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.

Newly Approved Pangenotypic HCV Therapies

Volume 5
Issue 11

In this Issue...

We've made exceptional progress in effectively treating most hepatitis C infections with relatively simple noninterferon, nonribivirin, direct-acting antiviral therapies. Now the focus has turned to those patients who remain "difficult to treat" — genotypes 1a and 3, prior DAA failures, and patients with renal disease.

In this issue, Dr. Ira M. Jacobson, Director of Hepatology at New York University School of Medicine, reviews the recent literature describing the uses of two newly approved regimens to treat these patients:

- SOF/VEL/VOX — a coformulated pill containing voxilaprevir (a protease inhibitor), velpatasvir (a previously approved NS5A inhibitor), and the nucleotide polymerase inhibitor sofosbuvir
- GLE/PIB — glecaprevir (a second generation protease inhibitor) and pibrentasvir (a second generation NS5A inhibitor)

LEARNING OBJECTIVES

- Describe the appropriate use of the sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) regimen in retreatment of prior HCV treatment failures.
- Describe the appropriate use of the glecaprevir/pibrentasvir (GLE/PIB) regimen across HCV genotypes in treatment-naïve and treatment-experienced patients with or without cirrhosis.
- Describe the appropriate use of each of GLE/PIB in the treatment of HCV infection in patients with renal disease.

GUEST AUTHOR OF THE MONTH

Commentary & Reviews

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

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. Jacobson has indicated that there will be no references to unlabeled or unapproved uses of drugs or products.

IN THIS ISSUE

Program Information
CME Information
Accreditation
Credit Designations
Intended Audience
Statement of Need
Internet CME/CE Policy
Faculty Disclosure
Disclaimer Statement

Length of Activity
1.0 hour Physicians
1.0 hour Nurses

Launch Date
December 28, 2017

Expiration Date
December 27, 2019

COMPLETE THE POST-TEST

Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST

COMMENTARY

POLARIS-2 AND POLARIS-3 (SOF/VEL/VOX)

POLARIS-1 AND POLARIS-4 (SOF/VEL/VOX)

EXPEDITION-1 (GLE/PIB)

SURVEYOR-I and SURVEYOR-II (GLE/PIB)

MAGELLAN-1, part 1 (GLE/PIB)

EXPEDITION-4 (GLE/PIB in CKD)

KEY TAKEAWAYS

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

COMMENTARY

The most recent developments in HCV therapy have featured the advent of pangenotypic regimens, which provide coverage of all the major HCV genotypes. The first-generation HCV regimens were highly effective against genotype 1, as their designers intended, with variable activity against other genotypes. While sofosbuvir (SOF), which remains the only nucleotide polymerase inhibitor available in late 2017, is pangenotypic in its coverage, the first generation protease and NS5A inhibitors were not. Genotype 3 in particular remained suboptimally addressed by such regimens as ledipasvir/sofosbuvir, simeprevir plus sofosbuvir, ombitasvir/paritaprevir/ritonavir and dasabuvir, and elbasvir/grazoprevir.

In mid-2016, sofosbuvir/velpatasvir (SOF/VEL) became the first approved pangenotypic regimen in the United States. In the ASTRAL series of trials, SVR rates of over 98% were noted with 12 weeks of SOF/VEL across all genotypes except genotype 3. ASTRAL-3 found that overall SVR for genotype 3 patients was 95%; higher in treatment-naïve patients without cirrhosis than in other GT3- infected patient groups, and with baseline resistance-associated substitutions (RAS) at the Y93 position (especially Y93H) having a slight but significant adverse impact on SVR. These results led to the AASLD/IDSA Guidance recommendation[1] for baseline testing for resistance-associated substitutions (RAS) in treatment experienced or cirrhotic patients with GT3, and the addition of ribavirin if this RAS was found (or the automatic addition of ribavirin in GT3 treatment-experienced patients with cirrhosis).

One year after the introduction of SOF/VEL we have seen the approval of two new pangenotypic regimens: a “triplet” regimen of (SOF/VEL/VOX) sofosbuvir, velpatasvir, and the pangenotypic protease inhibitor voxilaprevir (coformulated in a single pill taken once daily), and a “doublet” (GLE/PIB) regimen of the protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir (three tablets taken together QD). Both regimens were studied in extensive phase 3 trial programs — SOF/VEL/VOX in a set of four studies called POLARIS-1 through -4, and GLE/PIB in a number of studies with several acronyms bearing explorational themes (ENDURANCE, EXPEDITION, SURVEYOR, and MAGELLAN).

The POLARIS-2 and -3 studies of SOF/VEL/VOX in patients who were naïve to direct-acting antiviral agent (DAA) therapy were predicated on the hypothesis that a shortened, eight-week course of treatment with a pangenotypic triplet regimen would confer very high rates of SVR, equivalent to 12 weeks of treatment with SOF/VEL. POLARIS-2 did not vindicate the “reduced duration” hypothesis, but along with POLARIS-3 did reinforce, across all

genotypes, the excellent results of the comparator 12 week SOF/VEL dual regimen established in the ASTRAL studies (which led to the approval of this regimen in 2016).

For clarification: the eight-week triple regimen proved as effective as the 12 week dual regimen across all genotypes, with the important exception of genotype 1a. It was notably effective in genotype 3 patients, including those with cirrhosis. However, for equivalent levels of efficacy of eight weeks of SOF/VEL/VOX and 12 weeks of SOF/VEL across most genotypes, the advantage of an eight-week regimen is offset by the need to add a protease inhibitor. As a result of these considerations, the triple regimen did not garner approval for any DAA-naïve patients in July 2017 when the regimen, administered for 12 weeks, was approved for DAA-experienced patients. The POLARIS studies, published by Jacobson et al and Bourliere et al, are reviewed in this issue by Dr. Jacobson.

The explanation for the decrement in SVR with eight weeks of SOF/VEL/VOX in DAA-naive patients with genotype 1a remains unclear, as does the association of lower SVR in genotype 1a patients with the baseline NS3 Q80K polymorphism. This polymorphism emerged into clinical prominence when it was found to decrease rates of SVR in genotype 1a patients treated with simeprevir in combination with peginterferon and ribavirin, and to decrease SVR rates in patients treated with simeprevir and sofosbuvir for eight weeks. However, unlike with simeprevir, in vitro studies do not show a reduction in sensitivity of HCV genotype 1a to voxilaprevir.

The POLARIS-1 and -4 studies established 12 weeks of SOF/VEL/VOX as the first approved regimen for DAA-experienced patients, whether or not they had received an NS5A inhibitor previously. The absence of even a single virologic failure in the noncirrhotic NS5A-experienced patients in POLARIS-1 is striking, and the number of relapses in the cirrhotic cohort was small. The latter, however, does underscore the future need to identify “second generation” salvage regimens that will be effective in the few patients with SOF/VEL/VOX failure. The higher SVR rate with 12 weeks of SOF/VEL/VOX than SOF/VEL in POLARIS-4, which included DAA-experienced but NS5A inhibitor-naïve patients, is not altogether surprising because these patients, for the most part, had already failed a sofosbuvir-containing regimen. Whether because of host or viral factors, such prior failure lends plausibility to the hypothesis that adding two DAAs to sofosbuvir in a repeat course of therapy would be better than adding just one. Baseline sofosbuvir resistance was rare pretreatment, as was treatment-emergent resistance.

The findings from POLARIS-1 and -4 led to FDA approval of 12 weeks of SOF/VEL/VOX for patients with any HCV genotype who have failed a DAA regimen containing an NS5A inhibitor, and for patients with genotypes 1a or 3 who have failed a DAA regimen containing sofosbuvir without an NS5A inhibitor. In other genotypes, there was felt to be insufficient evidence for superiority of the triple regimen compared with SOF/VEL to warrant regulatory approval in those other genotypes.

The regimen of glecaprevir/pibrentasvir (GLE/PIB) is the other major addition to the therapeutic armamentarium for 2017. The SURVEYOR-1 and -2 studies (described by Kwo and colleagues and reviewed herein) affirmed the pangenotypic efficacy of the second generation combination regimen of glecaprevir and pibrentasvir and laid the foundation for the phase 3 trials of eight weeks of ribavirin-free treatment in patients without cirrhosis. Those phase 3 trials — ENDURANCE-1, -2, and -3 — have in fact been completed in patients with genotypes 1-6 in the aggregate, have been presented at international meetings but have not been published in the peer-reviewed literature at the time of writing (September 2017). Those presentations report:

- ENDURANCE-1 — Included over 600 patients with genotype 1 randomized to eight and 12 weeks of GLE/PIB and demonstrated 99.1% and 99.7% SVR12 rates, respectively. Only one in over 330 patients treated for eight weeks had virologic failure, compared with none of the 12-week patients.[2]
- ENDURANCE-2 — Provided similarly high efficacy rates obtained with 12 weeks of treatment with GLE/PIB in DAA-naïve GT2,4,5,6 patients.[3] The SURVEYOR 2, Part 4 study showed similarly high efficacy with eight weeks in patients with these genotypes (see below).
- ENDURANCE-3 — Compared eight or 12 weeks of GLE/PIB in DAA-naïve patients with genotype 3 versus 12 weeks of the (already approved for GT3) regimen of daclatasvir (DCV) plus sofosbuvir. SVR12 occurred in 95% of both the eight-week and 12-week GLE/PIB treatment groups, and in 97% of the DCV+SOF treated

patients.[4] These results were not significantly different from each other, although the number of virologic failures was numerically higher in the GLE/PIB groups than in the patients treated with DCV+SOF. Based on these findings, in August 2017 the Food and Drug Administration approved eight weeks of GLE/PIB across all six genotypes in DAA-naïve patients without cirrhosis.

The results of the EXPEDITION-1 study (described in the paper by Forns et al reviewed here) which evaluated 12 weeks of GLE/PIB therapy in patients with cirrhosis, are consistent with the very high SVR rates noted in an extensive phase 3 trial program of this regimen across a broad spectrum of HCV infected patient populations. The emerging algorithm for this regimen is relatively straightforward: eight weeks of therapy for noncirrhotic patients across genotypes 1-6 and 12 weeks for those with compensated cirrhosis (though somewhat more complicated for patients with prior DAA failure). As with other HCV protease inhibitors, treatment with glecaprevir is not recommended or contraindicated in patients with decompensated cirrhosis (Child-Pugh classes B and C).

The MAGELLAN-1, part 1 study (reviewed herein) showed promise for the pangenotypic GLE/PIB regimen in patients with prior DAA failure, setting the stage for the subsequent MAGELLAN-1, part 2 trial of the GLE/PIB regimen in this population. Results of the latter have been presented but not yet published (as of September 2017). In MAGELLAN-1, part 2, 91 patients with genotypes 1 or 4 were randomized to 12 or 16 weeks of GLE/PIB. In those with prior exposure to protease inhibitors but not an NS5A inhibitor, SVR occurred in 14/14 (100%) and 13/13 (100%) patients treated for 12 or 16 weeks, respectively. In patients treated with an NS5A but not a protease inhibitor, SVR occurred in 14/16 (88%) and 17/18 (94%), and in patients treated with an agent from each class, SVR rates of 11/14 (79%) and 13/16 (81%) were attained.[5]

In a companion abstract, the higher rates of failure in those with dual-agent exposure histories were shown to be related to dual class RASs. In patients with NS5A exposure only, baseline NS5A RASs were associated with SVR in 83% and 96% of 12-week and 16-week treated patients, respectively. As a result, the FDA approved GLE/PIB for 12 weeks in genotype 1 patients with a history of PI exposure and 16 weeks for those with NS5A exposure. However, approval was not granted for patients with a history of exposure to *both* an NS5A and a protease inhibitor.

Despite these advances in formerly “hard-to-treat” HCV genotypes, effective DAA treatment for hepatitis C-infected patients with advanced kidney disease has remained challenging. The NS5A and protease inhibitor classes are distinct pharmacokinetically from the nucleotide polymerase inhibitors by their hepatobiliary metabolism and/or excretion, whereas sofosbuvir is excreted renally. As a result, the major metabolite of sofosbuvir accumulates up to 20-fold in patients with renal failure, with the potential for adverse effects. Although case series reported from several centers have suggested that administration of sofosbuvir at either a reduced dose or standard dose of 400 mg/day is safe and effective in patients with renal failure, sofosbuvir is still not approved for patients with GFR < 30 ml/min. In contrast, the regimen of elbasvir/grazoprevir was approved for genotype 1 patients with CKD stage 4/5 as a result of very high SVR rates in the C-SURFER study.

In the EXPEDITION-4 study (reviewed herein), glecaprevir/pibrentasvir yielded SVR in 102 of 104 patients with severe renal impairment infected with various HCV genotypes (over half GT 1), with no virologic failures and good safety and tolerability. As a result, we now have a second approved DAA regimen, this one pangenotypic, for patients with CKD 4/5 across all viral genotypes.

As always, medical progress, including revolutionary progress, creates new questions. Which patients with renal failure should be treated with DAA therapy? An immediate instinct would be “all,” but HCV-infected patients who are candidates for kidney transplants can often receive HCV-positive kidneys much more quickly (enabling life-transforming discontinuation of dialysis) than HCV-negative kidneys. Therefore, therapy is being deferred for some such patients, especially in light of other recent studies indicating that very high SVR rates can be achieved posttransplantation, when the restoration of renal function removes the constraints on which HCV regimens can be used.

The most intriguing unexpected consequence of the advent of effective therapy both before and after kidney transplantation is the notion, now being explored at several centers under IRB-approved protocols, that antiviral therapy might best be deferred even in HCV-negative

patients in favor of giving them an HCV- positive kidney to facilitate their access to a new kidney. At the other end of the spectrum, there is no longer any reason to withhold HCV therapy from patients who are not candidates for kidney transplantation unless there are life-limiting morbidities.

References:

1. hcvguidelines.org
2. Zeuzem S et al, AASLD 2016, Abstract 2016.
3. Kowdley KV et al, AASLD 2016, Abstract 73.
4. Asselah T et al, AASLD 2016, Abstract 114.
5. Poordad F et al, EASL 2017, Abstract PS-156.

Back to top

POLARIS-2 AND POLARIS-3 (SOF/VEL/VOX)

Jacobson IM, Lawitz E, Gane E, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. *Gastroenterology* 2017;153:113-122.

View Journal Abstract View Full Article

The POLARIS-2 and -3 studies were phase 3 trials that evaluated the efficacy and safety of a fixed-dose, once-daily combination pill consisting of sofosbuvir (SOF) 400 mg, velpatasvir (VEL) 100 mg, and voxilaprevir (VOX) 100 mg for patients with chronic hepatitis C who had never been exposed to direct-acting antivirals (DAA) previously. Sofosbuvir is a pangenotypic nucleotide polymerase inhibitor approved initially in 2013, while velpatasvir is a pangenotypic NS5A inhibitor approved in 2016 in combination with sofosbuvir as a 12-week regimen for patients with all HCV genotypes.

Voxilaprevir, previously known as GS-9857, is a second-generation HCV protease inhibitor with pangenotypic coverage and activity against most of the resistance-associated substitutions (RAS) associated with exposure to first- generation agents in the class. The initial rationale for combining voxilaprevir with sofosbuvir and velpatasvir was that it might confer very high rates of sustained virological response (SVR) with shorter durations of therapy than possible with current regimens. Phase 2 trials by Gane et al (2016) and Lawitz et al (2016) showed that suboptimal rates of SVR were obtained with six weeks of triple therapy, but rates of SVR > 95% were noted with eight weeks of therapy in noncirrhotic and even cirrhotic patients with genotypes 1-6. Patients with cirrhosis also had very high rates of SVR with 12 weeks of therapy.

These findings led to the phase 3 POLARIS-2 and -3 trials, in which DAA-naïve patients, whether without or with cirrhosis and interferon-experienced or not, were randomized to eight weeks of SOF/VEL/VOX or 12 weeks of SOF/VEL. POLARIS-2 included patients across all genotypes, but genotype 3 patients with cirrhosis, historically a challenging group, were included only in POLARIS-3, which was dedicated exclusively to these patients.

In POLARIS-2, the intent was to assign, rather than randomize, patients with genotypes 4, 5, and 6 to the triple therapy arm, but the initial genotype screening assay erroneously identified a few patients as having genotype 1 and thus were randomized to receive SOF/VEL. Subsequent deep sequencing analysis postrandomization revealed that those patients had genotype 6.

Over 900 patients were included in POLARIS-2, with overall SVR rates of 95% for SOF/VEL/VOX and 98% for SOF/VEL. This difference represented a failure of the triple eight-week regimen to meet its protocol-specified noninferiority endpoint, and reflected 21 virologic failures of 501 patients in the triple therapy group vs three of 440 in those receiving the dual regimen. Subanalysis revealed that this difference was driven by lower SVR rates in the genotype 1a subpopulation. Patients with genotype 1a and the NS3 Q80K polymorphism in the protease molecule at baseline had lower SVR rates than genotype 1a patients without this polymorphism. Noncirrhotic patients with genotype 3 receiving triple therapy for eight weeks had a 99% SVR rate with no virologic failures, which also characterized the genotype

3 noncirrhotic patients who received SOF/VEL for 12 weeks. In POLARIS-3, genotype 3 patients with compensated cirrhosis had SVR12 in 96% in either group, with two virologic failures in each of the two arms, which consisted of 110 and 109 patients in the triple and dual therapy arms, respectively.

Resistance analyses in both studies showed that patients failing a course of treatment with SOF/VEL/VOX resistance-associated substitutions (RASs) treatment-emergent substitutions after an unsuccessful course of treatment.

In the comparison of adverse events between the two treatment arms in POLARIS-2 and -3, there was a higher frequency of nausea and diarrhea in the triple therapy group than with sofosbuvir and velpatasvir (15%-18% vs 5%-7% with diarrhea, 16%-21% versus 9% with nausea, respectively). However, most gastrointestinal side effects were graded mild, and there were no discontinuations as a result of gastrointestinal side effects.

Back to top

POLARIS-1 AND POLARIS-4 (SOF/VEL/VOX)

Bourliere M, Gordon SC, Flamm SL, et al; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *N Engl J* Med. 2017 Jun 1;376(22):2134-2146.

View Journal Abstract View Full Article

The POLARIS-1 and -4 studies were designed to evaluate a 12-week regimen of sofosbuvir, velpatasvir, and voxilaprevir, taken once daily in a fixed combination pill, in DAA-experienced patients with prior exposure to regimens with and without an NS5A inhibitor. The POLARIS-1 study included 415 patients with NS5A inhibitor treatment experience who were randomized to 12 weeks of SOF/VEL/VOX or placebo if they had genotype 1 infection (n = 300), and assigned to SOF/VEL if they had genotypes 2-6 (n = 115, of whom two received triple therapy). The trial was the only POLARIS study with a placebo control arm.

The SVR12 rate in the actively treated patients was 96%, reflecting 99% of the noncirrhotic patients (with no virologic failures) and 93% in cirrhotic patients (with six virologic failures). Among 101 genotype 1a patients, 96% had SVR; and among 45 genotype 1b patients, 100% had SVR. No patient treated with placebo attained SVR. Predictably in light of their earlier treatment experience, patients in POLARIS-1 had a much higher prevalence of NS5A resistance-associated substitutions than the DAA-naïve patients in POLARIS-2 and -3, but as in those studies these RASs had no impact on SVR, nor did baseline NS3 RASs. Also similar to POLARIS-2 and -3, treatment-emergent RASs were infrequent in patients with virologic failure, occurring in one of six patients who relapsed.

In POLARIS-4, patients were DAA-experienced but naïve to NS5A inhibitors. In total, 85% had taken sofosbuvir previously, either with ribavirin with or without peginterferon, or with simeprevir. A small number of patients had taken investigational therapies with agents that ultimately did not garner regulatory approval. Patients with genotypes 1, 2, or 3 (N = 163) were randomized to 12 weeks of SOF/VEL/VOX or SOF/VEL, while 19 patients with genotype 4 received SOF/VEL/VOX. As in the other POLARIS studies, ribavirin was not included.

The SVR12 rate with SOF/VEL/VOX was 97% versus 90% with SOF/VEL, reflecting a higher rate of relapse in the SOF/VEL group. Higher SVR rates for SOF/VEL/VOX versus SOF/VEL were limited to patients with genotypes 1a and 3, in which SVR occurred in 98% versus 89% for genotype 1a, and 96% vs 85% for genotype 3. Once again, baseline RASs did not affect SVR, and treatment- emergent RASs were infrequent.

As in POLARIS-2 and POLARIS-3, gastrointestinal side effects were associated with SOF/VEL/VOX at a similar incremental frequency as patients in the SOF/VEL group of POLARIS-4. Only one patient across both studies stopped therapy because of adverse events (angioedema after new exposure to the drug ramipril).

Back to top

EXPEDITION-1 (GLE/PIB)

Forns X, Lee SS, Valdes J, et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. *Lancet Infect Dis.* 2017 Oct;17(10):1062-1068.

View Journal Abstract View Full Article

The EXPEDITION-1 study evaluated a 12 week dual combination of glecaprevir and pibrentasvir in patients with compensated cirrhosis who had not been exposed to direct-acting agents (DAA) previously, except for sofosbuvir plus interferon with or without peginterferon. Glecaprevir is a second-generation protease inhibitor that covers all the HCV genotypes, including genotype 3, and covers most resistant variants associated with exposure to first-generation protease inhibitors. Its main resistance vulnerability is at the A156 position, where substitutions result in variants with poor replicative fitness, which mitigates the potential clinical impact of the reduced sensitivity of these variants to protease inhibitors. Pibrentasvir is a second-generation NS5A inhibitor with pangenotypic coverage and broad coverage against known NS5A RASs.

The study was a single-arm, open-label, 40-center study of 146 patients with genotypes 1, 2, 4, 5, and 6. Forty-eight patients had genotype 1a; 39 genotype 1b; 34 genotype 2; 16 genotype 4; two genotype 5; and seven genotype 6. The SVR12 rate was 99% (145/146), with one relapse at post-treatment week 8. The most common adverse events were fatigue and headache in 19% and 14%, respectively. Of the 11 (8%) with serious adverse events, none were considered related to study drugs. There were no ALT elevations and no premature treatment discontinuations for adverse events.

Back to top

SURVEYOR-I and SURVEYOR-II (GLE/PIB)

Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol.* 2017 Aug;67(2):263-271.

View Journal Abstract View Full Article

The SURVEYOR-I and SURVEYOR-II phase 2 studies reported in this paper were designed to evaluate the dual combination of glecaprevir and pibretasvir in DAA-naïve patients with genotypes 1 (SURVEYOR-1) or genotypes 2-6 (SURVEYOR-2) for eight or 12 weeks, with or without ribavirin. Patients with and without cirrhosis were included, but the present study focused exclusively on the patients without cirrhosis, as the results in cirrhotic patients were reported separately. In total, 449 patients were reported in this paper. In part 1 of each of the studies, different doses of GLE and PIB were assessed for 12 weeks, with or without ribavirin, following which optimized doses of GLE 300 mg and PIB 120 mg were given once daily in part 2 without ribavirin. In part 2, eight weeks of treatment was received by treatment naïve or interferon-experienced GT1 (n = 34) and GT2 (n = 54) patients, while only GT3 patients (n = 29) with no prior treatment were given eight weeks of therapy. In addition, 24 GT3 interferon-experienced patients and 34 GT4-6 patients received 12 weeks of treatment. Twelve-week treatment yielded SVR12 rates of 97%-100% (GT1), 96%-100% (GT2), 83%-94% (GT3), and 100% (GT 4-6). With eight weeks of GLE 300 mg and PIB 120 mg, SVR12 was attained in 97%, 98%, and 97% of patients with GT1, 2, and 3, respectively, by intent-to-treat analysis. Overall, of the 117 patients with genotypes 1, 2, or 3 who received eight weeks of treatment, none had virologic failure. Fatigue, nausea, and headache were the most common adverse events. Three patients discontinued prematurely for adverse events, one related to abdominal pain and heat sensation judged possibly related to DAA therapy. Serious adverse events occurred in seven patients, none considered related to DAAs. No ALT elevations suggesting a drug effect occurred.

Back to top

MAGELLAN-1, part 1 (GLE/PIB)

Poordad F, Felizara F, Asatryan A, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C genotype 1 virus infection and prior direct-acting antiviral treatment. *Hepatology*. 2017 Aug;66(2):389-397.

View Journal Abstract View Full Article

The MAGELLAN-1, part 1 study was a phase 2, open-label study in genotype 1 patients who had sustained virologic failure to a prior course of DAA therapy. Fifty patients without cirrhosis were randomized to three arms: (A) GLE 200 mg + PIB 80 mg; (B) GLE 300 mg + PIB 120 mg + RBV 800 mg; (C) GLE 300 mg + PIB 120 mg (the regimen that ultimately was approved after phase 3 studies). By intent-to-treat analysis, SVR12 occurred in 6/6 (100%) of arm A, 21/22 (95%) of arm B, and 19/22 (86%) of arm C. Virologic failure occurred in zero, one, and one patient in each of the three arms, respectively. No serious adverse events occurred, nor were there significant elevations in ALT or total bilirubin.

Back to top

EXPEDITION-4 (GLE/PIB in CKD)

Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. *N Engl J Med*. 2017 Oct 12;377(15):1448-1455.

View Journal Abstract View Full Article

The lack of dependence on renal excretion of NS5A and protease inhibitors led to the EXPEDITION-4 study, which evaluated a 12 week regimen of glecaprevir/pibrentasvir in DAA-naïve patients with stage 4 or 5 chronic kidney disease (CKD) who were previously untreated or had received interferon, ribavirin, and/or sofosbuvir but *not* other DAA classes. In a cohort of 104 patients, 82% were on hemodialysis, 19% had cirrhosis, and 52% had genotype 1 HCV, with most of the remainder having genotypes 2, 3, or 4. One hundred two patients (98%) achieved SVR12. One of the two patients failing to achieve SVR stopped treatment at week 4 because of diarrhea, and that patient had recurrent viremia at posttreatment week 5. Adverse events reported in at least 10% of patients were pruritus, fatigue, and nausea. Serious adverse events occurred in 24% of patients; none were considered to be drug-related. Four patients discontinued for adverse events, three of whom had SVR.

Back to top

KEY TAKEAWAYS

- Most patients who have failed previous direct-acting antiviral regimens for hepatitis C can now be treated effectively with newly approved regimens, regardless of HCV genotype
- An approved eight-week pangenotypic regimen (GLE/PIB) that can be used regardless of baseline viral level or interferon experience has been added to the treatment options for DAA-naïve, HCV-infected patients who do not have cirrhosis, including patients with severe renal impairment.
- Patients with cirrhosis remain ineligible for shortened duration of therapy with any available regimen.

Back to top

IMPORTANT CME/CE INFORMATION

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 DESIGNATION STATEMENT

Physicians

eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of *1.0 AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses

eNewsletter: This 1.0 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 0.5 contact hour, or a total of 3 contact hours for the 6 newsletters 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

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS

INTENDED AUDIENCE

HARDWARE & SOFTWARE REQUIREMENTS

COMPLETE THE POST-TEST

Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST

This activity was developed in collaboration with DKBmed.