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The Possible Association Between DAA Treatment for HCV Infection and HCC Recurrence

Robert S. Brown, Jr, MD, MPH
Gladys and Roland Harriman Professor of Medicine
Clinical Chief, Division of Gastroenterology and Hepatology
Weill Cornell Medicine
New York, New York

G&H How common is the coexistence of hepatocellular carcinoma and hepatitis C virus infection in a patient?

RB Among patients with hepatitis C virus (HCV) infection and cirrhosis, the risk of hepatocellular carcinoma (HCC) is estimated to be 1% to 3% per year. Thus, in any given year, the risk is relatively low, but over a decade, the risk is considerable. More importantly, with the rise in the number of baby boomers who have had HCV infection for more than 2 decades, we are seeing an increasing prevalence of HCC. Although the rate of new cases of HCV infection is falling, the prevalence of HCV infection with cirrhosis is still rising, as is the number of patients who have HCV infection and HCC.

G&H What is the current understanding of the relationship between HCV infection and HCC?

RB There is no evidence that HCV by itself can cause HCC. HCV does not integrate into the host genome the way that hepatitis B virus (HBV) does, and it does not have any proteins that have been linked to HCC. The mechanism by which HCV leads to HCC is likely through inflammation and cirrhosis. All forms of cirrhosis carry a risk of HCC, although cirrhosis due to HBV, HCV, hemochromatosis, and nonalcoholic fatty liver disease appear to have higher rates of HCC than other forms of cirrhosis.

It is also clear that the risk of HCC persists in cirrhotic patients infected with HCV even if they are cured of their HCV infection. Whether this increased risk of HCC will always persist or whether it just occurs in the short or midterm remains to be determined. The answer may come soon, as more and more patients are being cured of their HCV infection and are being monitored for longer periods of time.

Whether HCV infection can cause HCC in the absence of cirrhosis is controversial. If HCV infection can, the rate of HCC is likely very low. Medical societies do not recommend screening noncirrhotic HCV patients for HCC.

G&H Currently, how effective are direct-acting antiviral agents for treating patients infected with HCV in terms of different genotypes and special populations?

RB The development of direct-acting antiviral (DAA) agents has increased the cure rate above 90% in nearly all patient groups and above 95% in most groups. There are now effective all-oral treatment options for all genotypes (1-6) of HCV. DAA agents also appear to work in HCV patients who are coinfected with HIV, as well as in what were previously considered to be difficult-to-treat special populations, such as patients who have undergone liver or kidney transplant or who have end-stage renal disease.

However, some groups of patients may have fewer options based upon their comorbidities. For example, at the current time, patients with decompensated liver disease should not use protease inhibitors and patients with end-stage renal disease should not use nucleotides. These comorbidities may limit options for these groups based upon their genotype. However, with newer pangenotypic

regimens being developed, all patient groups should have a treatment option available now or very soon.

G&H Are there any significant adverse events associated with DAA agents?

RB All drugs have side effects, but these agents have very few and are exceedingly well tolerated. For example, the newest DAA agents have few drug-drug interactions. Many of them allow ribavirin to be eliminated from HCV treatment regimens. Although ribavirin has less toxicity when used without interferon, it still has some hematologic toxicity and more side effects than DAA agents alone. In addition, although some protease inhibitors can be used in all populations, there is a potential risk of hepatotoxicity, so these agents are avoided in patients with decompensated liver disease, as previously mentioned. Nucleotides also tend to be avoided in patients with end-stage renal disease because of the risk of accumulation, as these agents are excreted by the kidney.

In terms of direct toxicity, DAA agents are quite safe for the majority of patients. In clinical trials, discontinuations due to adverse events have comprised less than 0.5% of patients.

G&H Could you discuss the recent reports suggesting that there may be increased recurrence of HCC following DAA treatment for HCV infection?

RB Initially, it was thought that being cured of HCV would decrease the risk of HCC, but there have been conflicting data. There have been several reports of a decreased HCC risk, particularly in the long term. However, one would not expect a decrease in the risk of HCC in the very short term because a cancer found on imaging today was likely present a year or two ago at the cellular or molecular level. Thus, I did not expect to see a decrease in HCC in the first 2 to 5 years following sustained virologic response.

However, several recent reports from Europe have raised concern that there may be an increased risk of HCC or more diffuse HCC recurrence after treatment with DAA therapy. The most striking part of this has been an increase in the risk of tumor recurrence in patients who had been treated for their HCC, either with ablation or chemoembolization, and then had their HCV infection cured. In these studies, a higher rate of recurrence or more diffuse HCC was seen in patients who had their HCV infection cured than the rate expected in untreated control patients.

These recent European data are not supported by all of the research currently available, some of which shows equal or even lower rates of HCC, but they have raised some concern. One could imagine that perhaps curing HCV infection would decrease the level of immune surveillance of the liver and possibly increase the risk of HCC. I think these data have raised questions regarding the optimal timing of HCV treatment in patients with HCC, whether it should be done prior to or after successful HCC therapy once it is clear that the HCC is in remission. There is no clear evidence that HCV treatment per se does increase the risk of HCC, but I think that these recent data have left us with more questions than answers, and further research is certainly needed.

G&H If this relationship proves to be true, what might explain it?

RB No one believes that the drugs themselves cause HCC, and any speculation on how there could be an increased risk of HCC following DAA therapy is exactly that—speculation. However, one could imagine that the inflammation in patients with chronic HCV infection—although a risk factor for HCC in the long run—may actually have a protective effect that prevents HCC recurrence during the time of liver regeneration. Liver regeneration has been seen, both anecdotally as well as in case series, to promote rapid tumor growth or carcinogenesis after resection for HCC. If multiple lesions are seen in the remnant liver several months after a successful R0 resection that had no residual HCC, the surgeon did not cause those lesions from the resection; as the liver grew, they became clinically apparent.

Therefore, it is possible to imagine that as HCV infection is cleared and as the liver regenerates and repairs itself, small tumors that were present, but were not clinically apparent, might accelerate their growth. Similarly, now that HCV infection does not need to be controlled, the lack of immune surveillance and immune attack might allow tumors to grow more rapidly. If the relationship between HCC recurrence and DAA treatment proves to be true, it is likely because of either liver regeneration or the lack of immune surveillance, or both, that leads to the clinical appearance of tumors in an accelerated rate following sustained virologic response.

In the long term, I cannot imagine that once inflammation is removed, particularly if cirrhosis and fibrosis regress, that the risk of HCC would not be lowered. However, whether the aggressiveness of latent tumors is increased in the short term remains an open question needing further research.

G&H Have any earlier studies suggested that HCV treatment might be associated with HCC recurrence?

RB Earlier studies with interferon-based HCV therapy never showed this phenomenon, and that may be for more than one reason. One is that interferon has immune-stimulating and perhaps antitumor effects. That might explain why doctors might not see the possible aforementioned phenomenon with HCC recurrence and why they might see it with DAA agents (which lack immune-stimulating and antitumor effects) if indeed there is an increased appearance of tumors following DAA therapy.

However, there is a possible alternate explanation. Patients who were treated with interferon inherently had a lower risk of recurrent or de novo HCC because doctors could not use interferon in patients with the most advanced liver disease, who have the highest risk of HCC, and doctors certainly would not use interferon immediately after therapy for HCC.

G&H Are there any limitations to the European DAA studies that should be acknowledged?

RB First, all of those studies were observational; they were not randomized trials comparing patients who were treated and cured to patients who were not treated. It is important to remember that with DAA agents, the vast majority of patients can be cured, so patients need to be compared with historical controls or patients who for one reason or another were not treated, which will always instill bias in a study. Only a randomized trial can equalize confounders, both those that are known and those that are unknown.

Second, the HCC rates in some of the European DAA studies were higher than expected (certainly higher than those seen in other studies), which raises the question as to whether these findings were a chance occurrence. In the US transplant population, many patients with HCC have been treated for HCV infection while on the waiting list, and an increase in HCC recurrence has not been seen.

As with any preliminary, particularly retrospective, research, the European findings need to be replicated in different populations, and researchers need to make sure that the results are not due to biases, confounders, or chance occurrence.

G&H Even though more research is needed on this issue, should doctors make any adjustments to their management of patients?

RB Certainly doctors need to inform patients about the data (acknowledging their uncertainty) when treating patients for HCV infection, especially while administering ongoing HCC treatment, and/or managing any patients who may be at increased risk for HCC recurrence. In addition, in patients at the highest risk for recurrence of HCC, it might be best to consider waiting until it is clear that the tumor has been adequately treated without evidence of recurrence prior to undertaking HCV therapy. I am not recommending that doctors always wait or not wait; I think that clinicians need to balance the risks and benefits in each individual patient. Being that the data are uncertain on this issue, doctors might want to exert caution. Certainly all patients who have been treated for HCC need close follow-up, but until there is better understanding of this issue, doctors might want to follow patients who have had recent HCC therapy a little more closely after successful HCV treatment.

However, there are no new official recommendations at the current time to change the usual screening intervals or modalities based upon the presence or absence of HCV therapy. All HCV patients with cirrhosis should undergo at least standard surveillance for HCC, which is every 6 months. Many patients undergo more frequent screening after presumed curative or locoregional therapy for HCC. If a clinician is not sure whether to use intervals of 3 or 6 months in a high-risk subject, these new data may push him or her toward using shorter intervals.

G&H Are there any special considerations that should be kept in mind when managing these patients?

RB As clinicians, it is important to remember that even once HCV infection is cured, patients still carry a risk of HCC in the setting of cirrhosis. In addition, they still may have risks for ongoing liver disease. In particular, nonalcoholic fatty liver disease and alcoholic fatty liver disease are prevalent in the United States and worldwide. Therefore, even after HCV cure, patients require monitoring to make sure that their liver enzyme levels remain normal and that they do not have coexistent liver disease that would leave them at risk for further disease progression and liver-related morbidity and mortality.

Patients with cirrhosis need biannual imaging surveillance for HCC and tend to remain in the practice of hepatologists and gastroenterologists. Many patients who are noncirrhotic are discharged from specialist practices because they do not carry an increased risk of HCC. Therefore, it is important to instruct primary care doctors and other physicians involved in the care of these patients that if liver test results are abnormal or there are other risk factors for liver disease, these patients should continue to be followed or sent back to gastroenterologists or hepatologists. I have seen patients in my practice who have been cured of their HCV infection but still have abnormal liver function test results that have been attributed to the cured infection. That cannot be. We need to be aware and educate primary care providers, as well as other

gastroenterologists and hepatologists, that curing HCV infection does not eliminate the possibility of ongoing liver disease. If patients have abnormal liver function test results after being cured of their HCV infection, then investigation should be undertaken to determine the cause of those results.

G&H Are any studies being planned to further examine the possible relationship between DAA treatment and HCC recurrence?

RB All of the DAA agents have undergone study in cirrhotic patients, and most of the DAA manufacturers are following these patients long term, so these studies may provide some data on whether there is an increased risk of HCC occurrence or recurrence.

In addition, there will be data coming from other real-world experiences in the United States, such as HCV-TARGET (Hepatitis C Therapeutic Registry and Research Network), as well as possibly from national liver transplant and HCC databases, such as the Surveillance, Epidemiology, and End Results Program, to see whether HCV therapy has any impact on HCC recurrence. Large datasets and a period of time will be necessary to obtain a definitive answer on this issue.

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Suggested Reading

ANRS Collaborative Study Group on Hepatocellular Carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. *J Hepatol*. 2016;65(4):734-740.

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