ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Use of Statins in Hepatocellular Carcinoma

Abby B. Siegel, MD, MS
Assistant Professor of Medicine
Columbia University College of Physicians and Surgeons
New York, New York

G&H What prompted study of statin use in relation to hepatocellular malignancy?

AS Ironically, these studies were initially done because of concerns regarding statins and hepatotoxicity and, in particular, carcinogenicity. Animal models had initially shown evidence of hepatic necrosis and liver tumor development with statin use. Subsequent data in humans showed that, although elevations of aminotransferase levels up to 3 times the upper limit of normal may be seen in up to 3% of patients on statins, this laboratory abnormality is almost always asymptomatic. For instance, of more than 50,000 patients who received liver transplants between 1990 and 2002, only 1 transplant was thought to have been performed for treatment of toxicity associated with simvastatin therapy. Similarly, lovastatin has been estimated to cause about 2 cases per million patients of fulminant liver failure.

Around the same time that data on dispelling concerns about statins and hepatotoxicity came to the fore, data from several large epidemiologic studies, including the Nurse's Health Study and Physician's Health Study in breast and prostate cancers, suggested possible benefits of statin use in reducing cancer incidence. For patients with breast cancer, it was suggested that hydrophobic statins in particular (simvastatin, lovastatin, and fluvastatin) lowered the incidence of breast cancer. In prostate cancer, statins were thought to decrease the risk of advanced disease. Finally, studies on cell cultures and animal models also began to uncover biologic bases for anticancer properties of statins, as well as a possible benefit in treating hepatocellular carcinoma (HCC) with statins.

G&H How strong are the data on the value of statins in HCC?

AS Observational data are compelling that statins lower the risk of HCC in various patient populations (eg, those with diabetes, hepatitis B virus [HBV] infection, and hepatitis C virus [HCV] infection), but there are still no randomized trials showing that statins decrease HCC incidence. A large recent meta-analysis underlined these discordant findings. The authors examined 1,459,417 patients included in both randomized and observational trials. Large prevention benefits for statin use were seen in the observational trials (particularly in Asian populations), but there was no benefit seen in the randomized trials. Because of possible biases seen in observational studies, a large randomized trial is needed to prove a clear benefit.

G&H What can we learn about the relationship between statins and HCC from statin use in patients with nonalcoholic fatty liver disease?

AS Again, initially, studies were done because of concerns about hepatoxicity of statins, particularly in patients with elevated liver enzymes at baseline. In a landmark study, Chalasani and colleagues noted that, among patients who were hyperlipidemic, those with elevated liver enzymes who received statins had no significant increase in hepatotoxicity compared with patients with normal liver enzymes.

Growing data suggest that statins can be safely used in patients with well-compensated liver disease. In 1 randomized trial, 326 patients were randomly selected to receive high-dose pravastatin at a dosage of 80 mg/day

or placebo. Sixty-four percent of patients had underlying nonalcoholic fatty liver disease (NAFLD), and 23% had chronic HCV infection. All were well compensated, defined as having aspartate aminotransferase and alanine aminotransferase (ALT) levels less than or equal to 5 times the upper limit of normal, normal bilirubin levels, and no ascites or cirrhosis. Interestingly, the average ALT values decreased below baseline in the treatment group, while they went up in the control group.

The GREACE (Greek Atorvastatin and Coronary-Heart-disease Evaluation) trial, a prospective study of 1,600 patients with coronary artery disease who were randomly selected to receive a statin or "usual care" (which allowed statins), also showed a less than 1% risk of serious hepatotoxicity. Several observational studies also support this finding. It is not clear, however, whether patients with more serious underlying liver disease will have more problems, and this needs to be studied in more detail. The authors of the GREACE trial found that patients with moderately elevated liver enzymes at baseline (presumably from fatty liver disease) had improvements in liver enzymes with statin use.

Statins also seem to improve fibrosis in animal models of nonalcoholic steatohepatitis (NASH). However, no well-designed randomized trial in humans has yet shown that statins can prevent or improve pathologically defined fibrosis. Because some NAFLD-related HCCs may occur in the absence of fibrosis, improving the "steatosis" may be enough, in some cases, to prevent cancer, but this has not been proven either.

G&H Are some statins more beneficial than others in this setting, based on their unique mechanisms of action?

AS It was originally thought that hydrophobic/lipophilic statins might be more effective in preventing cancer than lipophobic statins because of better membrane permeability, and some preclinical studies do support increased anticancer activity with these subtypes. In addition, the lipophilic types of statins may have increased clinical benefits, such as reduction of oxidative stress. Interestingly, the lipophilic statins also seem to have more extrahepatic effects (including increased rates of myopathy), possibly due to increased metabolism by cytochrome p450. This, in turn, may cause increased levels of statin because of drug interactions.

However, clinically, these differences in cancer prevention have not yet been clearly shown. For instance, studies evaluating the incidence of breast and colon cancers for various types of statins have been conflicting. Further, a large meta-analysis by Dale and colleagues that evaluated randomized trials of statins did not show significant effects on cancer risk overall and also did not show differences related to the type of statin.

Data are limited in patients with HCC. One observational study in patients with HBV infection did not show a clear difference between various types of statins in prevention of HCC. Pravastatin was the only statin studied that did not have a statistically significant benefit, possibly because of its hydrophilicity, but it was also the least common statin prescribed, suggesting a possible sample size issue.

G&H What is the relationship between statin use, HBV and HCV virus, and protection against oncogenesis?

AS Statins have several potential anti-oncogenic effects. They have been shown to block the epidermal growth factor signaling pathway and the proteasome and induce apoptosis. Cholesterol is required for secretion of HBV, so statins may also help to prevent this. They also can block the formation of cholesterol and geranylgeranylated protein, both thought to be important for HCV replication. Statins also may improve response to therapy for HCV infection.

G&H Will patients at risk for HCC be selectively prescribed a statin or will data about statins and HCC translate into other novel therapeutic protocols?

AS Treatment of HBV infection has been shown to decrease the incidence of HCC. With the advent of new, more effective treatments for HCV infection, it will be worth investigating whether these treatments also provide a preventive effect. The degree of overlap between patients with HBV and HCV infection and steatosis is large, and whether patients with steatotic changes—in addition to other causes of liver disease—will be the most responsive to statins is also worth examining.

Without randomized data that show a benefit, patients should not yet be given statins purely for prevention of HCC. Even for those patients with NAFLD/NASH, consensus guidelines do not recommend use of statins other than for treatment of dyslipidemia. However, it is interesting to speculate whether patients who have more hepatic steatosis or other components of metabolic syndrome will respond better to statins. In addition, a genetic polymorphism in the 3-hydroxy-3-methylglutaryl coenzyme A reductase gene may help to predict who will have a better response to statins. It would also be interesting to study the effects of diet and exercise interventions with statin therapy in patients with underlying steatosis.

G&H What research might be warranted to further investigate the protective effects of statins in relation to HCC?

AS Smaller trials with pathologic endpoints to try to figure out whether statins affect the progression of liver disease to fibrosis are warranted. If it is found that statins affect progression to fibrosis, studies should address when to begin statin therapy and determine the optimal length of therapy. It is also important to study statins in patients with various underlying causes of HCC and in the context of other potential confounders, including other medications, body mass index, cigarette smoking, etcetera.

There are data that obesity is "carcinogenic" in animal models of liver cancer. Preliminary data also suggest that obese patients with liver cancer may have more aggressive tumors (specifically, vascular invasion of tumors). It would be interesting to see if statins also reduce the aggressiveness of tumors that develop.

A genetic polymorphism that encodes the patatin-like phospholipase domain-containing (PNPLA3) protein has been described. This polymorphism causes increased accumulation of hepatic fat and seems to be associated with HCC development. High-risk groups could be potentially selected based on *PNPLA3* gene status to see whether they are particularly responsive to statin therapy.

Interestingly, a study from Sweden reported an increased risk of HCC for obese patients with the *PNPLA3* variant, but for patients who underwent weight reduction surgery, the genetic polymorphism no longer seemed to affect risk. Whether other environmental modifications or possibly statin use could modify the expression of this gene are questions to consider. Ideally, we will need a randomized trial in a high-risk population to determine whether statins really do prevent HCC.

Dr. Siegel would like to thank Dr. Hashem El-Serag for his assistance in developing this commentary. *Dr. El-Serag is the Dan L. Duncan Professor of Medicine and Chief, Gastroenterology and Hepatology Section at the Baylor College of Medicine in Houston, Texas.*

Dr. Siegel has no conflicts of interest to disclose.

Suggested Reading

Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. *Hepatology.* 2005;41(4):690-695.

Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology.* 2012;142(7):1592-1609.

Dale KM, Coleman CI, Henyan NN, et al. Statins and cancer risk: a meta-analysis. *JAMA.* 2006;295(1):74-80.

Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. *Gastroenterology.* 2013;144(2):323-332.