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eViralHepatitis Review

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.

eViralHepatitis Review
VOLUME 4, ISSUE 3

ADVANCES IN MANAGING HARD-TO-TREAT HEPATITIS C: HIGHLIGHTS FROM THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD) MEETING NOVEMBER 2015

In this Issue...

Although treatment with effective and well-tolerated all-oral direct acting antiviral (DAAs) can benefit most patients with chronic hepatitis C virus infection, the infection remains difficult to cure in persons with HCV genotype 3 infection, those with advanced fibrosis or decompensated liver disease, patients with CKD or other major comorbidities, those who have previously not responded to HCV treatment, and those who use injection drugs.

In this Special Edition, *e*ViralHepatitis Review Program Director Dr. Mark Sulkowski reviews some of the important new research advances presented at the 2015 AASLD for treating these challenging patients. In addition, accessible directly from within this newsletter are brief audio discussions between Dr. Sulkowski and some of the study authors.

LEARNING OBJECTIVES

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

- Describe ongoing research into new therapies for patients with HCV genotype 3.
- Evaluate the development of new agents and agent combinations to better manage hard-to-treat patients with HCV.
- Summarize real-world use of DAA therapies to manage HCV.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

IN THIS ISSUE

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Program Information
CME Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Planners Disclosures
Disclaimer Statement

Length of Activity
1.0 hour Physicians
1.0 contact hour Nurses

Launch Date
December 29, 2015

Expiration Date
December 28, 2017

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NURSE POST-TEST

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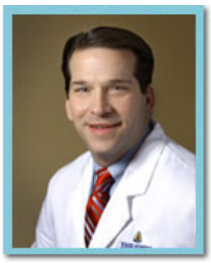

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Mark S. Sulkowski, MD has indicated that he has received research funding from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen, and Merck. He is a Gilead DSMB member and has served as a consultant/advisor to AbbVie, Cocrystal Pharma, ContraVir, Gilead, Janssen, Merck, and Trek.

Stephanie Petrou Binder, MD has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

Unlabeled/Unapproved Uses

The authors have indicated that there will be references to the unlabeled/unapproved uses of grazoprevir, MK-3682, MK-8408, elbasvir, and daclatasvir.

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ALLY-3+

All-Oral Treatment with Daclatasvir Plus Sofosbuvir Plus Ribavirin for 12 or 16 Weeks in HCV Genotype 3-Infected Patients With Advanced Fibrosis or Cirrhosis: The ALLY-3+ Phase 3 Study. Presented at the 66th Annual Meeting of the American Association for the Study of Liver Diseases AASLD; Nov 13-17, 2015, San Francisco.

Persons infected with HCV GT3, particularly those with advanced fibrosis or cirrhosis, are a challenging population in urgent need of effective therapies. While the combination of daclatasvir plus sofosbuvir in the ALLY-3 study led to SVR in more than 95% of patients with HCV genotype 3 without cirrhosis, the SVR rate among those with cirrhosis was only 63%, largely due to high rates of posttreatment relapse in this patient group.[1] Because of this disappointing result, the interim results of the ALLY-3+ study were eagerly anticipated. In the ALLY-3+ open-label, phase 3b study, 50 patients with HCV genotype 3 infection and evidence of bridging fibrosis/cirrhosis were randomized (1:1) to be treated with the triple drug combination of daclatasvir (DCV), sofosbuvir (SOF), and ribavirin (RBV) for 12 or 16 weeks. Eighty percent of the patients were male, 98%white, and 72% treatment experienced. Seventy-two percent of the participants had cirrhosis and 52% had HCV RNA of at least 6 million IU/mL. Baseline characteristics were comparable between the two arms.

Overall, the SVR4 rate was 92% (intention-to-treat analysis). SVR4 in the 12-week arm was 88% and 96% in the 16-week arms. In the 12-week arm, SVR4 was 83% in subjects with cirrhosis and 100% in subjects with advanced fibrosis, while in the 16-week arm, it was 94% and 100%, respectively.

There were no virologic breakthroughs. Relapse occurred in three patients, one from the 16-week group and two from the 12-week group. Four of five patients (80%) who had experienced relapse on SOF+RBV achieved SVR4. One death occurred in the 12-week arm; that death was not treatment-related.

Treatment was well tolerated. The most common adverse events (AEs) were insomnia (30%), fatigue (26%), and headache (24%). One patient had a grade-3 hemoglobin reduction. There were no discontinuations due to AEs or treatment-related serious AEs. SVR12 (primary endpoint) data are expected to be reported in the near future. Nonetheless, this interim analysis provides important evidence that supports the use of

ribavirin in combination with daclatasvir and sofosbuvir for the treatment of persons with HCV genotype 3 and advanced fibrosis.

Click here to hear *e*ViralHepatitis Review Program Director Dr. Mark S. Sulkowski discuss ALLY-3+ with study author Dr. Vincent Leroy

Click here to access the transcript version of the interview

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. *Hepatology*. 2015 Apr;61(4):1127–1135.

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C-CREST-1 & 2

Phase 2, Randomized, Open-Label Clinical Trials of the Efficacy and Safety of Grazoprevir and MK-3682 (NS5B Polymerase Inhibitor) with Either Elbasvir or MK-8408 (NS5A Inhibitor) in Patients with Chronic HCV GT1, 2 or 3 1nfection (Part A of C-CREST-1 & 2). Presented at the 66th Annual Meeting of the American Association for the Study of Liver Diseases AASLD; Nov 13-17, 2015, San Francisco

The success of treatment of hepatitis C virus infection hinges on the right drug combination that provides potent antiviral activity against a range of HCV variants, including those that harbor resistance associated variants (RAVs) that may confer decreased activity to one of the antiviral drugs in combination regimen. To this end, the combination of three antiviral drugs that inhibit three unique HCV targets — including NS3 protease, NS5A protein, and NS5B polymerase - are under investigation for treating patients infected with nearly any HCV genotype for durations as short as eight weeks. The triple-drug regimen of grazoprevir, MK-3682 (450 mg), and MK-8408 was highly effective and well-tolerated in treatment-naïve persons with chronic HCV GT1, 2, and 3-infection, without cirrhosis, according to the outcomes of a Phase 2 trial that compared two drug combinations for an eight-week treatment duration.

In this ongoing, open-label trial, patients with the genotypes GT1 (46 with GT1a and 47 with GT1b), GT2 (61), and GT3 (86) were randomized to receive either elbasvir (NS5A inhibitor, 50 mg) or MK-8408 (NS5A inhibitor, 60 mg) along with grazoprevir (NS3, protease inhibitor, 100 mg) plus MK-3682 (nucleotide analogue NS5B polymerase inhibitor, 300 mg or 450 mg) once daily, in Part A of the dose-ranging, parallel-group, multicenter C-CREST-1 & 2 Phase 2 study.

The outcomes across the study arms in patients with GT-1 patients revealed that 45 of 46 (98%) of patients with genotype 1a infection and 46 of 47 (98%) patients with genotype 1b infection achieved a sustained virologic response after 12 weeks of therapy (SVR12). In the two patients who did not achieve SVR and experienced HCV relapse, population sequencing did not detect NS3, NS5B, or NS5A resistance-associated variants (RAVs), conferring potency shifts of at least fivefold at baseline or following relapse, suggesting that longer treatment may have been needed for these persons.

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In patients with GT2, the grazoprevir plus MK-3682 (450 mg) plus MK-8408 regimen was highly effective, with 15 of 16 (94%) achieving SVR12. Interestingly, patients who were randomized to receive the lower dose (300 mg) of the nucleotide analogue NS5B inhibitor, MK-3682, and/or the first generation NS5A inhibitor elbasvir resulted in lower efficacy with only 29 of 45 (64%) patients with GT2 (60-71% across the three arms) achieving SVR12. In this group, HCV relapse was more common among patients who harbored the NS5A RAV at position 31 (L31M), which is common in persons with HCV genotype 2 infection prior to treatment.

In the patients with genotype 3 who had more difficult to cure infection, similar outcomes were noted across the study arms in which SVR12 was achieved in 78 of 86 (91%) patients. The response was comparable across arms (86%-95%), and eight patients experienced posttreatment relapse. SVR12 was lower among patients with GT3 who harbored an NS5A RAVs at positions 30, 31, or 93 (Y93H) at baseline compared with patients without these RAVs at baseline (5 of 11 [45%] versus 72 of 74 [97%], respectively). Among the eight patients with post-treatment relapse, two had treatment emergent NS5A RAVs at position 93 (Y93H).

With respect to safety and tolerability, all 240 patients enrolled completed the full eight weeks of dosing. The regimens were generally well tolerated, and no cardiac or renal safety signals were identified. The most frequent study drug-related adverse events (occurring in over 5% of all patients) were headache, fatigue, nausea, diarrhea, flatulence, and insomnia. There were no drug-related serious adverse events and no patients discontinued due to adverse events.

The phase 2 C-CREST 1 and 2 studies provide ample support for the further development of this once daily triple drug combination regimen ("triplet") in patients with the full range of HCV genotypes (1, 2, 3, 4, 5, and 6), as well as those with cirrhosis and HIV/HCV coinfection. Studies are also expected in persons who did not achieve cure with HCV DAA regimens.

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ASTRAL-1

A Phase 3 Double-Blind Placebo-Controlled Evaluation of Sofosbuvir/Velpatasvir Fixed-Dose Combination for 12 Weeks in Genotype 1, 2, 4, 5, 6 HCV-Infected Patients: Results of the ASTRAL-1 Study). Presented at the 66th Annual Meeting of the American Association for the Study of Liver Diseases AASLD; Nov 13-17, 2015, San Francisco

Many of the current HCV DAA regimens are effective for specific HCV genotypes and lack activity against other genotypes. For example, the fixed-dose combination tablet regimen of sofosbuvir/ledipasvir is approved for treating patients with genotype 1, 4, 5, or 6 infection but not for those with genotype 2 and 3. This is due to relatively limited antiviral activity of the NS5A inhibitor, ledipasvir, against genotypes 2 and 3; in contrast, the nucleotide analogue polymerase inhibitor, sofosbuvir, has pangenotypic activity. The ASTRAL studies (ASTRAL 1, 2, 3, and 4) were designed to evaluate the fixed-dose combination single tablet regimen of sofosbuvir (SOF) plus the investigational pangenotypic HCV NS5A inhibitor, velpatasvir (VEL; GS-5816).

In the ASTRAL-1 study, both treatment-naïve and treatment-experienced patients with genotype 1, 2, 4, or 6 HCV infection with and without cirrhosis were randomized (5:1) to receive a once-daily, all-oral single tablet of SOF/VEL (400 mg /100 mg daily) or placebo for 12 weeks. Due the low prevalence of genotype 5 infection, all patients with this strain were enrolled in the active SOF/VEL treatment group. The primary outcome measure was the superiority in SVR12 over placebo for patients treated with SOF/VEL.

Of the 740 patients enrolled at 81 sites in North America, Europe, and Hong Kong, 60% were male, 79% were white, 30% had IL28B CC genotype, 32% were treatment-experienced, and 19% had evidence of compensated cirrhosis. In the 624 patients treated with SOF/VEL, the genotype distribution was: 53% GT1, 17% GT2, 19% GT4, 6% GT5, and 7% GT6.

Overall, the SVR12 for patients treated with SOF/VEL was 99.0% (95% confidence interval: 97.9% to 99.6%) and the study met its primary efficacy endpoint (P < .001) with the superiority of SVR12 in the SOF/VEL-treated individuals to a prespecified SVR12 goal of 85%.

Only two patients had non-SVR due to virologic failure; both patients were infected with genotype 1 and experienced HCV relapse. The first patient had 1a infection and no cirrhosis, whereas the second had genotype 1b infection and cirrhosis. There was no virologic failure in any of the patients with genotype 2, 4, 5, or 6, including the 48 patients who had cirrhosis. Four patients did not achieve SVR12 for nonvirologic reasons (ie, lost to follow-up).

SOF/VEL treatment was well tolerated, and the type, frequency, and severity of adverse events (AEs) and laboratory abnormalities were similar to those observed in patients treated with placebo. Three patients (one treated with SOF/VEL and two with placebo) discontinued treatment due to adverse events. One SOF/VEL-treated patient died from an unknown cause eight days after completion of treatment. Fifteen (2.4%) patients treated with SOF/VEL experienced serious adverse events (SAEs); however, none was found to be related to the study drug.

This phase 3 study confirms the efficacy of the fixed-dose combination of SOF/VEL for the treatment of patients with genotype 1, 2, 4, 5, and 6 infection. Patients with genotype 3 were enrolled in the separately conducted ASTRAL-3 study (also discussed in this Special Edition).

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ASTRAL-3

Sofosbuvir/Velpatasvir Fixed-Dose Combination for 12 Weeks Compared to Sofosbuvir with Ribavirin for 24 Weeks in Genotype 3 HCV-Infected Patients: The Randomized Controlled Phase 3 ASTRAL-3 Study. Presented at the 66th Annual Meeting of the American Association for the Study of Liver Diseases AASLD; Nov 13-17, 2015, San Francisco.

The phase 3 ASTRAL-3 study compared a once-daily fixed-dose combination single tablet regimen of sofosbuvir (SOF) and the experimental agent velpatasvir (GS-5816, a pangenotypic HCV NS5A inhibitor; VEL) versus the standard of care regimen of SOF plus ribavirin in patients infected with hepatitis C genotype 3 (GT-3).

The study included 552 treatment-naïve and treatment-experienced patients with genotype 3 with and without cirrhosis from 75 sites in North America, Europe, Australia, and New Zealand. The enrolled patients were male, 62%; white, 89%; IL28B CC genotype, 39% had cirrhosis, 30%; 26% failed prior HCV treatment courses. Patients were randomized 1:1 to receive either a once daily oral, fixed dose single tablet combination of SOF/VEL (400 mg/100 mg daily) for 12 weeks or standard care: SOF (400 mg daily) plus ribavirin (RBV; 1000-1200 mg daily) for 24 weeks. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12) with a prespecified noninferiority margin of 10% for the comparison of the treatment regimens.

The investigators report that HCV RNA declined rapidly in both treatment groups, with 92% and 88% of patients achieving suppression of HCV RNA levels to less than the lower limit of quantification for the HCV RNA assay after four weeks of treatment in the SOF/VEL and SOF+RBV treatment groups, respectively. Overall, the rate of sustained virologic response in the SOF/VEL group was 95% (95% CI, 92 to 98), which was superior to the rate of 80% (95% CI, 75 to 85) in the SOF+RBV group (P < .001). Overall, SVR rates were higher in patients without cirrhosis compared to those with cirrhosis. Among patients who received SOF/VEL, the rate of sustained virologic response was 91% among those with cirrhosis, as compared with 97% among those without cirrhosis. Among patients who received SOF+RBV, the rates of sustained virologic response among patients with and those without cirrhosis were 66% and 87%, respectively.

Compared to patients treated with SOF/VEL, patients treated with SOF plus ribavirin had more side effects and were more likely to discontinue therapy. There were no discontinuations due to adverse events in the SOF/VEL arm, compared to eight discontinuations in the SOF+RBV treatment group. SOF/VEL-treated patients also reported an overall lower incidence of fatigue, insomnia and irritability. Five patients in the SOF/VEL treatment group and eight patients in the SOF+RBV treatment group experienced serious adverse events, including one case of generalized exanthematous pustulosis (in the SOF+RBV treated group, and related to the study drugs).

Click here to hear eViralHepatitis Review Program Director Dr. Mark S. Sulkowski discuss ASTRAL-3 with study author Dr. Graham Foster

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C-EDGE CO-STAR

C-EDGE CO-STAR: efficacy of grazoprevir / elbasvir Fixed Dose Combination for 12 Weeks in HCV-infected Persons Who Inject Drugs on Opioid Agonist Therapy. Presented at the 66th Annual Meeting of the American Association for the Study of Liver Diseases AASLD; Nov 13-17, 2015, San Francisco

Although injection drug use is a major route of HCV transmission, persons who inject drugs (PWID) have been considered difficult to treat due to concerns about adherence to the treatment regimen as well as the risk of reinfection following HCV cure among those successfully treated. In this context, the phase 3 C-EDGE COSTAR trial investigated the use of fixed-dose single tablet regime of grazoprevir 100 mg and elbasvir 50 mg (GZR/EBR) for the treatment of genotype 1, 4, or 6 infection in persons receiving opiate agonist therapy (OAT) such as methadone or buprenorphine.

Overall, 301 patients were enrolled and randomized to receive GZV/EBR (immediate treatment) or placebo (deferred treatment) in a double-blind fashion. At entry, the patient characteristics were, mean age; 47 years; male, 76%, Black race, male, genotype 1a, 76%; cirrhosis, 21%; HIV coinfection, 7%; methadone use, 79%; and buprenorphine use, 21%.

Study participants were randomized 2:1 to an immediate treatment group (ITG) which received GZR/EBR for 12 weeks or a deferred treatment group (DTG) which received placebo for 12 weeks followed by another 12 weeks of open label GZR/EBR. Primary endpoints were sustained virologic response (SVR) at follow up week 12 in the ITG, and the comparison of the SVR safety profile of GZR/EBR with placebo.

Study investigators assessed illicit drug use before and during the study through urine drug screening, but patients with positive drug screens were permitted to enroll and continue treatment in the study. At treatment entry, 60% of the 201 patients in the immediate treatment group had positive urine toxicology screens. During drug treatment, 79% of the treatment group had evidence of ongoing drug use (amphetamines 16%, benzodiazepines 39%, cannabinoids 40%, cocaine 19%, and opioids 41%). Nonetheless, 99% of patients (199 of 201) completed the full 12 weeks of treatment, and SVR was achieved in 91.5% (184 of 201) by intention-to-treat. In a modified, intention-to-treat analysis in which patients

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lost to follow-up (n = 3) were excluded and patients with molecular evidence of re-infection (n = 5) were counted as having achieved SVR (followed by reinfection), the SVR rate was 95.5% (189 of 198).

Among the patients in whom SVR was not achieved at posttreatment week 12, seven had posttreatment relapse, two discontinued due to adverse events, three were lost to follow-up, and five were reinfected.

Adverse events (AEs) were noted in both the ITG and DTG groups, with at least one AE reported by 83% of participants in both groups. Both groups reported serious AEs in 4% of patients, including one death in the deferred treatment group while on placebo. Drug-related AEs were reported by 41% of the ITG vs 34% of the DTG; the most common included fatigue (20%), headache (15%), nausea (12%) and diarrhea (12%). This groundbreaking study demonstrated that the once daily, fixed dose combination tablet of GZV/EBR could be safely and effectively delivered to PWIDs receiving opioid agonist therapy and led to high rates of treatment adherence and SVR despite ongoing illicit drug use in many participants. While reinfection was observed in five patients, these data provide direct evidence that persons with substance use should not be denied access to HCV treatments with oral DAAs.

Click here to hear eViralHepaitits Review Program Director Dr. Mark S. Sulkowski discuss C-EDGE CO-STAR with study author Dr. Gregory Dore

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HCV TARGET

Treatment Outcomes With 8, 12 and 24 Week Regimens of Ledipasvir/Sofosbuvir for the Treatment of Hepatitis C Infection: Analysis of a Multicenter Prospective, Observational Study. Presented at the 66th Annual Meeting of the American Association for the Study of Liver Diseases AASLD; Nov 13-17, 2015, San Francisco

HCV-TARGET is an international group of leading HCV investigators conducting a longitudinal observational study to help provide real-world evaluation of HCV therapies with direct acting antiviral agents. The study prospectively enrolls patients at the time of HCV treatment initiation in clinical practice and reports on how they were treated according to local standards of care at academic (n = 44) and community medical centers (n = 17) in North America and Europe.

Data from medical records becomes entered into a unique centralized database and is systematically reviewed by independent data monitors for completeness and accuracy. Demographic information, clinical data, adverse events (AEs) and virological data are collected throughout the treatment and posttreatment follow-up.

The investigators provided an analysis of 1074 patients with HCV genotype 1 infection who had completed eight (n = 154), 12 (n = 716), or 24 (n = 174) weeks of treatment with ledipasvir/sofosbuvir (LDV/SOF) with or without ribavirin and had also completed posttreatment follow-up to determine SVR or non-SVR outcomes. At the time of treatment initiation, patient characteristics were, 61% male; mean age of 60 years (age >65, 25%);

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20% black; prior HCV treatment experience, 44%; HCV genotype 1a infection, 66%; cirrhosis, 33%; HIV coinfection, 3%; and concurrent proton pump inhibitor use, 26%.

Among patients treated with LDV/SOF, the SVR rates were similar in patients treated for eight (97%), 12 (97%) and 24 (95%) weeks. Importantly, no difference was detected in the SVR rate among patients who qualified for eight weeks of LDV/SOF on the basis of 1) no prior HCV treatment; 2) no cirrhosis; 3) HCV RNA < 6 million IU/mL and received eight and 12 weeks of treatment (SVR rate, 97% with both durations; relapse rate, 3% with both durations). In a multivariable model of predictors of SVR, the investigators found that not using proton-pump inhibitors was associated with an increased likelihood of achieving SVR (adjusted odds ratio, 2.47, P .019). The overall difference in SVR in participants using PPIs (93%) and those not using PPIs (98%) was relatively small (~ 5%) but remained significant after adjustments for potential confounding. Overall, 65% of patients treated with this regimen reported at least one AE, with fatigue (22%) and headache (21%) being the most common.

These real-world data provide important evidence about the use of LDV/SOF. While both eight- and 12-week regimens are effective across a broad range of GT-1 infected patients, the findings suggest that eight-week regimens may be underused in the general population. The authors also note that HCV RNA findings at week four do not indicate treatment failure. Further, the study provided additional rationale to discontinue the use of PPIs prior to HCV treatment with LDV/SOF to better facilitate the absorption of LDV.

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