



Real-World HCV Care

In this Issue...

A recent development in hepatitis C management has been the emergence of several cohorts and registries that have effectively gathered real-world information about safety and efficacy outcomes for DAA therapies in actual clinical practice.

In this issue Dr. Andrew J. Muir from the Duke University School of Medicine reviews recent publications that help address current controversies and questions, including:

- the eight-week treatment duration recommendation for sofosbuvir-ledipasvir
- the response rates of African Americans
- outcomes in HIV-HCV patients
- the use of sofosbuvir-containing regimens in patients with chronic kidney disease
- DAA use in older patients



Volume 5 Issue 7

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Length of Activity

- 1.0 hour Physicians
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Expiration Date

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LEARNING OBJECTIVES

- Discuss the real-world data to support the recommendation for eight vs 12 weeks treatment duration of sofosbuvir-ledipasvir.
- Summarize current HCV treatment options for patients with advanced kidney disease for efficacy and safety.
- Describe the risks and benefits of HCV therapies in HIV-HCV patients and older patients.

GUEST AUTHOR OF THE MONTH

Commentary & Reviews



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Guest Faculty Disclosure

Dr. Muir has disclosed that he has served as a consultant/advisor to AbbVie, Inc. Gilead Sciences, Inc., and Merck & Co., Inc. He has also received grant/research funding from AbbVie, Inc., Gilead Sciences, Inc., and Merck & Co., Inc.

Unlabeled/Unapproved uses

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

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COMMENTARY

Hepatitis C virus (HCV) therapy has made tremendous progress in the last decade with the introduction of numerous potent, direct acting antiviral (DAA) therapies. These regimens were evaluated in large programs with trials in populations that included treatment-naïve and -experienced patients, HIV-HCV coinfecting patients, and patients with decompensated cirrhosis. Despite these robust development programs, the trials had typical inclusion and exclusion criteria that limited participation of patients with significant medical comorbidities. As a result, there were questions whether the regimens would be safe in the broader patient population in clinical practice because historically, outcomes in clinical practice have been reduced compared to those in trials. The recent emergence of large, observational cohorts has been an important development to increase our understanding of HCV outcomes in practice. In this issue we review several important analyses that demonstrate the value of these cohorts.

A major controversy was the FDA's recommendation to consider eight weeks of sofosbuvir-ledipasvir in treatment-naïve patients without cirrhosis and HCV RNA less than 6 million IU/ml. Concerns were raised, given the recommendation came from a post hoc analysis of the ION-3 study. Subsequently, multiple cohorts have demonstrated that this is a reasonable strategy.¹ In the analysis from the Veterans Administration by Backus and colleagues (reviewed herein), SVR rates were similar at eight and 12 weeks, and this analysis should give clinicians further confidence in the FDA recommendation. A key finding was the small but meaningful difference in response rates for African Americans. SVR rates among African Americans who received eight weeks (92.4%, 1065/1153) were significantly lower than in Caucasians receiving eight weeks (95.3%, 1504/1578, $P = .002$). SVR rates were similar among African Americans and Caucasians who qualified for eight weeks but received 12 weeks. As a result, the AALD/IDAA guidance panel recommended that African Americans should not receive the shortened course of eight weeks.²

Another area of controversy has been HCV treatment in advanced kidney disease. Even though sofosbuvir was not recommended for advanced chronic kidney disease because of its renal elimination, some clinicians and patients elected to use this agent. The (reviewed) study by Saxena et al reports the experience with this population in the HCV-TARGET study. Efficacy outcomes were similar for patients of all stages of kidney disease and revealed expected adverse events related to anemia with ribavirin. Serious adverse events were more than three-fold higher in patients with lower eGFR, and they also noted worsening

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renal function people in this low eGFR group who were not on dialysis. The observational nature of the study limits the ability to evaluate if renal dysfunction was related to sofosbuvir vs other relevant factors. Overall, the study highlights the potential risks for treatment of patients with advanced kidney disease with sofosbuvir and the need for close monitoring on treatment. For patients with genotypes 1 and 4, the paper by Munoz-Gomez et al demonstrates that an alternative to sofosbuvir was safe and effective in patients with advanced kidney disease in the real-world setting. This regimen and the more recently introduced elbasvir/grazoprevir regimen do not treat genotypes 2 and 3, but glecaprevir/pibrentasvir is expected later in 2017 and would be a pangenotypic regimen for patients with advanced kidney disease.

The high prevalence of HCV among HIV-infected patients and their aggressive natural history of liver disease has led to scrutiny on DAA regimens in this population. In the ION-4 study, the overall SVR rate was 96% with sofosbuvir-ledipasvir, but all 10 relapses in the study were in African Americans. Eight of these patients received efavirenz-containing regimens.³ The recent report by Bhattacharya et al from the Veterans Affairs Clinical Case Registry evaluated genotype 1 HIV-HCV patients treated with sofosbuvir-ledipasvir and ombitasvir/paritaprevir/ritonavir plus dasabuvir. The overall SVR rate was 90.9% and addressed the concerns of ION-4 with similar rates among the HCV regimens and racial groups. The SVR rate for African American patients receiving ledipasvir-sofosbuvir and an efavirenz-containing regimen was reassuring at 92.5% (124/134). Further support for DAA regimens in this population came from the French report of daclatasvir and sofosbuvir in 407 HIV-HCV patients. The study included 72% with cirrhosis and 18% with decompensated cirrhosis. The regimen was effective with SVR in 92% overall and well tolerated even in this population with advanced liver disease.

Another area of critical concern is the treatment of older patients with HCV. The reviewed study by Conti and colleagues examined the real-world experience of treating patients ≥ 65 years of age. The study demonstrated that efficacy rates for DAA regimens were similar for patients older or younger than 65 years. Serious adverse events were more common in older patients, and this report highlights the need for an evaluation for cirrhosis and comorbidities like chronic kidney disease in older patients.

Like the other studies in this review, this real-world cohort offers patients and their clinicians the opportunity to see both safety and efficacy outcomes in a large number of patients that are representative of our clinical panels. The recent developments with effective databases and registries that can report outcomes in an efficient manner have become a great companion to our clinical trial programs. With the data from these questions, controversies like the eight-week treatment regimen or the outcomes in African Americans with HIV-HCV can be addressed efficiently and help more patients and their clinicians understand how best to approach their care.

References:

1. Kowdley KV, Sundaram V, Jeon CY, et al. [Eight weeks of Ledipasvir/Sofosbuvir is effective for selected patients with genotype 1 Hepatitis C virus infection](#). *Hepatology*. 2017 Apr;65(4):1094-1103.
2. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. <http://www.hcvguidelines.org>. Accessed June 28, 2017.
3. Naggie S, Cooper C, Saag M, et al; ION-4 Investigators. [Ledipasvir and sofosbuvir for HCV in patients coinfecting with HIV-1](#). *N Engl J Med* 2015; 373:705–13.

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Sofosbuvir-Ledipasvir: 8 vs 12 Weeks

Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness and predictors of sustained virological response with all-oral therapy in 21,242 hepatitis C genotype-1 patients. *Antivir Ther.* 2016 Dec 9.

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The development of the fixed dose combination of sofosbuvir and ledipasvir was an important landmark for the treatment of HCV infection. This combination regimen offered a potent, ribavirin-free regimen to patients with genotypes 1a, 1b, 4, 5 and 6 and quickly became the most commonly prescribed HCV regimen in the United States. One area of controversy at the time of approval was the duration of therapy for treatment-naïve patients. The Food and Drug Administration (FDA) performed an analysis on the ION-3 phase 3 study, which evaluated sofosbuvir-ledipasvir for eight and 12 weeks. This analysis revealed that the relapse rate was higher for patients with baseline HCV RNA greater than 6 million IU/ml when treated for eight weeks (10%) when compared to 12 weeks of treatment (1%). The FDA therefore recommended that treatment-naïve patients without cirrhosis and with HCV RNA less than 6 million IU/ml could be considered for 8 weeks of therapy with sofosbuvir-ledipasvir. As a result of this recommendation, some payers mandated that patients with HCV RNA less than 6 million IU/ml should receive eight weeks of sofosbuvir-ledipasvir. However, since this recommendation came from a secondary analysis, many clinicians were uncomfortable with it.

This paper by Backus et al reports on 21,142 patients with genotype 1 HCV infection in the United States Veterans Health Administration and provides further insight into the question of treatment duration. The study was an observational intent-to-treat cohort analysis using data from the Veterans Affairs Clinical Case Registry for HCV. The treating clinicians determined the choice of antiviral regimens and duration of therapy. Overall, SVR rates were similar at 92.8% (3,401/3,664) at eight weeks and 93.6% (6,091/6,506) at 12 weeks. Further analysis revealed that among patients eligible for the eight-week duration (because they were treatment-naïve without cirrhosis and had HCV RNA less than 6 million IU/ml), 3,059 (55.2%) received eight weeks and 2,479 (44.8%) received 12 weeks. A key finding was a difference in response rates by race. SVR rates for African Americans who received eight weeks (92.4%, 1065/1153) were significantly lower than in Caucasians who received eight weeks (95.3%, 1504/1578, $P = .002$). Among patients who qualified for eight weeks but received 12 weeks, SVR rates were similar for African Americans (95.5%, 1106/1158) and Caucasians (95.1% 1018/1071, $P = .68$).

In an analysis limited to patients who received sofosbuvir-ledipasvir, African American race was a significant independent predictor of decreased odds of SVR (OR 0.80, 95%CI 0.70-0.92, $P < .001$). Although the difference in response rate for African American patients was small, this finding was felt to be significant and was one of the studies that led the American Association for the Study of Liver Disease and Infectious Disease Society of America to recommend that African American patients should not receive eight weeks of sofosbuvir-ledipasvir.

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Sofosbuvir Regimens in CKD

Saxena V, Koraisiy FM, Sise ME, et al; HCV-TARGET. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int*. 2016 Jun; 36(6):807-16.



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A major area of controversy for sofosbuvir has been its safety in patients with advanced chronic kidney disease. The main elimination for sofosbuvir is renal, and studies have demonstrated accumulation of the inactive metabolite GS-331007. The language in the sofosbuvir package insert for patients with severe renal impairment was that no dosage recommendation could be given for patients with estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m² or with end stage renal disease. Even with the introduction of other DAA regimens, genotype 2 and 3 patients still have not had an effective interferon-free regimen that did not contain sofosbuvir.

This report from the HCV-TARGET database provides insight into the use of sofosbuvir-containing regimens. HCV-TARGET is a longitudinal, observational study of HCV patients from academic and community clinics in North America and Europe. At the time of this report, renal function estimates were available for 1789 patients, and 73 (4%) had eGFR less than 45 ml/min/1.73m², with 18 with EGFR ≤ 30 ml/min/1.73m² and five patients on hemodialysis. The regimens were peginterferon in combination with sofosbuvir and ribavirin, sofosbuvir and ribavirin, and simeprevir/sofosbuvir with and without ribavirin. Efficacy outcomes were similar for patients with eGFR less than or greater than 45 ml/min/1.73m², and renal function was not a predictor in multivariate analysis. Among patients with eGFR less than 45 ml/min/1.73m², SVR12 rates were 50% (2/4) for peginterferon/sofosbuvir/ribavirin, 86% (12/14) sofosbuvir/ribavirin and 80% (28/35) for simeprevir/sofosbuvir, and 100% (11/11) with simeprevir/sofosbuvir.

Safety outcomes were a major focus of this analysis. Overall, 4% of patients discontinued treatment early, but this was similar for those with and without renal dysfunction. Among the 73 patients with eGFR less than 45 ml/min/1.73m², outcomes that were more common included anemia (30%), need for transfusion (10%), use of erythropoietin-stimulating drugs (12%), ribavirin discontinuation (12%), worsening renal function (15%), and any serious adverse events (22%). The difficulty with ribavirin dosing and anemia was not a surprise, given the renal clearance of ribavirin, but the three-fold increase in serious adverse events and the report of worsening renal function are important considerations. It should be noted that this observational cohort is limited in its ability to evaluate this renal finding in depth, and there are multiple potential contributing factors to renal dysfunction in this patient group. Although the efficacy outcomes were encouraging, this increase in serious adverse events warrants caution for this treatment strategy.

This study highlights the potential risks for treatment with sofosbuvir regimens in patients with advanced kidney disease and the need for discussion about these risks with patients, as well as close monitoring on treatment by experienced clinicians.

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HCV Therapy in Severe Renal Disease

Muñoz-Gómez R, Rincón D, Ahumada A, et al. Therapy with ombitasvir/paritaprevir/ritonavir plus dasabuvir is effective and safe for the treatment of genotypes 1 and 4 hepatitis C virus (HCV) infection in patients with severe renal impairment: A multicentre experience. *J Viral Hepat.* 2017 Jun; 24(6):464-471.

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Although many patients with HCV infection benefited early from the introduction of the DAA regimens, patients with advanced chronic kidney disease initially faced a disadvantage. The early DAA regimens in broad use contained sofosbuvir: as noted elsewhere in this newsletter, sofosbuvir has renal elimination and the package insert states that no dosage recommendation could be given for patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m² or with end stage renal disease. For patients with genotypes 1 and 4 infection and chronic kidney disease, an important breakthrough was the introduction of ombitasvir/paritaprevir/ritonavir for genotype 4, with the addition of dasabuvir for genotype 1. This regimen has minimal renal clearance and does not require dose adjustment for renal dysfunction.

In this retrospective study by Munoz-Gomez and colleagues from nine Spanish centers, 46 patients with chronic kidney disease stages 4 and 5 (including 34 on dialysis) were treated with ombitasvir/paritaprevir/ritonavir with or without dasabuvir according to genotype. Efficacy was impressive with SVR12 in 44/46 (96%). Both treatment failures discontinued therapy for an adverse event, with one at four weeks for atrial fibrillation and one at 13 days for severe heart failure. Ribavirin was added to the regimen for 21/46 patients, and these patients had a -2.28 ± 2.80 g/dl reduction in hemoglobin with treatment with dose reduction in 4/21 and suspension in 2/21. Transfusion was needed in three patients, and erythropoietin-stimulating agent doses were increased in 14/21 patients. Renal function was stable in the patients on dialysis.

This study highlights the need for ribavirin-free regimens in patients with chronic kidney disease but was reassuring otherwise in terms of safety and efficacy. It is also important to consider that both this regimen and the more recently introduced elbasvir/grazoprevir do not treat genotypes 2 and 3, but glecaprevir/pibrentasvir is expected later in 2017 and would be a pangenotypic, ribavirin-free regimen that has been studied in patients with advanced kidney disease.

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HIV/HCV Coinfection

Bhattacharya D, Belperio PS, Shahoumian TA, et al. Effectiveness of all-oral antiviral regimens in 996 human immunodeficiency virus/hepatitis c virus genotype 1-coinfected patients treated in routine practice. *Clin Infect Dis*. 2017 Jun 15; 64(12):1711-1720.



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Patients with HIV infection have appropriately received increased attention for HCV screening, linkage to care, and HCV DAA therapy. Patients with HIV-HCV have a more aggressive natural history of liver disease, and HCV therapy is strongly recommended. Several recently developed programs have included relatively large studies of DAA regimens in patients infected with HIV-HCV. From these studies a number of questions have emerged, with real-world cohorts and registries well positioned to provide answers. In the ION-4 study of sofosbuvir-ledipasvir for HIV-HCV patients, the overall SVR rate was 96% (322/335). Of the 13 patients who did not achieve SVR, all 10 relapses in the study were in African Americans. A key observation among these patients was that eight received efavirenz-containing regimens. Given that American HIV-HCV clinics treat many African Americans as well as patients with cirrhosis, there has been concern about the performance of these regimens in a real-world setting.

The recent report by Bhattacharya et al from the Veterans Affairs Clinical Case Registry evaluated treatment of genotype 1 HIV-HCV patients treated with either sofosbuvir-ledipasvir or ombitasvir/paritaprevir/ritonavir plus dasabuvir. The overall SVR rate of 90.9% was similar among the regimens. SVR was lower in patients with cirrhosis (85.9%, 176/205) compared to those without cirrhosis (92.4%, 674/700, $P = .006$). SVR rates for African Americans were 90.5% (546/603) and similar to other racial groups. The SVR rate for African American patients receiving ledipasvir-sofosbuvir and an efavirenz-containing regimen was 92.5% (124/134) and compared favorably to regimens without efavirenz.

The study had the opportunity to look at other questions, including the effect on tenofovir. Ledipasvir increases tenofovir disoproxil fumarate (TDF) exposure when coadministered with ritonavir-boosted atazanavir or darunavir, and there has been concern about the potential impact on renal function. An analysis of median creatinine during treatment revealed no difference when comparing sofosbuvir-ledipasvir in combination with TDF with or without a protease inhibitor or in the absence of TDF. Renal function was also stable in the ombitasvir/paritaprevir/ritonavir plus dasabuvir patients. This study was therefore important not only in providing confidence in the real-world results of HIV-HCV coinfection treatment but also in advancing our understanding around the issues of the African American response and potential harm with tenofovir.

The ability to address these issues so soon after the release of these medications into clinical practice is an important development in our ability to guide patients and clinicians about the therapies available to them.

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HIV/HCV Coinfection and Advanced Liver Disease

Lacombe K, Fontaine H, Dhiver C, et al. Real-world efficacy of daclatasvir and sofosbuvir, with and without ribavirin, in HIV/HCV coinfecting patients with advanced liver disease in a French early access cohort. *J Acquir Immune Defic Syndr*. 2017 May 1; 75(1):97-107.



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By virtue of the more aggressive natural history of liver fibrosis in patients with HIV-HCV infection, clinicians are likely to encounter HIV-HCV patients with cirrhosis and portal hypertension. Multiple studies have evaluated HCV-monoinfected patients with advanced liver disease and found that the currently available regimens are safe in compensated cirrhosis and the sofosbuvir-containing regimens are well tolerated in patients with decompensated cirrhosis. Experience has been more limited treating HIV-HCV coinfecting patients with advanced liver disease. As part of the French early access program that offered HCV therapy to more than 4000 patients and collected their clinical data, Lacombe and colleagues reported the experience of HIV-HCV patients treated with the pangenotypic regimen of daclatasvir and sofosbuvir. The recommended duration of treatment was 24 weeks, but the treating clinician could offer a shorter duration or add ribavirin. Of these 407 patients, 72% met criteria for cirrhosis, including 18% with decompensated cirrhosis. The cohort included 23% with MELD score greater than or equal to 15. The regimen was effective with SVR in 92% overall. In patients with compensated cirrhosis, SVR12 was 95% (134/141) without ribavirin and 100% (22/22) with ribavirin. Of the 33 patients with decompensated cirrhosis, only four received ribavirin. The SVR12 rate for the decompensated group was 94% (31/33).

Serious adverse events occurred in 9% of patients who received antiviral therapy. Most of the significant morbidity and mortality was related to complications of liver disease — progressive liver failure and hepatocellular carcinoma. Seven patients discontinued therapy because of an adverse event, and 10 patients died. Reasons for discontinuation were hepatocellular carcinoma, decompensated cirrhosis, respiratory distress, lymphopenia, renal insufficiency, attempted suicide, and anxiety.

In this population with advanced liver disease, the combination of daclatasvir and sofosbuvir was well tolerated and offered patients an opportunity for virologic cure and potential stabilization of their liver disease.

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HCV Therapy in Older Patients

Conti F, Brillanti S, Buonfiglioli F, et al. Safety and efficacy of direct-acting antivirals for the treatment of chronic hepatitis C in a real-world population aged 65 years and older. *J Viral Hepat.* 2017 Jun; 24(6):454-463.

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In the United States, the majority of HCV infections are present in the baby boomer generation born between 1945 and 1965. It is expected that many from this generation will have HCV diagnosed in their 70s and 80s. The tremendous impact from current HCV DAA regimens is related not only to their virology potency but also to their safety. Many patients previously ineligible for treatment with interferon-based regimens can now be treated. Following their release, DAA regimens have been associated with some concerning adverse events, including bradyarrhythmias with sofosbuvir-based regimens. Older patients are more likely to have comorbidities, and there was concern that this group might be at risk for complications related to DAA therapy.

In this report, Conti et al evaluated the efficacy and safety of DAA regimens in 282 older patients from a cohort with advanced fibrosis and cirrhosis from 11 centers in Italy. The cohort included 566 patients, and 566 received conventional regimens and were included in the analysis. Among these patients, 282 (50.7%) were ³ 65 years old, and 106 were 75 or older. The patients over 65 were more likely to have cirrhosis, diabetes mellitus, hypertension, chronic kidney disease, and history of hepatocellular carcinoma.

When considering safety, adverse events were more common in older patients but similar for the 65 to 74-year-old group (52.8%) and the group 75 years and older (57.5%, $P = .461$). Among patients who received ribavirin, dose reduction or discontinuation occurred in 25.9% of the older group and in 12.2% of younger patients ($P < .001$). Serious adverse events occurred in 14/282 (5%) of patients 65 and older and 12/274 (4.4%) of patients younger than 65. Discontinuation because of an adverse event occurred in seven (2.6%) younger than 65 and four (1.4%) aged 65 or older. The serious adverse events in older patients included four cases of hepatic decompensation, four of severe anemia, two with drug-related photosensitivity, and one each of pulmonary infection, atrial flutter, syncope, and abdominal pain. Deaths occurred in three patients in the younger group, two with worsening liver failure and one with intracerebral hemorrhage. Among patients 65 and older, two patients died because of worsening liver failure.

When considering efficacy, similar results were seen in younger and older patients. In the group 65 years and older, SVR rates were also similar for treatment-naïve (93.1%) and treatment-experienced patients (96.4%, $P = .290$). Lower SVR rates were observed in patients with cirrhosis and especially Child Pugh class B patients at 80.8% (21/26). This study highlights the effective outcomes in older patients and perhaps more important, that the regimens were well tolerated.

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KEY TAKEAWAYS

- Real world cohorts support the eight-week treatment duration for sofosbuvir-ledipasvir in treatment naïve patients without cirrhosis and with HCV RNA less than 6 million IU/ml, except for African Americans.
- Sofosbuvir-containing regimens are effective in patients with severe kidney disease but carry increased risk of serious adverse events and require close monitoring.
- Direct-acting antiviral regimens are safe and effective in real world cohorts of HIV-HCV patients.

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