JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eViralHepatitis Review
Jointly provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by educational grants from Gilead Sciences, Inc., Merck & Co., Inc., and AbbVie, Inc.

VOLUME 5 - ISSUE 12

LISTEN TO PODCAST | DOWNLOAD PODCAST | PHYSICIAN POST-TEST | NURSE POST-TEST

New Options for Patients with "Hard-To-Treat" Hepatitis C Infection

- Describe the key clinical considerations when selecting a retreatment regimen for patients who have failed previous therapy with DAA agents.
- Describe the key clinical considerations when selecting a retreatment regimen for patients who have failed previous therapy with peginterferon and ribavirin.
- Describe the key clinical considerations when selecting a treatment regimen for patients with renal impairment.

Guest Faculty Disclosure
Dr. Jacobson has disclosed that he has served as a consultant and/or advisor to AbbVie, Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen, Merck & Co., Inc., and Trek.

Unlabeled/Unapproved Uses
Dr. Jacobsonson has indicated that he will make reference to the unlabeled or unapproved uses of DAA combinations no longer in general use, experimental DAA combinations presented at recent society meetings, specific discrepancies between package inserts and the AASLD published guidelines, and the potential use of sofosbuvir outside of indication in patients with certain degrees of renal disease and uncompensated cirrhosis.

MEET THE AUTHOR

Ira M. Jacobson, MD
Director of Hepatology
New York University School of Medicine
New York, NY

Release Date:
January 25, 2018

Expiration Date:
January 24, 2020

LISTEN TO PODCAST NOW | DOWNLOAD PODCAST | SUBSCRIBE NOW | PHYSICIAN POST-TEST | NURSE POST-TEST

OTHER RESOURCES

Download the podcast transcript

Go to the companion newsletter

NEWSLETTER ARCHIVE | SHARE WITH A COLLEAGUE

PROGRAM DIRECTORS

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

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

Taryn Haselhuhn, BA, BSN, MSN, CRNP
Nurse Practitioner
The Johns Hopkins Hospital
Baltimore, Maryland

Podcast Transcript

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

I'm Bob Busker, managing editor of the program. Our guest today is Dr. Ira Jacobson, director of hepatology at the New York University School of Medicine. We're here to discuss how the new options for patients with "hard-to-treat" hepatitis C infection — as he described in his newsletter issue — can translate into clinical practice improvement.

***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 Gilead Sciences Inc., Merck & Co., and AbbVie, Inc.**

Learning objectives for this audio program include:

- **Describe the key clinical considerations when selecting a retreatment regimen for patients who have failed previous therapy with DAA agents.**
- **Describe the key clinical considerations when selecting a retreatment regimen for patients who have failed previous therapy with peginterferon and ribavirin.**
- **Describe the key clinical considerations when selecting a treatment regimen for patients with renal impairment.**

Dr. Jacobson has disclosed that he has served as a consultant and/or advisor to AbbVie, Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen, Merck & Co., Inc., and Trek. His discussion today will mention the unlabeled or unapproved uses of DAA combinations no longer in general use, experimental DAA combinations presented at recent society meetings, specific discrepancies between package inserts and the AASLD published guidelines, and the potential use of sofosbuvir outside of indication in patients with certain degrees of renal disease and uncompensated cirrhosis.

Dr. Jacobson, welcome to this *e*ViralHepatitis Review Podcast.

DR. JACOBSON: Thank you, Bob. It's a pleasure to be here with you.

MR. BUSKER: In your newsletter issue, you reviewed the recent studies that led to the approval of the two newest regimens for what used to be called the "hard-to-treat" patients with hepatitis C infection. I'm referring, of course, to sofosbuvir/velpatasvir/ voxilaprevir, or the SOF/VEL/VOX regimen; and the glecaprevir/pibrentasvir regimen, or GLE/PIB, also abbreviated as G/P. Our objective today is to look at how both regimens can work most effectively in clinical practice. So please start with a patient scenario.

DR. JACOBSON: I'd like to start with a 58-year-old man with hepatitis C virus phenotype 1A infection, stage 2 hepatic fibrosis, who failed a course of eight weeks of ledipasvir/sofosbuvir.

MR. BUSKER: Why do you think this patient failed eight weeks of ledipasvir/sofosbuvir? Was it the wrong choice of agent? Was it the wrong duration?

DR. JACOBSON: Your question gives us a good opportunity to remember that eight weeks of ledipasvir/sofosbuvir is still a perfectly viable approved regimen, as it has been for several years in genotype 1 infected patients who are treatment naïve, not even having been treated with interferon previously, who, like this patient with stage 2 fibrosis, are not cirrhotic, and who have baseline HCV RNA levels of less than 6 million IU/mL. About two-thirds of our HCV genotype 1 infected population have HCV RNA levels below this value.

I would remind everybody that the AASLD/IDSA Guidance document (online at hcvguidelines.org) — a very important reference source for all people who treat HCV — went further, based on several lines of evidence, to suggest that only nonblack patients should be treated with the eight-week regimen and that black patients should get 12 weeks; and similarly, that patients with HIV coinfection should get 12 weeks rather than eight. So there is nothing to suggest that this patient got an incorrect regimen. Provided the patient met the criteria I've enumerated, this was an appropriate regimen for his first exposure to direct acting antiviral agents.

MR. BUSKER: As you determine your retreatment strategy, what effect does the patient's stage 2 fibrosis have on your treatment selection?

DR. JACOBSON: That's a very important question. The recommendation for newly approved agents as of summer of 2017 for DAA-experienced patients like this one is: don't differentiate between noncirrhotic and cirrhotic patients. I'll specify how that plays out with each of the two approved regimens while also emphasizing that the two recently approved regimens for DAA failure patients are the first two approved regimens ever for that population.

For several years we've seen case reports or case series looking at existing regimens or modifications of existing regimens for DAA failure patients, but none of those were ever approved. Two regimens have recently been approved by FDA for DAA failure patients, such as this patient, who received ledipasvir, an NS5A inhibitor, and sofosbuvir, a nucleotide polymerase inhibitor.

The first is a triple combination incorporated into one tablet taken once daily of sofosbuvir, the nucleotide polymerase inhibitor; velpatasvir, a pangenotypic NS5A inhibitor; and voxilaprevir, a new pangenotypic HCV protease inhibitor that had not been marketed previously for hepatitis C. This triple regimen is approved for 12 weeks in patients who have previously been exposed to a DAA regimen containing an NS5A inhibitor like ledipasvir.

The other newly approved regimen that is approved for genotype 1 DAA failure patients is a pangenotypic regimen of a protease inhibitor called glecaprevir and an NS5A inhibitor called pibrentasvir. For patients who have previously received an NS5A inhibitor, as this patient did when he received ledipasvir and sofosbuvir, that regimen is now approved for 16 weeks, not 12 weeks, independent of whether the patient has cirrhosis. In general, this only covers Child-Pugh A cirrhotic patients or those with compensated cirrhosis. No protease inhibitor for hepatitis C is currently approved for decompensated cirrhosis in people with Child-Pugh B or C disease.

MR. BUSKER: With that as background, how would you treat this patient?

DR. JACOBSON: We've mentioned that two regimens have been recently approved as the first approved HCV treatment regimens for DAA experienced patients, and now we're talking specifically about a regimen that contained an NS5A inhibitor the first time around. We can talk later about other types of antiviral regimens to which patients may have been exposed, but almost all patients who currently take HCV therapy with direct acting antivirals get an NS5A inhibitor, so when we talk about patients exposed to NS5A inhibitors, we mean essentially all DAA experienced patients. The two regimens, again, are sofosbuvir/velpatasvir/voxilaprevir for 12 weeks and glecaprevir and pibrentasvir for 16 weeks in HCV genotype 1 infected patients.

The sustained virologic response rates are well over 90% with both of these regimens, but I should point out that there was a much larger database in the phase 3 trial that looked at SOF/VEL/VOX than for G/P.

MR. BUSKER: And baseline resistance testing?

DR. JACOBSON: In neither of these regimens is baseline resistance testing indicated, and happily for clinicians and patients everywhere, ribavirin is not indicated, either. And interferon, of course, is gone.

MR. BUSKER: And the actual SVR rate for the SOF/VEL/VOX regimen?

DR. JACOBSON: For SOF/VEL/VOX in a now famous study called POLARIS-1 that was published in the *New England Journal* earlier in 2017, the SVR rate was 96% in patients like ours who had been exposed to an NS5A inhibitor previously and had virologic failure. If we subdivide those patients into noncirrhotic and cirrhotic patients, it's worth pointing out that the SVR rate was 99% in the noncirrhotic patients. Indeed, the only patient who "failed" was actually not a virologic failure but was counted as a failure because he was either lost to follow-up or discontinued.

In contrast, the SVR rate was 93% in cirrhotic patients. The patient in our scenario was not cirrhotic, so the very high uniform rate of virologic success, minus the patient with nonvirologic failure, is worth emphasizing as having pertained to noncirrhotic patients like this one.

MR. BUSKER: And the SVR rate for G/P?

DR. JACOBSON: In the MAGELLAN 1 part 2 study, which was the main phase 3 trial that led to the approval of G/P in

genotype 1 patients who had failed a previous regimen with an NS5A inhibitor, the SVR rate was 94%. The SVR rates are nearly the same, but I want to underscore a point I made a moment ago: the database was quite a bit larger in the POLARIS-1 study of SOF/VEL/VOX. That study had a little over 100 patients in the active treatment arm. It was a placebo controlled trial, but over 100 patients were treated; whereas the arm in the MAGELLAN-1 part 2 study of G/P for 16 weeks that had the SVR rate of 94% had 18 patients, of whom 17 had a sustained virologic response.

MR. BUSKER: What can you tell us about other potential treatment regimens for prior DAA failures?

DR. JACOBSON: For several years we've looked at other treatment regimens because we've gotten greedy in this field—we want to cure everybody. We're not willing to settle for 2%, 3%, or 4% failure rates because you have to do something for those patients, too. In other words, we want to leave no patient behind.

We've looked at regimens like 24 weeks of ledipasvir/sofosbuvir. Or 24 weeks of sofosbuvir/velpatasvir plus ribavirin, which worked pretty well in a recent study presented at an international meeting. And people have looked at the triplet regimen of ombitasvir/paritaprevir/dasabuvir combined with a fourth element, sofosbuvir, for 12 weeks, which had excellent efficacy, as was a triplet regimen of elbasvir and grazoprevir combined with sofosbuvir for 12 weeks. All of those were presented at various meetings or published, but the problem is that none of them have been FDA approved. The ones combining elements from different sponsors, in particular, are going to be pretty expensive.

MR. BUSKER: So to wrap things up on the patient you presented: what would be your specific treatment recommendation?

DR. JACOBSON: For this noncirrhotic, genotype 1 patient who failed an NS5A inhibitor containing regimen, my answer is very straightforward. Of the two recently approved regimens, I prefer the triplet regimen of sofosbuvir, velpatasvir, and voxilaprevir because it's based on a much larger dataset and a more robust study led to its approval, so one might have more confidence in that regimen. In fact, I think the same line of reasoning was adopted by the expert panel that composes the constantly revised HCV treatment Guidance document from the AASLD and IDSA available at hcvguidelines.org, because they say flat out that their top-line recommended regimen for patients like this is SOF/VEL/VOX for 12 weeks.

MR. BUSKER: Thank you for that case and discussion. We'll return with Dr. Ira Jacobson from the New York University School of Medicine in just a moment.

MR. BOB BUSKER
This is Bob Busker, managing editor of *e*ViralHepatitis Review.

*e*ViralHepatitis 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.

In the month following each newsletter, a case-based podcast discussion, like the one you're listening to now, is available to help translate that new clinical information into practice. These podcasts are also available as downloadable transcripts.

Subscription to *e*ViralHepatitis Review is provided without charge or prerequisite.

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

Thank you.

MR. BUSKER: Welcome back to this *e*ViralHepatitis Review podcast. We've been speaking with Dr. Ira Jacobson from the New York University School of Medicine about how patients with hepatitis C infection who used to be classified as "hard to treat" can now more likely achieve SVR with newly approved therapies. So let's continue with another patient scenario.

DR. JACOBSON: This is a 49-year-old woman with genotype 3 hepatitis C infection and compensated cirrhosis who failed a regimen of peginterferon and ribavirin.

MR. BUSKER: What retreatment regimens are available for this patient?

DR. JACOBSON: Four treatment regimens have been approved for this scenario. Remember that genotype 3 at the beginning of this exciting era of direct acting antiviral therapy for hepatitis C was the most challenging genotype. It responded least well to regimens that were largely constructed to cover the highly preponderant genotype 1 in the United States and many other parts of the world, although genotype 1 is not the predominant genotype everywhere. As it

happened, the genotype 3 regimens didn't respond well to our initial exciting, indeed revolutionary, genotype 1 regimens.

When we introduced sofosbuvir and ribavirin as the first DAA regimen for genotype 3, we found that there was something about having genotype 3 and compensated cirrhosis, especially in patients who failed a previous course of interferon, that conferred very low rates of SVR. That's led to a very exciting late development in this revolution called DAA therapy for hepatitis C, which is the advent and recent approval of pangenotypic regimens — regimens that are capable of pretty equally covering all of the genotypes and conferring at least similar if not exactly the same high rates of sustained virologic response.

The two pangenotypic regimens now available and approved for genotype 3 are the combination of sofosbuvir and velpatasvir, the latter being an NS5A inhibitor that covers genotype 3 in vitro better than any previously approved NS5A inhibitor; and the newest regimen of G/P, where pibrentasvir and glecaprevir also cover genotype 3 very well — pibrentasvir very potently like velpatasvir; and glecaprevir better than any previous protease inhibitor on the market before voxilaprevir. Both of these are the preferred regimens for genotype 3, although I would add that a couple of years ago the first approved combination regimen in some parts of the world, including Europe and subsequently the U.S., for genotype 3 was daclatasvir, an older NS5A inhibitor that covers genotype 3 pretty well, combined with sofosbuvir.

For all practical purposes, the regimens that we now use for genotype 3 are either sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (G/P).

MR. BUSKER: In this patient with genotype 3 and compensated cirrhosis who previously failed peginterferon and ribavirin, is there a role for baseline resistance testing?

DR. JACOBSON: The short answer is no; that's the practical answer, and I could end it there. But I would point out that in the ASTRAL-3 study of SOF/VEL, if there was a resistant variant at the 93 position, generally the Y93H amino acid substitution, or another called the Y93N, there was a somewhat adverse impact on the chance for a sustained virologic response. That occurred more often in patients who had failed interferon and/or who had cirrhosis. That led to a rather complex set of recommendations in the AASLD guidance document, wherein patients who had failed interferon previously, even if not cirrhotic, or treatment naïve cirrhotics, should have a resistance test at baseline. And contrary to the package insert which just said SOF/VEL, they recommended adding ribavirin for those patients if they had a Y93 substitution.

They further recommended, in contrast to the package insert, that cirrhotic patients with genotype 3 and previous interferon failure should just take ribavirin without resistance testing. So for this particular population, baseline resistance testing hasn't been recommended either in the SOF/VEL package insert or the AASLD guidance document for these patients ever since it was approved in 2016. With G/P there is no recommendation for baseline resistance testing, nor has the suggestion been made.

At least until recently, some of us continued to get baseline resistance testing, so we can decide in whom to use ribavirin when we use SOF/VEL. The AASLD guidance document took it a step further in its most recent version by saying that in patients with a history of interferon/ribavirin failure, to use SOF/VEL/VOX instead of SOF/VEL and ribavirin, although you could use that as an alternative. That's very interesting because there is no approval for SOF/VEL/VOX in anybody except DAA experienced patients in the package insert for that product. That's an interesting divergence between the FDA approval language for that regimen of SOF/VEL/VOX and what the expert panel says in its document.

Finally, I would say that in genotype 3 patients who have compensated cirrhosis and have previously taken interferon, a regimen of 16 weeks of G/P is recommended as opposed to 12 weeks.

MR. BUSKER: For this patient, what other management measures are indicated?

DR. JACOBSON: That's really an important question because we talk about SVR rate and recommended regimens or non-recommended regimens and resistant variants all the time, but there is also a patient who needs to be taken care of in totality.

Most important, in a cirrhotic patient like this one, we have to remember to screen for hepatocellular carcinoma, or HCC, every six months with an imaging modality. I think a discussion of precisely which imaging modality to use at various time points is beyond our scope here. Suffice it to say that sonography is considered the standard, but plenty of us resort to CT or, from my point of view, even better yet, MRI such as in the event of obesity or difficulty seeing the liver under ultrasound. The important thing is every six-month imaging of some type.

Equally important is the admonition that screening must continue in patients with preexisting cirrhosis or advanced fibrosis beyond the point at which virologic cure has occurred, because we recognize that although the risk of liver cancer goes down by about 80% in cured patients, it doesn't disappear. There is a consensus among most experts nowadays that screening for liver cancer must continue indefinitely, even if cumulative evidence from clinical observation or noninvasive tests for fibrosis show that the cirrhosis may have regressed.

The second of the three points I'd like to mention about management measures is esophageal varices. All cirrhotic patients

should be screened for varices at baseline so preemptive measures can be taken to prevent variceal bleeding for the first time or to treat varices if bleeding has occurred previously. The patient should be to scoped least one time after virologic cure to make sure there are no new varices. If varices were present, particularly if they required treatment, you have to keep managing those varices with endoscopy and band ligation and/or beta blockade or whatever modality may have been used previously.

The third management measure is to continue to encourage abstinence from alcohol — or at least significant amounts of alcohol — in patients who had a lot of scar tissue or cirrhosis in their livers beforehand, with the possibility of greater flexibility as time goes by if evidence of regression of cirrhosis continues. But even then, we have to discourage people who have been heavy alcohol consumers in the past from drinking again.

MR. BUSKER: Thank you, Dr. Jacobson. We've got time for one more patient scenario.

DR. JACOBSON: This is a 76-year-old man with renal failure on hemodialysis. He has HCV genotype 1B and stage 3 fibrosis on elastography.

MR. BUSKER: Renal failure and on dialysis — these patients have always been considered especially challenging. What are the current treatment recommendations?

DR. JACOBSON: For a genotype 1 patient with renal failure, there are two recommended treatment options that don't contain sofosbuvir, the nucleotide polymerase inhibitor that has done so much to revolutionize the treatment of hepatitis C but is excreted predominantly through the kidneys. The metabolite of sofosbuvir demonstrated early in its development that it accumulates considerably, as much as 20-fold, in patients with renal failure, so there are potential safety concerns.

The two recommended treatment options for this patient with genotype 1 are the combination of elbasvir and grazoprevir for 12 weeks, or glecaprevir/pibrentasvir for eight weeks.

The latter regimen, glecaprevir/pibrentasvir, is approved across all genotypes, but the elbasvir/grazoprevir is approved only for genotypes 1 and 4.

MR. BUSKER: Can a sofosbuvir-based regimen be used at all for patients like this?

DR. JACOBSON: Yes, but there's an important difference between what can be used and what's approved. A number of case series from different investigators looked at variable numbers of patients with renal failure who have been given either the standard or lower doses of sofosbuvir to be on the safe side. No safety concerns have arisen, despite the known accumulation of the major metabolite of sofosbuvir (which I can always remember because the last three numbers of that metabolite are 007, and I was always a James Bond fan).

Sofosbuvir doesn't accumulate because it's metabolized quite quickly, so that's not the concern. But any time the metabolite of a drug accumulates as much as this one does, there are potential safety concerns that have not materialized in clinical case series. However, the approval language for sofosbuvir still stipulates that it's approved only for patients with glomerular filtration rates (GFR) of 30 mL/min and above; it is not approved for patients with lesser degrees of renal function characterized by a GFR of less than 30 mL/min.

In contrast, the protease and NS5A inhibitors that I've mentioned are approved, for patients with renal failure, are all excreted by the hepatobiliary route, not by the renal route, so we don't have these pharmacokinetic concerns. No distinctive safety issues have arisen in this population of renal patients when those two regimens have been used.

MR. BUSKER: Just for clarity, are there any instances where you might use a sofosbuvir-based regimen in a patient with renal failure?

DR. JACOBSON: I would hardly ever use a SOF-based regimen in a patient with renal failure, but there is one situation where you're between a rock and a hard place: patients with decompensated cirrhosis and renal failure. Remember, you are not supposed to use protease inhibitors in patients with decompensated cirrhosis, because those agents and their metabolites potentially accumulate in patients with advanced liver disease since they are excreted through the hepatobiliary route. There have been concerns that hepatobiliary excretion may result in safety issues in that population, and the FDA approval for all of the protease inhibitors stipulates that they're either not recommended or are contraindicated in patients with decompensated cirrhosis. That's the rock. The hard place is that sofosbuvir should not be used in renal failure. So if you have a patient with decompensated cirrhosis and renal failure and you still want to treat the patient, you have to choose one or the other. And in light of the data, albeit case series rather than any pivotal trial that's been incorporated into approval language for a sofosbuvir-containing product, I would go with the sofosbuvir in renal failure and feel more comfortable with that rather than with a protease inhibitor in decompensated cirrhosis.

So the answer is, I would use a sofosbuvir-based regimen in a patient with renal failure if they have decompensated cirrhosis and if we think they should not receive a course of antiviral therapy.

It is very important to stress that the comments I've just made do involve off-label use of either of the sets of drugs I've been talking about. Whether you use protease inhibitors in decompensated cirrhotic patients, which I've said specifically that I wouldn't use, or sofosbuvir in patients with renal failure, which I did say I might use in selected situations, you have to keep in mind that it's off label and not approved.

MR. BUSKER: Thank you for that caveat and also for today's cases and discussion. Let's wrap things up now by reviewing what we've talked about today in light of our learning objectives. So, to begin: clinical considerations when selecting a retreatment regimen for patients who have failed previous therapy with DAA agents.

DR. JACOBSON: I'm going to answer that question in the context of patients who have failed previous therapy with DAA agents that contained an NS5A inhibitor. As I've emphasized earlier, nearly all patients who have taken DAA regimens, especially in the last couple of years and currently, have taken an NS5A inhibitor as part of their regimens.

We have two recently approved regimens that represent the first two FDA approved regimens for patients who have failed an NS5A inhibitor-containing regimen of DAA therapy. Those are sofosbuvir/velpatasvir/voxilaprevir for 12 weeks, or glecaprevir/pibrentasvir for 16 weeks. Either is acceptable, but I think some clinical experts, including the experts who write the guidelines for the AASLD guidance document, give preferred status to the 12-week regimen of SOF/VEL/VOX. That's mostly because the trials on which these two approvals were based were much larger for SOF/VEL/VOX. Specifically, the POLARIS-1 trial with SOF/VEL/VOX was much larger than the trial, and therefore the dataset, on which the approval of G/P in this population is based. Note, however, that SOF/VEL/VOX is approved for prior NS5A inhibitor-containing regimen failures with any genotype while G/P is approved only for such DAA failures with genotype 1.

Still, both have conferred SVR rates well over 90% in this population and both have to be considered acceptable.

MR. BUSKER: And our second learning objective: the clinical considerations when selecting a retreatment option for patients who have failed previous therapy with peginterferon and ribavirin or who are treatment naïve.

DR. JACOBSON: The overarching consideration when selecting a regimen for either treatment naïve patients or a treatment regimen for patients who failed previous therapy with peginterferon and ribavirin, is that there are several excellent choices. In fact, at least four listed in the AASLD guidance document at hcvguidelines.org are all top line recommended regimens. They are top line because they have similar or equivalent very high degrees of efficacy in attaining sustained virologic response.

The nuances are things like potential drug/drug interactions that one regimen might have with a drug that a patient happens to be on, whereas another regimen might fit a little better. Perhaps the patient is on higher doses of proton pump inhibitors and can't stop them because of gastroesophageal reflux disease, because we have to remember that high doses of PTIs do impair the absorption of ledipasvir and velpatasvir. Sometimes it just gets down to which regimen the payer prefers, and as long as you don't feel that you're compromising the patient's chance of sustained virologic response, I think that's a reasonable consideration.

For patients in whom the clinician feels that duration is an overarching priority (which I think is usually not the case, but it's nice to be shorter if you can), we do have a newly approved pangenotypic regimen of glecaprevir/pibrentasvir that is approved for eight weeks in treatment naïve noncirrhotic patients across genotypes 1 through 6. We also have to remember that ledipasvir/sofosbuvir is still approved for eight weeks in genotype 1 noncirrhotic patients who are treatment naïve and have baseline viral levels below 6 million IU/mL.

At the end of the day, you don't want to use a regimen that has ribavirin if you don't have to, and that would be the last consideration I would underscore here.

MR. BUSKER: Finally: considerations when selecting treatment regimens for patients with renal impairment.

DR. JACOBSON: For patients with renal impairment, let's remember that sofosbuvir is not approved for patients with GFRs less than 30 mL/min because it depends almost entirely on renal excretion, and its major metabolite can accumulate many-fold when you use it in such patients. We do have two approved regimens, elbasvir/grazoprevir and glecaprevir/pibrentasvir, the latter of which is pangenotypic, that avoid that issue. Those two regimens have achieved extremely high levels of efficacy and safety in their clinical trials, and that constitutes the basis of their approval. For me in my practice, those are the two regimens that should be considered in any patient with renal impairment who is going to be treated for hepatitis C.

MR. BUSKER: Dr. Ira Jacobson from the New York University School of Medicine, thank you for participating in this *e*ViralHepatitis Review Podcast.

DR. JACOBSON: Bob, it's been a great pleasure to participate in this program and I appreciate the opportunity.

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*™. 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.eviralahepatitisreview.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 Gilead Sciences, Inc., and Merck, & Co., Inc., and AbbVie, Inc.**

CME/CE INFORMATION

ACCREDITATION STATEMENT

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 DESIGNATION STATEMENT

Physicians

Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit*™. 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 hour, or a total of 3 contact hours for the 6 podcasts in this program.

POLICY ON SPEAKER AND PROVIDER DISCLOSURE

It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the

speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the instructional materials.

INTERNET CME/CE POLICY

DISCLAIMER STATEMENT

STATEMENT OF RESPONSIBILITY

STATEMENT OF NEED

INTENDED AUDIENCE

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS

HARDWARE & SOFTWARE REQUIREMENTS

COMPLETE CME INFORMATION

This activity was developed in collaboration with DKBmed.