ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Overview of Current and Emerging Treatments for Hepatitis B Virus Infection

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G&H Have there been any recent trends in the incidence of hepatitis B virus infection in the United States?

RK The incidence of hepatitis B virus (HBV) infection in the United States is fairly low. For the most part, this disease is not very common. Transmission of HBV is relatively difficult, as it requires body fluid and blood, and universal vaccinations have been used in this country since the early 1990s. However, there is a discernible trend that the opioid epidemic and injection drug use have caused an upturning of the incidence curve, which had been going down over time.

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

RK In people who acquire the infection as an adult, only a few percent develop chronic infection, whereas people who acquire the infection early in their life are more likely to have chronic infection than recovery. Among those who end up with chronic infection, between 15% and 40% will develop progressive liver disease in terms of fibrosis over time, eventually developing cirrhosis and end-stage liver disease. In parallel with the progression of fibrosis, there is an increased risk of liver cancer.

G&H What are the current treatment options for HBV infection?

RK The most common treatment involves nucleoside/nucleotide polymerase inhibitors, which disrupt one step, namely reverse transcription of HBV RNA to DNA, in the viral life cycle. It has been shown that just that disruption significantly improves clinical outcomes. Patients who are typically treated have evidence of chronic liver damage, which is often demonstrated by abnormal liver enzymes and a high viral load (HBV DNA) in the serum. Liver biochemistry, HBV DNA, and, to some degree, quantitative hepatitis B surface antigen (HBsAg) are used to monitor response to therapy. In the past, clinicians performed liver biopsy to assess inflammation and fibrosis, but in current practice, noninvasive measures of fibrosis are useful and widespread.

The other treatment currently being used for HBV infection is interferon. However, its use is not as common because it requires injection, is inconvenient, and, in some patients, creates side effects that are uncomfortable.

G&H What are the most significant limitations associated with current treatment?

RK The main limitation is that treatment with nucleoside/nucleotide polymerase inhibitors is not curative; it is suppressive. These agents disrupt the viral life cycle, but do not eliminate the virus from the hepatocytes. That is in part because the virus replicates off of its own minichromosome, known as covalently closed circular DNA (cccDNA), and the treatment does not eliminate that genetic template. The treatment is essentially a temporary suppression. If it is stopped, viral replicative activity returns.

Another limitation may be that the pathogenesis of chronic HBV infection involves 2 aspects. One is the virus replicating in the cells. The other is that there is an immune reaction to the viral infection. In order to fundamentally overcome that infection, the immune response needs to be altered to fight the infection better. Current treatment with oral antiviral agents has no direct impact on the immune system.

In addition, some of the current medicines have long-term side effects—an example being the renal and bone toxicity of tenofovir disoproxil fumarate—so clinicians need to carefully weigh the risks and benefits of using them. The high economic burden associated with long-term suppressive medicine is another potential limitation.

G&H Are new treatment goals and endpoints for drug development needed? What should be the ultimate goal of HBV treatment?

RK It has been very encouraging to see the recent advances in the treatment of hepatitis C virus (HCV) infection, where cure has become possible because of the elimination of all viral genomic templates within hepatocytes. We are trying to do the same for HBV infection. The ideal endpoint is to eliminate anything related to the virus—any nonnative viral genetic material or proteins—from the cells. However, this is difficult to accomplish because of the cccDNA in the hepatocytes and because viral DNA often inserts itself into host DNA. As an intermediary step, we may have to accept that some genetic material of the viral DNA cannot be eliminated.

The common endpoint that is being talked about currently is functional cure. By and large, that means elimination of detectable HBsAg in the serum, which is the hallmark of HBV infection, with or without generating protective antibodies (anti-HBs). That does not necessarily mean that all evidence of HBV is eliminated in the liver cells; we are aiming for undetectable peripheral HBsAg in the serum. That being the goal, lowering HBsAg concentrations in the serum has become an important early signal for new compounds.

G&H Could you discuss the entry inhibitors that are currently in development for the treatment of HBV infection?

RK HBV enters hepatocytes through the NTCP receptor, which is a sodium/bile acid cotransporter. The compound furthest in development that targets this step is Myrcludex B (MYR Pharmaceuticals). By inhibiting the virus from being able to attach to the receptor, it may be possible to disrupt the viral life cycle differently than the polymerase inhibitors currently being used. As entry inhibitors do not kill the virus—they prevent the virus from infecting naive hepatocytes—this is not expected to be an efficient way of eliminating HBV infection.

Entry inhibition has mainly been studied in patients with HBV who are co-infected with hepatitis delta virus. Hepatitis delta virus is an RNA virus that requires HBsAg to be able to infect new hepatocytes. Late stage (phase 2b) clinical development is ongoing, and the data thus far are encouraging in hepatitis delta virus patients, who currently have few treatment options.

G&H Why are small interfering RNAs being studied to treat HBV-infected patients?

RK Small interfering RNAs (siRNAs) disrupt the part of the life cycle where HBV DNA is translated to RNA, which is then used to make viral proteins. Thus, siRNAs can reduce the production of HBV RNA as well as viral proteins, which can potentially have a profound effect on viral replication. This disrupts the viral life cycle in a new and effective way. We learned from initial data that more than one area of the viral DNA may need to be targeted. Some of the newer data have shown lowering of HBsAg concentrations. There are several compounds being tested in humans, including VIR-2218 (Alnylam and Vir Biotechnology), RG6004 (Roche), and ARO-HBV (Arrowhead).

HBV antisense oligonucleotides work in a similar way and prevent viral proteins from forming. At the recent meeting of the American Association for the Study of Liver Diseases, promising data were shown with GSK 3228836 (GSK and Ionis) being able to lower HBsAg concentrations.

G&H How can capsid inhibitors potentially treat HBV infection?

RK The HBV nucleocapsid consists of the core protein envelope and HBV RNA/DNA inside the envelope. Capsid assembly is a critical step in the HBV life cycle to form infectious virions. Thus, inhibiting this step by preventing encapsidation or disrupting the core proteins should have a significant impact on HBV replication. Thus far, the data show that this inhibition decreases the amount of circulating virus (ie, serum HBV DNA), which is an important pharmacodynamic marker for the effectiveness of capsid assembly inhibition. However, the effects on HBsAg concentration have been less than impressive. In my opinion, capsid inhibition may be an important component of HBV functional cure, perhaps in combination with other compounds being developed. Examples of capsid assembly inhibitors include Morphothiadin (HEC Pharma), JNJ-56136379 (Janssen), and ABI-H0731 (Assembly Biosciences).

G&H Could you discuss the HBsAg inhibitors currently being studied?

RK The frontrunners of this group are nucleic acid polymers (REP 2139/2165, Replicor). The mechanism by which they work is still unclear, but animal and human

data show that when these compounds are administered, HBsAg is not released outside the hepatocytes. When used with existing antiviral medications, HBsAg inhibitors can dramatically reduce HBsAg concentration in the blood and, in some cases, generate anti-HBs response. These data are very intriguing and suggest that by reducing exposure to HBsAg in the body, the human immune system may be able to overcome the immune tolerance that the virus causes in an infected patient.

G&H Has there been any research recently on immune modulators?

RK In general, immune activation is likely an essential component of HBV treatment. Therapeutic vaccines and other measures to improve the immune response against HBV will likely be an important component in a functional cure program by working on the immune side of treatment as opposed to on the virus itself. As far as I know, there has not been a human study showing a therapeutic vaccine alone affecting HBsAg concentration.

Traditional interferon aside, other immune modulators have been tested for the treatment of HBV infection. The retinoic acid–inducible gene I agonist Inarigivir (Spring Bank) has a dual action with interferon stimulation and antiviral activities, and was shown to reduce HBsAg concentrations in the serum. Other innate immune system modulators (Toll-like receptor agonists) are also being explored.

G&H Will a combination of drugs most likely be needed?

RK I think it is very likely that a combination of drugs will be needed. HCV is often said to be an easier virus to cure, but its treatment currently consists of at least 2 antiviral medications. To the degree that HBV is a harder virus to kill, I think it is very likely that a combination will be needed. I could be wrong, however; in the early days of the current polymerase inhibitors, many doctors thought that those medications would need to be used in combination, but that did not turn out to be true. Perhaps we will need 1 or more drugs to kill or suppress the virus in conjunction with 1 or more drugs to boost the immune system to eliminate the remaining virus.

G&H Do you think achieving functional cure is a feasible goal within the next 5 years or so?

RK Obviously, it is difficult to predict the future. I would like to see if we could get to an intermediate stage, where we may not be able to readily eliminate HBsAg, but we might be able to add an effective drug to a polymerase inhibitor so that viral replication is halted without continuous, lifelong treatment. If we could get to a stage where HBV DNA remains undetectable off of all treatment, that would be significant progress compared to what we have now, even if HBsAg cannot be completely eliminated.

G&H What are the most important next steps in research in terms of HBV treatment?

RK It would be useful to have an easily accessible, accurate biomarker to understand the biology of the virus (ie, gauge what is happening inside the hepatocytes). For example, we do not have a good tool to measure the quantity or activities of cccDNA, which is the culprit for maintenance of infection.

In addition, because many researchers are hypothesizing that combination treatment will be necessary, it would be helpful to be able to predict which combinations might work best. This might involve systems biology or mathematical modeling, and will hopefully reduce many iterations of trial and error with different combinations.

In terms of unmet needs, I think research on immune-tolerant patients, including children, is urgently needed. It has been shown that HBV DNA integration occurs early in life, which may set in motion the process leading to liver cancer development. Trials to date have not suggested changes in long-term outcomes. Immune-tolerant patients make up the patient group in which novel therapeutic agents may have a large impact.

Finally, although a cure is still needed for HBV infection, it should be kept in mind that our current treatment is actually quite good and usually able to make a large impact when used appropriately. It is important to remember that of the estimated 250 million people currently living with HBV infection, only a fraction have been diagnosed, properly evaluated, and given effective medications. By all means, we should work on finding the cure to HBV infection, but in the mean time, we should also work on delivering the treatment currently available to HBV patients who need it.

Dr Kim has served on advisory boards for Gilead and Roche.

Suggested Reading

Cornberg M, Lok AS, Terrault NA, Zoulim F; 2019 EASL-AASLD HBV Treatment Endpoints Conference Faculty. Guidance for design and endpoints of clinical trials in chronic hepatitis B—report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference [published online November 12, 2019]. *J Hepatol.* doi:10.1016/j.jhep.2019.11.003.

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