and would not convince skeptics.

Despite the fact that most of those who treat HBV have accepted that suppression of viral replication is a useful surrogate marker of improved outcomes, there are those who have reservations about this. At the recent American Association for the Study of Liver

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Address reprint requests to: Morris Sherman, M.B., B.Ch., Ph.D., F.R.C.P. (C), Toronto General Hospital, 585 University Ave., Toronto, ON, M5G 2N2, Canada. E-mail: morris.sherman@uhn.on.ca; fax: 416-591-2107.

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Diseases (AASLD) meeting in Boston in 2012 a Cochrane-type systematic review and meta-analysis was presented as a poster.<sup>8</sup> This study came to the conclusion that the evidence showed only a minor reduction in HCC incidence in cirrhosis patients and no effect in noncirrhosis patients. This analysis included 27 trials and more than 7,000 patients. Another abstract showed that the natural history of HBV in Olmstead County, Minnesota, was similar before and after the introduction of hepatitis B antivirals,<sup>9</sup> again suggesting that HBV treatment had no effect. However, the uptake of appropriate treatment was not mentioned.

In addition to the difficulty in performing a randomized controlled trial there are other obstacles to proving that HBV treatment reduces HCC incidence. In theory, one should not expect a major reduction in HCC incidence in cirrhosis patients. Cancer development is a drawn-out process that does not initiate in the months prior to the diagnosis of even small lesions. Rather, the oncogenic process starts years earlier. A cirrhotic liver probably contains many clones of cells carrying genetic abnormalities that predispose to cancer. There is even data suggesting that the whole liver, or a great part of it, may be one abnormal clone that carries the predisposition to cancer.<sup>10</sup> Thus, stopping the process at a late stage, such as in cirrhosis, should not be expected to have a major impact on HCC incidence. Of course, since the period of follow-up required to document these outcomes is relatively short, this effect will be more easily demonstrated than in noncirrhosis patients, in whom it may take many years to document the difference in outcomes. This, then, is one of the other major obstacles to proving the effect of antiviral therapy in noncirrhosis patients, the time required to see the development of HCC. If one institutes treatment early enough to reduce the incidence, e.g., in 30-year-olds or 40-year-olds, the study would have to follow the cohort for 10+ years to be certain of an effect or no effect.

In this issue of HEPATOLOGY Hosaka et al.<sup>11</sup> describe a study in which they document that treatment of chronic HBV with entecavir reduces the incidence of HCC. This is a retrospective analysis of a sufficiently large number of subjects and of historical controls with an adequate length of follow-up. Controls had to be obtained from an era before HBV treatment was available. However, the controls were propensity matched to the treated subjects. In propensity matching subjects are matched according to the likelihood that they might develop the outcome of interest rather than simply matching on demographic factors. The authors took advantage of the fact that the HCC risk

in HBV has been quantitated in at least three different studies in different populations. These studies developed scores that can be used to determine the likelihood that an individual might develop HCC. The authors looked at propensity matching for all three scores, and their results were consistent whatever score was used. In the absence of randomization this is the next best method of ensuring that the experimental and control groups are similar.

The study showed that treatment with entecavir did in fact reduce the incidence of HCC and did so to a greater extent than lamivudine did. Furthermore, the magnitude of the risk reduction increased as risk scores increased. This means that patients at higher risk for HCC, i.e., those with cirrhosis, those who were older, and who had more active disease obtained greater benefit from treatment than younger patients and those without cirrhosis. These results are consistent with the discussion above describing that it is easier to demonstrate the effect of antiviral suppression in cirrhosis (and other patients at higher risk). The study also suggests that the effect of antiviral therapy is mediated by viral suppression. This is implicit in the finding that entecavir had a greater effect than lamivudine. This report is the first study that demonstrates a reduction in HCC incidence with one of the newer, more potent antiviral agents.

Given that we will never have an additional randomized controlled data for outcomes of HBV treatment, is the Hosaka study<sup>11</sup> the last word on the subject? Do we still need a similar study using tenofovir? It seems clear that the effect of antiviral therapy is related to a reduction in viral load, and that anything that reduces viral replication will have a beneficial effect. Furthermore, the stronger the antiviral effect, the greater the improvement in outcomes. If we accept this, then it is probably not necessary to undertake a similar study with tenofovir (although I am sure someone will do such a study). Do we need a study comparing the effects of entecavir and tenofovir on HCC incidence? Again, probably not! Such a study would need a very long follow-up and a very large sample size, and even then the difference, at best, will be small.

Thus, we can summarize the evidence from this current study and from others as follows: Suppression of viral replication in HBV cirrhosis patients reduces but does not eliminate the risk of HCC. Suppression of viral replication in noncirrhosis also reduces the risk of HCC, but since the risk of HCC is not as high as in cirrhosis patients, the magnitude of the risk reduction is less. It is not yet clear whether treatment of noncirrhosis, if instituted early enough, can eliminate the risk of HCC altogether. Given the difficulty of

performing such a study, we may never get that answer. However, that should not stop us from providing treatment for those with active disease.

MORRIS SHERMAN, M.B., B.CH., PH.D., F.R.C.P.(C)  
*Department of Medicine*  
*Division of Gastroenterology University of Toronto*  
*Toronto, ON, Canada*

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