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 Bristol-Myers Squibb, Gilead Sciences, Inc. and Merck & Co, Inc.

VOLUME 4 — ISSUE 2: TRANSCRIPT

Featured Cases: The New DAAs and HCV Genotype 2/3 Patients

Our guest author is David L. Wyles, MD, Associate Professor of Medicine, Division of Infectious Diseases at the University of California San Diego.

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

- Evaluate the treatment options for patients with genotype 2 and genotype 3 HCV infection, including those with cirrhosis.
- Summarize the phase 3 clinical trial data investigating the new DAA regimen of grazoprevir plus elbasvir.
- Describe the limitations in currently available retreatment options for patients failing interferon-free DAA regimens, including the importance resistance may play in retreatment success.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of new DAA regimens for the treatment of genotype 2 and genotype 3 HCV infection, as well as their potential use in retreatment in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 4, Issue 1 *eViralHepatitis Review* newsletter—New HCV DAA Regimens, Retreatment, and Optimizing Treatment of Genotype 2/3 Infection.

MEET THE AUTHOR

David L. Wyles, MD
Associate Professor of Medicine
Division of Infectious Diseases
University of California
San Diego
San Diego, California

Unlabeled/Unapproved Uses

Dr. Wyles has indicated that there will be references to the use of grazoprevir plus elbasvir for the treatment of HCV infection – this combination in not currently FDA approved for the treatment of HCV infection and is still considered investigational.

Faculty Disclosure

Dr. Wyles has disclosed that he has received grant and/or research funding from AbbVie, Bristol-Myers Squibb, Gilead, and Merck, and has provided advisory consult for Janssen.

Release Date
November 24, 2015

Expiration Date
November 23, 2017

CME/CE INFORMATION ⇩ **PROGRAM BEGINS BELOW**

ACCREDITATION STATEMENTS

Physicians

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership 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.

CREDIT DESIGNATIONS

Physicians

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

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.

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

Today's program is a follow-up to our newsletter issue reviewing the *New DAA Regimens for the Treatment of Genotype 2 and Genotype 3 HCV Infection,* as well as their potential use in retreatment. Our guest today is that issue's author, Dr. David Wyles, Associate Professor of Medicine in the Division of Infectious Diseases at the University of California San Diego.

*e*ViralHepatitis Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Bristol-Myers Squibb, Gilead Sciences, and Merck & Company.

Learning objectives for this audio program include:

- Evaluate the treatment options for patients with genotype 2 and genotype 3 HCV infection, including those with cirrhosis.
- Summarize the phase 3 clinical trial data investigating the new DAA regimen of grazoprevir plus elbasvir.
- Describe the limitations in currently available retreatment options for patients failing interferon-free DAA regimens, including the importance resistance may play in retreatment success.

Dr. Wyles has indicated that he has received grant and/or research funding from AbbVie, Bristol-Myers Squibb, Gilead, and Merck, and that he has provided advisory consult for Janssen. He has further indicated that there will be references to the use of grazoprevir plus elbasvir for the treatment of HCV infection – this combination is not currently FDA approved for the treatment of HCV infection and is still considered investigational.

I'm Bob Busker, managing editor of *e*ViralHepatitis Review. Dr. Wyles, thank you for joining us today.

DR. WYLES: Thanks very much, Bob. It's my pleasure to be here, and I'm looking forward to our discussion today on some new HCV therapies that are available.

MR. BUSKER: In your newsletter issue, Dr. Wyles, you reviewed the key studies investigating what have been called "hard to treat" patients with hepatitis C — those with non-genotype 1 virus, hepatic or renal disease, or who have failed an initial DAA treatment. Our focus today is on how to translate some of that information into clinical practice. So start us out, if you would doctor, with a patient scenario.

DR. WYLES: Our first patient is a 52 year old Hispanic gentleman. He's never been treated for his HCV and he has genotype 3. He also has cirrhosis based on a FibroScan done as well as a confirmatory FibroSure test which also suggested cirrhosis.

His cirrhosis is well compensated, his Child-Pugh score is A, and he had recent imaging with no evidence of masses and a negative EGD looking for varices. Pertinent laboratory studies include a platelet count of 187,000, an albumin of 4.2, and a normal INR of 0.9. He works full time and is very concerned about side effects related to HCV treatment. He is here today to discuss some treatment options.

MR. BUSKER: This patient is genotype 3 — let me ask you give us some context, if you would doctor. How has the treatment of genotype 2 and genotype 3 evolved since 2013 when sofosbuvir was introduced?

DR. WYLES: I'll even go back before 2013. Before 2013 and the arrival of sofosbuvir, pegylated interferon plus ribavirin was the standard of care for both genotype 2 and 3 infections. Generally the treatment approach was 24 weeks of that combination, which resulted in pretty high cure rates or sustained virologic response rates in both populations, to the point that genotype 2 and 3 infections were often lumped together as a so-called "easier to treat" form of hepatitis C compared to genotype 1.

With the arrival of sofosbuvir in 2013, we started to realize that at least with direct acting antiviral-based therapies, genotype 2 and 3 no longer responded similarly. In fact, genotype 3 was recognized as the hardest to treat. We saw this in studies that looked at patients who were treatment naïve and treatment experienced, where patients with genotype 2 responded very well to sofosbuvir plus ribavirin for 12-16 weeks, with SVR rates in general around 90 percent or better. In patients with genotype 3, particularly those with cirrhosis who had previously been treated with an interferon based therapy, the best SVR rates we could attain with the sofosbuvir/ribavirin based regimen were around 60 percent, even if that treatment was extended to

24 weeks. That highlights some of the gaps we have in treatment efficacy if we're just talking about a sofosbuvir plus ribavirin based regimen after 2013.

MR. BUSKER: Genotype 2 versus genotype 3 — are there differences in the epidemiology?

DR. WYLES: Yes, a couple of major differences are important to recognize. First, in the United States we don't see that much genotype 3, but it's important to recognize that globally genotype 3 is the second most prevalent genotype; it accounts for somewhere between 20 percent to 30 percent of all hepatitis C infections globally behind genotype 1, which is the most prevalent. Here in the United States, genotype 1 is significantly more prevalent, with about 70 or 75 percent of our infections being genotype 1, and then genotype 3 accounts for maybe 10 percent to 15 percent.

MR. BUSKER: And the clinical differences?

DR. WYLES: Clinically, progression of genotype 3 has been studied, and some recent data indicates that genotype 3 is associated with a more aggressive form of hepatitis C or an accelerated natural history. We've known for a while that genotype 3 infections are associated with hepatic steatosis, or fat accumulation in the liver. Then two large studies from the Veterans Affairs population have shown that genotype 3 HCV was associated with an increased risk of developing cirrhosis or hepatocellular carcinoma compared to genotype 1. In fact, the second study showed that patients with genotype 3 were more likely to die from their hepatitis C than patients with genotypes 1 or 2.

Lastly, if you're able to intervene and cure genotype 3 hepatitis C, you see a big improvement in overall patient survival, and that was a larger improvement than seen in patients with genotype 1 or 2 who were cured of their HCV.

MR. BUSKER: In the newsletter you reviewed the ALLY-3 study. How might those results influence treatment approaches for genotype 3?

DR. WYLES: Yes, ALLY-3 was a phase 3 study that looked at taking sofosbuvir, an NS5B nucleotide inhibitor that has been the standard of care for treatment of genotype 3, now with sofosbuvir plus ribavirin, and added an NS5A antagonist called daclatasvir, which has pangenotypic activity, including against genotype 3.[1] The ALLY-3 study was a single arm study that looked at patients with genotype 3 who were both treatment naïve and treatment experienced, including those with cirrhosis, and treated them with 12 weeks of sofosbuvir 400 mg once daily, with daclatasvir 60 mg once daily for 12 weeks with no ribavirin. In this study overall, excellent responses were seen with about 90 percent of treatment naïve patients and 86 percent of treatment experienced patients attaining SVR-12 or cure.

The main highlight, though, is the continued difference in responses based on cirrhosis status in patients with genotype 3. Patients without cirrhosis, whether they were treatment naïve or treatment experienced, had excellent response rates of about 96 percent combined. Unfortunately, the patients with genotype 3 who had cirrhosis, regardless of whether they were treatment naïve or experienced, did not fare as well and only had a 63 percent SVR rate in patients with cirrhosis combined between treatment naïve and treatment experienced.

So while the non-cirrhotic data looks great and allows us to get to a 12 week regimen we can omit ribavirin from, and it both shortens the duration and removes ribavirin for patients without cirrhosis, we still see that same population of patients with genotype 3 who have cirrhosis not responding optimally to this regimen. That suggests we still need further work on an optimal treatment for patients with genotype 3 who have cirrhosis, despite the ALLY-3 data.

MR. BUSKER: You also reviewed the Boson study in your newsletter issue. How might the results of that study impact current treatment approaches?

DR. WYLES: As we just pointed out, patients with genotype 3 and cirrhosis are particularly problematic, because even with sofosbuvir plus daclatasvir, their responses are not optimal. The BOSON study aimed to evaluate patients with the toughest to treat genotypes, 2 and 3.[2] In particular, the BOSON study was large, almost 600 patients. They enrolled any patient with genotype 3, as well as genotype 2 treatment experienced patients who also had cirrhosis. That study looked at three treatment approaches for those patients: 16 weeks of sofosbuvir plus ribavirin; 24 weeks of sofosbuvir plus ribavirin; or 12 weeks of sofosbuvir plus pegylated interferon with ribavirin.

The overall responses of all the patients combined in the three treatment arms of the BOSON study was that sofosbuvir plus pegylated interferon and ribavirin was statistically superior in terms of SVR rates to either 16 or 24 weeks of sofosbuvir plus ribavirin. Overall, 93 percent of patients treated with pegylated interferon plus sofosbuvir and ribavirin attained an SVR.

In the patients with genotype 3 and cirrhosis, 12 weeks of interferon with sofosbuvir and ribavirin looks better than either 16 or 24 weeks. Specifically 88 percent of patients with genotype 3 and cirrhosis who were treated with the 12 week regimen including interferon achieved a cure. That's the highest SVR rate we've seen thus far in treatment of patients with genotype 3 and cirrhosis.

Based on these results, current guidelines now reflect that this should be considered one of the first line therapies in a patient with genotype 3 who has cirrhosis, either treatment naïve or experienced.

The final point I'll add is a lot of patients as well as providers are concerned about interferon tolerability. At least in the BOSON study it's important to point out that discontinuations because of adverse events were no higher in the interferon-containing arm; in fact, they were less than 1 percent for the study. Of course, applicability to the real world may be slightly different — but still, 12 weeks of an interferon-based regimen does appear to be tolerated relatively well by patients.

MR. BUSKER: Based on the studies you've just described, doctor, how would you treat this 52 year-old genotype 3 patient?

DR. WYLES: I think the compelling point for our patient and listeners are appreciating, is the fact that he has not only genotype 3 but also cirrhosis. He is treatment naïve, but he is also continuing to work and is very concerned about the side effects. I would approach this by talking with him and telling him, based on study data we have, his best chance for being cured appears to come with a 12 week regimen that includes interferon along with sofosbuvir and ribavirin.

I would then take the discussion to the tolerability. If he is averse to trying interferon, the other option for the patient would be to try sofosbuvir plus daclatasvir. But although this is not based on a significant amount of trial data, we think extension to 24 weeks would be appropriate, and that would be recommended in the guidelines. So sofosbuvir plus daclatasvir with or without ribavirin for 24 weeks would be the other options, or a 12 week regimen containing interferon.

At that point, it just comes down to a discussion and the patient and the provider coming to a decision about which they'd prefer to try. Approvals for 24 weeks of sofosbuvir plus daclatasvir with insurance may also be problematic.

MR. BUSKER: Thank you for that case and discussion, doctor. And we'll return with Dr. David Wyles from UC San Diego 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 email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to hepatologists, infectious disease specialists, primary care physicians, nurses, nurse practitioners, and other clinicians caring for patients with viral hepatitis.

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

Subscription to *e*ViralHepatitis 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 to and receive eViralHepatitis Review without charge, and to 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. And I'm here with Dr. David Wyles from the Division of Infectious Diseases at the University of

California San Diego. We've been discussing how the findings from recent studies can impact the management of "hard to treat patients." let's continue, if you would doctor, with another patient situation.

DR. WYLES: Our second case today involves a 62 year old African American gentleman. He also has diabetes and hypertension which have resulted in end stage renal disease requiring hemodialysis. He has HCV genotype 1A with bridging fibrosis on a biopsy he had in 2013. The patient currently is on the kidney transplant list but is also interested in HCV treatment.

MR. BUSKER: The connection between hepatitis C and kidney disease — would you summarize that for us, doctor?

DR. WYLES: A number of aspects of hepatitis C disease may affect the kidneys as well as many other extrahepatic organs. Specifically talking about the kidney, we know hepatitis C can result in direct kidney injury through membranoproliferative glomerulonephritis; HCV though is also associated with insulin resistance and the development of diabetes mellitus, and obviously diabetes is another leading cause of kidney injury.

Finally, data from large-cohort studies out of Taiwan indicate that in patients with diabetes who have been followed for a long time, those who also have HCV are at increased risk for developing renal disease over 10 years of follow-up.

Perhaps most important from that study, though, is patients who had an intervention in which their HCV was treated and cured, their risk of developing incident renal disease over the 10 year follow-up period was dramatically reduced. These highlight a number of the interactions with HCV and the kidney and why it's important to try to treat HCV to prevent some of those outcomes.

MR. BUSKER: The patient you described — he's got end stage renal disease, he's on dialysis and the transplant list. How do those factors impact HCV treatment with the currently available options?

DR. WYLES: End stage renal disease presents a number of complications with our currently approved HCV treatment option. First, sofosbuvir, which is a common component of many interferon free regimens currently, undergoes metabolism in cells, and a metabolite nicknamed 007 comes back out of the cells. What we know is that this metabolite accumulates to high levels in patients with end stage renal disease, so a creatinine clearance less than 30, or those on hemodialysis.

We don't know at this point what are the ramifications for the patient with this high level accumulation. In other words, we don't know if that accumulation has any associated toxicities or whether it's safe in patients with renal disease. Studies with sofosbuvir are ongoing in this patient population, but at this point it's generally not recommended to use sofosbuvir in somebody with end stage renal disease or who is on hemodialysis.

For the other main currently interferon-free regimen available, the so-called 3D regimen that looks at a combination of a protease inhibitor plus an NS5A antagonist with a nonnucleoside inhibitor, all these components are metbolized hepatically, so they're not excreted by the kidneys to any large extent. Some preliminary data suggests good responses with this treatment regimen. The problem for our patient, in particular, since he has genotype 1A, most would recommend including ribavirin with this regimen, and ribavirin in patients with end stage renal disease is a problem because of difficulties in dosing and an enhanced side effect profile, particularly anemia, in this population. So we need better options than our currently available DAAs for patients with end stage renal disease.

MR. BUSKER: But as you discussed in your newsletter, those "better treatment options" for patients with ESRD may be coming in the near future.

DR. WYLES: Yes. Grazoprevir plus elbasvir is a new fixed dose combination treatment that is currently investigational, but we do expect regulatory approval sometime in early 2016. I think this regimen is exciting, particularly for patients with end stage renal disease, because both components are metabolized hepatically and cleared, so issues surrounding end stage renal disease and changes in pharmacokinetics of the regimen are not prominent.

And based on some phase III data we already have in patients with end stage renal disease, this regimen seems to do very well and also seems to allow us to omit ribavirin from the treatment regimen, which can be particularly problematic in patients with end stage renal disease.

Specifically, the phase 3 study C-SURFER which was reviewed in the newsletter, showed a very high cure rate in patients with end stage renal disease: 99 percent were cured in a phase 3 study. When we looked at the per protocol or completing treatment analysis, a strict intention to treat analysis still showed a 94 percent SVR12 rate with this regimen in patients with end stage renal disease.[3]

MR. BUSKER: So for patients like the one you described — ESRD, dialysis, transplant list — the fixed-dose grazoprevir plus elbasvir combination would likely be appropriate, yes?

DR. WYLES: Sure. As I indicated, both are cleared hepatically, so I think that gives us an advantage in patients with end stage renal disease. The key from the C-SURFER study is that ribavirin can be omitted. In evaluating the 3D regimen in patients with end stage renal disease, it was a relatively small study and all patients with genotype 1A were required to receive ribavirin. That study showed that the majority of patients with genotype 1A on ribavirin who also had end stage renal disease ended up either dose adjusting or discontinuing ribavirin because of enhanced side effects, particularly anemia.

So data from the C-SURFER study provides the first phase data available with any HCV treatment regimen in an end stage renal disease population and allows us to omit the ribavirin from this regimen, which should result in much better tolerability. In fact, in the C-SURFER study, the regimen appeared very well tolerated. There was a placebo arm, and there was no difference between active treatment and placebo arms in side effect profiles or discontinuations of the study medications because of side effects.

One aspect to keep in mind about this patient, or in general patients with end stage renal disease who might be on the transplant list, is always to discuss these patients with the transplant nephrologist. An interesting aspect with HCV and end stage renal disease is that if patients and their transplant providers are willing to accept an HCV-positive organ, there may actually be some benefit for the patient to remain HCV-positive until they get their kidney transplant, and then it could be considered to treat the patient's HCV after their transplant. There may be better access to HCV-positive kidneys, decreasing the wait times on the transplant list, so that's an important consideration when thinking about this patient.

MR. BUSKER: Thank you for that case and discussion, Doctor. Let me ask you to bring us one more patient situation now, if you would, please.

DR. WYLES: Our last case is a 63 year old gentleman who has genotype 1B hepatitis C and compensated cirrhosis. This gentleman was previously treated for his HCV in a clinical study with a DAA regimen that consisted of sofosbuvir plus ledipasvir for 12 weeks. In that study he did not receive any ribavirin. He relapsed in that study and now he's returning to clinic after about six months wondering what are his current treatment options for his hepatitis C. He had viral sequencing after he failed the initial treatment; he has an NS5A resistance mutation, a Y93H. He does not have NS5B resistance, and his cirrhosis remains well compensated, although laboratory values included a platelet count of 66,000, albumin of 4.1, and INR of 1.1.

MR. BUSKER: Before we discuss retreatment options for this patient, Dr. Wyles, let me ask you to give us some basic background on how DAAs target the various aspects of the hepatitis C lifecycle.

DR. WYLES: Our currently available DAAs target three main viral processes or enzymes, including the NS3 protease, which essentially chops up the viral protein into its functional components; the NS5B RNA polymerase, which replicates the viral RNA or reproduces it; and then NS5A inhibitors, which target a protein that's essential for both replication and release of virions from the cell.

It's important to consider these different mechanisms of action and at least have a general understanding of each DAA and which viral protein it targets, because when we're considering retreating a patient, we're worried about resistance. For a lot of these direct acting antivirals that are available now, patients who fail one class of inhibitors will develop resistance to that inhibitor, particularly protease inhibitors and NS5A inhibitors, so the concern becomes trying to find treatment options or retreatment options that do not involve those mechanisms of action, if possible, because of the concern of resistance and then cross-resistance to any second treatment option you present the patient.

MR. BUSKER: Thank you for that explanation, doctor. Let's turn to the data now. What have the current investigations shown about retreating patients who, like the one you've described, have failed a prior direct acting antiviral-containing regimen?

DR. WYLES: We have a couple of layers of data. First, for patients who failed a DAA in combination with interferon and ribavirin, we have quite a bit of data that suggests the approved DAA interferon-free regimens will be quite efficacious. Particularly with protease inhibitor plus interferon failures, retreating patients with a nucleotide plus NS5A based regimen appears very efficacious, and there aren't many unique considerations in that population.

Additionally, patients who were treated with sofosbuvir plus ribavirin or sofosbuvir plus interferon and ribavirin also seem to do very well if they're retreated, even if it's a sofosbuvir-containing regimen such as sofosbuvir plus ledipasvir.

Patients for whom it is particularly difficult to identify an appropriate retreatment regimen are ones who have failed interferon-free, DAA-containing regimens, specifically sofosbuvir plus ledipasvir, or have failed the 3D regimen of paritaprevir with ritonavir plus ombitasvir and dasabuvir. Patients failing those regimens are likely to have NS5A resistance, and it's this population that we don't have proven retreatment options for.

MR. BUSKER: In your description, you specified an NS5A resistance mutation this patient has — a Y93H. What's the significance of that Y93H mutation?

DR. WYLES: The Y93H is a specific resistance mutation in the viral NS5A protein. This resistance mutation is frequently selected, but perhaps is more problematic because once selected, it tends to cause a high level of resistance to nearly all currently available NS5A inhibitors. That would include ledipasvir, daclatasvir, or even the investigational agent we talked about earlier, elbasvir.

The other particular problem with NS5A resistance mutations, including the Y93H, is that once they're selected, they seem to persist for a long time. By its nature when HCV replicates it does not integrate and does not have a long-lived viral reservoir, so many resistance mutations naturally tend to dissipate over time. This is seen with protease inhibitor mutations where after a year and a half or two years, the majority of patients have lost those resistance mutations.

But recent data on persistence of NS5A resistance mutations suggests that they remain enriched in patients for at least two years after they fail an NS5A containing regimen, with about 85 percent of patients still having resistance after two years from failure with an NS5A containing regimen.

And as we'll discuss and as was reviewed in the newsletter, it seems that these NS5A mutations affect impact responses if you try to retreat patients with an NS5A inhibitor-containing regimen.

MR. BUSKER: Clinical trial data to guide therapy for the patient you described — what currently exists?

DR. WYLES: For this patient, who failed sofosbuvir plus ledipasvir for 12 weeks, — again, an interferon free DAA containing regimen that had an NS5A antagonist — only one study looked at trying to retreat this population. That was the so-called 1118 study that Dr. Lawitz presented at the International Liver Congress in 2015.[4]

The 1118 study looked at 41 patients who had failed sofosbuvir plus ledipasvir and tried to retreat them with the same regimen, sofosbuvir/ledipasvir, but extending the duration to 24 weeks. The majority of the patients had been treated with sofosbuvir plus ledipasvir, with about 70 percent receiving only eight weeks of therapy in their previous treatment. In a somewhat disappointing result, the overall response rate with retreatment of 24 weeks of sofosbuvir and ledipasvir resulted in a cure rate of only 71 percent.

In terms of factors that predicted who would respond and who would fail, NS5A resistance turned out to be a key predictor in response rates. Patients entering the retreatment phase of the study who did not have detectable NS5A resistance, all were cured with retreatment of 24 weeks of that regimen. However, if patients did have NS5A resistance, the cure rate was only 60 percent with retreatment.

We alluded to the Y93H mutation before. This mutation causes a very high level resistance to ledipasvir and other NS5A antagonists, and if patients specifically had that mutation and were retreated, the response rate was only 33 percent. This was a small

study, so the numbers tended to be very small. If you look at these subgroups, only six patients in the whole study who were retreated and had the Y93H, but again, the results suggest that NS5A resistance and retreating with another NS5A inhibitor-based regimen may be problematic for patients who fail interferon free DAA therapies.

MR. BUSKER: So based on what we've been discussing, how would you advise a patient like this? Are there better treatment options on the horizon?

DR. WYLES: This is obviously a difficult position. This patient has cirrhosis and a relatively low platelet count, so we are worried about the chances that his liver disease will progress further and he'll decompensate. The issue, of course, is that there are no proven retreatment options. You could consider retreating the patient with switching away from an NS5A inhibitor-containing regimen, so the option would probably be something like sofosbuvir plus simeprevir, which is a protease inhibitor, for 24 weeks of treatment. Most, I think, would throw in ribavirin as well if they were going to attempt this, and that is probably one of the better treatment options available currently. However, it's important to point out that we have no clinical trial data to help us talk to this patient in an informed manner about what we might expect the treatment success rates to be. So that is one option, but unproven.

The other potential consideration is to wait for this patient until we have better therapies. Investigational therapies are just entering trials that look at triple combinations — an NS5B nucleotide inhibitor plus an NS5A inhibitor plus a protease inhibitor. Many of these NS5A inhibitors are next generation inhibitors, so they do do better against some of the resistance mutations, although the Y93H remains particularly problematic.

So we could wait with this patient, but that obviously involves risk that he could decompensate or have progression of his liver disease as we're waiting for better therapies.

MR. BUSKER: Treat or wait — which would you do with this specific patient?

DR. WYLES: I think the compelling issue for this patient is his low platelet count and cirrhosis. We know that patients with platelet counts less than 100,000 tend to be at higher risk for going on to have decompensation. I think I would probably attempt to retreat this patient. Trying sofosbuvir plus simeprevir with ribavirin for six months is probably the best option right now if he can't immediately get into a study of one of these more potent treatment options.

MR. BUSKER: Thank you, Dr. Wyles, for today's cases and discussion. Let's wrap things up by looking at what we've talked about today in light of our learning objectives. So to begin: treatment options for patients with genotype 2 and genotype 3 infection, including those with cirrhosis.

DR. WYLES: For patients with genotype 3, I think sofosbuvir plus daclatasvir is an optimal treatment option because it allows us to shorten the duration and remove ribavirin for patients with genotype 3 without cirrhosis. Of course, for patients with genotype 3 and cirrhosis or those with very difficult to treat genotype 2, it does look like the best response rates will be seen with interferon plus sofosbuvir and ribavirin, assuming patients can tolerate and are willing to take interferon.

That brings up the important discussion with patients about the risks and benefits of using interferon-based regimens, versus the unproven efficacy of the extension of sofosbuvir and daclatasvir to 24 weeks in patients with difficult to treat HCV, particularly genotype 3.

MR. BUSKER: And our second learning objective: the phase III clinical trial data investigating grazoprevir plus elbasvir.

DR. WYLES: Grazoprevir and elbasvir is a fixed dose combination that is currently investigational, but we do expect approval in 2016. A number of phase 3 studies have been completed looking at its efficacy in both treatment naïve and treatment experienced patients who have genotype 1 as well as 4 and 6, although the number of genotype 4 and 6 patients was small. These studies show overall that 12 weeks of this regimen without ribavirin is efficacious in treatment naïve patients with genotype 1 infection in particular. There are some potential issues with baseline NS5A resistance and responses with this regimen that still need to be worked out.

Another highlight of this regimen is, it is not cleared renally, and we have the first phase 3 data in a

population with end stage renal disease, showing that this treatment regimen for 12 weeks without ribavirin looks particularly efficacious in this population which currently does not have excellent treatment options.

MR. BUSKER: And finally: the currently available retreatment options for patients who have failed interferon-free DAA regimens and the problem of resistance.

DR. WYLES: Our last case highlighted the problems clinicians face with trying to come up with a retreatment option for patients who have failed interferon-free DAA regimens. NS5A resistance in particular seems to be a problem for these patients, and it's difficult to devise an optimal retreatment strategy that either omits an NS5A inhibitor because of concerns of cross resistance or will be potent enough to cure these patients, since most of them will be expected to have advanced disease with cirrhosis.

Perhaps it is most important for clinicians just to realize that there is no accepted approach because we don't have adequate data yet to devise optimal retreatment options.

MR. BUSKER: Dr. David Wyles, from the Division of Infectious Diseases at the University of California San Diego, thank you for participating in this *e*ViralHepatitis Review Podcast.

DR. WYLES: Thanks very much, Bob. I enjoyed participating in the podcast, and I hope we have been able to convey some of the exciting advances that surround treatment of genotype 3 and new regimens we should see in 2016.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.eviralhepatitisreview.org/test.

This podcast is presented in conjunction with the *e*ViralHepatitis 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 developed for primary care physicians, gastroenterologists, infectious disease specialists, OB/GYNs, physician assistants, nurse practitioners and nurses, and other clinicians diagnosing or managing patients with viral hepatitis.

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership 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.

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 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 *e*ViralHepatitis Review via email, 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 the 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.

*e*ViralHepatitis Review is supported by educational grants from Bristol-Myers Squibb, Gilead Sciences, Inc., and Merck, & Co., Inc.

REFERENCE

1. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatol Baltim Md*. 2015 Apr;61(4):1127–35.
2. Foster GR, Pianko S, Brown A, et al. Efficacy of Sofosbuvir Plus Ribavirin With or Without Peginterferon-alfa in Patients With HCV Genotype 3 Infection and Treatment-Experienced Patients with Cirrhosis and HCV Genotype 2 Infection. *Gastroenterology*. Epub 2015 Aug 4.
3. Roth D, Nelson D, Bruchfeld A, et al. LP02 : C-surfer: grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease. *J Hepatol*. 2015 Apr;62, Supplement 2:S263–S264.
4. Lawitz E, Flamm S, Yang JC, et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks. *J Hepatol*. 2015 Apr;62, Supplement 2:S192.