JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eViralHepatitis Review
Podcast Issue
Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by educational grants from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

VOLUME 3 — ISSUE 4: TRANSCRIPT

Featured Cases: The Role of Prediction Models: Best practices in Identifying Cirrhosis and HCC in Patients Infected with HBV

Our guest author is Anna Suk-Fong Lok, MD, FRCP Professor in the Department of Internal Medicine and Director of Clinical Hepatology in the Division of Gastroenterology at the University of Michigan Health System in Ann Arbor.

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

- Identify which patients with chronic hepatitis B virus infection have high risk for cirrhosis and hepatocellular carcinoma
- Discuss the utility and limitations of prediction models for cirrhosis and HCC in patients with chronic HBV infection
- Describe how to incorporate predicted risk of HCC into decisions regarding hepatitis B treatment

This discussion, offered as a downloadable audio file and companion transcript, covers predictive models for cirrhosis, as well as case-study scenarios for the clinical practice. This program is a follow up to the Volume 3, Issue 3 *eViralHepatitis Review* newsletter—Should this Patient be Treated? Best Practices in Identifying Cirrhosis and HCC in Patients Infected with HBV – Role of Prediction Models.

MEET THE AUTHOR

Anna Suk-Fong Lok, MD, FRCP
Professor, Department of Internal Medicine
Director, Clinical Hepatology
Division of Gastroenterology
University of Michigan Health System
Ann Arbor, Michigan

Faculty Disclosure

Dr. Suk-Fong Lok has indicated that she has received research grants from Bristol-Myers Squibb, Gilead Sciences, and Merck, and that she has served on advisory panels for Gilead Sciences and Merck.

Unlabeled/Unapproved Uses

Dr. Suk-Fong Lok has indicated that in today's discussion she will not reference the unlabeled or unapproved uses of any drugs or products.

Release Date
November 26, 2013

Expiration Date
November 25, 2015

PROGRAM DIRECTORS

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

Raymond T. Chung, MD
Associate Professor of Medicine
Director of Hepatology,
Harvard Medical School
Vice Chief of Gastroenterology
Massachusetts General Hospital
Boston, Massachusetts

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

CME INFORMATION

⇩ PROGRAM BEGINS BELOW

ACCREDITATION STATEMENTS

Physicians

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

The Institute for Johns Hopkins Nursing and the American Nurses Credentialing Center do not endorse the use of any commercial products discussed or displayed in conjunction with this educational activity.

CREDIT DESIGNATIONS

Physicians

eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 1.0 *AMA PRA Category1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses

eNewsletter: This 1 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each newsletter carries a maximum of 1 contact hour or a total of 6 hours for the six newsletters in this program.

Podcast: This 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hours a total of 3 contact hours for the six podcasts in this program.

SUCCESSFUL COMPLETION

To successfully complete this activity, participants must read the content, and then link to the Johns Hopkins University School of Medicine's CME website or the Institute for Johns Hopkins Nursing's website. to complete the post-test and evaluation. Once you receive a passing grade, you can access and print your certificate of credit.

NOTE: If you have already registered for other Hopkins CME programs on their prospective websites simply enter the requested information when prompted.

There are no fees or prerequisites for this activity.

This activity is supported by educational grants from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., and Genentech, Inc.

LAUNCH DATE

August 27, 2013; activities expire 2 years from the date of publication.

INTENDED AUDIENCE

The target audience (clinicians) for the HBV curriculum includes:

- Primary: primary care physicians (PCPs), OB/GYNs, physician assistants (PAs), nurse practitioners (NPs), community gastroenterologists and others who care for patients of Asian and West African descent in areas of high HBV prevalence
- Secondary: gastroenterologists, infectious disease specialists, and other clinicians involved in the care of patients at risk for HBV

The target audience for the HCV curriculum includes:

- PCPs, OB/GYNs, NPs, PAs, hepatologists, gastroenterologists, infectious disease physicians, and others involved in the care of patients with hepatitis.

INTERNET CME POLICY

The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine is committed to protecting the privacy of its members and customers. The Johns Hopkins University SOM maintains its Internet site as an information resource and service for physicians, other health professionals, and the public.

Continuing Medical Education at the Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in an Internet-based CME program. Your information will never be given to anyone outside of the Johns Hopkins University School of Medicine program. CME collects only the information necessary to provide you with the services that you request.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of the Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information for specific drugs or combinations of drugs, including indications, contraindications, warnings, and adverse effects, before administering pharmacologic therapy to patients.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

STATEMENT OF NEED

Through discussions with experts in the specialty of HBV, a survey of participants from previous Johns Hopkins CME activities, and a review of current literature, the following core learning gaps have been identified:

HCV

- Clinicians do not adequately identify which of their patients are at highest risk for HCV infection or effectively interpret testing results.
- Clinicians need to understand best practices in how to identify and manage HCV treatment-related side effects.
- Clinicians need improved awareness of how newly emerging therapies impact therapeutic decision-making in HCV infected and HIV/HCV co-infected patients.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HCV.

HBV

- Clinicians do not effectively identify their patients at risk for HBV.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HBV.

PLANNER DISCLOSURES

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of the Johns Hopkins University School of Medicine Office of Continuing Medical (OCME) to require signed disclosure of the existence of financial relationships with industry from any individual in a position to control content of a CME activity sponsored by OCME. Members of the Planning Committee are required to disclose all relationships, regardless of their relevance to the activity content. Faculty are required to disclose only those relationships that are relevant to their specific presentations. The following relationships have been reported for this activity:

- **Mark S. Sulkowski, MD,** has disclosed that he has served as a consultant for AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck and Vertex Pharmaceuticals Incorporated. He has received grant/research funding from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck and Vertex Pharmaceuticals Incorporated, and has served on a steering committee for Pfizer, Inc.
- **Raymond T. Chung, MD,** has disclosed that he has served as a consultant for AbbVie, Inc. and Idenix and has received grant/research funding from Gilead and Mass Biologics.

No other planners have indicated that they have any financial interests or relationships with a commercial entity.

CONFIDENTIALITY DISCLAIMER FOR CME CONFERENCE ATTENDEES

I certify that I am attending a Johns Hopkins University School of Medicine CME activity for accredited training and/or educational purposes.

I understand that while I am attending in this capacity, I may be exposed to "protected health information," as that term is defined and used in Hopkins policies and in the federal HIPAA privacy regulations (the "Privacy Regulations"). Protected health information is information about a person's health or treatment that identifies the person.

I pledge and agree to use and disclose any of this protected health information only for the training and/or educational purposes of my visit and to keep the information confidential.

I understand that I may direct to the Johns Hopkins Privacy Officer any questions I have about my obligations under this Confidentiality Pledge or under any of the Hopkins policies and procedures and applicable laws and regulations related to confidentiality. The contact information is: Johns Hopkins Privacy Officer, telephone: 410-735-6509, e-mail: HIPAA@jhmi.edu.

"The Office of Continuing Medical Education at the Johns Hopkins University School of Medicine, as provider of this activity, has relayed information with the CME attendees/participants and certifies that the visitor is attending for training, education and/or observation purposes only."

For CME Questions, please contact the CME Office at (410) 955-2959 or e-mail cmenet@jhmi.edu.

For CME Certificates, please call (410) 502-9634.

Johns Hopkins University School of Medicine
Office of Continuing Medical Education
Turner 20/720 Rutland Avenue
Baltimore, Maryland 21205-2195

Reviewed & Approved by:
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

HARDWARE & SOFTWARE REQUIREMENTS

PC: Internet Explorer (v6 or greater), or Firefox, MAC: Safari or Firefox

MR. BOB BUSKER: Welcome to this *eViralHepatitis Review* Podcast.

eViralHepatitis Review is presented by The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. This program is supported by educational grants from AbbVie Inc., Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

Today's program is a companion piece to our eViralHepatitis Review newsletter issue: *The role of prediction models: Best practices in identifying cirrhosis and HCC in patients infected with HBV*.

Our guest is one of that issue's authors, Dr. Anna Suk-Fong Lok from the University of Michigan.

This activity has been developed for primary care physicians, gastroenterologists, infectious disease specialists, OB/GYNs, physician assistants, nurse practitioners, community gastroenterologists, clinicians who care for patients of Asian and West African descent in areas of high hepatitis B prevalence, and other HCPs involved in the care of patients with or at risk for hepatitis B infection.

There are no fees or prerequisites for this activity.

The Accreditation and Credit Designation Statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies and expiration dates, and to take the post-test to receive credit online, please go to our website newsletter archive, www.eviralhepatitisreview.org, and click on the Volume 3, Issue 4 podcast link.

Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:

- Identify which patients with chronic hepatitis B virus infection have high risk for cirrhosis and hepatocellular carcinoma
- Discuss the utility and limitations of prediction models for cirrhosis and HCC in patients with chronic HBV infection
- Describe how to incorporate predicted risk of HCC into decisions regarding hepatitis B treatment

I'm Bob Busker, managing editor of eViralHepatitis Review. On the phone we have with us Dr. Anna Lok, Professor in the Department of Internal Medicine and Director of Clinical Hepatology in the Division of Gastroenterology, at the University of Michigan Health System in Ann Arbor.

Dr. Lok has indicated that she has received research grants from Bristol-Myers Squibb, Gilead Sciences, and Merck and that she has served on advisory panels for Gilead Sciences and Merck.

She has also indicated that her presentation today will not reference the unlabeled or unapproved uses of any drugs or products.

With all that said: Dr. Lok, welcome to this eViralHepatitis Review Podcast.

DR. ANNA LOK: Well thank you for having me with you today.

MR. BUSKER: In your newsletter issue, Doctor, you reviewed recent investigations into predictive models for cirrhosis and hepato-cellular carcinoma in patients with hepatitis B. What we'd like to do today is discuss how that information can be applied to clinical practice. So if you would, Doctor Lok, start us out by describing a patient.

DR. LOK: So the first patient that we have is a 32 year old Asian man, he was found to be hepatitis B surface antigen positive, E antigen positive, with high viral load of HBV DNA, 8.5 $\log_{10}$, roughly 300 million IU/mL and a normal ALT of 28 U/L.

MR. BUSKER: My first question is about evaluating this patient. Would you consider liver biopsy or noninvasive testing for fibrosis?

DR. LOK: Well this is a very young patient with high DNA level and normal ALT, so he is likely to be in the immune tolerant phase. I would not recommend a liver biopsy if the serum ALT levels on follow-up are persistently in a normal range.

The reason for that is, most patients in the immune-tolerant phase have minimal liver injury, and a prognosis is favorable during a follow-up of up to 10 years. In a prior study of 40 patients, liver biopsies

showed no fibrosis in half of the patients and mild fibrosis in the other half.

Another study showed that follow-up biopsies of these patients who remain in the immune tolerant phase did not show progression five years after the initial biopsies. As we know, liver biopsies do carry a risk; therefore, biopsies are not recommended.

There is, however, growing interest in the use of noninvasive tests for fibrosis, such as serum biomarkers and liver stiffness measurement to assess hepatic fibrosis as an alternative to liver biopsy. But the performance of these tests in differentiating different stages of fibrosis is low, and these tests can be influenced by the degree of hepatic inflammation. So it is not clear whether these noninvasive tests would help in evaluating this patient. At this stage, the likelihood of liver injury for this patient is fairly low, and I would just monitor him every six months.

The noninvasive tests of fibrosis were covered in the newsletter.

MR. BUSKER: What can you tell us about the predicted risk of HCC in this patient, doctor?

DR. LOK: Well if we applied the REACH-B HCC prediction score, derived from the REVIEW HBV study — and this was discussed in the newsletter — this patient's score would be 9.1 The projected risk of HCC is 0.5% at three years, 1.2% at five years, and 2% at 10 years for this particular patient.

MR. BUSKER: And the predicted risk of cirrhosis?

DR. LOK: Currently there is only one published scoring system to predict the risk of cirrhosis. In addition to the variables that we mentioned in the REACH-B model for HCC prediction — sex, age, E antigen status, DNA level and ALT — the cirrhosis model also includes HBV genotype and hepatitis B surface antigen levels.

Hepatitis B surface antigen level is not associated with the risk of cirrhosis in patients positive for the E antigen as in this particular case. However, we need to know which HBV genotype he's infected with. If he's infected with genotype C, then the risk of cirrhosis is roughly twice that of genotype B.

MR. BUSKER: This patient who you've described for us — 32 year old Asian male, hepatitis B surface antigen positive, and E antigen positive, with a high HBV DNA viral load, and a normal ALT — would you advise treating this patient?

DR. LOK: I would not treat this patient at this time. Antiviral therapy can certainly decrease serum HBV DNA level; however, for patients in immune tolerance phase, the likelihood of E antigen seroconversion with either pegylated interferon or nucleoside/nucleotide analogs is low.

Furthermore, it is not clear whether treatment during the immune tolerance phase will improve the outcome, as some of these patients might eventually go on to spontaneous seroconversion on their own.

MR. BUSKER: How then would monitor this patient?

DR. LOK: Since we decide not to treat the patient at this time, it is important to monitor him. I would monitor him every six months. If during follow-up the ALT increases to more than two times the upper limit of normal, I would monitor him more frequently and recommend treatment if spontaneous E seroconversion is not observed after three to six months.

Considering his Asian ethnicity, I would also recommend HCC surveillance if he's more than 40 years old.

MR. BUSKER: The issue of the patient's age, doctor. How would you manage this patient differently if he was, as you said, older than 40?

DR. LOK: If he's older than 40 and his HBV DNA level remains as high as he is now, which is some roughly 300 million IU/mL, I would recommend a liver biopsy and antiviral treatment if there is moderate or severe inflammation and/or advanced fibrosis on a biopsy. That's because, if he is over the age of 40 it would mean he's been infected for much longer, and if the virus level remains so high the risk of cancer increases.

MR. BUSKER: What if this patient was instead a young woman who's now pregnant? She's got the same high virus level — would you recommend antiviral therapy for her, in order to reduce the risk of perinatal transmission?

DR. LOK: This is an area that's unsettled, but increasingly the evidence suggests that if a young woman who is pregnant has a very high virus level, antiviral therapy in the late second or the early third trimester of pregnancy through delivery might further reduce the risk of perinatal transmission in addition to HBeAg and vaccination to the baby.

MR. BUSKER: Thank you, Dr. Lok, for that case and that discussion. Let me ask you to bring us another patient now, if you would, please.

DR. LOK: Sure. Well the second patient that I'm going to discuss is a Caucasian man who is 45 years old, found to be hepatitis B surface antigen positive, E antigen negative, with an ALT of 29 u/L and HBV DNA of less than 2,000 iu/mL. In fact, the HBV DNA was only 150 iu/mL at presentation.

MR. BUSKER: Would you consider this patient to be in the "inactive carrier" phase? How would you make that determination?

DR. LOK: It is not possible to determine that with one set of lab values, because patients with chronic hepatitis B do have fluctuations in DNA and ALT levels, particularly in a patient who is E antigen. I would monitor this patient by checking ALT every three months and HBV DNA every six months over a one-year period. If the ALT is persistently normal and DNA persistently less than 2,000 IU/mL, I would consider that he's truly in an inactive carrier phase.

Some other experts would argue that we monitor the patient for a longer period of time, perhaps two to three years, before we can declare that a patient is in the active carrier phase.

MR. BUSKER: Should this patient be considered free of HCC risk?

DR. LOK: This patient is not free of HCC risk, although high levels of HBV DNA have been shown to be a strong, independent predictor of cirrhosis, HCC, and liver-related mortality. Patients with lower DNA, for example, less than 2,000 IU/mL, may also develop HCC.

MR. BUSKER: Tell us more, if you would, about the factors associated with disease progression and HCC.

DR. LOK: Many other factors contribute to HCC development. For example, age, gender, alcohol consumption, family history of HCC, DNA level, ALT, and HBV genotype.

The recent studies in Taiwan also show that for patients like this one, who is considered to be in an inactive carrier phase with E antigen negative, low DNA, and normal ALT, additional testing for HBS antigen level would further stratify the risk of disease progression as well as HCC. So if he were found to have low HBS antigen level, then his risk of HCC would be much lower than if he had a high HBS antigen level.

MR. BUSKER: Let's say that after a full year of observation this patient does appear to be in the inactive carrier phase. How would you continue to monitor?

DR. LOK: All patients with chronic hepatitis B should have long-term follow-up. So even if he's found to be truly in the inactive carrier phase after one year, I would continue to monitor this patient by testing for ALT and HBV DNA every six to 12 months.

It is important to emphasize to the patient the importance of regular follow-up, because HBV DNA and ALT levels can go up in the future, either spontaneously or if he is diagnosed to have cancer or other medical conditions that require long-term steroids or immunosuppressive therapy, or cancer chemotherapy.

If he has evidence of cirrhosis, I would consider cancer surveillance; if not, I would not recommend HCC surveillance.

MR. BUSKER: Are there any circumstances where you might consider the need for a liver biopsy?

DR. LOK: If he remains in the inactive carrier phase with persistently normal liver enzyme and low DNA level, I would not do a liver biopsy. However, if during follow-up the ALT increases to one to two times the upper limit of normal or higher, I would recommend a liver biopsy.

A liver biopsy is most useful if his ALT is minimally elevated to guide whether treatment is necessary. Because if the biopsy shows moderate or severe inflammation or significant fibrosis, I would consider treatment.

As we discussed in the first case, noninvasive tests of fibrosis such as serum biomarkers or a liver stiffness measurement can also be considered, and these tests are particularly helpful when the ALT is normal or minimally elevated, because there wouldn't be the confounding effect of inflammation.

We have to, however, bear in mind that these noninvasive tests are very good at differentiating patients with cirrhosis versus no cirrhosis, but they are less reliable in differentiating various stages of fibrosis. And the accuracy is lower in patients with very high ALT.

MR. BUSKER: Thank you, doctor. And we'll return with Dr. Anna Lok from the University of Michigan Health System, 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 *eViralHepatitis Review*.

eViralHepatitis Review is a combination newsletter and podcast program delivered via e-mail 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, nurse, nurse practitioners and other clinicians caring for patients with viral hepatitis

Bi-monthly 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. Subscription to eViralHepatitis Review is provided without charge or prerequisite.

Continuing education credit for each issue and each podcast is provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. For more information on this educational activity, to subscribe and receive eViral Hepatitis Review without charge, and access back-issues, please go to our website: www.eviralhepatitisreview.org

MR. BUSKER: Welcome back to this eViralHepatitis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Anna Lok from the University of Michigan. And our topic is: the role of prediction models in identifying cirrhosis and HCC in patients with HBV.

We've been looking at how some of the new information Dr. Lok discussed in her newsletter issue can be applied in clinical practice. So if you would, Doctor, please describe another patient for us.

DR. LOK: This patient is a 48 year old man with no symptoms, but during a routine test he was found to be positive for hepatitis B surface antigen. In fact, he requested a test because one of his brothers was recently found to be positive for hepatitis B surface antigen.

He's negative for E antigen, negative with an HBV DNA of 3.7 log10 IU/mL, which translates into roughly 5,000 IU/mL. His ALT was elevated at 80 U/mL and he had a normal platelet count, normal bilirubin, albumin, and prothrombin time.

Because of the elevated ALT, and the fact that he's a little older, a liver biopsy was performed and surprisingly, it showed evidence of cirrhosis. He has no history of ascites, variceal bleeding, or encephalopathy, indicating that he has compensated liver disease.

There is also no evidence of portal hypertension, because in addition to your normal platelet count, ultrasound showed that his spleen size was within normal limits.

MR. BUSKER: In this patient, would you consider starting antiviral therapy?

DR. LOK: This is a very simple, straightforward case, and I would definitely recommend treatment, based upon the finding of cirrhosis and high ALT, as well as high HBV DNA level. Although the HBV DNA level is not very high, only 5,000 IU/mL, this is considered to be high for someone with cirrhosis.

The guidelines of American Association for Study of Liver Disease or the ASLD, and the Asian-Pacific Association for Study of the Liver, or APASL, recommend antiviral therapy in patients with cirrhosis, an HBV DNA of more than 2,000 iu/mL, regardless of the ALT.

For patients with cirrhosis who have increased ALT levels, the ASLD guidelines recommend treatment

regardless of HBV DNA level. So even if his DNA level were lower, treatment would be recommended because of the increased ALT.

The EASL guideline has a lower threshold for starting treatment, and they recommend treating patients with cirrhosis and any detectable level of serum HBV DNA, regardless of ALT.

So he would be someone that every single guideline would recommend starting on antiviral therapy.

MR. BUSKER: Which antiviral therapy would you recommend for this patient?

DR. LOK: This patient has compensated liver disease with no evidence of portal hypertension, so he could be cautiously treated with pegylated interferon or a nucleoside or nucleotide analog. Pegylated interferon is contraindicated in patients with decompensated cirrhosis or those with compensated cirrhosis and evidence of portal hypertension. But phase 3 clinical trials show that peginterferon can be used safely in patients with compensated cirrhosis, as long as there's no sign of portal hypertension as in this patient.

Many experts, however, prefer to use a nucleoside or nucleotide analog to be more careful, since many of these patients do require long-term therapy. And if he decides on a nucleoside or nucleotide analog, I would recommend either entecavir or tenofovir because he'll need long durations of therapy, and a drug with a low rate of antiviral resistance would be important.

MR. BUSKER: The evidence basis that long-term antiviral treatment can actually reverse cirrhosis. Talk to us about that, if you would, please.

DR. LOK: There is growing evidence that long-term nucleoside/nucleotide analog can reverse fibrosis and cirrhosis. Although in the past we had thought that cirrhosis is irreversible stage of liver damage, recent studies have shown that this is not the case. In particular, recent data from a follow-up report of a phase 3 tenofovir trial in which roughly 350 patients had paired biopsies over entry into the trial and at year five. After five years of continuous treatment, using the Ishak scoring system they found that roughly half of the patients had decreased fibrosis stage by at least one point. The Ishak fibrosis staging system goes from 0 to 6, with 5 and 6 showing cirrhosis. Furthermore, they had almost 100 patients with cirrhosis on a baseline biopsy, and three-quarters of these patients decreased their fibrosis stage to a level where they are no longer considered to have cirrhosis.

That is very clear evidence that with long-term viral suppression, fibrosis and cirrhosis can be reversed.

MR. BUSKER: Even if the HBV DNA is suppressed, is this patient still at risk of HCC?

DR. LOK: Antiviral therapy can prevent or reduce the risk of cancer, but does not completely eliminate that risk. Based on his initial laboratory values, his REACH-B score, which is a predictive score for HCC, is 10, and his predicted risk of HCC in 5 and 10 years without antiviral treatment, would be 2% and 5.2%, respectively. However, the REACH-B score was derived from data of patients without cirrhosis, and its accuracy in patients with cirrhosis is lower. I would expect that given this patient had cirrhosis, his risk of HCC would be higher than what the REACH-B score would have predicted.

There is insufficient data at this time to counsel patients how much that risk will be reduced, if HBV DNA became undetectable after he started antiviral therapy. Therefore, it is important to continue to perform HCC surveillance on these patients.

MR. BUSKER: Again — in this patient — is there a time when you would consider stopping the antiviral treatment?

DR. LOK: I would recommend lifelong nucleoside/nucleotide analog therapy, as this patient has cirrhosis. I might consider withdrawing treatment if hepatitis B surface antigen clearance is achieved. This, however, is achieved in only a very small percentage of patients.

One could argue whether it would be worthwhile repeating a liver biopsy a few years down the line to see whether cirrhosis is reversed, and if that is the case, whether we could contemplate stopping treatment. But right now, we don't really have any evidence to support that approach.

What is important, though, is if for any reason we decide to stop treatment, the patient must be monitored closely for relapse, and treatment should be reinitiated immediately if relapse occurs, particularly since this patient did have cirrhosis in the beginning. In fact, I usually tell my patients that

I need to monitor them more closely during the first few months after stopping treatment than when they are on treatment, to detect early relapse.

MR. BUSKER: Dr. Lok, thank you for bringing us those cases and your insight into them. I'm going to ask you now to look to the future for us, if you would please, and tell us what you think is going to happen with the incorporation of prediction models into clinical practice?

DR. LOK: One of the biggest dilemmas with hepatitis B treatment is to know whom we should start on treatment and what is the right time, and certainly these prediction models might give us additional information, because so many factors contribute to disease progression and HCC.

But one has to really understand the limitations of these prediction models. Almost all of the currently available prediction models have been derived from Asian patients, and they have not been validated in western patients who differ in genetic background, age at the time of infection, and the predominant HBV genotypes. And even for Asian patients, those prediction models might not apply to the very young patients who are less than 30 years old, or who are older than 55, because the models were derived from patient populations with an age group between 30 and 65.

In the future, we hope to have risk prediction models that further fine tune, that might incorporate genetic markers associated with risk of liver fibrosis and HCC that may permit physicians to make even more personalized decisions regarding whom to treat and when to initiate treatment.

MR. BUSKER: Thank you for sharing your thoughts, doctor. To wrap things up, I'd like to review what we've talked about today in light of our learning objectives. So to begin: identifying which patients with chronic HBV infection are at high risk for cirrhosis and HCC.

DR. LOK: We talk about the goals of antiviral treatment, which is to prevent cirrhosis and hepatocellular carcinoma. Therefore, it is important to identify who might be at risk. But to determine whether treatment works, we also have to have surrogate of more short-term endpoints, which is really looking at suppression of virus, normalization of liver enzymes, E antigen seroconversion, and S antigen loss.

In deciding whom to treat and not to treat, we're looking at who has active or advanced liver disease right now. People with life-threatening liver disease need to be treated now, but for those who do not have active or advanced liver disease, we are then relying on the prediction models to see what the risk would be in the near future, and those with high predictive risk obviously would be started on treatment.

We also discussed the importance of lifelong monitoring, because a patient who is predicted to have a low risk now may end up having a higher risk in the future if their liver enzymes or the virus level becomes elevated in the future.

MR. BUSKER: And our second learning objective: the utility and the limitations of prediction models for cirrhosis and HCC.

DR. LOK: We mentioned that prediction models would help us identify the patients who ought to be put on treatment; however, many of these models have not been validated, particularly in Caucasian patient populations, and how well these models work in real life has not been tested.

So the limitations of all these prediction models have to be recognized, and whatever information we get from a prediction model is to be just used as additional information, but not necessarily the only information that would guide the treatment decisions, and we've illustrated some of the utility of these models in a case in our discussions.

MR. BUSKER: And finally: incorporating predicted risk of HCC into decisions regarding HBV treatment.

DR. LOK: We discussed some of the limitations of these methods and their utility. One of the problems with incorporating these risk models is whether we apply these risk models only one time when we see the patient or do we apply these models sequentially during follow-up with changes in the lab values.

This way of utilizing the prediction models has not been studied, but that's actually what we do clinically. When we see the patient initially, we'll assess the patient and make some prediction, but during follow-up, we, as physicians, tend to revise those predictions

if the patient's condition changes. And obviously as the predicted risk of disease progression and cancer increases, we would need to rediscuss the treatment options for this patient. And I hope those case discussions illustrate how we use those prediction models in clinical practice.

MR. BUSKER: Thank you Dr. Anna Lok from the University of Michigan Health System for participating in this eViralHepatitis Review Podcast.

DR. LOK: It was a pleasure, and I hope that the audience found this useful.

MR. BUSKER: This podcast is presented in conjunction with the eViralHepatitis Review Newsletter, a peer-reviewed literature review certified for CME/CE credit, emailed monthly to clinicians treating patients with viral hepatitis.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education, through the joint sponsorship of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

For physicians, The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credits™*. Physicians should claim credit commensurate only with the extent of their participation in this activity.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

For nurses, this 0.5 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

This educational resource is provided without charge, but registration is required. To register to receive eViralHepatitis Review via e-mail, please go to our website, www.eViralHepatitisReview.org.

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of names of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing implies review of educational format, design, and approach. Please review the complete prescribing information for specific drugs, combinations of drugs, or use of medical equipment — including indication, contraindications, warnings, and adverse effects — before administering therapy to patients.

Thank you for listening.

eViralHepatitis Review is supported by educational grants from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., and Genentech, Inc.

REFERENCE

1. Yang HI, Yuen MF, Chan HLY, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011;12(6):568-574.