Hepatitis delta virus (HDV) is a defective virus that needs the helper function of hepatitis B virus (HBV) in the form of hepatitis B surface antigen (HBsAg) production to propagate and cause disease in humans. In addition, HDV needs the host RNA polymerase for its replication because its genome does not code for an RNA polymerase of its own. Yet, HDV causes the most severe form of viral hepatitis both in the acute and chronic hepatitis settings. The importance of HDV and the severe liver disease it causes are exemplified by cohort studies demonstrating that HDV is associated with higher rates of cirrhosis and complications of cirrhosis compared to HBV monoinfection. Despite these observations and in striking contrast to HBV or hepatitis C virus, treatment for HDV has not changed in more than 3 decades and consists of the off-label use of conventional or pegylated interferon alfa (PEG-IFN alfa) for the chronic viral hepatitis setting. Given the nonspecific antiviral and immunomodulatory effects of interferons, it is fair to say that currently there is no specific treatment for acute and chronic hepatitis delta (CHD). Although delta hepatitis or the disease caused by HDV is actually a consequence of co-infection of HDV with HBV, with the exception of rare instances, the dominant virus is HDV; therefore, treatment needs to be tailored toward HDV. Without a doubt, there has been a lack of interest among the biomedical industry to develop new drugs for this most serious viral hepatitis form. One reason may be the fact that HDV is the least encountered of the five human hepatitis viruses; according to a recent study, 12 million people (or 4.5%) infected with HBV are anti-HDV positive. CHD has received orphan disease status in the European Union and the United States. Another reason for the lack of interest may be the absence of a readily available “easy” viral target for drug interference.

IFNs remain a suboptimal treatment option for CHD, and although they have been used for more than 30 years, even the optimal way to use them has not been thoroughly investigated. Their use is hampered by frequent adverse events and suboptimal treatment responses. Viral relapse is common and may occur quite late. Treatment is mainly for a duration of 1 year, although a total treatment duration of more than 10 years has been reported, which may be seen as a desperate attempt to get the most out of a suboptimal single-treatment option despite the accompanying adverse events. It is clear that new treatment options are needed, and it is fortunate that we are finally witnessing the active transformation of bench-side work into clinical practice. Two drugs, the farnesyl transferase inhibitor lonafarnib and the hepatocyte entry inhibitor bulevirtide, are currently going through phase 3 studies. Bulevirtide has received conditional approval by the
European Medicines Agency for the treatment of compensated CHD as of July 2020. In recent study of *Hepatology Communications*, data on long-term follow-up of CHD treatment with another new compound, the nucleic acid polymer (NAP) REP 2139, is reported. Briefly, 12 patients with compensated CHD received 15 weeks of REP 2139, followed by 15 weeks of a combination of REP 2139 and PEG-IFN alfa 2a. After 30 weeks, REP 2139 administration was stopped and PEG-IFN was continued for another 33 weeks, for a total of 48 weeks of PEG-IFN treatment. REP 2139 was given as 2-hour intravenous infusions once per week. At the end of treatment, or 63 weeks, 6 of 12 patients were HBsAg negative and had developed protective (>10 mIU/mL) antibodies to hepatitis B surface antigen (anti–HBs) titers. One year after treatment discontinuation, HBsAg negativity and anti–HBs positivity were maintained in 5 patients. Similarly, at the end of treatment and 1 year of follow-up, HDV RNA was undetectable by polymerase chain reaction in 9 and 7 patients, respectively. These data were presented in the original manuscript 3 years ago. The current paper describes 3.5 years of follow-up data after treatment discontinuation of the same cohort and basically reports that HBsAg negativity and anti–HBs were maintained in 4 patients and HDV RNA was maintained in 7 patients. Maintaining undetectable HDV RNA is very important clinically and may herald prevention of complications of liver disease in these patients. It is, however, not equal to a cure for HDV because the virus may remain infective at titers well below the most sensitive HDV RNA assays. Supporting this observation, viral relapse has been reported as late as 9 years after treatment discontinuation.

Available data are very striking, but there are also unanswered questions, concerns, and deficiencies. First, the mechanism of action of NAPs is not well understood. It is suggested that NAPs exert their effect most likely by blocking the release of HBsAg mainly as subviral particles from hepatocytes. It is assumed that blocking HBsAg extrusion into the circulation will counteract HBsAg-induced inhibition of the host immune system and pave the way for host-immune control of HBV/HDV infection. However, the mechanism by which release of subviral particles from hepatocytes is blocked is not clear. NAPs are oligonucleotides in which an oxygen atom normally linking two consecutive nucleotides is replaced with sulfur. The introduction of the sulfur atom makes these “phosphorothioate oligonucleotides” hydrophobic and allows them to interact with hydrophobic surfaces of proteins in a sequence-independent, phosphorothioate-dependent manner. Data so far suggest that the antiviral efficacy of NAPs in HBV and HDV is without any apparent effect on HBV or HDV viral components. Further, despite the early HBsAg clearance and development of protective anti–HBs titers in some patients, no immunoreactive properties are known for NAPs. It is speculated that NAPs may target a host protein for their antiviral effects in HBV as well as HDV. This protein remains to be discovered.

Second, a clinical concern might be the fate of retained HBsAg in hepatocytes. Retained HBV envelope proteins may stimulate oncogenic pathways and could lead to the development of hepatocellular carcinoma; however, data indicate effective HBsAg tissue clearance. Maintenance of safety for 3.5 years after treatment is also confirmatory.

A third concern is the observed on-treatment hepatitis flares, in particular in patients with advanced liver disease (in the current study, patients with cirrhosis were avoided). These flares were more pronounced when PEG-IFN was added to REP 2139 and appeared to be beneficial. The mechanism of the flares during monotherapy with REP 2139 and its timing, association with virologic response, and incidence need to be assessed in a larger study.

Fourth, the effect of monotherapy with REP 2139 has to be compared to combination treatment with PEG-IFN to better understand the roles of NAP monotherapy and combination therapy with PEG-IFN in the management of CHD. Optimal treatment duration may differ according to treatment regimen. It may be shorter with combination treatment with PEG-IFN but longer with monotherapy.

Finally, we do not know if combination treatment using a staggered approach is better than simultaneous combination treatment. The rationale behind a staggered approach may be to decrease immune epitopes (inhibiting HBsAg release from hepatocytes) by using REP 2139 first and consequently restoring the “immune exhaustion” described for chronic hepatitis B (CHB), thus setting the stage for optimal treatment efficacy for PEG-IFN.

These theoretical considerations need to be addressed in future clinical studies. With lonafarnib and bulevirtide, the best results were obtained in...
combination with PEG-IFN. This is also likely the case with REP 2139, although this needs to be better demonstrated. However, there will also be a place for monotherapy with the new compounds, such as patients with low baseline HDV RNA for lonafarnib and patients with compensated cirrhosis who have thrombocytopenia for bulevirtide. The possible role of REP 2139 monotherapy also needs to be addressed in future studies. REP 2139 and other similar compounds have been assessed in the last 10 years in small patient cohorts from Moldova and Bangladesh. These compounds have been tested in approximately 60 patients and appear to be relatively safe, but it is time now for larger studies to address the many questions that have arisen. The company developing NAPs is working on a subcutaneous formulation, and a drug applied subcutaneously is definitely better suited for treating CHB or CHD. Meanwhile, we may see new classes of NAPs to be tested in CHB or CHD. The fact that the race for treating CHB or CHD more efficiently has gained momentum is promising. Last but not least, it is important to remember that the best and cheapest way of preventing HDV-related disease is to prevent acquisition of HDV, and high coverage of HBV infant vaccination in HBV-endemic countries is key.

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