JOHNS HOPKINS MEDICINE
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eViralHepatitis Review
Podcast Issue
Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
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VOLUME 3 — ISSUE 2: TRANSCRIPT

Featured Cases: European Association for the Study of the Liver HCV Update

Our guest author is Mark S. Sulkowski, MD, Professor of Medicine and Medical Director of the Viral Hepatitis Center, Divisions of Infectious Diseases and Gastroenterology/Hepatology at The Johns Hopkins University School of Medicine in Baltimore.

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

- Summarize the evidence describing newly emerging therapies for hepatitis C
- Assess how these newly emerging therapies may affect therapeutic decision-making in patients with HCV genotype 3
- Assess how these new therapies may affect therapeutic decision-making in patients with HCV genotype 1

This discussion, offered as a downloadable audio file and companion transcript, covers advancements in hepatitis C therapy presented at EASL, as well as case-study scenarios for the clinical practice. This program is a follow up to the Volume 3, Issue 1 *eViralHepatitis Review* newsletter—European Association for the Study of the Liver (EASL)/ HCV Update.

Faculty Disclosure
Dr. Sulkowski has indicated that he has received grant and or research support from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck, and Vertex Pharmaceuticals Incorporated. He has served on consulting or advisory boards for AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck, and Vertex Pharmaceuticals Incorporated. And he has also served on a steering committee for Pfizer, Inc.

MEET THE AUTHOR

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Unlabeled/Unapproved Uses
Dr. Sulkowski has indicated that in today's discussion he will be referencing the unapproved or non-indicated uses of sofosbuvir plus peginterferon/ribavirin (currently being reviewed by the FDA, but not yet approved), simeprevir plus peginterferon/ribavirin (also currently being reviewed by the FDA and not yet approved), interferon-free regimens including sofosbuvir plus daclatasvir and sofosbuvir plus ledipasvir, as well as other experimental interferon-free HCV treatment regimens, some including the addition of ritonavir.

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CME INFORMATION

⇩ PROGRAM BEGINS BELOW

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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

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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

- linicians 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

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- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HBV.

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

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

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Today's program is a companion piece to our eViralHepatitis Review newsletter issue: *European Association for the Study of the Liver HCV Update*.

Our guest is that issue's author, Dr. Mark Sulkowski from The Johns Hopkins University School of Medicine.

This activity has been developed for primary care physicians, OB/GYNs, nurse practitioners, physician assistants, hepatologists, gastroenterologists, infectious disease physicians, and others involved in the care of patients infected or at risk for infection with hepatitis C.

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

- Summarize the evidence describing newly emerging therapies for hepatitis C
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- Assess how these new therapies may affect therapeutic decision-making in patients with HCV genotype 1

I'm Bob Busker, managing editor of eViralHepatitis Review. On the phone we have with us Dr. Mark Sulkowski, Professor of Medicine and Medical Director of the Viral Hepatitis Center in the Divisions of Infectious Diseases and Gastroenterology/Hepatology at The Johns Hopkins University School of Medicine in Baltimore.

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Dr. Sulkowski, welcome to this eViralHepatitis Review Podcast.

DR. MARK SULKOWSKI: Thank you. It's great to be here.

MR. BUSKER: As you pointed out in your newsletter issue, doctor, advances in hepatitis C therapy are moving forward very fast. I'd like to start out today by asking you to recap some of the new treatments that were discussed at EASL 2013 and any updates that may have occurred since that meeting.

DR. SULKOWSKI: Well certainly, this has been a very dynamic and rapidly moving year. Hepatitis C advances have really been coming every six months in a rapid format, and in general these advances have been broken down into the European Liver Meeting, the so-called International Liver Congress, or EASL, which occurs in the spring, and then in the fall we have the American Liver Meeting or AASLD, and that typically occurs in late October/early November, as it will this year.

So the advances are really challenging to keep up with in those six- month intervals. This year at EASL, which was held in Amsterdam, a tremendous number of studies pointed the direction for new therapeutics. We're also gearing up again for more advances at the AASLD meeting.

Let's start by recapping what we saw at EASL. In my mind, one way to break down these rapidly advancing multiple regimens is to think of them as refinement to the current therapy, which is a hepatitis C protease inhibitor, plus peginterferon, plus ribavirin. While I know that many patients and hepatitis C treating clinicians are very anxious to get rid of interferon and go to what we refer to as interferon free, it's important to note that there is this intermediate step of significant and very important advances with refinements to peginterferon and ribavirin as a backbone.

As we outlined in the newsletter, the first of these refinements is the so called NEUTRINO study. This was presented at the European liver meetings and also published in the *New England Journal of Medicine*. It is the combination of a once daily polymerase inhibitor known as sofosbuvir, plus peginterferon and ribavirin. What's important about this particular regimen is that it is taken for only 12 weeks. We've been accustomed to response-guided therapy with telaprevir and boceprevir. With telaprevir the treatment is taken for 24 weeks if the patient achieves a rapid virologic response. But here we're dropping this paradigm of so-called response-guided therapy and the treatment regimen for all patients is going to be sofosbuvir, peginterferon, and ribavirin.

The study was conducted in patients who were treatment naïve and had hepatitis C genotype 1, 4, 5, and 6. The only patients who weren't included in the NEUTRINO study were those with genotypes 2 and 3, and we'll get to them a little later. The results with this 12-week, triple therapy regimen were very impressive The SVR rate for genotype 1 was around 90%, and the SVR rate for genotypes 4, 5, and 6, which was the smaller number, was above 95%. So SVR rates were very high, and the treatment was well-tolerated. We all know about the side effects of peginterferon and ribavirin, but during the 12 week interval the dropout rate for side effects was less than 3%.

There were some important predictors of response. We saw that individuals who had cirrhosis responded a little less well, but still a very good 80% SVR. Individuals who were IL28BCC responded a bit better than those who were CT and TT.

This regimen is part of a package for sofosbuvir that has been submitted to the FDA, and we anticipate that the FDA will be discussing this regimen in the fall of 2013, and perhaps approval for prescription in the United States by the end of the year.

Now the other refinement to peginterferon/ribavirin was simeprevir. Now simeprevir is a second-generation protease inhibitor, so it works at the same target as telaprevir and boceprevir, but some important refinements are that it's taken once daily, it does not cause anemia, and it does not cause a rash as we've seen with telaprevir.

It is a well-tolerated oral once daily protease inhibitor. Now it was studied in a classic response-guided therapy format for either 24 or 48 weeks. Simeprevir was taken with peginterferon and ribavirin for the first 12 weeks and then simeprevir was stopped. If the patient had a rapid virologic response, the treatment was 24 weeks; if the patient was a slow responder, treatment was extended to 48 weeks.

Now the majority of patients, more than 75 percent, qualified for the 24 week treatment course. The other important point about these studies, the so-called QUEST-1 and QUEST-2 studies that are also reviewed in the newsletter, is that they were compared to a placebo plus PEG-interferon and ribavirin. Now, not surprisingly, the simeprevir group did better with respect to SVR, but what I think was equally surprising was that the tolerability of placebo and simeprevir were very similar.

So like sofosbuvir, this regimen has been submitted to the FDA and is planned to be discussed in the fall of 2013 by the FDA, and we may see approval for prescription in the United States by the end of calendar year 2013. So we'll certainly get more information about these regimens. Some details still have to be sorted out. For example, in the simeprevir study, patients with genotype 1 subtype A who had a baseline mutation that occurs naturally and spontaneously called Q80K, appeared to respond less well. So we're going to have to really dig into that data, but these refinements should be available by the end of calendar year 2013.

MR. BUSKER: Now interferon-free therapies — as you mentioned, there's a lot of interest there. Update us on those if you would, please.

DR. SULKOWSKI: Well certainly the gold standard, if you will, or the goal of hepatitis C treatment is to get rid of the interferon-alpha. It's been the cornerstone of hepatitis C therapeutics since the early 1990s, and has a lot of side effects. So at the EASL meeting in 2013 we saw some major advances towards interferon-free regimens.

Now the first group of patients that will get access to interferon-free therapy is expected to be patients infected with genotype 2 or 3. There were several studies that were conducted with the combination of sofosbuvir plus ribavirin in patients with genotype 2 or 3 infection who were both treatment naïve, as well as patients who had failed previous peginterferon and ribavirin therapy.

The third group of patients that was studied were patients who were determined to be interferon-unwilling, -ineligible or -intolerant. And of course, as many clinicians have observed, there are many patients who are unwilling to take interferon because of its side effects.

These studies were presented individually but actually published in the *New England Journal of Medicine* as a group of studies. As we reviewed in the newsletter, these studies included the FISSION study. FISSION was a treatment naïve trial, genotype 2 and 3 patients, the majority were genotype 3, who were randomized to peginterferon and ribavirin vs sofosbuvir and ribavirin. Now, sofosbuvir and ribavirin was given for a period of 12 weeks, whereas the PEG-interferon and ribavirin was given for the standard 24 weeks.

The remarkable data from the FISSION study was that the SVR rates were essentially identical when one looked at the overall population. There were a couple of surprises. The first is that genotype 2 infected patients responded much better to sofosbuvir and ribavirin, SVR rates in the ball park of 95 percent, and genotype 3 infected patients with both peginterferon and ribavirin, as well as sofosbuvir and ribavirin responded less well, overall 56%. And then while one looked at the subgroup of patients with genotype 3 and cirrhosis, we saw SVR rates as low as 30 to 35%.

So the one thing we learned from this particular study was that genotype 3 and genotype 2 are truly different viral infections, and we can certainly talk more about that.

The next group of studies was the POSITRON study. This was for interferon-unwilling, -ineligible, and -intolerant patients, and this was compared to placebo. The SVR results were very similar to those in FISSION, so I won't get into the details here, but what I found interesting about the POSITRON study was that the major side effects observed were some anemia with ribavirin, as we would expect, but the major side effects were fatigue, headache, and nausea. The same three side effects were also seen in the patients who received placebo, but they occurred more commonly in the patients who received sofosbuvir and ribavirin, but overall the regimen was very well tolerated.

The final study of this trio of genotype 2 and 3 studies was the FUSION study. Now this looked at genotype 2 and 3 affected patients who had failed previous peginterferon and ribavirin. This group of patients certainly has no treatment options using current therapeutics. What we did see in this study was an important comparison of 12 weeks of sofosbuvir and ribavirin vs 16 weeks.

This study yielded a very interesting result. For genotype 2 and 3, the results were quite different. For genotype 2 infection, the results showed outstanding SVR rates above 95% for 12 weeks and not a substantial gain with 16 weeks, although perhaps among patients with cirrhosis. But for patients with genotype 3 with and without cirrhosis, there was a substantial increase in the SVR rate with 16 weeks of therapy up to 61%.

It's anticipated that when the sofosbuvir and ribavirin regimen is considered by the FDA for approval in the United States, we may see a 12-week duration of therapy for genotype 2 and a 16-week duration of therapy for genotype 3, given these outcomes. But nonetheless, this group of patients becomes the first in the United States to actually get access to interferon-free therapy on an approved basis.

The majority of patients in the United States have genotype 1 infection, and here we saw some very exciting data at the European Liver Meetings. It's important to note that the phase 3 clinical trials for

the regimens I'll discuss have not been completed; they're ongoing in 2013, and we do not anticipate approval of these regimens for prescription probably until the end of 2014, and of course that's speculation on my part.

The first regimen that garnered attention was a combination of sofosbuvir, the polymerase inhibitor we discussed earlier, plus ledipasvir. Ledipasvir is an NS5A inhibitor, and what we saw at EASL was a relatively small study of treatment naïve and had peginterferon and ribavirin failure patients, this was presented by Professor Gane using his cohorts in New Zealand, and he reported 100% response rates in these groups; but again, these were small numbers of patients.

This regimen was also studied in a protocol called the LONESTAR Study that was not presented at EASL, it's only been discussed in a press release, but the press release also looked quite promising with 95 percent or greater, so we look forward to seeing the full dataset from this additional phase 2 study known as LONESTAR. Stay tuned for that after the AASLD meeting.

A couple of other regimens I think are worth discussing. The Aviator study was a very large phase 2 study of nearly 500 patients who were treated with a combination antiviral regimen using three direct antiretrovirals. This regimen included a protease inhibitor known as ABT450, which is boosted by ritonavir and used to inhibit CYP3A4 and thereby allows once daily dosing.

ABT450 has been combined with ABT267, which is an NS5A inhibitor, and in the study, multiple regimens were evaluated. Patients with genotype 1 got various combinations. Some got all the medications, ABT450; ABT267 plus ABT333 (a nonnucleoside polymerase inhibitor), plus ribavirin. Other patients had one of the drugs dropped out. For example, some patients did not take ribavirin, other patients were randomized not to take 333, and some did not take ABT267.

The results were quite interesting. Patients were treated for 8, 12, or 24 weeks. The group that did best was the group that took all the medications for 12 weeks. They had a 98% SVR rate in both genotype 1A and 1B. If the duration was reduced to 8 weeks, the relapse rate was a bit higher and the SVR rate dropped by roughly 10%, so 12 weeks was better than 8.

When one of the drugs was removed, either ABT267 or ABT333, or ribavirin, there was in general a 10% decline in SVR. Studies are ongoing to clarify which patients need all the medications. For example, there were some hints in the study that perhaps patients with genotype 1 subtype B don't need the full regimen, so we'll see where this ends up, but it was a very exciting study.

The last regimen that's interferon-free is sofosbuvir plus an NS5A inhibitor called daclatasvir. This regimen was important because it was tested in patients who had failed telaprevir and boceprevir plus peginterferon and ribavirin. Certainly those patients have no treatment options today.

This study looked at 41 patients who had virologic failure to telaprevir and boceprevir. Half of them still had evidence of resistance to those first-generation protease inhibitors. Importantly, after 24 weeks of therapy, all patients achieved SVR 24. This was a very successful combination that I think gives great hope to patients who have failed peginterferon or ribavirin.

However, none of these interferon-free oral regimens for genotype 1 are expected to be approved in this calendar year. But stay tuned; they're moving very quickly and we expect to see more data, both at the American Liver Meetings in the fall and also coming to our clinics sometime in late '14, early '15.

MR. BUSKER: And we'll return with Dr. Mark Sulkowski from the John Hopkins University School of Medicine 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. Mark Sulkowski from The Johns Hopkins University School of Medicine. And today we're talking about new information on hepatitis C presented at the 2013 EASL meeting in Amsterdam.

Before the break, doctor, you gave us a very comprehensive update on emerging HCV treatments. What I'd like to do now is ask you to talk about how some of that new information might affect current clinical practice. So if you would, please start us out with a patient scenario.

DR. SULKOWSKI: The first patient I'd like to discuss has genotype 3 infection. This is a 58 year old man with advanced fibrosis. His history is in many ways very typical of patients in the United States. He was infected around 1975 through injection drug use but has not used drugs in decades.

The patient's HCV was diagnosed in 1995 but not treated, primarily because of a desire to avoid interferon. But in 2012, his primary physician was aware of hepatitis C, spurred in part by the recent CDC discussion of screening, and recommended further evaluation.

The initial evaluation included a noninvasive seromarker known as HCV FibroSURE, which indicated the potential for cirrhosis. This was further suggested by a low platelet count. Further evaluation determined that he had compensated cirrhosis with genotype 3 infection. He was referred for medical evaluation and treatment.

MR. BUSKER: Before we get specifically into this patient, let me ask you a more general question: how common is genotype 3 infection and what's unique about it?

DR. SULKOWSKI: Genotype 3 infection is shaping up to be a very interesting hepatitis C strain. It occurs in roughly 10 to 15% of American patients with HCV, it's very common in other parts of the world, as well, and we've always known it's unique in that it causes hepatic steatosis, or fatty liver. There is also some data to suggest that the prognosis is worse in patients with genotype 3 patients, and it's more aggressive in leading to cirrhosis and potentially end-stage liver disease.

The other unique factor is what I already discussed with respect to sofosbuvir and ribavirin: genotype 3 appears to respond less well and also responds less well to peginterferon and ribavirin. So it's emerging as a unique viral strain with respect to its characteristics and natural history and also its treatment responsiveness.

MR. BUSKER: The patient you described — 58 years old, genotype 3A, long-term infection, advanced fibrosis, compensated cirrhosis — how should he be evaluated? Do you see any need for biopsy? And what about screening for hepatocellular cancer?

DR. SULKOWSKI: This is a very good point. We often focus on hepatitis C treatment but there is medical care that needs to be delivered for the cirrhotic patient. The first question is how confident are we he has cirrhosis and I think we're getting to a point where noninvasive blood tests and the noninvasive test known as elastography to measure liver stiffness can really give us a good idea. So I don't think this patient needs a liver biopsy, he does need regular cancer screening, that is hepatocellular carcinoma screening, and I recommend ultrasound, typically with AFP every six months.

And what I tell patients like this, as I told this individual, is you need to think of this as the same way women think about mammography. Every six months, ultrasound to look for hepatocellular carcinoma. Of course, the reason we do that is if we can find a liver cancer early, it can be treated. He also needs to be vaccinated against hepatitis A and B if he is not immune, and, of course, should abstain from any and all alcohol.

MR. BUSKER: What are his treatment options now — and what may be available in the next couple of months?

DR. SULKOWSKI: This is an interesting time for this patient. The current therapy is peginterferon and ribavirin. We know that this is a challenging course of therapy because of side effects and a relatively low SVR rate, so the data that would apply to this patient most succinctly would be the data from the FUSION study and from the FISSION study with sofosbuvir and ribavirin.

We know from these clinical trials that genotype 3 did not respond as well as genotype 2, and we know that patients with cirrhosis did better with 16 weeks and patients with genotype 3 did better with 16 weeks of therapy. So drawing from the data from the FUSION study, if we were to treat this patient with sofosbuvir and ribavirin, we would certainly consider 16 weeks of treatment. And I should point out there's a study being conducted in Europe that's actually looking at 24 weeks for genotype 3 infected patients. So clearly if we're going to use interferon-free therapy, longer therapy, at least 16 weeks, in my mind would be better.

Another interesting option is the possibility of using sofosbuvir, peginterferon, and ribavirin. The NEUTRINO study excluded patients with genotype 3, but a study now published in *Lancet Infectious Diseases,* called the PROTON study1, that did look at sofosbuvir, PEG-interferon and ribavirin for 12 weeks in genotype 2 and 3 infected patients. Now a small number, only 25 patients, but all achieved SVR.

So in my mind this patient needs to move toward treatment, and I would probably wait until sofosbuvir is available and then consider either sofosbuvir and ribavirin, and maybe discuss with him the inclusion of peginterferon, albeit an off-label use of that drug.

MR. BUSKER: I want to let our listeners know that a link to the PROTON study published in *Lancet* that Dr. Sulkowski referred to can be found in the transcript version of this podcast. Aside from sofosbuvir, what else is in the pipeline for genotype 3?

DR. SULKOWSKI: Genotype 3 is an interesting strain. Unfortunately, the current protease inhibitors and some of the current NS5A inhibitors are not particularly active against genotype 3, so there is a major push to develop new direct antivirals.

One that's being studied is an NS5A inhibitor called GS5816, and another NS5A inhibitor from a company called Idenix, that appear to be quite active against genotype 3 infection, but these were in phase 2 trials. In other words, the next generation of drugs for genotype 3 is not going to be available in the near future, maybe two years or more down the road. So I think it's important when we look at a patient with genotype 3 and cirrhosis, we should move forward with treatment with these current options, adding sofosbuvir to that list.

For this particular patient I elected not to defer treatment any further. I indicated that we should wait until sofosbuvir is approved, given that there are plans for the FDA to discuss this in the fall of 2013, and then have recommended moving forward with a sofosbuvir-and-ribavirin-based regimen for a minimum of 16 weeks with the potential for adding peginterferon to the mix.

MR. BUSKER: Thank you, doctor, for bringing us that case. Let me ask you to describe another scenario, if you would, with a patient who has a different genotype.

DR. SULKOWSKI: Another patient who was recently evaluated in our office was a 45 year old man with genotype 1, subtype B. He is interesting that he has IL28BCC, which is very responsive to peginterferon, but also minimal liver disease. He is otherwise healthy. His liver disease stage is stage 0 or 1, very minimal for fibrosis, but he really wants to be cured. I think the discussion this brings up is what are his options for treatment.

As I outlined earlier, we are expecting some refinements with peginterferon and ribavirin in late 2013, so could this patient be treated with peginterferon, ribavirin and sofosbuvir or simeprevir, or potentially wait until late '14, early '15 for interferon-free oral regimens? That's the discussion we're having today with patients like this.

MR. BUSKER: Considering that his liver disease stage is mild — why not wait for interferon-free therapy? What are the other considerations in the decision to treat or not to treat the HCV in this patient?

DR. SULKOWSKI: I think in my mind, this decision, you have a genotype 1 infected patient, and the question is treat now or defer therapy until later. Now I would start with the premise that most patients who are hepatitis C affected want to be treated and want to

be cured. The question really is how much they're willing and able to put into that, can they take interferon-alpha, can they take treatment for a full 48 weeks, and those type of issues?

But I'll start with the premise that most patients desire to be cured; they don't want to be infected with chronic hepatitis C. So in that sense I think the patient's decision does matter, I do consider the treatment decision to be a conversation with the patient, understanding their desires to be cured.

Now that said, there are a number of patients in whom I feel quite comfortable waiting for the availability of oral interferon free regimens and these are patients who say, yes, I want to be cured, but I really don't want to take interferon. There may be many reasons for that.

But another group of patients — and this patient may be one of them — who say, I understand my liver disease is mild, but I'm concerned about this virus, and perhaps because of family reasons or other considerations want to pursue treatment, I think it's perfectly acceptable to treat that patient.

In fact, I think as we move forward into greater efficacy and better tolerability of hepatitis C treatment, we're going to be discussing more and more the question of what else does hepatitis C do to patients. We all know that it causes liver disease, that's a fact that is not in dispute. It can lead to cirrhosis, liver cancer, end stage liver disease, and in some patients, death.

An intriguing body of literature is beginning to grow that suggests hepatitis C may be linked to higher mortality from other diseases. A study from Taiwan suggested increased risk of malignancy — not liver cancer — and increased risk of renal disease. Other studies suggest hepatitis C can affect the brain and still other studies suggest it can lead to diabetes mellitus.

So as we get into these better treatments I think we'll be asking what else hepatitis C is doing to this patient. I believe that as we talk to patients in the current era, liver disease stage is by far the driver of our treatment decisions, but that will change as treatment evolves.

MR. BUSKER: To wrap things up on this patient: how did you decide to proceed?

DR. SULKOWSKI: Well in discussing this individual I think it was very clear that treatment was a major priority, and the individual was not particularly concerned about interferon. And as we talked through the potential side effects and benefits of interferon, we made the decision to proceed with a regimen of sofosbuvir plus peginterferon and plus ribavirin. The advantages were that he's got IL20BCC, so he should respond quite well, at least based on the NEUTRINO study, and it's 12 weeks long.

In my mind it did make sense to pursue telaprevir or boceprevir today because that treatment course would be as long as 24, or if he was a slower responder, 48 weeks, so we decided to wait a little bit until the next generation of therapies were here, but because of his strong desire to be cured, we elected not to wait until the interferon-free, all-oral therapies are available.

For another patient we might decide to wait. I think this highlights the need to actually sit down and individualize the approach to treatment for patients infected with chronic hepatitis C.

MR. BUSKER: Thank you, Dr. Sulkowski, for presenting those patients and for your insight into their treatment options. Now I'd like to recap what we've talked about today in light of our learning objectives. To begin: describe newly emerging therapies for hepatitis C.

DR. SULKOWSKI: We focused on the emerging refinements to peginterferon and ribavirin with sofosbuvir and simeprevir and also looked ahead to the interferon-free, oral direct antiretroviral regimens. And although these are still about a year to a year and a half down the road, we saw very exciting phase 2 data for regimens based on sofosbuvir and ledipasvir, as well as ABT450/ritonavir. We're looking forward to these coming forward, and the future looks bright for these interferon-free oral regimens.

MR. BUSKER: And our second learning objective: how these newly emerging therapies might affect therapeutic decision-making in patients with genotype 3.

DR. SULKOWSKI: Certainly, genotype 3 infected patients do have improved treatment options or at least will have improved treatment options and we see approval of new drugs. But what we're learning is a bit paradoxical. For years, we always thought of

genotype 1 as the most difficult to treat strain of hepatitis C globally, but because many of these new direct acting antivirals were engineered, if you will, to target genotype 1, we actually see that there are less drugs in the pipeline for genotype 3.

It's intriguing to think about it this way, but genotype 3 may emerge as one of the more difficult-to-treat strains of hepatitis, and genotype 1 may actually shift to an easier-to-treat strain. And that is a true paradigm shift in how clinicians and patients have thought about this disease. So genotype 3 is a hot topic following EASL 2013.

MR. BUSKER: And finally: how these new therapies might affect the therapeutic decision-making in patients with genotype 1.

DR. SULKOWSKI: Clearly when a health care provider sits down with a patient with chronic hepatitis C, yes, we're going to discuss the current approved therapies and the current standard of care, but when a therapeutic area is moving as quickly as hepatitis C is, we also need to be aware of and discuss what's coming in the not too distant future. I think patients need to consider the full array of options, both in terms of what they are, what the pros and cons are, the potential benefits and risk, if you will, but also the timelines when they're expected. So a comprehensive discussion with patients should include current treatments, but also treatments expected in the not too distant future.

MR. BUSKER: One more question, Dr. Sulkowski. For clinicians treating patients with HCV, what's the single most important thing they should be aware of?

DR. SULKOWSKI: Well, Bob, I think my parting word of advice to hepatitis C treating clinicians would be stay tuned. Medicine always has a rapid learning curve and we know the importance of staying up on the field. Certainly, hepatitis C is moving at a pace that is quite quick. I think the key in hepatitis C treatment today is education and staying tuned to advances in therapy.

MR. BUSKER: Dr. Mark Sulkowski, from the Johns Hopkins University School of Medicine, thank you for participating in this eViralHepatitis Review Podcast.

DR. SULKOWSKI: Thanks, Bob, I've really enjoyed it.

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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