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Emerging Therapeutic Approaches for Chronic Hepatitis B

Our guest author is Chloe Thio, MD, Professor of Medicine, Divison of Infectious Diseases at the Johns Hopkins University School of Medicine

After participating in this activity, the participant will demonstrate the ability to:

- Describe the differences between TAF (tenofovir alafenamide) and TDF (tenofovir disoproxil fumarate).
- Explain the key concepts and challenges of achieving hepatitis B cure.
- Discuss both the virological and immunological approaches to HBV cure.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of Emerging Therapeutic Approaches for Chronic Hepatitis B in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 4, Issue 11 eViralHepatitis Review newsletter - New and Emerging Therapeutic Approaches for Chronic Hepatitis B.

Unlabeled/Unapproved Uses

Dr. Thio has indicated that there will be references to the currently unlabeled or unapproved uses of TAF for hepatitis B, as well as the unapproved experimental uses of Myrcludex B and cyclosporine A.

MEET THE AUTHOR

Chloe L. Thio, MD
Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, Maryland

Guest Faculty Disclosure

Dr. Thio has indicated that she has received grant support from Gilead Sciences, Inc.

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PROGRAM DIRECTORS

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and
Gastroenterology/Hepatology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Raymond T. Chung, MD
Director of Hepatology and Liver Center
Vice Chief, Gastroenterology
Kevin and Polly Maroni Research Scholar
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Julie McArthur, MS, CRNP
Adult Nurse Practitioner
Division of Infectious Disease
Johns Hopkins University
School of Medicine
Baltimore, Maryland

Podcast Transcript

MR. BOB BUSKER: Welcome to this *e*ViralHepatitis Review podcast.

Today's program is a follow-up to our newsletter on New and Emerging Approaches for Chronic Hepatitis B. I'm Bob Busker, managing editor of *e*ViralHepatitis Review. Our guest today is that newsletter issue's author, Dr. Chloe L. Thio, Professor of Medicine in the Division of Infectious Diseases at Johns Hopkins University.

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Learning objectives for this audio program include:

- **Describe the differences between TAF (tenofovir alafenamide) and TDF (tenofovir disoproxil fumarate).**
- **Explain the key concepts and challenges of achieving hepatitis B cure.**
- **Discuss both the virological and immunological approaches to HBV cure.**

Dr. Thio has indicated that she has received grant support from Gilead Sciences, Inc. She has indicated that there will be references to the currently unlabeled or unapproved uses of TAF for hepatitis B, as well as the unapproved experimental uses of Myrcludex B and cyclosporine A.

Dr. Thio, thank you for joining us today.

DR. CHLOE THIO: It's my pleasure to be here, Bob I'm looking forward to discussing with you some new therapies for hepatitis B.

MR. BUSKER: In your newsletter issue, you reviewed recent publications on a new therapy to manage hepatitis B infection, as well as the research underway to develop an HBV cure. Let's start by focusing on management with a patient situation.

DR. THIO: This is an interesting patient to discuss in relationship to the newsletter. A patient I'm currently seeing, a 63 year old Asian female with hepatitis HBeAg-negative chronic hepatitis B who has compensated cirrhosis. She was infected with hepatitis B as a child. Her hepatitis B DNA in 2003 before starting tenofovir disoproxil fumarate, or TDF, was 155,000 IU/mL.

Her current hepatitis B DNA is undetectable, she remains HBsAg-positive, and has osteoporosis for which she was previously receiving bisphosphonate therapy but is now only taking calcium and vitamin D. Her DEXA scans have been stable. She also notably has a family history of hepatocellular carcinoma in her father.

MR. BUSKER: This patient has been on TDF, and that treatment has been successful. In your newsletter, you talked about tenofovir alafenamide, or TAF, which at the time of this recording is approved for HIV treatment and is under FDA review for use in hepatitis B. Would you consider changing this patient to TAF, if and when it's approved? And if so, why would you do that?

DR. THIO: That's a good question and very relevant in today's therapeutic time period. TAF, just so everybody knows, is tenofovir alafenamide. It's a newer form of tenofovir basically, and the things I think about with TAF vs TDF are, how long does the patient need therapy, and what risk factors does she have for side effects from TDF vs TAF?

People with HBeAg-negative chronic hepatitis B, like this patient, need treatment lifelong. It's pretty clear from most studies that if you take people off therapy who have HBeAg-negative chronic hepatitis B, their hepatitis B rebounds. In addition, she has compensated cirrhosis, so she doesn't have the luxury of being able to have a rebound because she could decompensate. For her I look at lifelong therapy, so I want a drug that's as safe as possible.

We know that TDF leads to decreases in bone mineral density, and she already has a history of osteoporosis for which she's been on bisphosphonate therapy but she is off of it now. So minimizing the risk of further bone mineral density decreases would be useful. At the recent EASL Conference, which is the European Association for the Study of Liver Diseases, there were two studies, one in HBeAg-negative patients and one in HBeAg-positive patients, both of which showed that there were smaller decreases in bone mineral densities with TAF than with TDF. I think she's a good candidate for TAF for that reason.

To review those two studies in a little more detail, the HBeAg-negative study was presented by Dr. Buti, in which 425 e antigen-negative patients were randomized to receive either 25 mg of TAF vs 300 mg of TDF. They were randomized in a 2:1 ratio, and we'll talk later on in this podcast about why there was such a difference in the dosage of those two drugs.

These patients were mainly Asian men and had mainly genotype B and C hepatitis B. After 40 weeks of treatment, 94% of the TAF and 93% of the TDF group achieved undetectable hepatitis B DNA, which was defined as less than 29 IU/mL%, so they were equivalent.

The companion study of 873 e antigen-positive patients used the same study scheme and demographics as the e antigen-negative patients. The proportion with undetectable hepatitis B DNA at 48 weeks was 64% in the TAF group and 67% in the TDF group; once again, no difference between those two drugs. So TAF is not only safer for bone toxicity, it also is equivalent in efficacy.

Although it's not relevant to our patient here, it's important to point out that TAF is also safer for renal toxicity. In those studies the median change in the estimated glomerular filtration rate from baseline to 48 weeks was lower in the TAF group than in the TDF group.

It's also important just to know that, TAF has not been approved for patients with creatinine clearances less than 30. So if you have a patient who is in renal failure, TAF could not be used.

MR. BUSKER: The studies show that TAF is less toxic to bone and kidney than TDF. From your analysis, why do you think that's so?

DR. THIO: That's a good question. Both TAF and TDF are prodrugs of the active drug tenofovir, which causes the toxicity. Earlier I mentioned the difference in our patient's dosage of drug, 25 mg of TAF vs the 300 mg of TDF. That's because when TDF is given, it's converted to tenofovir in the blood and is then taken up into cells. So to get adequate intracellular concentrations of tenofovir, you need much higher doses of tenofovir in the blood. That is why we give much higher doses of TDF.

TAF, on the other hand, is first taken up into the cells as TAF and is then converted to tenofovir inside the cells. Cells that

take it up include T cells and macrophages, and certain other specific cells such as hepatocytes, which is why it is also useful against hepatitis B.

Once the TAF is taken up by the cells, it is converted to tenofovir and then becomes phosphorylated to the active forms of tenofovir diphosphate. Because of this, the plasma levels of tenofovir are 90% lower with the 25 mg of TAF than they are with the 300 mg of TDF, but the intracellular levels of the active form, tenofovir diphosphate, are fivefold higher with TAF than with TDF.

MR. BUSKER: The patient, as you described her, has osteoporosis. TAF, as we've said, is currently not approved for hepatitis B treatment. But for our discussion, let's assume that TAF is available. So my question is, if you were starting this patient on therapy today and she did not have osteoporosis, how would you manage her?

DR. THIO: As I mentioned, because she has HBeAg-negative chronic hepatitis B, her treatment would be lifelong, and I would want to minimize any potential for side effects. So if I knew she did not have lamivudine-resistant hepatitis B, the two options I would consider, if TAF were approved, would be TAF or entecavir. If she does have lamivudine resistant hepatitis B, I would use TAF because entecavir is not the drug of choice in that situation. If TAF were available, I would avoid giving TDF because of the long-term toxicities that occur in some people.

MR. BUSKER: Your newsletter issue presented a thorough overview of the challenges faced and the progress being made toward a cure for hepatitis B, and we'll go into that in more detail in just a few moments. But my question right now is, do you think HBV polymerase inhibitors — pols like TAF or like entecavir — will be included in the treatment plans that eradicate the virus?

DR. THIO: It's difficult to predict exactly which components of therapies will be included in an eventual cure for hepatitis B, but I do think that a cure will need a multipronged approach, similar to what we use with HIV, where you're attacking different parts of the life cycle or boosting the immune system. Since hepatitis B pol inhibitors have a very long and safe track record, and replication is an important part of stopping the life cycle of hepatitis B, I can see that there's a likelihood that a pol inhibitor like TAF or entecavir could be part of a combination treatment plan.

MR. BUSKER: Thank you for that case and discussion. We'll return with Dr. Chloe Thio from Johns Hopkins in just a moment.

Ms. Julie McArthur
Hello. I'm Julie McArthur, adult nurse practitioner in the Division of Infectious Diseases at Johns Hopkins University. I'm one of the program directors of *e*ViralHepatitis Review.

*e*ViralHepatitis Review is a combination newsletter and podcast program delivered by email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to hepatologists, infectious disease specialists, primary care physicians, nurses, nurse practitioners, and other clinicians caring for patients with viral hepatitis.

Bimonthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new clinical information into practice in the exam room and at the bedside.

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BOB BUSKER: Thank you, Julie. I want to jump in here for a moment to tell our listeners about the new GetSMART app for Apple iOS, Android, or desktop. It's about prescribing Extended Release and Long Acting Opioids — GetSMART stands for Safe Means of Administering the Right Therapy. The GetSMART app is available for CME/CE/MOC credit at no cost. You

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MR. BUSKER: Welcome back to this *e*ViralHepatitis Review podcast. I'm Bob Busker, managing editor of the program. We've been talking with Dr. Chloe Thio from the Division of Infectious Diseases at Johns Hopkins University about Emerging Therapeutic Approaches for Chronic Hepatitis B.

Before our break, we touched on the idea of a cure for hepatitis B. I'd like to step away from our normal case-based format now to continue that discussion.

To my mind, the advances in understanding the HBV life cycle are key to the development of a cure. In your newsletter issue, you reviewed a 2016 article by Hayes and colleagues that reported on our current state of HBV life cycle knowledge. Please summarize that information for us.

DR. THIO: The important point the Hayes paper brings out is the steps that lead to the development of the covalently closed circular DNA, or cccDNA, in the hepatocyte nucleus. This podcast isn't the appropriate forum to discuss all of those steps in detail, but I refer you to the newsletter to learn what some of those steps are. But I do want to hit home the point that the cccDNA is used as the transcription template to form all of the mRNA that are used either replication or that form the various proteins including surface antigen, e antigen, the X protein, and the core antigen. So without the cccDNA, the hepatitis B replication and life cycle would stop.

MR. BUSKER: Keeping in mind what you just said about cccDNA, how should we define the word "cure" in regard to hepatitis B?

DR. THIO: I think you can think of cure in two ways. The first would be what I would call a functional cure, which is what we see in the majority of people who have natural hepatitis B recovery — people who develop surface antibody and lose surface antigen after an acute infection. These people, for the most part, still retain cccDNA in the nucleus of some but not all hepatocytes.

We know this because when these people become immunosuppressed either with medications or with an immune suppressive disease such as HIV, or they are put on immunosuppressive therapy after transplant, their hepatitis B can reactivate because cccDNA is still present in some hepatocytes.

So a functional cure would be to a point where we're stopping replication after discontinuing medicaitons but we're not getting rid of that cccDNA. We are achieving that with a very small proportion of people with the currently available therapies for hepatitis B.

The other type of cure, which I think is more difficult to achieve, is what we would call an eradication cure, which would eliminate the cccDNA to the point where it doesn't exist in the nuclei of any hepatocytes.

MR. BUSKER: What are the research approaches for either a functional cure or an eradication or elimination cure?

DR. THIO: In the big overview there are two basic approaches: the virological approach or the immunological approach. The virological approach is just what it sounds like. The idea would be to attack the virus at various steps in the replication cycle. As I mentioned, the Hayes paper talks about some of the steps toward building up to the cccDNA, and several other steps also occur after the cccDNA is established in the nucleus. Attacking the cccDNA directly would also be one of the virological approaches. Any of those steps could be targeted to block the replication life cycle for hepatitis B.

The current hepatitis B polymerase inhibitiors attack one of those steps, but many more steps could also be attacked.

The important thing to understand with the immunological approach is that the immune system in chronic hepatitis B is defective in that it's tolerant to the hepatitis B antigens. So the idea in the immunological approach would be to boost the immune response to hepatitis B, which could be done either by boosting the general immune response or by boosting a hepatitis B-specific immune response.

MR. BUSKER: Tell us about some of the virological approaches that are currently being investigated.

DR. THIO: On the bright side, a lot of approaches are currently being studied. Some of those will eventually fall by the wayside, but it's important that we understand at least what people are doing at this point.

One of the approaches would be to block the entry of the hepatitis B virus into the hepatocyte. When the hepatitis B enters the hepatocyte, and this is reviewed in the Hayes paper, it binds to the NTCP receptor. This receptor is used as a bile acid transport receptor, but something that also binds hepatitis B and allows it to enter.

A compound called Myrcludex B was synthesized before the receptor was identified because we knew at that point which part of the hepatitis B virus bound to an unknown receptor. Myrcludex B was synthesized to match this pre-S1 region of hepatitis B where this binding occurs. This compound basically blocks the binding of hepatitis B to the NTCP receptor.

Another drug, cyclosporine A, which is already available and used, also binds the NTCP receptor, and some studies have looked at that.

In the newsletter I discuss a paper, a phase 2a clinical trial that was presented at the American Association for the Study of Liver Diseases conference, which looked at Myrcludex B as a treatment for hepatitis B. The authors studied patients who were HBeAg-negative and had chronic hepatitis B, all with hepatitis B DNA levels greater than 2000 and did not have cirrhosis. They were given increasing doses of Myrcludex-B subcutaneously, from 0.5 mg to 10 mg. All of these doses were given once daily for 12 weeks; the 10 mg group received an additional 12 weeks of treatment. They found that the response was best in the 10 mg group. Six of eight people who received 10 mg achieved greater than a 1 log decline of hepatitis B DNA at 12 weeks, compared to only about 21% of all the other people in the other groups. No changes in hepatitis B surface antigen levels occurred, and the tolerability was excellent, except for three people who had some injection site reaction.

This study is interesting because it shows you can lead to declines in hepatitis B DNA levels, but whether it will be an important component of a cure needs to be studied. Certainly longer durations of this drug also need to be studied. That's one virological approach, just block the receptor.

Another approach would be to silence the mRNAs. I mentioned that the cccDNA is the transcript for making all the mRNAs. And as probably many of you know, in other diseases people are working to silence these mRNAs so the downstream effects of the mRNAs are no longer present. With hepatitis B, if we can silence the mRNAs, we can stop replication because the pre- genomic RNA can't encapsulate, and could stop more surface antigen particles from being produced.

It's important to understand that because more than one mRNA is produced from the cccDNA, sometimes these surface antigen particles are produced but don't contain any hepatitis B DNA; these are called empty particles. These empty particles are important because they are thought to play a role in immune tolerance. If you can decrease the number of these empty particles, perhaps there might be a way to boost the immune system toward eliminating hepatitis B.

Other virological approaches being considered include capsid inhibitors. I've been mentioning that the pregenomic RNA needs to be encapsulated, and one approach is to prevent this encapsulation with capsid inhibitors. Other approaches include degrading the cccDNA itself, and also blocking release of hepatitis B surface antigen particles.

Those are some of the virologic approaches that are currently under development.

MR. BUSKER: What about the immunological approaches? What can you tell us about those?

DR. THIO: There are many immunologic approaches, as well. As I mentioned earlier in this podcast, you can either stimulate the general immune system or you can stimulate the hepatitis B-specific immune system.

One of the approaches is to activate the general immune response by blocking the toll-like receptor-7 or TLR-7. TLR-7 is a pattern recognition receptor that increases both the adaptive and the innate immune response. If you can stimulate TLR-7, hopefully you can increase the immune response, which would allow elimination of infected hepatocytes.

One study reviewed in the newsletter looked at this TLR-7 agonist in 100 people, 84 of whom received either one or two

doses of the drug. They found no change in hepatitis B DNA, but that probably wouldn't be expected with just one dose. They did notice, however, an increase in a particular interferon-stimulated gene called ISG-15 mRNA, and the mRNA in the people who received the highest doses of TLR-7 increased, suggesting that this drug was stimulating the immune system to some degree. More studies will be needed to see whether that immune stimulation leads to a reduction in hepatitis B DNA.

The other general approach is to block the immune checkpoint markers. The important thing to understand is that in chronic hepatitis B, these inhibitory pathways or immune checkpoint markers are up-regulated. When there is chronic stimulation by some antigen, in this case hepatitis B, the T cells become tolerant to this by up-regulating these markers. The idea is, if you can block these markers, perhaps you can reverse this tolerance or immune-exhausted state and allow the T cells then to attack the infected hepatocytes.

One example reviewed in the newsletter is blocking the PD-1/PD-L1 pathway, which has been used in various cancer chemotherapies and is now being studied with hepatitis B. In general, this study showed that patients who received this immune checkpoint blocker along with other medications, including a therapeutic vaccine and a polymerase inhibitor, did have some increase in their immune control of hepatitis B virus. But whether this leads to a cure for hepatitis B also needs more study.

The other important point to know about trying to stimulate the general immune system against hepatitis B is concern that this could lead to fulminant hepatitis. If someone has many infected hepatocytes and you unleash immune tolerance and the T cells begin attacking the infected hepatocytes, that leads to a fulminant hepatitis. So I think up-regulating the general immune system will be a balance between too much immune response and not enough immune response, because you don't want too much, which then leads to a fulminant hepatitis situation.

The other approach, if you're not going to activate the general immune system, is to activate the hepatitis B-specific T cells. These studies are just starting to be under development and weren't reviewed in the newsletter, but I will just say that the basic ideas here are either to give a therapeutic vaccine that takes parts of the hepatitis B virus that are thought to be the most immunogenic or most likely to stimulate the immune system, and give that as a therapeutic vaccine in the hope that you can stimulate the hepatitis B-specific T cells to attack the hepatocytes.

The other way is to engineer T cells themselves, and put them back into the patient to stimulate an immune response to hepatitis B.

MR. BUSKER: There's an impressive amount of research going on. How close do you think we are to developing a cure for hepatitis B?

DR. THIO: I don't think we're very close. As you can tell from the papers we have discussed here and are discussed in the newsletter, most of them are still in very early phase trials, trying to find the correct dose and trying to understand the side effects of these various drugs. So I think we're many, many years away from curing hepatitis B.

There are no current studies of these new agents demonstrating that they can cure hepatitis B on their own. As I mentioned with the current polymerase inhibitors, some people can achieve this functional cure, but 5% of people actually lose surface antigen and develop surface antibody with just a polymerase inhibitor. So we know it can be achieved, but we certainly would want to achieve it in more people than that, and these newer drugs are a long way from being able to do either a functional or an eradication cure.

MR. BUSKER: But are you confident that a cure is possible?

DR. THIO: Yes. As I mentioned, we can already achieve a functional cure with some of the polymerase inhibitors. It is not very common but it is possible, so you need to believe that we should be able to achieve a functional cure in more people. We also know that 90% to 95% adults who get infected achieve what we are aiming for: functional cure. They don't develop chronic hepatitis B; they develop surface antibodies, and even if they still have cccDNA present in some of their hepatocytes, their livers do not suffer any consequences of having that cccDNA.

Because most people can naturally achieve what we would call a functional cure, I think we should be able to figure out how to achieve this in more people who have chronic hepatitis B. An eradication cure will be more difficult, because even

people who naturally develop surface antibody and recover from hepatitis B don't eradicate the cccDNA, but I think it will be possible with some of the newer technologies.

MR. BUSKER: A fascinating topic, doctor, and thank you for sharing your insights. Let's wrap things up now by reviewing the key points of today's podcast in light of our learning objectives. So to begin: the differences between TAF and TDF.

DR. THIO: They're similar or equivalent in efficacy in treating hepatitis B, at least up to 48 weeks; we don't have longer term studies yet. They're equivalent in both e antigen-negative and e antigen-positive hepatitis B, as well as in patients who are either treatment experienced or treatment naïve.

The differences are that TAF has less toxicity to the bone and kidney than does TDF.

MR. BUSKER: And our second learning objective: the key concepts of achieving an HBV cure.

DR. THIO: The most important thing is cccDNA in the hepatocyte nucleus, which is central to replication, and the types of cure are focused on that. There's a functional cure and the eradication cure. The eradication cure is what it sounds like — we eradicate that cccDNA. With the functional cure, cccDNA is still present but we stop its replication so that the hepatitis B virus is no longer being produced in large amounts. The idea with the functional cure is that we could stop therapy but would still not have replication from the cccDNA.

MR. BUSKER: And our final learning objective: the virological and the immunological approaches to HBV cure.

DR. THIO: With the virological approaches, the aim is stop the virus from replicating by hitting various parts of the hepatitis B replication cycle. In this podcast today we discussed some of the ways that's being done, including blocking the NTCP receptor, silencing MRNAs, inhibiting the capsid, and preventing release of hepatitis B surface antigen particles. We've also talked about immunological approaches that boost the general immune system by stimulating the toll-like receptor TLR-7 or by blocking immune checkpoint markers.

The other immunological approach is rather than a general immune response, to increase the hepatitis B-specific immune response, using methods such as therapeutic vaccination or engineering T cells that are specific against hepatitis B. Whether any of those will end up being part of the hepatitis B cure remains to be seen.

MR. BUSKER: Dr. Chloe Thio from Johns Hopkins University, thank you for participating in this *e*ViralHepatitis Review Podcast.

DR. THIO: It's been my pleasure, Bob, I've enjoyed talking to you about upcoming therapies leading towards a hepatitis B cure.

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