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VOLUME 3 — ISSUE 6: TRANSCRIPT

Featured Cases: Cure of Hepatitis B: Is it Achievable?

Our guest author is Fabien Zoulim, MD, PhD, Professor, Head of INSERM Viral Hepatitis Laboratory at the Medical School of Lyon, Lyon 1 University, Hepatology Department, Hospices Civils de Lyon in Lyon, France.

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

- Describe expectations in terms of hepatitis B surface antigen loss with nucleotide/nucleoside therapies, alone or in combination with interferon.
- Explain the risk factors for the development of hepatocellular carcinoma after hepatitis B surface antigen clearance.
- Discuss non-eradication of the HBV genome and reactivation after surface antigen clearance.

This discussion, offered as a downloadable audio file and companion transcript, covers the topic of HBV cure, as well as case-study scenarios for the clinical practice. This program is a follow up to the Volume 3, Issue 5 *eViralHepatitis Review* newsletter—Cure of Hepatitis B: Is it Achievable?

Unlabeled/Unapproved Uses
Dr. Zoulim has indicated that in today's discussion he will reference the unlabeled or unapproved uses of quantification of surface antigen testing and the testing of combination therapies with interferon currently in trial.

MEET THE AUTHOR

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Faculty Disclosure
Dr. Zoulim has indicated that he has received research grants from Roche, Gilead Sciences, Inc., Novira Therapeautics, Inc., and Scynexis, Inc. He has served as a consultant to Gilead Sciences, Inc. and Roche, and received honoraria from Gilead Sciences, Inc. Roche and Bristol-Myers Squibb.

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CME INFORMATION

⇩ PROGRAM BEGINS BELOW

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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:

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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.

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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, *Cure of Hepatitis B: Is it Achievable?*

Our guest is one of that issue's authors, Dr. Fabien Zoulim from the Medical School of Lyon, Lyon 1 University.

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.

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

- Describe expectations in terms of hepatitis B surface antigen loss with nucleotide/nucleoside therapies, alone or in combination with interferon.
- Explain the risk factors for the development of hepatocellular carcinoma after hepatitis B surface antigen clearance.
- Discuss non-eradication of the HBV genome and reactivation after surface antigen clearance.

I'm Bob Busker, managing editor of eViralHepatitis Review. On the phone we have with us Dr. Fabien Zoulim, professor and head of the Hepatology Department at Lyon University Hospital, and also head of the INSERM Viral Hepatitis Laboratory at the Medical School of Lyon, Lyon 1 University, in Lyon, France.

Dr. Zoulim has indicated that he has received research grants from Roche, Gilead Sciences, Inc., Novira Therapeutics, Inc., and Scynexis, Inc. He has served as a consultant to Gilead Sciences, Inc. and Roche, and received honoraria from Gilead Sciences, Inc., Roche and Bristol-Myers Squibb.

He has indicated that his presentation today will reference the unlabeled or unapproved uses of quantification of surface antigen testing and the testing of combination therapies with interferon currently in trial.

Dr. Zoulim, welcome to this eViralHepatitis Review Podcast.

DR. ZOULIM: I'm delighted to be here today and discuss with you whether a cure of hepatitis B is achievable.

MR. BUSKER: Let me ask you to start that discussion, Doctor, by describing a patient for us, please.

DR. ZOULIM: This is the case of Mr. X, a 40 year old man of Turkish origin, who was diagnosed with chronic hepatitis B in 1999. The results of laboratory analysis were the following: the patient was found to be detected to be hepatitis B surface antigen positive, HBeAg negative, anti-HBeAb positive, with HBV DNA fluctuating above 2000 UI/mL, he was infected with genotype D, with pre-core stop codon mutant. HIV, HDV and HCV tests were all negative. ALT levels were fluctuating between normal values and 3 times the upper limit of normal values. Liver biopsy was performed and the histopathology evaluation showed lesions of chronic hepatitis B with a Metavir score A1F3. Ultrasound analysis did not show any sign of liver tumor or portal hypertension.

MR. BUSKER: This 40 year old patient was initially diagnosed in 1999. How was he treated then?

DR. ZOULIM: At that time we were in 2000, and we decided to do a course of 12 months pegylated interferon alpha. We observed an on-treatment

virologic response with normalization of ALT levels, but this was followed by a rebound of viral replication and re-elevation of ALT levels three months after treatment cessation.

MR. BUSKER: So he was treated with interferon, but his viral replication rebounded and his ALT levels went back up. How did you proceed?

DR. ZOULIM: So we could define this as a failure of pegylated interferon alpha therapy, so we decided to follow the patient off treatment. In 2005, a new line of therapy was started with adefovir dipivoxil, a nucleotide analog, which was associated with a decrease in viral load and normalization of ALT levels. When newer viral load assays became available, we found that the HBV DNA levels were found to be persistently detected at low levels, approximately 3 log IU/mL.

Therefore, in 2008, because of the persistence of detectable HBV DNA, adefovir dipivoxil was stopped and switched to tenofovir disoproxil fumarate. Three months after the initiation of this new line of therapy, HBV DNA became undetectable by real-time PCR with a detection limit of 15 IU/mL. The virologic and biochemical responses were maintained until the last visit, and HBsAg remained positive.

At that time we performed a noninvasive assessment of liver damage by FibroScan and FibroTest, which showed a progressive improvement, with elasticity values declining from 9 kPa to 4 kPa on the FibroScan evaluation, and the FibroTest score declined from F3 to F1. Regular six-monthly ultrasound screening showed no sign of liver tumor development or portal hypertension.

Because of the excellent results, the patient then asked us whether treatment could be stopped at some point or if we could do something else to achieve this goal.

MR. BUSKER: This patient's clinical presentation and course — would you say those are typical for chronic hepatitis B?

DR. ZOULIM: Yes, this is a typical situation for patients from the Mediterranean basin or Middle East who are usually infected with a genotype D strain which favors the selection of precore mutants. Generally, precore mutant infections are associated with a clinical presentation of HBeAg negative chronic hepatitis B with fluctuating levels of HBV DNA and ALT. Pegylated interferon therapy generally leads to a good virologic response and biochemical response during therapy but is often followed by a relapse of viral replication and reinitiation of liver disease activity, which was the case in our patient.

MR. BUSKER: In a patient like this, how should the clinician interpret the results of nucleotide or nucleoside antiviral therapy?

DR. ZOULIM: In this patient, adefovir dipivoxil administration significantly decreased viral load and normalized ALT levels; however, as we mentioned, virologic response was not complete, as low levels of HBV DNA were persistently detected, which defined a partial virologic response. This is consistent with the observation made in the major clinical trials and cohort studies with adefovir dipivoxil.

The switch to tenofovir disoproxil fumarate led to undetectable HBV DNA levels and normalization of ALT levels for more than four years, and this is also consistent with observations in clinical trials and other clinical studies with tenofovir.

The improvement in noninvasive markers of liver fibrosis should be taken with caution, as this may not completely reflect a true regression of liver fibrosis; however, some studies using liver histology during long-term nucleoside therapy have shown an improvement of liver fibrosis and even a regression of liver cirrhosis in some patients.

MR. BUSKER: The expectations — in terms of surface antigen clearance — what would those be in a patient receiving nucleotide or nucleoside antiviral therapy?

DR. ZOULIM: Clinical experience and results of clinical studies with nucleoside or nucleotide analogs with a high genetic barrier to resistance, such as entecavir or tenofovir, have shown that the rate of HBsAg decline is very low and that only 10% of patients may achieve HBsAg clearance after six years of nucleoside analog administration.

Results of clinical trials with tenofovir also showed that HBsAg clearance was essentially confined to the population of HBeAg positive patients of non-Asian origin. Clinical experience and studies of other nucleoside analogs showed that HBsAg clearance

may still be achieved with nucleoside analog monotherapy in HBeAg negative patients but at a lower frequency. This was also discussed in the newsletter issue.

MR. BUSKER: Could HBsAg quantification be used to predict surface antigen loss?

DR. ZOULIM: Yes, it would be very relevant assays to predict HBsAg loss. Several assays to quantify serum HBsAg are commercially available but not yet approved in all countries. The use of these assays demonstrated that in most patients, prolonged nucleoside analog therapy for several decades would be needed to achieve HBsAg clearance or cccDNA clearance. The kinetics of HBsAg decline might be useful to predict at the individual level the time to HBsAg loss. However, in the majority of patients, the levels of HBsAg seem to be pretty stable over time during nucleoside analog administration.

The level of baseline HBsAg was also studied as a predictor of clearance during nucleoside analog therapy, but conflicting results were obtained in the different studies.

MR. BUSKER: What are the expectations with interferon — again, in terms of surface antigen clearance?

DR. ZOULIM: A few studies have looked at the impact of interferon administration on HBsAg loss. The rate of HBsAg clearance is also low, approximately 11%, when patients are followed up to five years after the end of the one-year course of interferon. Among the patients who achieve undetectable HBV DNA at the end of interferon therapy, the chance of clearing HBsAg was increased to 66%.

Some studies have shown that the chance of HBsAG loss are high with genotype A versus the other genotypes, which was also observed with some of the studies with nucleoside administration. Host genetic studies which are reviewed in the newsletter also could identify that IL28B polymorphism could predict interferon induced HBsAg clearance. However, this patient already received a course of interferon without virologic success, prior to nucleoside analog therapy.

MR. BUSKER: One more question on this patient, Doctor — and that's to ask you about the potential role of interferon combination therapy?

DR. ZOULIM: Combination therapy with interferon and nucleoside analog has been discussed for several years. Trials of de novo combination therapy of first generation nucleoside analogs such as lamivudine with pegylated interferon have not shown an added benefit over monotherapy on the off-treatment virologic response.

A few pilot studies using de novo combination strategy followed by a nucleoside analog monotherapy tail, even in patients who failed a previous course of interferon, showed, very interestingly, an increased rate of HBsAg decline and loss, accompanied by a significant decline of cccDNA in the liver of patients.

Another possibility could be possibility could be to envisage an add-on interferon therapy after a lead-in phase of nucleoside analog monotherapy. Indeed, some clinical immunology studies have shown that long-term nucleoside analogy therapy induced virologic response, which is needed to obtain the restoration of specific CD4/CD8 T cell responses, which could pave the way to add-on strategies with interferon.

However, most of these studies that were mentioned were noncontrolled pilot studies. It is therefore necessary to wait for the results of ongoing trials, evaluating the interferon add-on strategies in patients who achieve viral suppression during nucleoside analog therapy.

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

DR. ZOULIM: Yes, so let's talk about the second case. It is a 68 year old man of Portuguese origin, presenting with chronic hepatitis B, HBeAg negative, followed for 20 years in our outpatient clinic. On his initial liver biopsy in 1998 he was cirrhotic. The patient has an overweight with a BMI 33 and arterial hypertension.

In 1999, antiviral therapy was started with lamivudine, but was followed by a virologic breakthrough three years after the initiation of treatment. At that time adefovir dipivoxil was added to lamivudine, but virologic response remained partial. When tenofovir disoproxil fumarate was available, tenofovir was started and virologic response

occurred with HBV DNA becoming undetectable by real time PCR during entire follow-up. Nevertheless ALT levels stayed at 1.5 times the upper limit of normal and insulin resistance was documented. Finally, in 2008, HBsAg clearance was observed.

MR. BUSKER: A question, Dr. Zoulim. The surface antigen clearance occurring in this case — how do you explain it?

DR. ZOULIM: Well this case demonstrates perfectly that long-term viral suppression by nucleoside analog can lead to hepatitis B seroclearance. In this study by Dr. Seto, et al, that is discussed in the newsletter issue, has shown that in the lamivudine-treated population, 10% of patients may achieve HBsAG clearance after 10 years of therapy.[2] Our patient had about 10 years of treatment with different lines of nucleoside analog therapy which maintained virologic response over time. Unfortunately, we did not use HBsAg quantification at that time yet to determine the kinetics of HBsAg clearance, which could have given us some useful information in terms of prediction of HBsAG clearance in the patient.

MR. BUSKER: Thank you, Doctor. What happened next with this patient?

DR. ZOULIM: Four years after clearance of HBsAg, the patient developed a hepatocellular carcinoma which needed treatment by percutaneous radiofrequency ablation.

MR. BUSKER: So this patient developed HCC despite a complete virologic response and surface antigen clearance. Would you talk to us more about how and why this happened, Doctor?

DR. ZOULIM: I think this is a very important issue in patients who have lost hepatitis B surface antigen. So there are two types of arguments that need to be discussed. The first is the pathobiology of HBV induced liver cancer which rely on several factors. The first one the HBV genome integration in the host genome, which occurs in the early phase of infection. And this can be one of the mechanisms involved in the deregulation of host gene expression. The second one is the ongoing chronic inflammation associated with chronic hepatitis B. The third one is hepatocyte lysis and hepatocyte turnover, which occurs during chronic hepatitis, and which are associated with the development of liver cirrhosis as a consequence of long-term liver damage. So all these factors are very important in the development of hepatocellular carcinoma.

Clinically there are risk factors that are known and can be divided into different categories: host related, virus related factors, and environmental factors. Host factors mainly include age of the patient or duration of viral infection, male gender, family history of hepatocellular carcinoma, persistence of ALT elevation, low albumin levels, high bilirubin levels, and co-factors such as alcohol consumption and presence of liver cirrhosis.

The viral factors also are well known and include the persistence of elevated HBV DNA levels, positivity of HBeAg, infection with the genotype C HBV, the presence of precore promoter mutations which have been described as important risk factors. The other main environmental factors are aflatoxin exposure and cigarette smoking.

MR. BUSKER: In the patient we've been discussing — what were his specific HCC risk factors?

DR. ZOULIM: In our patient we could find risk factors such as a long-lasting infection with HBV, which was probably acquired during childhood, and associated with liver cirrhosis. Furthermore, the patient did not normalize liver enzymes in spite of correct hepatitis B controlled by antiviral therapy. And the persistence of liver enzyme elevation was attributed to a steatohepatitis in the context of an obvious metabolic syndrome. And all these elements constitute risk factors for hepatocellular carcinoma development.

And it was interesting that in one of the papers that is discussed in the newsletter it was shown that antiviral therapy can decrease the incidence of hepatocellular carcinoma but does not completely eliminate the risk over time.[1]

MR. BUSKER: How would you monitor a patient who has lost HBsAG?

DR. ZOULIM: In our clinical practice we stay with a six-month interval of ultrasound surveillance in spite of HBsAg clearance, especially if the patient was shown to be cirrhotic or to have advanced fibrosis on liver histology. I believe that the key message of this case is the importance of follow-up, even in patients who clear the HBsAg. Thanks to the recently published studies that are also discussed in the

newsletter, we know that cirrhosis may revert with long-term antiviral treatment, and that the incidence of hepatocellular carcinoma can also decrease.[1] But the persistence HBV DNA integrated in the host genome has been described as factor predisposing to the development of liver cancer. It will be important in the future to identify risk factors in each individual patient to better define a surveillance algorithm to be adapted to each individual patient.

For our patient, the main arguments for remaining with the six- month interval for liver imaging were the following: a long-lasting infection with HBV, a pre-existing cirrhosis before starting therapy, the existing steatohepatitis, and the lack of normalization of liver enzyme that was observed even during nucleoside analog therapy.

MR. BUSKER: In this patient did you stop the antiviral treatment? And what would you recommend to clinicians who have similar patients?

DR. ZOULIM: In our experience and in our institution, we recommend in these patients to stop antiviral treatment only if the patient develops sufficient antibody level against HBsAg. For our patient that was not the case, and antiviral treatment was therefore maintained after HBsAg loss. And then we continue monitoring the patient every three months and in case of anti-HBs antibody seroconversion on two sequential results, we stop the nucleoside analog.

MR. BUSKER: And along those lines, how would you monitor the patient after treatment withdrawal?

DR. ZOULIM: After treatment withdrawal, the monitoring would be in the first year identical to a patient under treatment, which means a blood test is performed every three months to quantify HBV DNA, HBsAg, and HBsAb. In case of stable antibody level, we can then loosen the follow-up to a six-month interval. But we must be aware of the possibility of seroreversion in case of immune depression, and we will talk about this situation in the next case.

MR. BUSKER: And we'll return with Dr. Fabien Zoulim and that next case 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 down-loadable 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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MR. BUSKER: Welcome back to this eViralHepatitis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Fabien Zoulim from the Medical School of Lyon, Lyon 1 University. And our topic is *Cure of Hepatitis B: Is it Achievable?*

We've been looking at how some of the new information Dr. Zoulim discussed in his newsletter issue can be translated into clinical practice. So let me ask you now to continue, Doctor, by bringing us another patient.

DR. ZOULIM: Yes, so our third patient is a 50 year old man of Asian origin, living in France since early childhood. He suffers from arterial hypertension with nephroangiosclerosis and severe renal impairment and kidney hemodialysis is ongoing on for two years. Finally, he underwent kidney transplantation last autumn. His hepatitis B status before transplantation was HBsAg-negative, HBsAb-positive, HBcAb-positive. HBV DNA was negative. At six months after transplantation, he came to the hospital emergency

ward for fatigue and jaundice, with ALT levels more than ten-fold the upper limit of normal.

EBV/CMV/HCV/HIV/HDV/HAV and HEV serology tests were all negative. HBsAg assay was also negative, as well as HBsAb, and interestingly, HBcAb of IgM type were positive. Ultrasound examination of the liver was normal, and liver function were still maintained.

MR. BUSKER: You've brought us a fairly challenging case, Doctor. What diagnosis was made?

DR. ZOULIM: In this type of situation we might have to acknowledge the diagnosis of HBsAg mutant. Indeed if the HBsAg is negative with the presence of anti-HBC IgM antibodies, we have to check for hepatitis B virus reactivation. HBV DNA was not quantified at the time when the patient came to the emergency ward, which was a mistake. This patient had been monitored only on the HBsAg, but unfortunately in that situation occult HBV infection can be missed.

MR. BUSKER: So the HBV DNA needs to be quantified to identify occult HBV.

DR. ZOULIM: Yes, indeed, HBV DNA needs to be quantified, and this is essential in the post-transplantation follow-up. In our case, it finally turned out to be elevated at approximately 6 log IU/ml. To confirm the diagnosis, viral genome sequencing found mutations in the HBs gene, and these mutations were responsible for immune escape, explaining the persistence of HBV despite the anti-HBsAb response, and the false negativity of the HBsAg assay and the false negativity of the laboratory diagnosis.

MR. BUSKER: Viral reactivation — talk to us about that, if you would, please.

DR. ZOULIM: One important message that needs to be remembered is that the HBV genome is never completely eliminated, even after HBsAg clearance. Indeed, the covalently close circular DNA, also called cccDNA, is a replicative form of HBV DNA which plays a crucial role in natural history of HBV infection. During infection, the viral cccDNA accumulates in the nuclei of infected hepatocytes and acts as a template for the transcription of viral genes, and it is considered as a viral minichromosome from which viral replication can restart in the case of loss of immune control.

It is interesting to see that in a study from 2004 which examined 98 patients with liver biopsies at different stages of HBV infection, it showed that patients with HBsAg clearance had extremely low levels of cccDNA compared to patients who were HBeAg positive. It was interesting to see that cccDNA did persist in these patients who lost HBsAg. And as it was mentioned before, in case of severe immune depression and loss of immune control of viral infection, HBV replication can reinitiate from the viral cccDNA template, leading to reactivation.

Another factor in addition to the persistence of cccDNA in the liver of infected patients is the HBV genome variability. And as mentioned earlier, mutations hepatitis B surface gene may be responsible for immune escape and the persistence of the viral genome despite anti-HBsAb seroconversion. So these two factors may be very important to explain not only to persistence of the virus, but also the reactivation of viral replication in the case of severe immune depression as was the case in our patient who received a kidney transplantation.

MR. BUSKER: What are the recommendations for the prophylaxis of HBV reactivation in surface antigen negative patients?

DR. ZOULIM: The American and European Association for the Study of the Liver recommended the following prevention. While HBV reactivation can occur in persons who are HBsAg negative but anti-HBc and anti-HBs positive, and in those with isolated anti-HBc antibodies, this is infrequent, and there is not enough information to recommend routine prophylaxis for these individuals. However, these patients should be monitored and antiviral therapy initiated when serum HBV DNA becomes detectable.

Nevertheless, some authors and experts suggested that antiviral treatment should be systematically initiated if the monitoring cannot be guaranteed, or if the immunosuppression will be for long-term.

It was shown in a retrospective Chinese cohort study that 15 out of 322 occult HBV carriers had HBV reactivation after kidney transplantation. Among the recipients with HBV reactivation, serum HBV DNA became positive in 10 cases, and serum HBsAg

became positive in 13 cases. Twelve cases had liver function impairment, and nine of these cases had HBV reactivation occurring within the first six months after kidney transplantation. And patient survival was significantly lower in HBV reactivation group.

So the results of this study really emphasize the need for cautious monitoring and management of these serologically cured patients, and that decisions for the monitoring and for prophylaxis must take into consideration not only the international recommendations, but also the clinical profile of each individual patient. The monitoring should comprise at least viral load, HBsAg, and HBsAb every month within the first six months posttransplantation and then every three months. So this is the minimal monitoring that should guarantee a good management of the patient.

Obviously, as it was said before, some experts would recommend to start prophylactic antiviral treatment in many patients to make sure that the risk of reactivation is minimized.

MR. BUSKER: I want to let our listeners know that a link to that retrospective Chinese cohort study Dr. Zoulim just referred to, can be found in the transcript version of this podcast. Doctor, I want to thank you for today's cases and discussion. Let me ask you now to look to the future for us: achieving a cure for HBV — what do you see happening?

DR. ZOULIM: Well I believe it appears more and more clear that a clinical cure might be achievable in the future for hepatitis B. The results of nucleoside analog or pegylated interferon therapy are really encouraging, with an improvement in liver fibrosis, a decreased risk of hepatocellular carcinoma, which represents strong arguments to convince patients to be screened and treated.

The rate of HBsAg clearance on the other end remains low, and the clearance of HBsAg typically requires long-term therapy. The results of new combination trials with a novel nucleoside analog and pegylated interferon, we are waiting to see if this can change the management of our patients. And we have also to keep in mind that major research efforts are ongoing to identify new targets and novel compounds to design true combinations to be evaluated in clinical trials with the aim of increasing the rate of HBsAg loss.

MR. BUSKER: Thank you for sharing your thoughts, Dr. Zoulim. Let's wrap things up now by summarizing what we've talked about today in light of our learning objectives. So to begin: the expectations — in terms of hepatitis B surface antigen loss — with nucleotide/nucleoside therapies, alone or in combination with interferon.

DR. ZOULIM: I believe we've seen that HBsAg clearance can be achieved with the current antiviral treatments; however, the rate of HBsAg loss remains low and requires, in any case, long-term antiviral treatment.

MR. BUSKER: And: the risk factors for the development of hepatocellular carcinoma after hepatitis B surface antigen clearance?

DR. ZOULIM: The risk factors for the development of hepatocellular carcinoma after HBsAg clearance are the presence of integrated viral genome in the host genome, the long duration of infection, the preexisting liver cirrhosis or advanced fibrosis, an infection with viral genotype C, as well as additional cofactors such as alcohol consumption, cigarette smoking, aflatoxin exposure or additional liver disease such as nonalcoholic steatohepatitis.

MR. BUSKER: And finally: the noneradication of the HBV genome and reactivation after surface antigen clearance.

DR. ZOULIM: The main determinants to explain HBV reactivation after HBsAg clearance are the persistence of viral cccDNA, which is the viral minichromosome in the liver of infected patients, even after hepatitis B surface antigen loss. But also the viral genome heterogeneity and the possibility of many mutations occurring on the viral genome which may provide selective advantage to the virus. And all these elements can explain the reactivation of the viral replication in case of loss of immune control of the infection.

Therefore, in patients who have lost HBsAg and who are undergoing immunosuppressive therapy, frequent monitoring is required, and in some cases antiviral prophylaxis can be discussed.

MR. BUSKER: Dr. Fabien Zoulim, from the Medical School of Lyon, thank you for participating in this eViralHepatitis Review Podcast.

DR. ZOULIM: Thank you very much. I also really enjoyed this discussion and I hope that this will be helpful for practitioners involved in hepatitis B management as well as for patients.

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.

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