HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Hepatocellular Carcinoma and Hepatitis Delta Virus

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G&H Is hepatitis delta virus oncogenic?

NR The simple answer is yes, although hepatitis delta virus (HDV) is not yet labeled as a carcinogenic virus. It is well known that hepatitis B virus (HBV) is oncogenic; it is strongly linked to causing cancer, which is why hepatitis B vaccination is considered to be an anticancer vaccine. HDV is an obligate virus; the development of HDV infection requires HBV infection. It is challenging to separate HDV from HBV. However, it is known that individuals who are coinfected with HDV and HBV have higher hepatocellular carcinoma (HCC) rates than those who are only infected with HBV, strongly supporting the idea that HDV is also a cancer-causing virus.

G&H What proportion of patients infected with HDV develop HCC?

NR Epidemiologic data in this area are limited. It is not well understood how many individuals are infected with HDV in the first place, including among those infected with HBV, as HDV testing has not been widely performed for many reasons. In addition, there is always the chance of skewed perception of risk when looking retrospectively at a population of people with HCC. However, it has been found that the rates of HCC and cirrhosis are significantly higher in patients coinfected with HBV and HDV compared with patients only infected with HBV (up to 3 times the rate of HCC and 10 times the rate of cirrhosis). Not all patients who are exposed to HDV develop HCC or cirrhosis, but the risk of each is much higher.

G&H What risk factors are associated with the development of HCC in patients who are infected with HDV?

NR The most significant risk factor is cirrhosis. However, other factors associated with HCC increase rates of this disease in HBV/HDV-coinfected patients. For example, factors such as hepatitis C virus (HCV), fatty liver disease, alcohol use, smoking, older age, and male sex are all linked to higher HCC rates. In addition, demographic data have shown that genetics or environmental exposure can increase the risk of HCC in some individuals in certain parts of the world. This is seen most commonly in sub-Saharan Africa, where aflatoxin B_1 exposure is common and associated with HCC. HCC develops at a much earlier age in sub-Saharan Africa than in other parts of the world. Accordingly, HBV guidelines recommend starting HCC screening at age 20 years in Africans compared with age 40 years in Asian men and age 50 years in Asian women. Mongolia has the highest incidence of HCC in the world, which reflects the high prevalence of HCV as well as HBV/HDV coinfection. All of these factors compound the risk of HCC with HDV infection.

G&H Does HBV/HDV treatment affect the risk of HCC?

NR Treating HBV has clearly been shown to reduce HCC in patients with chronic HBV infection. However, this is a more challenging question for patients coinfected with HBV/HDV, as effective treatments for HDV are not widely available. It is also important to note that

treating HBV does not have an impact on HDV, although it is certainly preferable for HBV to be well controlled. Medications that are used for HBV will not slow HDV disease progression. Natural history studies show that clinical outcomes are better in patients who are HDV antibody-positive but HDV RNA–negative, suggesting that it is viral replication, not just disease exposure, that causes complications. Traditionally, only interferon-based treatment was available, and it worked in few patients. If HDV replication was reduced and liver enzyme levels were improved, better clinical outcomes could be achieved. There is excitement because 2, and hopefully more, HDV medications are currently in the pipeline. If these medications can control viral replication and decrease inflammation in the liver, clinical outcomes, including HCC rates, should be improved.

G&H What are the possible mechanisms by which HDV may increase the risk of HCC?

NR It is recognized that HBV increases HCC risk both by causing liver damage from inflammation, oxidative stress, and fibrosis as well as by damaging DNA. HBV integrates into host DNA, which can separate pathways so that cancer-promoting ones can be turned on and anticancer pathways can be turned off. How HDV promotes HCC is not fully understood, although recent data suggest that the mechanism is distinct from that of HBV. Genes that are upregulated with HDV coinfection involve DNA replication and DNA damage and repair, suggesting that genome instability contributes to hepatocarcinogenesis.

> HDV infection increases HCC rates enough that it triggers an earlier time point to begin screening.

G&H What are the clinical implications of the relationship between HCC and HDV, particularly in terms of screening?

NR As discussed, the risk of HCC is much higher in an individual who has HDV infection. This impacts when individuals begin screening but does not change how they are screened; ultrasonography with or without alpha-fetoprotein at 6-month intervals is still standard. However, once coinfection with both HBV and HDV is established, guidelines support screening at the time of diagnosis as opposed to individuals who have only HBV monoinfection, in whom the recommendations to start screening are often based on age or a combination of family history and other factors. HDV infection increases HCC rates enough that it triggers an earlier time point to begin screening.

It should also be pointed out that there is a substantial need for biomarkers and better modalities that are more accurate to use for HCC screening. Currently, ultrasonography is used, although it is recognized that this modality is not as accurate as computed tomography (CT) scan or magnetic resonance imaging (MRI). However, using CT scans and MRI at 6-month intervals is not financially or physically feasible.

G&H Have there been any recent advances or changes in the understanding of HCC and HDV?

NR With better diagnostic tools and large clinical cohorts, providers are starting to understand more about HDV, including the variable and heterogenous risk of disease progression and HCC. Until prospective epidemiologic information suggests otherwise, HDV coinfection should be considered a much higher-risk condition than HBV monoinfection. Unfortunately, this increased risk does not yet translate to a change in management (outside of earlier HCC screening). In noncirrhotic patients, viral replication is associated with both progression to cirrhosis and HCC. Once cirrhosis is established, the risk of HCC will remain, even if replication can be eliminated. Thus, management will change when effective therapies are available to control viral replication and decrease disease progression. Ideally, therapy should be started prior to significant fibrosis to most effectively prevent negative clinical outcomes.

G&H What are the most important remaining questions regarding the relationship between HCC and HDV?

NR There are many unanswered questions. It is necessary to start more effectively identifying individuals who have HDV infection to better understand disease progression and explain the heterogeneity within that progression. For example, is the disease different if the patient acquired it at an early age or at an older age (eg, through injection drug use)? Is it different if the patient acquired HDV infection and also has fatty liver disease? Is it different if the patient has HDV infection and low levels of replication, compared with HDV that has high levels of replication? More data are needed. Our understanding has been limited by the lack of screening of HBV-infected patients for HDV,

lack of large prospective natural history cohorts, and lack of effective therapy. There are still also questions regarding potential oncogenic mechanisms that could drive both therapeutics as well as chemoprevention. It is obvious that an at-risk population should limit additional risk through smoking and alcohol cessation, but what if using a statin or aspirin could also decrease HCC rates?

G&H Are you aware of any studies currently underway or upcoming in this area?

NR There is a lot of excitement around HDV, and this has led to investigations into every aspect of the HDV care pathway. Multiple studies are looking at treatments for HDV either directly or by achieving hepatitis B surface antigen (HBsAg) clearance. Studies are looking at various screening strategies such as whether a reflex test from HBsAg to HDV antibody could facilitate diagnosis. There is also exciting research into genomics and the molecular signaling pathways driving hepatocarcinogenesis. HCC therapy is also expanding. Most importantly, there is a push to determine whether guidelines should be changed to support more-inclusive screening for HDV in HBV-infected individuals, as prevention and early identification will always be best.

Improved screening is important because curative measures are available for early-stage HCC; in contrast, there are limited treatment options when cancer is found at an advanced stage, although systemic chemotherapy is improving.

G&H Are there any misconceptions in the general gastroenterology or hepatology community about this topic?

NR Many US physicians think that HDV is extremely uncommon, likely because there is a lack of testing for it. They also may feel that they should not screen for it because they cannot do anything if they find it because of the current lack of effective treatments. Being that the rates of cirrhosis and HCC are much higher in patients who are infected with HDV, identifying individuals who are at higher risk is very important. This will require commercially available tests covered by insurers, guidelines that outline appropriate screening, and a clear care pathway for infected individuals. An educational campaign needs to be started so that providers look for HDV in HBV-infected individuals and do not miss the opportunity to take better care of patients. Improved screening is important because curative measures are available for early-stage HCC; in contrast, there are limited treatment options when cancer is found at an advanced stage, although systemic chemotherapy is improving. Better therapeutics are expected shortly. Finally, I want to emphasize that HDV and HBV are vaccine-preventable infections. It is important to screen for HBV and vaccinate patients who are not protected.

Disclosures

Dr Reau has received research funding (paid to her institution) from Eiger. She has also consulted for Gilead.

Suggested Reading

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