ADVANCES IN HEPATOLOGY

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Emerging Therapeutic Targets for Hepatitis Delta Virus Infection

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

JG Estimates are that approximately 70,000 to 100,000 people in the United States and approximately 15 to 20 million people worldwide are infected with hepatitis delta virus (HDV). This virus can be found across the entire world; the countries that do not report it either do not test for it or their tests do not work properly.

G&H What are the potential consequences of HDV infection?

JG This virus is responsible for the worst form of human viral hepatitis. HDV has its own genome and coat-like structure, but its lipid envelope uses the same envelope proteins that hepatitis B virus (HBV) does; in fact, HDV steals them from HBV. Thus, HDV infects cells the same way that HBV does and uses the same receptor as HBV. The net effect is more severe disease than with HBV monoinfection. In addition, HDV accelerates the progression of fibrosis to cirrhosis compared to monoinfection with HBV. With HDV infection, the patient may have earlier complications of end-stage liver disease and liver decompensation. Also, the patient will have decreased survival and higher rates of liver cancer compared with infection with HBV alone.

G&H Which patients should be tested for HDV infection?

JG Anyone who has HBV infection should be considered for HDV testing, especially people who have elevations of alanine aminotransferase (ALT; a liver enzyme that is released when the liver is damaged), exacerbations or more serious forms of their disease, or earlier onset of disease. Until recently, many physicians, including hepatologists, did not screen their patients for HDV infection because effective therapies were not readily available. Now that effective therapies are on the horizon, the rates of HDV testing are starting to increase.

G&H Why are new therapies needed for HDV infection? How effective is current treatment?

JG No treatment has been approved by the US Food and Drug Administration. The only treatment currently being used in clinical practice that has been shown to have some efficacy is interferon α in its regular or pegylated form. The treatment duration is usually at least 1 year, and response rates are approximately 20% to 30%, with a high rate of posttreatment relapse. In addition, the side effects of interferon α are considerable, typically including flu-like symptoms, myalgias, headaches, depression, and cytopenias, which can be very significant. Prolonged therapy may require dose reduction.

G&H Which new therapeutic targets are currently being considered for HDV infection?

JG A good deal of work has been done trying to understand the molecular biology of HDV and its life cycle. This has led to the identification of several targets that form the basis of new therapies that have entered clinical trials. The first target is entry, and the class of entry inhibitors is exemplified by Myrcludex B (Hepatera/MYR GmbH), which is designed to compete with HDV and HBV entry into the hepatocyte.

The next class of drugs consists of nucleic acid polymers, which are exemplified by REP 2139 (Replicor).

These compounds may have multiple mechanisms of action, but they appear to inhibit the secretion of hepatitis B surface antigen envelope proteins.

The third class of drugs consists of prenylation inhibitors, which are exemplified by lonafarnib (Eiger BioPharmaceuticals, Inc). These agents target prenylation, a host process that the virus is critically dependent on in order to form and release a new virus particle.

The fourth class of drugs is pegylated interferon λ (Eiger BioPharmaceuticals, Inc). In clinical trials of other hepatitis viruses, this type of interferon has shown roughly comparable antiviral effects as interferon α but with fewer side effects. This is likely because the receptors for interferon λ are less widely distributed throughout the body than those for interferon α.

G&H What have studies reported to date regarding the use of Myrcludex B?

JG The first pilot study of this agent involved 24 weeks of treatment (2-mg daily subcutaneous injections) vs standard pegylated interferon α vs the combination of these drugs. After this treatment period, the patients continued on pegylated interferon α alone for a total of 48 weeks. The primary endpoint of the study was a decrease in hepatitis B surface antigen, but no statistical change was seen at week 24. There was a 1.67 log reduction in HDV RNA with Myrcludex B alone, a 2.17 log reduction with pegylated interferon α alone, and a 2.59 log reduction in the combination at week 24.

Of note, all of these patients had a relatively low baseline HDV RNA level, with the mean being 10^4 copies/mL. Two patients on Myrcludex B monotherapy, 2 patients on pegylated interferon α monotherapy, and 5 patients on the combination went below the limit of quantitation. This study was the first demonstration of Myrcludex B's in vivo antiviral activity against HDV in patients. However, when treatment was stopped, viral RNA increased.

More recently, a larger, phase 2B, open-label study was initiated with Myrcludex B plus an anti-HBV nucleoside. In this study, all patients are on a HBV nucleoside plus either 2, 5, or 10 mg of Myrcludex B administered by daily subcutaneous injections for 24 weeks. The primary endpoint is a 2 log decline of HDV RNA at the end of the treatment period. Interim data presented at the 2017 meeting of the American Association for the Study of Liver Diseases (AASLD) showed a 1.8 log median HDV RNA decline for the 2-mg dose, a 1.6 log median decline for the 5-mg dose, and a 2.7 log median decline for the 10-mg dose. ALT levels generally improved, but hepatitis B surface antigen did not change. Bile acids increased, which is consistent with how the mechanism of this drug works (ie, by targeting the receptor for bile acid uptake, which is used by both HDV and HBV), but there was no report of significant pruritis. Further data are awaited on this drug.

G&H What research has been conducted thus far on REP 2139?

JG The nucleic acid polymer REP 2139 has been tested in a pilot study of 12 patients in Moldova. The study consisted of 15 weeks of 500 mg of the drug given intravenously once a week, followed by another 15 weeks at half the dose plus standard pegylated interferon α, the latter of which was continued for a total of 48 weeks. Four of 12 patients had an impressive decrease (up to 5 logs) in hepatitis B surface antigen during intravenous monotherapy. These declines were associated with HDV RNA becoming negative. Response was mostly maintained during the pegylated interferon α phase of the study, although 5 patients rebounded after cessation of REP 2139.

G&H What clinical trial data are currently available on lonafarnib?

JG Lonafarnib is an oral agent that has been given to over 2000 patients in previous oncology studies. A placebo-controlled proof-of-concept study by the National Institutes of Health (NIH) demonstrated a strong correlation between the amount of drug in the serum and the mean viral load decline, and showed no evidence of resistance. This study was followed by the phase 2 LOWR HDV (Lonafarnib With Ritonavir in HDV) –1, –2, –3, and –4 studies, which included over 120 HDV-infected patients across multiple international sites. This agent has dose-limiting gastrointestinal toxicities of diarrhea, nausea, and weight loss. Because CYP3A4 extensively metabolizes lonafarnib, coadministration with ritonavir, a well-established CYP3A4 inhibitor, allows for the use of a lower lonafarnib dose with better gastrointestinal tolerability but higher postabsorbed drug levels that allow for increased efficacy. In these studies, doses from 25 mg twice daily up to 100 mg twice daily have been investigated, all with ritonavir.

Several of these regimens have shown promise in various studies, but 2 are likely to be focused on in subsequent larger-scale studies. One regimen consists of 50 mg twice daily of lonafarnib with ritonavir 100 mg twice daily, both administered orally. At 24 weeks of treatment, multiple patients were HDV RNA–negative, and the majority of patients had normalized ALT levels.

The other most promising regimen is the combination of low-dose lonafarnib (25 mg) and ritonavir (100 mg), both administered orally twice daily, with pegylated

interferon α. All of the patients went below the limit of quantitation. Three of 5 patients were HDV RNA–negative at week 24. Two of those 3 patients stopped treatment at week 24 and were HDV RNA–negative at week 48, while the other patient continued treatment to week 48 and was HDV RNA–negative. In this triple combination therapy, the majority of patients also normalized their ALT levels.

Surprisingly, approximately 15% of patients who did not become HDV RNA–negative during the earlier trials of lonafarnib experienced transient ALT elevations after stopping treatment, followed by ALT normalization and a decline in HDV RNA to undetectability. Patients who experienced this phenomenon and continued to remain HDV RNA–negative with normal ALT levels showed evidence of fibrosis reversal on liver biopsy.

G&H Have there been any studies on pegylated interferon λ?

JG Pegylated interferon λ is currently being studied in 33 patients in New Zealand, Pakistan, and Israel, and an interim analysis of this study was presented at the most recent AASLD meeting. Ten patients had reached at least 24 weeks of treatment with pegylated interferon λ. At 24 weeks, 6 of 10 patients (60%) responded and had a HDV RNA decline of greater than 2 logs or had become HDV RNA–negative. Three patients showed evidence of rebound on treatment, and 1 had no significant response to treatment. There was a mean 2 log decline in HDV RNA at week 24. Many of these patients had been on interferon α in the past and experienced fewer side effects with pegylated interferon λ.

G&H What side effects have been reported with these emerging drugs?

JG Myrcludex B is associated with an increase in bile acids. Thrombocytopenia, lymphopenia, eosinophilia, and neutropenia have been described, but were usually mild and transient. Hair loss, dysphagia, and dysgeusia have been reported with nucleic acid polymers. In addition, mild pancytopenias have also been reported, and required dose reductions of pegylated interferon α. Gastrointestinal side effects (eg, diarrhea, nausea, anorexia, weight loss) have been described with higher lonafarnib doses, but have usually been mild with lower doses. The main side effects of pegylated interferon λ are possible increases in the level of transaminases and bilirubin, but these resolve with dose reduction.

G&H Are any of these new drugs close to being approved?

JG This coming year, there will likely be registration studies for lonafarnib with ritonavir as an oral treatment as well as lonafarnib/ritonavir in combination with pegylated interferon λ, although these studies will wait concordance with the US Food and Drug Administration. To my knowledge, there is no open investigational new drug application in the United States for the other aforementioned drugs at this time.

G&H Do these drugs reflect any other new concepts involving HDV?

JG The targeting of prenylation with lonafarnib is an example of targeting a viral infection with a drug that inhibits a host-cell target (ie, not something in the actual virus). One of the predictions of such an approach is that it is targeting a genetic locus that is not under the control of the virus; thus, it may be a much harder evolutionary task for the virus to develop resistance or to evade this inhibition. This is predicted to translate into a higher barrier to the development of clinical resistance. The first empiric data in humans are now available from studies conducted at the NIH and in Turkey in which virus isolates from every patient were sequenced at every time point, and indeed no evidence of resistance was revealed. Thus, targeting a host-cell function upon which the virus depends can translate into a very high barrier to the development of resistance. This can enable the drug to be used at progressively lower doses. This targeting concept is also being applied to other viruses.

Dr Glenn is the scientific founder of Eiger BioPharmaceuticals, Inc; is on the Board of Directors; and has an equity interest in the company.

Suggested Reading

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