ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Using Immunomodulatory and Antiviral Strategies in the Quest to Cure Hepatitis B Virus Infection

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G&H What should be the endpoint of hepatitis B virus treatment?

AG This is an important question. Several meetings were convened by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases to define the endpoint of hepatitis B virus (HBV) treatment, which is cure. The final definition came down to functional cure, which is essentially elimination of HBV DNA as well as hepatitis B surface (HBs) antigen from the serum of patients in the absence of ongoing treatment. This is the endpoint that the entire hepatology community is aiming for at this point.

G&H Why is it difficult to achieve cure of HBV infection?

AG The difficulty lies in the biology of the virus. Covalently closed circular DNA (cccDNA) establishes an episomal template in the cellular nucleus that looks very much like host chromosomes. This template then produces virus progeny and viral antigens that are consistent with chronic infection. Eliminating the viral template within infected hepatocytes is challenging because of the difficulty of discriminating the viral template from host DNA. Thus far, no drug has been able to successfully target the template.

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

AG The currently approved therapies are nucleos(t)ide analogues and type 1 interferon. Nucleos(t)ide analogues are highly effective at reducing viral load and resolving liver damage, which is important in the progression of disease, but they do not target cccDNA. Thus, these agents are not achieving cure and are not changing the level of antigen production in patients because they hit a downstream step in the viral life cycle. Type 1 interferon, which is a finite treatment, has the potential to achieve loss of hepatitis B e antigen, and potentially HBs antigen. However, HBs antigen loss is a rare event with type 1 interferon and cannot be predicted from clinical biomarkers. Because of its side effects, which are not well tolerated, and because HBV cure remains a rare event, type 1 interferon is no longer widely used.

G&H What is the rationale for using an immunomodulatory approach to try to achieve HBV cure?

AG This strategy is based on data from patients, as well as small and large animal models, pointing to immune response in terms of effective viral control because it can eliminate infected hepatocytes or control antigen production by producing antibodies and neutralizing surface antigen. There is also good evidence that the immune response can eliminate infected hepatocytes in transplant patients, although these data come from small case report studies. Patients with chronic HBV infection who receive a bone marrow transplant from HBV-immune donors with fully functional immune response, as well as livers infected with chronic HBV that are transplanted into HBV-immune recipients with fully functional immune response, are able to clear their chronic HBV infection.

G&H What are the challenges associated with the development of immunomodulatory therapy for HBV infection?

AG One challenge is overcoming how decades of infection have skewed the virus-specific immune response in patients with chronic HBV infection. Most patients were infected at birth, so their HBV-specific immune response has encountered viral antigen their entire lives. This leads to a level of dysfunction that will likely require aggressive targeting to try to restore in order to achieve viral control.

Another challenge is that we do not know what is needed from the immune system, in terms of restoration, to achieve functional cure of chronic HBV infection. We are highly confident that restoring virus-specific T- and B-cell immune responses will be important, but we do not know the specific functional feature of these cells (cytokines, cytotoxicity, proliferation, etc) or the magnitude that will be required to achieve viral control.

G&H What types of immunomodulatory therapies are currently in development to cure HBV infection?

AG There are 4 primary categories currently in development. One consists of therapeutic vaccines that target virus-specific T- and B-cell responses. Another category consists of innate immunomodulators that target pattern recognition receptors such as Toll-like receptors (TLRs), stimulator of interferon gene (STING), and retinoic acid–inducible gene I (RIG-I). These can be expressed primarily in immune cells, but sometimes in parenchymal cells such as hepatocytes or epithelial cells. Also in development are checkpoint inhibitors, which have been widely used in oncology. In HBV, this approach targets programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) to promote T- and B-cell responses. Finally, the most recent entry into immunotherapies consists of anti-HBs monoclonal antibodies. These have the potential to bind circulating HBs antigen in serum and potentially target it to immune cells, such as dendritic cells, monocytes, and macrophages, which could use it to boost T- and B-cell responses.

G&H In which phases of development are these therapies?

AG Therapeutic vaccines are being developed by multiple companies to provide potential options for boosting immunity. Most of the vaccines are entering phase 1 studies, but some are in early phase 2 clinical studies. Unlike previous vaccine attempts that mainly used recombinant HBs antigen or plasmid DNA, new vaccines use more immunogenic delivery strategies. Examples include chimpanzee adenoviral vectors, modified vaccinia Ankara, virus-like particles, or peptide depot technology. Many of the new generation of vaccines use a heterologous prime boost strategy. This means that they deliver the antigen using different delivery vehicles in subsequent doses. For example, the first dose could be recombinant antigen and the second dose a viral vector. This way, the immune system sees antigens slightly differently, which provides a stronger boost than repeating the same formulation.

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In addition, there are multiple innate immunomodulatory molecules targeting TLR-7 and TLR-8 in phase 2 studies or moving into phase 1 and 2 trials. Checkpoint inhibitors that have been approved to target PD-1 or PD-L1 in oncology are now entering phase 1 studies for chronic HBV infection. Likewise, anti-HBs monoclonal antibodies are entering phase 1 studies. Thus, many of these immunomodulatory therapies are quite early on in the development process, and data are anxiously being awaited.

G&H Do there appear to be any safety issues with using an immunomodulatory approach for curing HBV infection?

AG Safety concerns differ based on the class of immune-targeting drugs. HBV-specific therapies, such as therapeutic vaccines, are likely to have good safety profiles because of their specificity. As mentioned previously, it is known that a specific immune response can clear an acutely infected liver without inducing liver failure. Concern for significant liver damage is higher with nonspecific drugs such as innate immunomodulators or checkpoint inhibitors. However, thus far, liver damage has not proven to be an issue. Nevertheless, it is still early on in the development process for many of these compounds, and doctors should be cautious and aware of the potential for liver damage, particularly in patients with fibrosis and cirrhosis. In my

opinion, it is highly unlikely that induction of a strong HBV-specific immune response will result in liver failure. Some liver damage may occur, but I think it is highly unlikely that inducing HBV-specific immunity (T and B cells) will cause fulminant hepatitis.

G&H What lessons have been learned from previous generations of antiviral HBV therapies?

AG We know that reducing viral replication with nucleos(t)ide analogues also decreases liver damage and thus improves patient outcomes. However, merely suppressing viral replication is not sufficient to cure HBV infection and does not eliminate the disease.

In addition, we have learned that nucleos(t)ide analogues do not affect HBV antigens in the circulation of patients with chronic infection because these agents do not affect cccDNA in the nucleus. This is a gap that new antiviral therapies are trying to fill. Although none of them have been able to target cccDNA yet, current strategies are trying to completely suppress viral replication and viral antigens in the circulation. The thinking is that further suppression of viral replication, as well as the removal of viral antigens, will improve the potential for combinations with immunotherapies.

Some of the most anticipated combination therapies that are entering trials now are therapeutic vaccines with siRNAs.

G&H What antiviral therapies are currently in development for HBV infection?

AG Antiviral therapies have advanced further than immunotherapies at this point. Strategies such as RNA interference with small interfering RNAs (siRNAs) or antisense oligonucleotides have been through phase 2 studies and are now entering combination strategies in which they are being combined with multiple direct-acting antiviral therapies. Capsid assembly modulators have also been through phase 2 studies and are in combination studies as well.

In addition, small molecules are being developed that target HBV polymerase. These agents do not work as chain terminators like nucleos(t)ide analogues but instead inhibit viral polymerase itself to prevent chain elongation. This is a different strategy to inhibit viral replication. These molecules are still early in development.

G&H What further research is needed on the latest generation of antiviral therapies for HBV infection?

AG Strategies involving RNA interference with siRNAs or antisense oligonucleotides, HBs secretion inhibitors, and anti-HBs monoclonal antibodies reduce or remove HBV antigens from the circulation. This has been hypothesized to improve the ability to boost immunity, particularly with therapeutic vaccines. Animal model data have been encouraging in terms of trying to reduce antigen and boost immune response simultaneously, but have been challenging to translate to humans. What is needed is immunologic studies in patients receiving these new drugs demonstrating a reduction of HBV antigens in phase 1 and 2 clinical trials, which were severely lacking in the past because these drugs were considered antivirals and not immunomodulatory. I also think that ongoing research using liver fine-needle aspirate sampling and effective use of omics technologies will help identify biomarkers associated with antiviral responses in patients with HBV.

G&H Could you discuss any recent research on combination antiviral and immunomodulatory treatments for HBV infection?

AG At this point, the vast majority of combination treatments that have been tested involve nucleos(t)ide analogues because they are the standard of care. They have been combined with both innate immunomodulators and therapeutic vaccines, but these combinations have not been sufficient to achieve cure.

Some of the most anticipated combination therapies that are entering trials now are therapeutic vaccines with siRNAs. It will be important to follow the immune response in these patients to determine whether modulating antigens in the circulation can improve the effects of therapeutic vaccines.

There are also studies on combinations with new antiviral therapies, which are progressing into combinations of direct-acting antivirals. There was recently a study with a triple combination of an siRNA, a capsid assembly modulator, and a nucleos(t)ide analogue. However, thus far, combinations of direct-acting antivirals have not been able to achieve functional cure of chronic HBV infection.

It should be acknowledged that it is still quite early on in the development process, and optimal combinations have not yet been identified. Nevertheless, I think this also supports the notion that although potent direct-acting antiviral therapies suppress viral replication, they will need a boost from the patient's immune system to achieve functional cure.

G&H What are the priorities of research in terms of developing immunomodulatory and antiviral therapies to cure HBV infection?

AG We need to be ready to seize on any combination that achieves functional cure in a reasonable percentage of patients. We currently hypothesize what is required for functional cure based on a large volume of literature, but to validate hypotheses, it is necessary to study patients who have achieved functional cure. Having patients who achieve cure will allow scientists to investigate what is responsible for that cure and allow the field to refine what to target in the immune response.

Collaboration and partnerships for drug development are increasing, particularly with smaller biotechnology companies. Although large pharmaceutical companies have the ability to target different aspects of the HBV life cycle, there has been an increase in discussion of collaboration for trials to test combination therapies to move forward more quickly, rather than starting from scratch with individual assets. This is an encouraging sign. There has also been an increase in community engagement, and patient advocacy groups are also involved in discussions regarding clinical trials and drug development. This field is obtaining many different perspectives and is maturing. I think there is potential to start achieving functional cure with some of the new therapies that are being developed.

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Suggested Reading

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