ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Hepatitis Delta Virus Testing and Research

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G&H How prevalent is hepatitis delta virus in the United States?

JG The exact number is not known, but approximately 100,000 individuals in the United States are currently infected with hepatitis delta virus (HDV), which has been referred to as the worst form of human viral hepatitis. Thus, it certainly qualifies as an orphan disease, but the number of individuals infected is not insignificant. The disease is more prevalent in other parts of the world.

G&H Why has there been undertesting and underreporting of HDV?

JG The practical and historical legacy of HDV is likely to blame. In the past, there was not much awareness of the disease, and if people were aware, they often did not think that identifying infected individuals was important; after all, effective treatment was not available, so management would not change. This thinking is changing now because there are several exciting therapies that will likely become available in the near future. Thus, it is becoming important to identify individuals who have HDV.

G&H How do hepatitis delta antibody tests and RNA tests compare in terms of specificity and sensitivity?

JG Some of the commercial hepatitis delta antibody tests that are currently available are suboptimal. Although they tend to be relatively inexpensive, many of the enzyme-linked immunoassay (ELISA)-based tests have significant false-positive and false-negative rates as compared with the gold standard of HDV RNA testing or even standard Western blot testing, which can assess the specificity of the antibody.

As mentioned, the HDV RNA test is the gold standard for active infection as well as treatable infection. Not too long ago, commercial tests were not available in this country, but now there are several commercial tests that are very good in terms of both specificity and sensitivity. However, they are expensive. If money is not a concern, HDV RNA testing should be used right away. Otherwise, an antibody test is better than nothing, but if the clinical suspicion is high and the antibody test is negative, additional testing should be pursued to ensure that the antibody test is not a false-negative.

My colleagues and I recently developed an alternative test, which is a quantitative microarray antibody capture (Q-MAC) assay. Essentially, the test quantitates the amount of hepatitis delta antigen–specific immunoglobulin G that is present in a patient's serum. This assay has been shown to be very sensitive and quantitative, and has several thresholds that are very practical. If the antibody titer is above a first threshold, there is a 100% chance that the patient will test positive on a standard Western blot. As a result, we no longer perform routine Western blots. In addition, if the Q-MAC assay shows an antibody titer above a higher second threshold, there is a 100% chance that the patient will test positive for HDV RNA. Thus, this assay is very useful because by performing just one test, it is possible to predict with certainty who will test positive for HDV RNA and whether he or she will test positive for a standard Western blot, indicating that the patient has been exposed to HDV at some point.

Measuring HDV RNA is important from a practical clinical perspective because it indicates which patients need to be treated. From an epidemiologic perspective,

however, just accurately knowing who has antibodies that are specific for delta antigen is useful. Although the Q-MAC assay is not yet commercially available, it has been used on a research basis for screening large populations and cohorts from different countries to determine estimates of prevalence of HDV-infected individuals from a given region of the world. It has also been useful on an individual patient basis when a clinician performs a commercial ELISA for HDV that comes back negative, but the clinician still suspects that the patient has the disease based on other clinical criteria. As mentioned, one of the challenges for some commercial ELISAs is that false-positives and, even more concerningly, false-negatives may occur.

G&H Will commercial genotype tests be needed for HDV?

JG It is unclear. In the United States, a large percentage of patients with HDV currently have genotype 1, although that could change with immigration from parts of the world where other genotypes are more prevalent. All genotypes are expected to be equally sensitive to the therapies in development, at least for the therapies that I am most involved with, such as the prenylation inhibitor lonafarnib (Eiger BioPharmaceuticals) or interferon lambda (Eiger BioPharmaceuticals). Genotype is unlikely to have clinical significance for those drugs. It remains to be seen if there are particular genotypes that are more or less sensitive to other drugs in development.

G&H Is there a need for rapid diagnostic tests?

JG There are several that are being developed, and I suspect that the pace with which they will become available may increase, piggybacking on the push to develop rapid diagnostic tests for COVID-19. These tests could be useful in remote settings for epidemiologic testing or in low-resource areas. In addition, these tests could potentially be used at the point of care in the doctor's office, coupled with initiation of treatment. However, for therapeutic purposes, it is most important to monitor HDV RNA, which ideally needs to be done in a quantitative manner (ie, in terms of monitoring response to therapy using a quantitative polymerase chain reaction [PCR]-based assay).

G&H Should commercial laboratories implement reflex testing of hepatitis B surface antigen to antibodies to HDV and then PCR testing?

JG That is a good idea. It is probably an efficient way to make sure not to miss people who could benefit from the new therapies. The only caveat is what type of HDV testing to perform. If an antibody test is validated to have very low false-positive and false-negative rates, then that is a reasonable approach. Anyone who has antibodies for HDV should undergo PCR testing.

G&H Is there a role for direct-acting antivirals in the treatment of HDV?

JG There are no direct-acting antivirals (DAAs) for HDV, in part because the virus does not encode any classical targets against which to develop DAAs. The DAAs that are currently available for hepatitis B virus have a minimal role because they do not have an effect on HDV. All that HDV needs from hepatitis B virus is a source of hepatitis B surface antigen, which HDV is very efficient at coopting from hepatitis B virus in the same cell. Therefore, unless a DAA can completely eradicate every trace of surface antigen, it is not expected to have any effect on HDV. All of the studies to date have shown this.

G&H Is HDV RNA negativity a cure for HDV?

JG This is a challenging question because HDV behaves differently than other viruses, where RNA negativity sustained for 6 months has typically been what is used to define a cure. For example, when a patient tests negative for hepatitis C virus RNA for a certain period of time following treatment, we know that the patient is cured—in other words, the virus does not come back. For HDV, that is not the case. Even patients who test negative for HDV RNA 6 months following cessation of treatment can have late relapses. In fact, late relapse has historically been quite common with HDV. With the newer therapies, that may be different, but for the time being, even patients who test negative for HDV RNA following treatment should be monitored for a long time to watch out for a late relapse.

G&H What are the priorities of research in terms of HDV testing?

JG An important priority is developing better-performing, low-cost screening assays for hepatitis delta antibody that are not subject to significant false-positive and false-negative rates. When a clinician has confidence in an assay, another priority is using it and screening as many appropriate people as possible. Now that effective therapies are in development, it is important to make sure that every patient who could benefit from treatment has access to it.

G&H What are some of the promising treatments in development for HDV?

JG Historically, the only drug that has been available is interferon alpha, which is difficult to take, needs to be used for a long time (at least a year), and is associated

with high relapse rates in the minority of patients who respond. However, it is not approved by the US Food and Drug Administration for use in HDV.

There are several new agents in advanced development. One is the entry inhibitor bulevirtide (formerly Myrcludex-B; Hepcludex, Gilead), which is a peptide therapy delivered by daily or twice-daily subcutaneous injection for at least a year. In addition, an intravenous nucleic acid polymer treatment showed quite promising efficacy in one study, but further clinical studies are needed. It also has the drawback of having to be given intravenously, which is very inconvenient because many months of repetitive dosing are required.

The only oral therapy that is currently in phase 3 development is lonafarnib. In addition to being the most convenient therapy, it is synergistic with interferon alpha. However, going forward, interferon alpha may be substituted with interferon lambda, which has the same antiviral efficacy as alpha but is much better tolerated. It is administered via subcutaneous injection just once a week. It has shown exciting findings in patients with HDV. A study that combined lonafarnib and interferon lambda was recently completed at the National Institutes of Health. It showed evidence of significant synergy between the 2 drugs, and the combination achieved profound antiviral responses with only 6 months of treatment, as opposed to most other regimens, which are given for a year or more.

One or a combination of the aforementioned agents may offer hope to patients with HDV. These agents have different mechanisms of action, so there is the potential for various combinations. I think some patients may need only an oral drug; however, some patients may need more than 1 drug.

Disclosures

Dr Glenn is the founder of Eiger BioPharmaceuticals, has an equity interest in the company, and is on the board of directors.

Suggested Reading

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