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New Therapies, Evidence, and Guidance in Hepatitis C Management: Expert Practices and Insights from an Educational Symposium at the AMCP 27th Annual Meeting & Expo

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Norah Terrault, MD, MPH; Alex Monto, MD; Michael R. Stinchon, Jr., RPh; Erica Rusie, PharmD; and Kathleen Moreo, RN-BC, BSN, BHSA, CCM, Cm, CDMS

Learning Objectives

- Apply evidence-based and consensus recommendations to identify hepatitis C virus (HCV) patients who can benefit from direct-acting antiviral (DAA) therapies
- Describe the accuracy and utility of new and emerging noninvasive methodologies for assessing liver fibrosis and prognosis for liver-related mortality
- Evaluate current evidence, guidelines, and expert recommendations to differentiate HCV antiviral therapies as part of patient-centered decision making
- Implement established leading practices in managed care for improving care coordination and patient adherence to HCV therapy and monitoring regimens

Forum

This article summarizes the presentations and discussions from an educational symposium that was conducted by PRIME Education, Inc. (PRIME) at the 27th Annual Meeting & Expo of the Academy of Managed Care Pharmacy (AMCP) in San Diego, California, on April 7, 2015.

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New Therapies, Evidence, and Guidance in Hepatitis C Management: Expert Practices and Insights from an Educational Symposium at the AMCP 27th Annual Meeting & Expo

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ABSTRACT

BACKGROUND: The 2013-2014 approvals of new direct-acting antiviral (DAA) therapies for hepatitis C virus (HCV) infection have engendered a paradigm shift in HCV treatment and management, offering the potential for a cure at a population level. The availability of the highly effective and relatively safe DAAs prompted revisions to guidance recommendations based on new clinical trial evidence. In the context of this paradigm shift and considerations of the costs associated with the new DAAs, managed care professionals face new questions and challenges regarding HCV treatment and management approaches. To address the continuing education needs of this group, PRIME Education, Inc. (PRIME) conducted a symposium on HCV at the 27th Annual Meeting & Expo of the Academy of Managed Care Pharmacy. Moderated by Michael R. Stinchon, Jr., RPh, the program panel featured 2 internationally recognized leaders in hepatitis C treatment and research: Norah Terrault, MD, MPH, and Alex Monto, MD.

OBJECTIVE: To summarize the educational symposium presentations and discussions.

METHODS: This article is organized by key questions that the panelists and attendees raised for discussion during the 2-hour symposium. The questions addressed methods for assessing liver fibrosis; comprehensive patient assessment to inform treatment decisions; the influence of viral load on decisions about treatment duration; the role of ribavirin in optimizing treatment efficacy; unmet treatment needs for patients with HCV genotype 3 or advanced liver disease; and managed care strategies for patient education, adherence promotion, and care coordination. In answering attendee questions on these issues, the expert panelists presented established evidence, and recognizing limitations to current evidence and guidance recommendations, they discussed applications of clinical judgment and offered their views and practices regarding individualized care for patients with HCV.

SUMMARY: In response to questions about the utility of noninvasive methods for assessing liver fibrosis, the expert panel presented a comparative overview of the methodology, accuracy, risks, limitations, and costs of noninvasive tests and liver biopsy. Discussion highlighted the strengths of noninvasive methods for diagnosing advanced disease and cirrhosis and the methods' limitations that pose barriers to ensuring that patients receive necessary antiviral therapy. Based on guidance recommendations, treatment should be prioritized in patients with advanced fibrosis or cirrhosis (Metavir score F3 to F4). While acknowledging the importance of this recommendation, the symposium panelists also argued that making effective decisions about whom, and when, to treat requires a more comprehensive clinical approach to patient assessment and adjusting recommended priorities according to individual patient considerations. This approach involves evaluating outcomes such as extrahepatic complications, including those affecting quality of life, functional status, and work productivity. In response to questions regarding decisions about DAA therapy duration based on viral load, the panel engaged the audience in thinking critically about evidence-based cutoff values and natural fluctuations of HCV RNA concentrations. Discussions centered on the importance of clinical judgment to ensure that the treatment duration promotes the highest efficacy and avoids risks of relapse. The panel responded to several audience questions about the role of ribavirin in new DAA regimens. Evidence-based presentations and discussions focused on patient-specific factors that must be considered to inform effective decisions about adding ribavirin. The panel took a similar approach to answering questions about emerging challenges and the difficult-to-treat populations of patients with HCV genotype 3 or advanced liver disease. The symposium concluded with presentation of, and discussion on, managed care strategies for educating patients about appropriate HCV medication use, improving adherence, and coordinating care provided by the interprofessional team.

CONCLUSIONS: The availability of new DAAs for HCV raises new questions and challenges for managed care professionals, especially regarding prioritizing patients for immediate therapy as well as treatment and management approaches that account for the needs of individual patients and subpopulations. The educational symposium summarized in this article directly addressed key questions and challenges through presentations of evidence, guidance recommendations, and interactive discussions on the views and practices of international leaders in HCV treatment and research.

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The widely recognized paradigm shift in the treatment and management of patients with hepatitis C virus (HCV) infection was ushered in by the late-2013 U.S. Food and Drug Administration (FDA) approvals of 2 direct-acting antiviral (DAA) therapies—simeprevir and sofosbuvir. The new era of HCV care has been further advanced by the approvals of the combined use of simeprevir and sofosbuvir, the fixed-dose combination of ledipasvir/sofosbuvir, and combination paritaprevir/ritonavir/ombitasvir and dasabuvir (or PrOD). As demonstrated in clinical trials, the new DAA therapies offer the potential for accomplishing the primary goals of hepatitis C treatment, which are to achieve sustained virologic response (SVR) at a population level and to thereby eradicate the virus. With regard to clinical, economic, and quality-of-life outcomes, the benefits of accomplishing these goals are substantial.[1]

The availability of the new DAA therapies has prompted revisions to the guidance recommendations of the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA), in collaboration with the International Antiviral Society-USA (IAS-USA).[2] Moreover, given the remarkable efficacy and safety of the new DAAs, along with resource issues associated with their high costs, they have engendered novel challenges for providers and

managed care professionals in their efforts to accomplish the primary goals for HCV care. Pressing issues for managed care professionals include appropriately prioritizing patients for immediate antiviral therapy and understanding optimal approaches to HCV treatment and management that account for the needs of individuals and subpopulations of patients defined by genotype, stage of liver disease, symptoms, comorbidities and complications, quality of life, and various other factors.

To support managed care professionals in meeting these challenges, PRIME Education, Inc. (PRIME), a national medical education company and accredited provider of continuing medical education (CME/CE) for health care professionals, conducted a symposium on HCV treatment and management at the 27th Annual Meeting & Expo of the Academy of Managed Care Pharmacy (AMCP). The 2-hour CME/CE-accredited program, entitled "New Therapies, Evidence, and Guidance in the Management of Hepatitis C," was moderated by Michael R. Stinchon, Jr., RPh, who is Pharmacy Service Manager of Clinical Programs at Aetna Medicare in Hartford, Connecticut. Two internationally recognized leaders in hepatitis C treatment and research served on the symposium panel: Norah Terrault, MD, MPH, who is Professor of Clinical Medicine and Surgery and Director of Viral Hepatitis Center at the University of California, San Francisco, and Alex Monto, MD, who is Associate Professor of Clinical Medicine at the University of California, San Francisco.

In parts of the educational symposium, Dr. Terrault and Dr. Monto gave brief presentations to update attendees on AASLD/IDSA/IAS-USA guidance recommendations and new evidence from clinical trials on recently approved and investigational DAA therapies. (Between the symposium date of April 7, 2015, and the publication of this article, the HCV guidance recommendations were updated. This article reflects recommendations that were available on July 16, 2015.) Most of the program involved panelist and audience discussions about key questions that underscore current challenges in HCV clinical and managed care. These discussions were designed to support attendees in (1) identifying the most accurate and appropriate methods for staging liver fibrosis; (2) making decisions about treatment eligibility based on comprehensive patient assessments; (3) accounting for variations to the standard of care, specifically by assessing the influence of viral load on decisions about treatment duration and by applying evidence on the role of ribavirin in optimizing treatment efficacy; (4) addressing unmet treatment needs for patients with HCV genotype 3; (5) selecting appropriate therapies for patients with advanced liver disease; and (6) implementing effective managed care strategies for educating patients about appropriate medication use, promoting adherence, and coordinating patient care through communication with other members of the health care team. Recognizing limitations to current evidence and guidance recommendations, Dr. Terrault and Dr. Monto offered their views and practices regarding individualized care for patients with HCV. Although the panel recognized the concerns of treatment cost in HCV care, the symposium was not designed to address this issue directly.

This article summarizes the educational symposium presentations and discussions, with an emphasis on issues related to prioritizing patients for immediate antiviral therapy and providing individualized HCV care for patients in groups defined by virus and disease characteristics.

Assessment of Liver Fibrosis

One of the strongest predictors of hepatitis C disease progression and clinical outcomes is the patient's extent of liver fibrosis.[3] Thus, AASLD/IDSA/IAS-USA guidance recommendations call for pretreatment assessment of fibrosis using noninvasive methods or liver biopsy.[2] Guidance-directed decisions about which patients should receive immediate therapy are based partly on Metavir fibrosis scores, ranging from a score of F0 (no fibrosis) to F4 (cirrhosis). Patients with Metavir F3 or F4 staging, indicating advanced fibrosis or cirrhosis, are designated as having the "highest" priority for immediate antiviral treatment. Patients with F2 staging are designated as "high" priority. On this topic, the symposium attendees asked the following questions: Which methods are clinicians using to evaluate and stage liver fibrosis? Which tests do the experts consider as the gold standard? How do biopsies and noninvasive methods compare in accuracy, risks and complications, and costs?

Liver biopsy has historically been considered the gold standard for assessing the degree of fibrosis and for diagnosing advanced disease and cirrhosis. However, this invasive method is now widely recognized as an imperfect standard due to limitations including intraobserver and interobserver variability in histopathological interpretation, sampling errors, and high cost.[2,4-13] Accurate staging of fibrosis on the biopsy requires sufficient length and portal triads; thus, understaging of fibrosis can occur if the sample is too small.[4-6] In 1 study, for example, 30% of patients undergoing liver biopsy were understaged by 1 Metavir stage, and 2.4% were understaged by 2 Metavir stages.[4] In addition, this invasive test requires the patient to be monitored as an outpatient for several hours after the procedure and is associated with small but well-recognized risks, such as bleeding and pain.

Recent advances and FDA approvals of noninvasive methods offer safer and less expensive options for assessing fibrosis. Commonly used noninvasive methods include abdominal imaging, direct or indirect biomarkers, and advanced imaging techniques such as vibration-controlled transient elastography (VCTE). A recently FDA-approved software system (HEPATIQ) assesses the severity of liver disease by quantitative analysis of nuclear medicine liver-spleen images.[14] A comparative overview of noninvasive methods and biopsy for assessing fibrosis is presented in Table 1.

VCTE uses shear wave velocity to measure liver stiffness.[2] The results, expressed in kilopascals (kPa), are translated into clinical information that correlates with fibrosis staging. AASLD/IDSA/IAS-USA recommendations identify correlation values of 8.7 kPa

TABLE 1 Invasive and Noninvasive Fibrosis Measurements

	Liver Biopsy	Serum Markers	Transient Elastography
Methodology	Direct observation	Measures direct and indirect serum markers of fibrosis	Measures liver stiffness by detection of ultrasound-propagated shear waves
Accuracy for detecting cirrhosis	High	Moderate (APRI) to high (FibroSURE, ELF)	High
Accuracy for detecting intermediate fibrosis	High	Low	Moderate to high
Risk of complications	Bleeding, bile leak, pain	Minimal	Minimal
Contraindications	Coagulopathy, infection, biliary obstruction, ascites, vascular lesions, morbid obesity, patient refusal to consent	None	Patient habitus that precludes performing test NPO < 4 hours before procedure
Limitations	Sampling error, observer variation	False-positives with hemolysis, inflammation, Gilbert's syndrome	False-positives with inflammation, congestion, obesity, fatty liver
Longitudinal monitoring	Low patient acceptance as repeat measure	Indices may change with disease progression or therapy	Liver stiffness changes with disease progression or therapy
Cost	Highest per-test cost	Lowest per-test cost	High initial equipment cost

APRI = aspartate aminotransferase-to-platelet ratio index; ELF = enhanced liver fibrosis; NPO = nothing to eat or drink.

for Metavir F2, 9.5 kPa or higher for F3, and 14.5 kPa or higher for F4 or cirrhosis; however, other values may be used in clinical applications.[2] A commonly used VCTE system in clinical settings is FibroScan (Echosens, Paris, France), which was approved by the FDA for liver fibrosis assessment in 2013. This VCTE technique has several advantages, including being painless, speed (taking approximately 10 minutes), and ease of administration. Because the test results are provided instantaneously, clinicians can use them immediately to guide decisions about treatment. Studies have demonstrated that VCTE is moderately to highly accurate in diagnosing advanced fibrosis and cirrhosis.[15-17] However, VCTE is less able to discriminate between the intermediate stages of fibrosis (F1 and F2).[18-20] In addition, several factors and conditions may confound the accuracy of VCTE in determining fibrosis. These include steatosis, active viral hepatitis, high body mass index, and food consumption prior to the test.[21-26]

A common current application of biomarkers in fibrosis assessment involves FibroTest (BioPredictive, Paris, France), which is also called FibroSure in the United States. This method involves a calculation based on 5 indirect markers of fibrosis: α2- macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, and gamma glutamyl transpeptidase, which are adjusted for age and sex. FibroSure has been demonstrated to have moderate to high accuracy for assessing advanced fibrosis and cirrhosis.[17,27] However, similar to VCTE, this method and the use of other biomarkers are limited in accuracy for detecting low- or intermediate-stage fibrosis.[28]

The AASLD/IDSA/IAS-USA guidance recommendations indicate that combining direct biomarkers and VCTE is "the most efficient approach to fibrosis assessment."[2] The guidance calls for biopsy in patients with discordant results between these methods and for cases in which more accurate fibrosis staging is needed to inform treatment decisions.

In response to questions about fibrosis assessment from the symposium audience, Dr. Terrault and Dr. Monto discussed the central importance of identifying which patients are cirrhotic. The panelists talked about their experiences in diagnosing advanced disease and cirrhosis through clinical assessments, routine laboratory tests, and abdominal imaging. In physical examination, they said, cirrhosis signs include a firm liver edge, splenomegaly, spider angiomata, and palmar erythema. Dr. Terrault explained the diagnostic value of a low platelet count, pointing to a cutoff value of less than 140,000/μL as a sign of portal hypertension and cirrhosis. Dr. Terrault views these clinical and laboratory findings or abdominal imaging showing signs of cirrhosis and portal hypertension as sufficient for making a diagnosis of cirrhosis and establishing need for immediate treatment. Thus, for patients with these signs, she questions the need for further tests, including FibroSure or FibroScan. The panelists acknowledged the value of biomarkers and VCTE for patients whose clinical signs and abdominal imagings do not clearly indicate advanced disease or cirrhosis. In agreement with AASLD/IDSA/IAS-USA recommendations, they view liver biopsy as helpful when the results of different noninvasive tests do not agree.[2]

Addressing the limitations of noninvasive methods for assessing fibrosis, Dr. Terrault described potential barriers to ensuring that patients receive necessary antiviral therapy. She raised the case of patients who undergo noninvasive tests that indicate a Metavir stage of F2. Because biomarkers and VCTE are least accurate for intermediate stages of fibrosis, she explained, it is possible that the F2 results may inaccurately understage fibrosis; consequently, the patient would not be designated as the highest priority category for treatment and miss the opportunity to be treated immediately despite actually having advanced fibrosis.[18-20] Similarly, it is possible that the higher fibrosis scores may be inaccurate and overstaged, and as a result, individuals could be treated prior to developing advanced fibrosis.[21,25]

"We make it sound like we're so precise on knowing what's an F3 and what's an F2, and that is just not the reality—especially because most of us are using noninvasive tests. While these tests perform very well at the extremes, in the middle they make errors. As an example, for some patients I do FibroTest or FibroScan, and their results show that they're an F2. That's the range of the test that performs least well. So, maybe they're really an F3. If they were an F3, they would be eligible for immediate treatment. So, some clinicians find it frustrating that we are drawing this line at F3. I'd like to see us move away from an arbitrary F3 cutoff, especially based on tests that are not perfect."

—Norah Terrault, MD, MPH

Comprehensive Patient Assessment to Inform Treatment Decisions

As described earlier and summarized in Table 2, AASLD/IDSA/IAS-USA guidance recommendations designate the highest priority for HCV treatment to patients with advanced fibrosis or cirrhosis, corresponding to Metavir stages F3 or F4.[2] The recommendations for highest priority also include cryoglobulinemia with end-organ manifestations, such as vasculitis and renal disease (proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis).[2] Consistent with the guidelines, Dr. Terrault and Dr. Monto acknowledged the importance of prioritizing patients with advanced fibrosis or cirrhosis. However, they also argued that making effective decisions about whom, and when, to treat requires a more comprehensive clinical assessment. This approach involves evaluating the impact of HCV and HCV-related extrahepatic complications, including those affecting quality of life, functional status, and work productivity.[2,29-31]

When Dr. Terrault presented the guidance recommendations for highest priority treatment, she commented on her experiences with some health plans that base approvals of immediate HCV treatment strictly on whether patients have F3 or F4 fibrosis staging. Advocating for a more comprehensive approach in these cases, she discussed the clinical relevance of the high priority criteria listed in the AASLD/IDSA/IAS-USA guidance recommendations. This indication is designated for patients with Metavir F2 fibrosis, HIV-1 or HBV coinfection, other coexistent liver diseases such as nonalcoholic steatohepatitis (NASH), debilitating fatigue, type 2 diabetes mellitus (insulin resistance), and porphyria cutanea tarda. As reviewed in the AASLD/IDSA/IAS-USA guidelines, recent reports suggest that treating HCV patients with lower stage fibrosis may extend the benefits of SVR and improve survival.[2,32-35] In a long-term follow-up study (up to 20 years), the 15-year survival rate was statistically significantly better for patients with Metavir stage F0 or F1 fibrosis who achieved SVR compared with those who were untreated or failed treatment (93%, 88%, and 82%, respectively; $P=0.003$).[32] In addition, the guideline authors cited modeling studies that show a lower risk of mortality in patients who initiated treatment before Metavir F3.[33-35]

TABLE 2 AASLD/IDSA/IAS-USA Recommendations for Prioritizing HCV Patients for Treatment

Highest Priority for HCV Treatment	High Priority for HCV Treatment	Persons at Elevated Risk of HCV Transmission
Advanced fibrosis or cirrhosis (Metavir F3-F4)	Fibrosis (Metavir F2)	Men who have sex with men, with high-risk sexual practices
Organ transplant	HIV-1 coinfection	Active injection drug users
Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (e.g., vasculitis)	HBV coinfection	Incarcerated persons
Proteinuria, nephritic syndrome, or membranoproliferative glomerulonephritis	Other coexistent liver disease (e.g., NASH)	Persons on long-term hemodialysis
	Debilitating fatigue	HCV-infected women of child-bearing potential wishing to get pregnant
	Type 2 diabetes mellitus (insulin resistant)	HCV-infected health care workers who perform exposure-prone procedures
	Porphyria cutanea tarda	

AASLD = American Association for the Study of Liver Diseases; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus-1; IAS-USA = International Antiviral Society-USA; IDSA = Infectious Diseases Society of America; NASH = nonalcoholic steatohepatitis.

"Many health plans draw a line indicating that the patient must at least be at Metavir stage F3 for immediate treatment. We need to go beyond looking at Stage 3 or 4. Look into the patient, at what's going on in terms of comorbidities and symptoms related to hepatitis C. If patients have HIV, fatty liver disease, or fatigue, they need the treatment, even if they are less than stage 3 or 4."

—Norah Terrault, MD, MPH

To highlight the need for comprehensive assessment and individualized treatment decisions, the panel discussed a case of a working mother with chronic HCV infection who was suffering from debilitating fatigue. The patient was having difficulty being productive at work, helping her children with schoolwork, and being active with her family. However, because of moderate fibrosis (Metavir F2), she was denied coverage for treatment. The panel discussion focused on the potential positive influence of treatment for this patient, including outcomes such as reduced symptoms and improved quality of life, productivity, and ability to care for her family.[29]

Patients at high risk for transmitting HCV are further identified as a high priority treatment group (Table 2).[2] The underlying rationale and potential public health benefit of this recommendation is clear. Together with other interventions, treating to prevent HCV transmission is likely to decrease HCV disease prevalence.[36] Even modest increases in SVR among injection drug users have been shown to reduce HCV prevalence.[36-38] Furthermore, treating HCV-infected women who intend to become pregnant can relieve the burden of HCV in newborns, although treatment is not recommended for women who are already pregnant.[2]

Evidence suggests that treatment at early and late fibrosis stages can yield favorable clinical and economic benefit.[2,32-35,39] There is wide variability among health plans in eligibility criteria for HCV treatment with some being comprehensive and others, such as many state Medicaid programs, that are more restrictive.[40,41] In light of these and other benefits of SVR, and with additional DAA agents forthcoming, the symposium panelists suggested that managed care pharmacy professionals consider other factors in addition to stage of fibrosis when determining access to treatment for HCV patients.

Variations to Standard of Care

The rapid evolution of interferon-free DAA treatment regimens has changed the perception and approach to the treatment of patients with HCV, particularly those with genotype 1. In the context of ongoing changes, several variations to the standard of care have been explored to optimize treatment outcomes, minimize side effects, and encourage compliance. This section summarizes the symposium discussions and evidence on variations involving the influence of viral load on decisions about treatment duration and the utility of ribavirin in new DAA regimens.

Influence of Viral Load on Decisions About Treatment Duration

For treatment-naïve patients with HCV genotype 1, the AASLD/IDSA/IAS-USA guidelines recommend ledipasvir/sofosbuvir for 12 weeks (Table 3).[2] The prescribing information for ledipasvir/sofosbuvir indicates that shortening the treatment duration from 12 to 8 weeks may be considered in noncirrhotic treatment-naïve patients with baseline HCV RNA concentrations less than 6 million IU/mL.[42] This recommendation was based on the ION-3 study, which revealed that among those patients with baseline HCV RNA less than 6 million IU/mL, relapse rates were similar for those receiving 8 and 12 weeks of treatment.[43] However, due to limitations of the study, the guidelines advise caution when shortening the treatment to less than 12 weeks in patients without cirrhosis. With respect to this recommendation, the symposium attendees asked the following questions to the expert panel: What do you see as the distribution of viral load less than 6 million versus greater than 6 million IU/mL? How do you accurately identify patients who may be treated for 8 weeks with the promise of efficacy? In the

TABLE 3 AASLD/IDSA/IAS-USA HCV Treatment Recommendations for Treatment-Naïve Patients and Retreatment in Patients for Whom Prior PEG-IFN and RBV Therapy Has Failed

Genotype	Regimen	Duration
Treatment-Naïve		
Genotype 1a	ledipasvir/sofosbuvir	12 weeks
	paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV	12 weeks (no cirrhosis) 24 weeks (cirrhosis)
	simeprevir + sofosbuvir ± RBV	12 weeks (no cirrhosis) 24 weeks (cirrhosis without Q80K polymorphism)
Genotype 1b	ledipasvir/sofosbuvir	12 weeks
	paritaprevir/ritonavir/ombitasvir + dasabuvir	12 weeks (no cirrhosis)
	paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV	12 weeks (cirrhosis)
	simeprevir + sofosbuvir	12 weeks (no cirrhosis)
	simeprevir + sofosbuvir ± RBV	24 weeks (cirrhosis)
Genotype 2	sofosbuvir + RBV	12 weeks (no cirrhosis) 16 weeks (cirrhosis)
Genotype 3	sofosbuvir + RBV + PEG-IFN	12 weeks
	sofosbuvir + RBV (alternative regimen)	24 weeks
Retreatment for Prior Treatment Failure with Peg-IFN plus RBV		
Genotype	**Regimen**	**Duration**
Genotype 1a (no cirrhosis)	ledipasvir/sofosbuvir	12 weeks
	paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV	12 weeks
	simeprevir + sofosbuvir	12 weeks
Genotype 1b (no cirrhosis)	ledipasvir/sofosbuvir	12 weeks
	paritaprevir/ritonavir/ombitasvir + dasabuvir	12 weeks
	simeprevir + sofosbuvir	12 weeks
Genotype 1a or 1b (compensated cirrhosis)	ledipasvir/sofosbuvir	24 weeks
	ledipasvir/sofosbuvir + RBV	12 weeks
	paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV	24 weeks (genotype 1a) 12 weeks (genotype 1b)
	simeprevir + sofosbuvir ± RBV	24 weeks (without Q80K polymorphism)
Genotype 2	sofosbuvir + RBV	12-16 weeks
	sofosbuvir + RBV + PEG-IFN	12 weeks
Genotype 3	sofosbuvir + RBV + PEG-IFN	12 weeks
	sofosbuvir + RBV (alternative for IFN ineligible)	24 weeks

Note: Recommendations accessed on July 16, 2015.[2]
PEG-IFN = pegylated interferon; RBV = ribavirin.

real world, do you use baseline HCV RNA less than 6 million IU/mL for determining treatment duration?

In response to these questions, Dr. Monto and Dr. Terrault discussed the problems of fluctuations in HCV RNA levels, viral load distribution in the real world, and how they determine shortening treatment duration from 12 to 8 weeks. Dr. Monto shared that in his practice setting, the San Francisco Veterans Affairs Health Care System, approximately 10%-15% of HCV patients have a baseline HCV RNA of greater than 6 million IU/mL. He added that it is important to consider the natural fluctuations in viral load during infection and to not attach clinical significance to small changes (<0.5 $\log^{10}$) in HCV RNA levels.[44-46]

Dr. Terrault engaged the audience in thinking critically about how, in the ION-3 study, the researchers arrived at 6 million IU/mL as the cut-point for selecting patients to be treated with a shorter duration of therapy. She reiterated that viral load can fluctuate, so using a single RNA HCV level as a definitive criterion for deciding treatment duration may result in negative outcomes. Consider, for example, a patient whose viral load fluctuates in a range around the 6 million IU/mL level. If the patient's baseline measurement of viral load is slightly under 6 million IU/mL, a strict application of the cut-point value would indicate that 8 weeks of treatment is appropriate. However, given the potential for higher virus concentrations with normal fluctuation, an 8-week treatment course for this patient may compromise efficacy and increase risks of relapse. In practice, Dr. Terrault explained that she chooses a very low viral load (<1 million IU/mL) to be most comfortable and confident that patients can be treated for 8 weeks without compromising efficacy.

"What's still not clear to me in the ION-3 study is how the researchers arrived at exactly 6 million IU/ml as the cut-off for shorter duration therapy. Is 6.0 really different than 6.1 million? Or, is it really different than 5 million? Obviously, the researchers chose a cut-point that gave them the greatest proportion of patients that were going to end up with an SVR. It's an informative study because it gives us a sense of who can be treated for a shorter period of time. But it's important to consider that viral loads do fluctuate. Also, we haven't had validation studies that show that 6 million is the perfect choice. In my practice, we aim for defining a low viral load versus a high viral load. I actually pick 1 million as a cutoff and low stage of disease. I feel that by choosing a lower cutoff of viral load, it increases the chances of achieving success with 8 weeks of therapy."

—Norah Terrault, MD, MPH

The Role of Ribavirin in Optimizing HCV Treatment Efficacy

Ribavirin has traditionally been considered a critical component of HCV treatment with interferon-based therapy. However, its use requires high pill burden and, even without peg-interferon, is associated with considerable side effects. With more potent DAAs, the role of ribavirin becomes less clear and more marginalized. On this topic, attendees at the symposium asked several questions: What types of side effects are there with ribavirin alone (without peg-interferon)? What are the consequences of adding ribavirin or extending the duration of therapy? How does adding ribavirin impact cost and adherence?

In response to questions about the role of ribavirin, Dr. Terrault and Dr. Monto stressed the importance of comprehensive patient assessment of factors that may negatively affect adherence and/or tolerability. Some patients may not be candidates for ribavirin; thus, the decision to use this agent should be made by the patient and the medical team based on the patient's comorbid conditions, likelihood of adherence, and overall assessment of risks and benefits. Several conditions are contraindications for ribavirin, including pregnancy and significant or unstable cardiac conditions that may worsen ribavirin-induced anemia. However, for those patients who are eligible, adding ribavirin may improve SVR rates and shorten duration of treatment. Summarized as follows, completed and ongoing studies provide data and help to answer questions about the utility of ribavirin with DAAs.

A post hoc analysis of data from previous clinical trials of ledipasvir/sofosbuvir that included patients with HCV genotype 1 and compensated cirrhosis was performed to evaluate the safety and efficacy of ledipasvir/sofosbuvir, as well as optimal treatment duration and the potential benefit of adding ribavirin.[47] Overall, response rates were similar among HCV genotype 1 treatment-naïve and treatment-experienced groups (SVR12 rates ranged from 95%-98%). However, treatment-experienced patients who received 12 weeks of ledipasvir/sofosbuvir without ribavirin had a noticeably lower SVR12 rate (90%) compared with that observed when ribavirin was added or the treatment was extended to 24 weeks (96%-100%).[47] In addition, an association was found between low platelet count (<75,000/ μL) and lower likelihood of SVR12.[47] This finding was also observed in the phase 2 SIRIUS trial that evaluated ledipasvir/sofosbuvir plus ribavirin for 12 weeks and ledipasvir/sofosbuvir for 24 weeks in patients with HCV genotype 1 and compensated cirrhosis who previously failed protease inhibitor therapy.[48] While ledipasvir/sofosbuvir (without ribavirin) for 12 weeks may be the optimal regimen for many HCV genotype 1 patients with cirrhosis, these findings highlight the benefit of adding ribavirin and/or extending treatment duration to 24 weeks in cirrhotic patients who are treatment-experienced and/or have low platelet counts.[47,48]

With the PrOD regimen, the rates of SVR12 were found to be statistically superior to the historical control, with the SVR12 ranging from 90%-100% with 12 weeks of treatment.[49-53] Rates of SVR for HCV genotype 1a, the more difficult to treat genotype 1 subtype, have been found to be lower than that for HCV genotype 1b. For patients with genotype 1a (irrespective of cirrhosis),

adding ribavirin to PrOD results in high rates of SVR.[49,50,54] For genotype 1b, the addition of ribavirin to PrOD does not appear to provide additional benefit for noncirrhotic treatment-naïve and treatment-experienced patients.[50,51] In treatment-naïve patients with cirrhosis, the June 2015 AASLD/IDSA/IAS-USA guidance recommended PrOD and ribavirin for 24 weeks in HCV genotype 1a and 12 weeks for HCV genotype 1b infection.[2] This recommendation also applies to treatment-experienced patients in whom pegylated interferon and ribavirin has failed. However, in the recently presented TURQUOISE-III study, the PrOD regimen, without the use of ribavirin, given for 12 weeks achieved 100% SVR12 in HCV genotype 1b patients with compensated cirrhosis, including treatment-experienced patients.[55] This data would suggest ribavirin may not be required with the PrOD regimen for HCV genotype 1b patients with cirrhosis.

"For a lot of us who have treated hepatitis C patients over the years, ribavirin has been a part of our approach since 1998. We've been trying to treat without ribavirin for a long time because it's a pretty toxic drug. It causes dose-dependent hemolytic anemia, dropping hemoglobin by about 25% in a lot of patients. It turns out that using ribavirin without interferon produces less anemia but still some, in addition to affecting mood and sleep. The downside includes pill burden. In some DAA regimens, the pill burden can be significant. Granted the treatment duration is relatively short, but in some patient populations they already have a laundry list of medications. But for patients with advanced disease—who are cirrhotic and are close to needing a transplant—those are the patients who can't wait for therapy. The evidence shows that in those patients, some of whom are treatment-experienced, if you add in ribavirin you may be able to limit the duration of therapy to 12 weeks. For a patient whose viral load isn't dropping by week 4, we may consider adding ribavirin to the current regimen."

—Alex Monto, MD

Unmet Treatment Needs for Patients with Genotype 3

Historically, genotype 1 was considered the difficult-to-treat genotype, with genotypes 2 and 3 achieving higher rates of SVR. However, new DAAs and combination regimens provide high rates of SVR in patients with genotype 1 and 2, but treatment for HCV genotype 3, particularly in patients with cirrhosis who are treatment-experienced, has been far less successful, with lower rates of SVR and higher rates of relapse.[56-59] It is now recognized that genotype 3 is an aggressive genotype associated with increased rates of steatosis and a disproportionately higher risk for hepatocellular carcinoma.[57,60,61] On this topic, participants at the symposium expressed concerns and asked the following questions: What are the AASLD/IDSA/IAS-USA guidance recommendations for treatment of HCV genotype 3? What therapies are under investigation for the treatment of HCV genotype 3? In recent clinical trials on approved and investigational DAAs, what were the SVR rates in patients with cirrhosis?

At the time of the presentation, the AASLD/IDSA guidance recommendation for HCV genotype 3 was sofosbuvir plus weight-based ribavirin (1,000 mg [<75 kg] to 1,200 mg [>75 kg]) for 12 weeks.[2] The recommendation was based on results from the VALENCE study, which investigated sofosbuvir with ribavirin for 24 weeks in treatment-naïve and treatment-experienced patients with HCV genotype 3.[57] High SVR rates were achieved in those who were treatment naïve with or without cirrhosis (92% [n=12/13] and 95% [n=87/92], respectively); however, treatment-experienced, noncirrhotic patients achieved SVR at a slightly lower rate of 87% (n=85/98), and the rate was only 62% (n=29/47) in those who were cirrhotic. In June 2015, the AASLD/IDSA guidance recommendation for patients with HCV genotype 3 who are treatment naïve or for whom prior peg-interferon and ribavirin treatment has failed, with or without cirrhosis, was updated to daily sofosbuvir and weight-based ribavirin (1,000 mg [<75 kg] to 1,200 mg [>75 kg]) plus weekly peg-interferon for 12 weeks or daily sofosbuvir and weight-based ribavirin (1,000 mg [<75 kg] to 1,200 mg [>75 kg]) for 24 weeks as an alternative regimen for those who cannot tolerate interferon (Table 3).[2] The updated recommendation is supported by results of the BOSON trial.[62]

In 2014, results from the ELECTRON-2 trial in HCV genotype 3 patients were presented.[59,63] In treatment-naïve patients, ledipasvir/sofosbuvir alone for 12 weeks achieved an SVR12 rate of 64% (n=16/25), with 8 relapses; adding ribavirin achieved SVR12 in all (100%; n=26/26) patients with genotype 3 infection.[59] In treatment-experienced patients, this regimen of ledipasvir/sofosbuvir plus ribavirin for 12 weeks achieved an overall SVR rate of 82% (n=41/50).[63] Rates were considerably influenced by the presence of cirrhosis, with SVR12 rates of 73% in cirrhotic patients compared with 89% in noncirrhotic patients.[63] In presenting these data, Dr. Terrault explained that because this study was performed in New Zealand, there is a regional effect to consider. As demonstrated in other studies in patients with HCV genotype 1, response to treatment may vary by geographic region.[64,65] Referring to the 100% SVR12 rate in treatment-naïve patients using ledipasvir/sofosbuvir plus ribavirin, she suggested that genotype 3 viruses in this geographically isolated country may be more sensitive to this DAA combination than in other places in the world and may respond differently. Hence, patients with HCV genotype 3 infection, particularly those with cirrhosis, remain a population in need of additional strategies to achieve SVR.

The all-oral regimen of the NS5A inhibitor daclatasvir, in combination with sofosbuvir, was recently approved by the FDA for the treatment of HCV genotype 3. In the ALLY-3 study, this all-oral 12-week regimen achieved SVR12 rates of 90% (n=91/100) in treatment-naïve patients and 86% (n=44/51) in treatment-experienced patients (overall rate of 89%).[66] Lower

SVR12 rates were reported in HCV genotype 3 patients with cirrhosis (63%; n = 20/32) compared with those without cirrhosis (96%; n = 105/109). Further analysis of cirrhotic patients showed that SVR12 was achieved in 58% (n = 11/19) of treatment-naïve patients and 69% (n = 9/13) of treatment-experienced patients—response rates similar to those observed in the current recommended regimen.[57,58,67] Results of these studies underscore the need for more improved therapies in genotype 3, shorter duration of therapy (≤ 12 weeks instead of current 24 weeks), and higher efficacy in patients with cirrhosis and prior treatment experience.

Treatment for HCV Patients with Decompensated Cirrhosis

Patients with decompensated cirrhosis have traditionally been considered difficult to treat. Due to poor tolerability and efficacy of interferon-based regimens, treatment options were especially limited for this patient population. In response to attendee questions about treatment for HCV patients with advanced liver disease, Dr. Terrault, a leading expert in viral hepatitis in the liver transplantation setting, explained how all-oral interferon-free regimens are highly tolerable leading to changes in treatment approaches and improving patient outcomes. However, it is important to remember that this subset of patients, particularly those with decompensated cirrhosis (Child-Pugh B and Child-Pugh C), require specialized care and management.[2]

Unlike compensated cirrhosis, for which 3 oral treatment regimens are recommended, the AASLD/IDSA/IAS-USA-recommended treatment options for HCV genotype 1 patients with decompensated cirrhosis are currently limited to ledipasvir/sofosbuvir with or without ribavirin, although not specifically FDA approved for this indication.[2] For those treatment-naïve patients expected to tolerate ribavirin, the AASLD/IDSA/IAS-USA guidance recommends ledipasvir/sofosbuvir plus ribavirin (600 mg initial dose, increasing as tolerated) for 12 weeks. Alternatively, the guidance recommends ledipasvir/sofosbuvir without ribavirin for 24 weeks in patients with poor tolerance to ribavirin.[2] For treatment-experienced patients, the AASLD/IDSA/IAS-USA guidance recommendation is ledipasvir/sofosbuvir plus ribavirin (600 mg initial dose, increasing as tolerated) but extended for 24 weeks.[2] Currently, other regimens are not recommended by the AASLD/IDSA/IAS-USA for patients with decompensated cirrhosis due to safety concerns.[2]

In contrast to the guidelines, Dr. Terrault explained a slightly different approach that she takes with treatment-experienced patients who have decompensated cirrhosis in her clinical practice. Her approach for this group is similar to the guidance recommendation for treatment-naive patients, using ledipasvir/sofosbuvir plus ribavirin for 12 weeks, unless the platelet count is less than 75,000/μL. In this case, she extends treatment to 24 weeks because low platelet count has been associated with lower SVR rates.[48] For treatment-experienced patients unable to use ribavirin, Dr. Terrault follows the recommended strategy of ledipasvir/sofosbuvir for 24 weeks.[2]

The recommended regimen of ledipasvir/sofosbuvir and other interferon-free regimens under investigation, notably daclatasvir plus sofosbuvir and grazoprevir/elbasvir, yield high cure rates that exceed those of interferon-based therapy for HCV genotype 1 patients with decompensated cirrhosis.[66,68,69] Moreover, achievement of SVR with these regimens improves liver function (Model for End-Stage Liver Disease [MELD] and Child-Pugh scores) and possibly results in delisting patients from the orthotopic liver transplantation waiting list.[68,70]

The recently presented SOLAR-2 trial investigated ledipasvir/sofosbuvir plus ribavirin for 12 or 24 weeks in HCV patients with decompensated cirrhosis who were awaiting or had received liver transplants.[68] The overall SVR12 rate was 85% (n = 61/72) and 88% (n = 60/68) in patients treated for 12 or 24 weeks, respectively. Sustained viral suppression is also associated with improved liver function, evident by an improvement in MELD and Child-Pugh scores.[68]

In the ALLY-1 study, investigational daclatasvir, sofosbuvir, and ribavirin for 12 weeks produced SVR rates of 82% (n = 37/45) for HCV genotype 1 patients with advanced liver cirrhosis (Child Pugh class A, B, or C), with similar cure rates for those with hard-to-treat HCV genotype 3 (83% [n = 5/6] for advanced cirrhosis).[66] The C-SALT study of investigational grazoprevir/elbasvir combination reported that 90% (n = 27/30) of patients with HCV genotype 1 and advanced cirrhosis (Child Pugh class B) achieved SVR12 with a 12-week course of treatment.[69]

Dr. Terrault also added that many issues remain unresolved for the treatment of patients with advanced liver disease, particularly those with decompensated cirrhosis. As examples, she raised questions about the appropriate therapies, investigational treatment regimens, the optimal length of treatment, and the role of ribavirin. Although decompensated cirrhosis is listed as a contraindication to ribavirin, since these patients are more prone to develop hematologic side effects, with close monitoring and dose modifications, this antiviral agent can be given safely to these patients.[2,71]

New Issues in HCV Treatment

The introduction of oral DAA therapy has dramatically changed HCV treatment and promises cure in most patients. However, with new therapies come new challenges. As noted earlier, special characteristics of genotype 3, including a more rapid progressive disease, increased rates of steatosis, and a disproportionately higher risk for hepatocellular carcinoma, have made it particularly difficult to treat. Effective treatment for patients with genotype 3 is still needed. Patients with renal impairment or those with end-stage-renal disease also present a challenge and are areas of intense research.[72,73] Currently, there is a lack of data in this patient population, and there are concerns about the renal elimination of sofosbuvir.[2] Moreover, new questions and concerns about potential drug interactions, drug resistance, and reinfection have emerged.[2,74,75]

Managed Care Strategies: Patient Education, Adherence Promotion, and Care Coordination

The symposium concluded with a presentation and discussion led by Michael R. Stinchon, Jr., RPh, on managed care strategies for improving the treatment and outcomes of patients with HCV. Stinchon began by highlighting evidence presented earlier on the high rates of SVR that have been reported in clinical trials on new DAAs. He echoed the message that these therapies offer remarkable potential for accomplishing the primary goals of HCV care—achieving SVR on a population basis and eradicating the virus. However, commenting on real-world experiences of health plan members, Mr. Stinchon pointed out major barriers to achieving SVR that require effective managed care strategies to overcome. As summarized in this section, he focused on barriers of inadequate patient education, challenges in promoting medication adherence and receipt of follow-up care after treatment initiation, and gaps in care coordination. Regarding needs for patient education and interprofessional care coordination, he gave the example of a member who tried to refill her sofosbuvir 7 days after it was first filled. Ensuing consultation with the plan's case managers and the member's physician revealed that the patient did not receive adequate instructions on how to take the sofosbuvir, so she took it in concert with her ribavirin. In this case, Mr. Stinchon emphasized that proper education on appropriate use must be accompanied by coordinated follow-up involving all members of the health care team.

"It is especially unfortunate when we have patients with hepatitis C and we get them access to the right medication, but they don't take the medication correctly, or they don't have the right support to know how to take it. Then you end up with waste in the system, where you have a patient who started out in a negative cohort and is still sick. And, we all know that when patients with hepatitis C track, they end up in the more severe categories in which their costs increase and their health and quality of life are worsened."

—Michael R. Stinchon, Jr., RPh

Mr. Stinchon also suggested approaches to overcoming potential barriers to patient nonadherence to new DAAs and scheduled receipt of follow-up care. Clinical trials have revealed relatively low rates of side effects in patients taking these medications. In addition, compared with interferon-based regimens, the new medication regimens are less complex and shorter in duration. Thus, it is not surprising that adherence rates are high in clinical trials of all-oral DAA regimens.[76,77] However, in real-world settings these therapies pose barriers to adherence that require coordinated solutions involving providers and managed care professionals. Mr. Stinchon emphasized encouraging physicians to have upfront discussions with patients about their cost burdens in starting DAA therapy, following through with scheduled follow-up appointments, and completing the treatment course.[78] These discussions should directly address the negative implications of nonadherence and provide information about opportunities for financial assistance. Mr. Stinchon also emphasized the vital services that specialty pharmacies provide for patient education, monitoring to identify potential adherence deviations based on utilization, and coordinating therapeutic regimens for HCV patients with comorbid conditions.

In addressing the importance of dialogue between managed care professionals and providers, Stinchon outlined key aspects of communication, including verification of the member's diagnosis, therapy dose, treatment regimen, duration of treatment, specific symptoms (e.g., degree of fatigue), presence of comorbidities and coinfection, and treatment history. He gave the example of a member with extreme fatigue that was not documented in precertification notes. Communication with the physician to verify patients' symptoms, such as fatigue, may influence decisions about access to HCV therapy. In the initial stage of care, Mr. Stinchon emphasized communicating with physicians to request a full picture of the patient so the member obtains appropriate preauthorization for necessary services and treatment. In follow-up stages, he spoke about the importance of interprofessional communication about members' on-treatment monitoring, including viral load evaluations, barriers to adherence such as costs and complexity of medication regimens for patients with comorbidities, adverse effects, and appropriate monitoring after treatment completion.

"As we move forward in this changing landscape for hepatitis C treatment, it is imperative that managed care pharmacy professionals play a key role. The new agents have proven to be highly effective and well tolerated. They have also driven significant cost across the health care system. Creating clinically sound guidelines to reflect the most current literature can help ensure that appropriate patients will receive treatment while remaining mindful to cost. The most severe patients should be prioritized, but other factors should be considered for those with complicating variables.

This patient population—due to high incidence of comorbidities, history of substance abuse, potential significant out-of-pocket expenses, and other factors—can benefit greatly from high-touch support services. Managed care pharmacy professionals should look to support patients with these resources whenever possible to fortify patients with the tools necessary to achieve desired outcomes. Whether it be through targeted case management services or additional specialty pharmacy mechanisms, these high-touch support services will add expenses in the short term but reduce incidence of misuse and waste, as well as create benefit for the patient and increase the likelihood of successful treatment."

—Michael R. Stinchon, Jr., RPh

Conclusions

The educational symposium held at the 2015 AMCP Meeting & Expo addressed important clinical and managed care questions that have arisen with the availability of all-oral, interferon-free DAA regimens. Considering the pivotal roles of managed care professionals in decision making about eligibility for immediate treatment in patients with HCV, the expert panel emphasized a comprehensive approach to patient assessment. In addition to fibrosis stage, key patient-specific factors include comorbidities; coinfections; complications of liver disease; extrahepatic manifestations; prior treatment history; risk of transmission; and the impact of HCV and HCV-related symptoms on quality of life, functional status, and work productivity. Considerations of unique treatment needs among subpopulations, including patients with HCV genotype 3 or advanced liver disease, are also fundamental to effective decision making. Whereas the new therapies are significantly more effective and safer than previous options, they pose new sets of challenges for managed care professionals in areas of patient education, adherence, and interprofessional communication. Moreover, the high costs of the therapies will continue to factor into treatment decisions. In response to new and emerging challenges, ongoing and future research aims to recognize patient populations with unmet needs, identify more effective treatment options for these groups, and base treatment and management decisions on cost-effectiveness evidence.

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