Do Hepatitis C Antivirals Pose Risk for Hepatocellular Cancer Recurrence and Hepatitis B Reactivation?

April 25, 2016 By Lucinda K. Porter RN

I am rattled by a recent announcement by the European Medicines Agency (EMA), which is the agency in Europe that oversees drugs much like the FDA does in the U.S. There have been reports of hepatitis B reactivation in patients who have been infected with hepatitis B and C viruses, and who were treated with hepatitis C direct-acting antivirals (DAAs). Hepatitis B re-activation refers to a return of active infection in a patient who formerly had inactive HBV. This has triggered a review of DAA use.

Unfortunately, there is more. Data released at the 2016 meeting of the European Association for the Study of the Liver (EASL) reported an unexpected higher risk of recurrence of hepatocellular carcinoma (HCC or liver cancer). The study (Development of Hepatocellular Carcinoma in HCV Cirrhotic Patients Treated with Direct-acting Antivirals - Federica Buonfiglioli et al.) brings up this question: Are patients who had HCC and were treated with DAAs at increased risk of cancer returning earlier than patients who were not treated with DAAs? (A smaller, second study showed similar results: Unexpected Early Tumor Recurrence in Patients with Hepatitis C Virus-related Hepatocellular Carcinoma Undergoing Interferon-Free Therapy: A Note of Caution - María Reiga et al.)

The data are confounding. I am not even going to pretend to have an opinion about the HBV reactivation. Speculation without evidence is a waste of time, and I'll leave that to the EMA. I pray that we find answers to that soon.

As for the HCC reactivation, there isn't enough data to form an opinion in this case either. However, there are ways to look at this that knock the fear down a notch. Let's begin with what we know:

According to the World Health Organization, liver cancer accounts for 662,000 deaths and is the third leading cause of cancer-related death in the world. Most HCC cases occur in patients with chronic liver disease, and most of these are in people with chronic hep B or C. Approximately 80% to 90% have cirrhosis, and most of the remainder have moderate to advanced fibrosis.

The bulk of the data regarding HCC recurrence following DAA treatment came from an Italian

study. Medical records were investigated from 344 patients with HCV-related cirrhosis, who did not have active HCC. They were all HIV-negative. All were treated with one of the following combinations: sofosbuvir and simeprevir (34%), ABT-450/r, ombitasvir, dasabuvir and ribavirin (22%), sofosbuvir and ribavirin (17%), sofosbuvir and daclatasvir (16%) and sofosbuvir and ledipasvir (10%). HCC was assessed by comparing baseline ultrasounds and MRI/CT-scans with those taken during the six-month post treatment follow-up.

Sustained virologic response (SVR) was achieved in 89% of patients at 12 weeks post-treatment. At 24 weeks post treatment, active HCC was detected in 7.6% of all patients (n=26) without a history of HCC. This is considered a standard rate for cirrhotic patients. The 59 patients who had a previous history of HCC, the recurrence rate was 29% (n=17). The HCC recurrence rate is normally about 30% but it does not generally happen this quickly. Normally, it takes a few years for lesions of this size to appear.

Important points to consider:

- The people who are at risk here are cirrhotic patients who were in remission for HCC and were treated with DAAs. This study is NOT saying that all patients who were treated with DAAs are at risk for liver cancer.
- This is a small study. We need more data, and we need data from other countries, including the U.S. Also, we need data that include a control group of people who did not get treated for HCV.
- To date, the data overwhelmingly support the notion that SVR is associated with lower all-cause mortality. However, most of the data used interferon-based treatment. Does this change with DAA use?

The bottom line:

- All patients with cirrhosis, regardless of SVR-status, need to be monitored for HCC.
- If you had HCC and were treated with DAAs, you need extra monitoring for HCC. Imaging is an essential part of this monitoing. In the study, alphafetoprotein (AFP) was increased in only 2/26 (8%) subjects at the time of HCC detection.
- Alert the FDA if you have HCC recurrence following DAA use. You don’t need to speculate as to whether it was related or unrelated; all you need to do is make the report.
- Stay tuned for the European Medicines Agency findings regarding these issues.

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