Inactive HBV Elevates Risk of Liver Cancer

BY SHARON WORCESTER

Carriers of inactive hepatitis B virus are at increased risk of hepatocellular carcinoma and liver-related death, compared with noncarriers, according to findings from a large, prospective cohort study.

The annual incidence rates of hepatocellular carcinoma and liver-related death in 20,069 participants in the study, which had a mean follow-up of more than 13 years, were 0.06% and 0.04%, respectively, among 1,932 carriers of inactive hepatitis B virus (HBV). The annual incidence rates were 0.02% for hepatocellular carcinoma and 0.02% for liver-related death among 18,137 controls, wrote Dr. Jin-De Chen of National Taiwan University Hospital, Taipei, and colleagues.

Multivariate-adjusted hazard ratios for carriers, compared with controls, were 4.6 and 2.1 for hepatocellular carcinoma and liver-related death, respectively, the investigators reported (Gastroenterology [doi: 10.1053/j.gastro.2010.01.042]).

The authors used data from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL–HBV) Study for their analysis. Inactive HBV carriers were those who had seronegative hepatitis B e antigen status, anti–hepatitis C virus (HCV)-seronegative status, serum levels of HBV DNA less than 10,000 copies/mL without cirrhosis, hepatocellular carcinoma, or increased serum alanine transaminase (ALT) levels. Controls were participants who were seronegative for HB surface antigen and antibodies against HCV, but who had similar clinical liver features (normal serum ALT, without cirrhosis or hepatocellular carcinoma at study entry). Together, the groups contributed 262,122 person-years of follow-up.

VITALS

Major Finding: Annual incidence rates of hepatocellular carcinoma and liver-related death were 0.06% and 0.04%, respectively, among 1,932 carriers of inactive hepatitis B virus (HBV). The annual incidence rates were 0.02% for hepatocellular carcinoma and 0.02% for liver-related death among 18,137 controls.

Data Source: A prospective cohort study involving 20,069 subjects.

Disclosures: This study received grant support from Bristol-Myers Squibb Co.; Department of Health, Executive Yuan, National Health Research Institutes, Taiwan; and Academia Sinica, Taiwan. The investigators reported that there were no financial or other disclosures related to the study.

Significant predictors of hepatocellular carcinoma in the entire cohort, compared with controls, were older age (hazard ratio of 2.7/10-year increment), high-normal baseline ALT level (HR 2.2), and alcohol drinking habit (HR 2.4). Significant predictors in inactive HBV carriers, compared with controls, were older age (HR 2.6/10-year increment) and drinking habit (HR 3.7).

The risk of hepatocellular carcinoma was higher in those with baseline serum HBV DNA levels of 300-10,000 copies/mL, compared with those with undetectable serum HBV DNA at baseline, but the difference did not reach statistical significance (HR 1.6). In inactive carriers with undetectable serum HBV DNA at baseline, alcohol drinking habit was a significant predictor of hepatocellular carcinoma (HR 6.9).

Significant predictors of liver-related death in the entire cohort, compared with controls, were similar to those for hepatocellular carcinoma, and included older age (HR 2.3/10-year increment), high-normal baseline serum ALT level (HR 1.9), and alcohol drinking habit (HR 2.1). Among inactive HBV carriers, only older age (HR 2.6/10-year increment) and alcohol drinking habit (HR 5.8) were significant predictors.

The inclusion of hepatocellular carcinoma as a time-dependent event in the analysis revealed that it was the most striking risk predictor for liver-related death (HR 611 for the entire cohort, and 451 for inactive HBV carriers), as would be expected, the investigators noted.

In those without newly developed hepatocellular carcinoma, older age (HR 2.0/10-year increment) and alcohol drinking habit (HR 2.3) were significant risk factors for liver-related death; in inactive carriers without hepatocellular carcinoma, only older age was a significant predictor (HR 2.4).

No significant differences were seen in the development of hepatocellular carcinoma or liver-related death between inactive carriers with undetectable and detectable serum HBV DNA, the investigators noted.

The study is limited by a lack of histologic data, since liver biopsies were not applicable in the large community-based study. Also, serial HBV DNA measurements were not taken to assess for continued inactive carriage, and other risk factors, such as HBV genotypes, were not assessed in those with HBV DNA levels greater than 100,000 copies/mL to determine an association with hepatocellular carcinoma in inactive carriers.

Future studies that include serial measurement of hepatitis B surface antigen serostatus and serum HBV DNA levels would help clarify the natural history of inactive HBV carriage, they concluded. ■

Reports of Drug-Induced Liver Injury Lack Essential Data

BY SHARON WORCESTER

Key clinical information is often lacking in published reports of drug-induced liver injury, Dr. Vijay K. Agarwal and his colleagues reported.

The finding is concerning, because accurate reporting of drug-induced liver injury—the single leading cause of acute liver failure in the United States—is essential for the development of reliable, interpretable data to help promote early detection and awareness of drug-induced hepatotoxicity, said Dr. Agarwal of Duke University, Durham, N.C., and colleagues.

For the study, which was conducted on behalf of the Drug-Induced Liver Injury Network, the investigators developed a list of 42 elements necessary for evaluating causality of drug-induced liver injury, and they analyzed 97 published case reports or series of such injuries for the presence of these elements.

VITALS

Major Finding: None of 97 analyzed case reports or series reports of drug-induced liver injury included all 42 elements, which the investigators deemed necessary for evaluating causality of such events. A median of 48% of the elements were missing in the reports.

Data Source: Retrospective analysis.

Disclosures: Funding for the Drug-Induced Liver Injury Network is provided by the National Institute of Diabetes and Digestive and Kidney Diseases; the study was conducted on behalf of this network. One author, Dr. John G. McHutchison, reported receiving research support from, and acting as a scientific adviser for, GlaxoSmithKline and Merck & Co.

Basic disease, drug, and demographic information was present in the vast majority of reports, but numerous important elements for determining causality and eliminating alternative causes of liver injury were lacking. These elements included bilirubin level (missing in 12% of reports), initial alkaline phosphatase level (missing in 58% of reports), and competing viral etiologies (missing in more than 50% of reports).

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The reports evaluated included 23 single case reports, 7 brief communications, 46 small case series, and 21 letters to the editor, and they focused on six drugs from three drug classes: amoxicillin/clavulanic acid (35 reports), troglitazone (32), rosiglitazone (10), pioglitazone (8), zafirlukast (8), and montelukast (4). The first two drugs are known to cause clinically apparent drug-induced liver disease, while the other four rarely cause liver injury, but case reports have been important in documenting the medications' potential for hepatotoxicity, the investigators noted.

Some studies included only vague descriptions of how certain diagnoses were excluded, and data on abnormal results from serial liver tests often were not included. Single case reports had significantly fewer missing elements than letters to the editor and small case series (a median of 33% vs. 50% and 48% of the elements were missing, respectively).

No significant differences were observed on the basis of journal type: The median percentage of missing elements was 50% for major internal medicine journals, 48% for gastroenterology and liver subspecialty journals, and 45% for other types of journals.

The authors noted that unless the essential details for interpreting the findings are included in such reports, it will be impossible to determine if episodes of hepatotoxicity can be causally assigned to a specific drug or combination of drugs. In addition, opportunities to identify rare events that might not be apparent in clinical trials, and to increase awareness of issues possibly associated with a drug early in its development and use, will be missed, the investigators said. They argued that a more standardized approach to the reporting of drug-induced liver injury is needed.

A checklist of minimal elements for diagnosing drug-related liver injury and for assessing causality should be developed, and a secondary list of elements that are helpful in many situations—such as results of assays for anti–hepatitis E virus antibodies to exclude hepatitis E, or magnetic resonance cholangiopancreatography to fully exclude biliary obstruction—would be useful, they said.

Such standards, which have been suggested in the past but not widely adopted, could be posted on a publicly funded Web site, with the goal that they would ultimately be adopted by journal editors, the authors suggested. ■