ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Emerging Therapies Toward a Functional Cure for Hepatitis B Virus Infection

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G&H Currently, what is the burden of hepatitis B virus infection in the United States?

RK Population surveys have suggested that there are between 700,000 and 800,000 people living with hepatitis B virus (HBV) infection in the United States. However, those population surveys tend to miss people with a high prevalence of HBV infection, including recent immigrants and institutionalized people.

> ... ideally, the treatment goal would be to cure HBV infection.

Altogether, it has been suggested that up to 1.5 to 2 million people in the United States may actually have HBV infection.

G&H What should be the goal of HBV treatment?

RK The current goal is limited by the tools that are available to treat the disease. These tools, namely oral HBV polymerase inhibitors, are very effective at suppressing the virus from replicating and preventing damages to the liver, but they are not curative (unlike hepatitis C virus [HCV] treatment). Thus, the current treatment goal is remission of liver disease by effective suppression of HBV. It is important to keep in mind that this treatment goal can only be achieved in patients who are diagnosed with HBV infection and are being followed, and that there are many people living with HBV infection who have not even been diagnosed or connected to the health care system. Therefore, a larger health care system–wide goal is to provide treatment to all people at risk of future complications so that they can be prevented.

It should also be pointed out that, ideally, the treatment goal would be to cure HBV infection. Although achieving that goal is not currently possible, there are many compounds being tested at the present time. Hopefully in the next decade, there will be a cure for this disease.

G&H How can functional cure of HBV infection be defined?

RK The prevailing definition of functional cure at the present time is loss of hepatitis B surface antigen (HBsAg) in the blood. However, what this means biologically is not completely understood. There are several barriers to cure, one of which involves covalently closed circular DNA, a sort of viral chromosome in the liver cells of an infected person. This replication template is not affected by the current polymerase inhibitors. Another barrier is that some of the viral genome is inserted into host chromosomes, which can generate viral proteins. The extent to which this contributes to the maintenance of chronic infection is unknown, as is whether it is possible to achieve

Table. Partial List of HBV Direct-Acting Antiviral Candidate Compounds in Human Trials

Drug	Company	Latest Trial Phase
siRNAs		
ARB-1467	Arbutus Biopharma	Phase 2
ARB-1740	Arbutus Biopharma	Phase 2
RG6004 (HBV LNA)	Roche	Phase 1/2
ARO-HBV	Arrowhead	Phase 1/2
Entry Inhibitor		
Myrcludex B	Hepatera/MYR	Phase 2
Capsid Inhibitors		
NVR 3-778	Janssen	Phase 2
JNJ-56136379	Janssen	Phase 1
ABI-H0731	Assembly Biosciences	Phase 1
AB-423	Arbutus Biopharma	Phase 1
HBsAg Inhibitors		
REP 2139	Replicor	Phase 2
REP 2165	Replicor	Phase 2

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LNA, locked nucleic acid; siRNAs, small interfering RNAs.

Adapted from Hepatitis B Foundation. Drug watch. Compounds in development for chronic hepatitis B. http://www.hepb.org/treatment-and-management/drug-watch/. Updated May 2018. Accessed June 20, 2018.

functional cure by interrupting the viral cycle at different points. Functional cure may not translate to complete cure because of the viral genome fragments that persist in the host cells.

G&H What treatment approaches or targets are currently being used for HBV infection, and what are their functional cure rates to date?

RK Currently, only 2 classes of HBV treatment agents are available. One is interferon, which is an immunomodulatory drug as well as an antiviral agent. Interferon has a low functional cure rate, but the rate varies according to the host phase of infection. People who are younger and have more active underlying liver inflammation tend to respond better, whereas older people with less inflammatory activity have a lower cure rate. After interferon therapy, the functional cure rate is, at most, 20%. In functional cure with interferon, a certain percentage of HBsAg loss can occur after treatment is completed. The other class of medicine for current HBV treatment consists of HBV polymerase inhibitors, often called nucleoside or nucleotide analogues. These agents are very effective at suppressing the virus by blocking the viral enzyme needed for the virus to replicate itself. However, they do nothing directly to the host immune system, and their functional cure rate is lower than that of interferon (<10% over many years of follow-up).

G&H What treatment approaches or targets are currently being investigated for HBV infection?

RK There are many classes of targets currently under investigation, some of which are listed in the Table. One class blocks the entry of HBV into hepatocytes, as the virus usually takes advantage of a receptor to insert itself into the cytoplasm of a hepatocyte. One agent in this class (Myrcludex B, Hepatera/MYR) is being tested in a phase 2 clinical trial.

Another class undergoing fairly active investigation involves small interfering RNAs. This class targets the viral genome in different areas to disrupt viral protein production and interrupt its life cycle. Within this class, there are several compounds being tested, and the difference between them relates to the region of the RNA that each is targeting and how the RNAs are introduced into hepatocytes.

Capsid inhibitors comprise another class of agents currently undergoing investigation for HBV treatment. Capsid, the protein surrounding the viral genome, plays multiple roles, allowing capsid inhibitors to have multiple modes of inhibiting HBV. Currently, several of these agents are being tested.

Another class in clinical development consists of HBsAg inhibitors. The last step of the HBV life cycle is for the virus (or surface protein) to be exocytosed, and this particular class of chemical inhibits HBsAg from being processed and released outside of the cell. Interestingly, this seems to trigger an immune reaction from the host, as the viral proteins circulating in the body may play a role in paralyzing the immune response. Preliminary studies indicate that, when combined with other antiviral agents, a HBsAg inhibitor may help patients restore their immune function, leading to HBsAg loss and sometimes hepatitis B surface antibody production.

In addition, there are a number of agents purported to improve host immune response against HBV. Some of them are innate immune enhancers, including Toll-like receptor agonists. Also in early development is a RIG-I activator that triggers interferon response, as well as directly interrupts HBV replication. Finally, there are a number of agents targeting the adaptive immune system. For example, programmed cell death protein 1 and

programmed death-ligand 1 inhibitors are checkpoint inhibitors that have led some patients to lose HBsAg by breaking the immune tolerance that perpetuates the infection. A number of therapeutic vaccines are under development as well.

Once HBV is incorporated into the host genes, it is a challenge to remove it.

G&H What clinical trial data are available on these agents?

RK The clinical trial data are either phase 1 or 2 at most, so they are not very mature, but they are promising. However, there have not yet been large-enough trials to conclusively tell us that any of these molecules will consistently provide high rates of functional cure that are clinically meaningful.

G&H Overall, what appears to be critical for achieving functional cure?

RK The data to date seem to indicate that 2 components are needed. One is to fundamentally disrupt the viral life cycle, and the other is to encourage the host immune system to try to break through the tolerance that is preventing cure of the infection. My interpretation of the emerging data is that both of these components have to work together. Therefore, some element of immunomodulators is likely necessary, at least in the beginning stages of the cure effort, as well as direct-acting antiviral agents with viral or intracellular targets. Identifying what may be the ideal combination seems to be what most researchers are trying to figure out because none of the compounds previously mentioned appear to completely eliminate the virus by themselves. The data are promising for curing the virus, as compared to merely suppressing it, but we are not there yet. We would like to be able to achieve what we have come to expect with HCV.

A major unknown factor in functional cure of HBV is the integration of HBV DNA into the host. Once HBV is incorporated into the host genes, it is a challenge to remove it. This is thought to be an important barrier to achieving functional cure, but it remains to be seen whether this will continue to be the case as better treatments are developed. Another issue is at what cost we should try to achieve functional cure. Currently, there are very effective viral suppressive medicines that drive the hepatitis B viral load to zero (ie, undetectable levels) as well as cause the patient's liver inflammation to disappear and the progression of liver disease to halt (and sometimes even reverse). Those agents achieve very good outcomes without too many long-term safety concerns, so the bar is set fairly high that (1) functional cure should actually provide more advantage to the patient and (2) functional cure could be achieved safely. It is unknown what it means to have HBsAg disappear if all that it accomplishes is status quo plus cosmetic disappearance of the antigen. Does that simply mean patients would be able to stop taking suppressive medicine long term? Or does functional cure really mean fundamental alteration of the natural history of the infection (ie, eliminating the risk of liver cancer, which would be groundbreaking)? This issue remains to be sorted out.

G&H Are there any data showing that the elimination of HBsAg is actually meaningful?

RK Proponents of functional cure as the next endpoint point to data obtained from people who experience HBsAg loss, untreated or treated with the currently available medications. They observe that patients who lose HBsAg have much better outcomes over time than patients who fail to lose HBsAg. However, these 2 groups of people are often too different to compare. People who lose HBsAg on their own, or even those who are taking the currently available antiviral agents (particularly nucleoside/nucleotide analogues), may have something in their body, perhaps in their immune system, that lets them achieve functional cure. Their underlying ability (ie, a host factor) may be what is driving the apparent benefit of HBsAg loss rather than the fact that the HBsAg has become undetectable in their blood.

G&H Is it possible that a single drug may be able to achieve functional cure of HBV?

RK Thus far, the data seem to suggest that none of the compounds being tested may be sufficient individually to achieve functional cure. At the present time, I think it is likely that some type of combination will be needed, perhaps one that works on intracellular targets and another on host immune cells.

G&H Is achieving functional cure a feasible goal for all HBV patients in the near future?

RK It depends on how the near future is defined. I have been telling my patients that a functional cure may come within 5 years for the past 5 years, so I have stopped

trying to predict the future. However, I suspect that patients whose disease activity is controlled on their own or by long-term antiviral medications will likely be the easiest to lead to functional cure.

Nevertheless, it is important to keep in mind that HBV is a difficult disease to cure. People may have unrealistic expectations due to the recent success of HCV drugs for completely eliminating the disease in the vast majority of patients. However, these 2 diseases are quite different. Even if functional cure of HBV is achieved, the viral genetic material is likely to remain in the host; therefore, the extent of risk reduction associated with functional cure is likely to be smaller. The biggest concern for HBV patients is liver cancer. There is a real risk of liver cancer, even when the virus is suppressed.

G&H What are the most important next steps in research in this area?

RK One of the most important next steps is to determine what combination of drugs may be most effective for HBV treatment. As previously discussed, there are many compounds being developed, but a combination will likely be needed. Then, I think the next challenge will be to take the tools that are developed and apply them to people living with HBV infection throughout the world. The latest statistics from the World Health Organization state that 250 to 300 million people in the world are infected with HBV, making this disease a significant public health problem worldwide.

Dr Kim has served on advisory boards of Gilead, Roche, and Inovio.

Suggested Reading

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