CASE IN POINT

Treating Hepatitis C Virus Reinfection With 8 Weeks of Ledipasvir/Sofosbuvir Achieves Sustained Virologic Response

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Three patients reinfected with hepatitis C virus after a sustained virologic response were considered treatment naïve and treated with a short-course direct acting antiviral regimen.

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To decrease the incidence and prevalence of hepatitis C virus (HCV) in the United States, hepatology experts, public health officials, and patient advocates agree that linkage to care is essential for treatment of people who inject drugs (PWID). The most recent surveillance report from the Centers for Disease Control and Prevention (CDC) estimates that injection drug use accounts for the transmission of approximately 72% of new HCV infections.[1,2]

Although recent studies of direct-acting antiviral (DAA) agents have not been designed to investigate the long-term rates of reinfection in this population, various population-based studies in multiple countries have attempted to describe the rate of reinfection for this cohort.[3-7] This rate varies widely based on the defined population of PWID, definition of reinfection, and the prevalence of HCV in a given PWID population. However, studies have consistently shown a relatively low historic rate of reinfection, which varies from 1 to 5 per 100 person-years in patients who have ever injected drugs, to 3 to 33 per 100 person-years in patients who continue injection drug use (IDU). Higher rates are found in those who engage in high-risk behaviors such as needle sharing.[3-7] Yet, the US opioid crisis is attributable to a recent rise in both overall incidence and reinfections, highlighting the importance of determining the best treatment strategy for those who become reinfected.[1]

Current HCV guidelines from the American Association for the Study of Liver Diseases AASLD) and Infectious Diseases Society of America (IDSA) encourage access to retreatment for PWID who become reinfected, stating that new reinfections should follow treatment-naïve therapy recommendations.[8] However, to date this recommendation has not been validated by published clinical trials or patient case reports. This is likely due in part both to the small number of reinfections among PWID requiring retreatment and barriers to payment for treatment, particularly for individuals with substance use disorders.[9] While this recommendation can be found under the key population section for the "Identification and Management of HCV in People Who Inject Drugs," health care providers (HCPs) may easily miss this statement if they alternatively refer to the "Treatment-Experienced" section that recommends escalation to either sofosbuvir/velpatasvir/voxilaprevir or glecaprevir/pibrentasvir in patients who are NS5A inhibitor DAA-experienced.[8] Anecdotally, the first instinct for many HCPs when considering a treatment regimen for a reinfected patient is to refer to treatment-experienced regimen recommendations rather than appreciating the reinfected virus to be treatment naïve.

A treatment-escalation approach could have the consequence of limiting the number of times a patient could undergo treatment on successive reinfections. Additionally, these retreatment regimens often are more expensive, resulting in further cost barriers for payors approving retreatment for individuals with HCV reinfection. In contrast, demonstrating efficacy of a less costly short-course regimen would support increased access to initial and retreatment

TABLE Characteristics of Initial Infection, Treatment, and De Novo Retreatment

Cases	Initial Genotype	FibroScan Score, kPa	Initial DAA Treatment (wk)	Initial DAA SVR, wk	Evidence of Reinfection	Risk Factors	Reinfection Genotype	Reinfection Treatment (wk)	Final SVR, wk
1	1a	5.6	ledipasvir/ sofosbuvir (8)[a]	24	Viremic	Injection drug use	1a	ledipasvir/ sofosbuvir (8)	12
2	3	4.7	sofosbuvir/ velpatasvir (12)	12	Viremic; change in genotype	Injection drug use	1a	ledipasvir/ sofosbuvir (8)	24
3	2	4.9	sofosbuvir/ velpatasvir (12)	24	Viremic; change in genotype	Intransal drug use	1a	ledipasvir/ sofosbuvir (8)	12

Abbreviations: DAA, direct-acting antiviral; SVR, sustained virologic response.
[a]Initial infection was treated with inteferon for 76 weeks prior to initial DAA treatment.

courses for PWID. The implications of enabling improved access to care is essential in the setting of the ongoing opioid epidemic in the United States.

Given the perspective that the virus should be considered treatment naïve for patients who become reinfected, we describe here 3 cases of patients previously achieving sustained virologic response (SVR) being retreated with the cost-effective 8-week regimen of ledipasvir/sofosbuvir following reinfection.

CASE REPORTS

Case 1

A 59-year-old male presented for his third treatment course for HCV genotype 1a. The patient initially underwent 76 weeks of interferon-based HCV treatment in 2007 and 2008, from which he was determined to have achieved SVR in 24 weeks (SVR24) in April 2009. His viral load remained undetected through February 2010 but subsequently had detectable virus again in 2011 following relapsed use of alcohol, cocaine, and injection drugs. The patient elected to await approval of DAAs and eventually completed an 8-week regimen of ledipasvir/sofosbuvir from May to July 2016, achieving SVR24 in December 2016. The patient's viral load was rechecked in October 2018 and he was again viremic following recent IDU, suggesting a second reinfection.

In preparation for his third HCV treatment, the patient was included in shared decision making to consider retreating his de novo infection as treatment naïve to provide a briefer (ie, 8 weeks) and more cost-effective treatment given his low likelihood of advanced fibrotic liver disease—his FibroScan score was 6.5 kPa, whereas scores ≥ 12.5 kPa in patients with chronic HCV suggest a higher likelihood of cirrhosis.[10] At week 4, the patient's viral load was undetected, he completed his 8-week regimen of ledipasvir/sofosbuvir as planned and achieved SVR12 (Table). He had reported excellent adherence throughout treatment with assistance of a pill box and validated by a reported pill count.

Case 2

A 32-year-old male presented with HCV genotype 1a. Like case 1, this patient had a low FibroScan score of 4.7 kPa. He was previously infected with genotype 3 and completed a 12-week course of sofosbuvir/velpatasvir in November 2016. He achieved SVR12 as evidenced by an undetected viral load in February 2017 despite questionable adherence throughout and relapsed use of heroin by the end of his regimen. He continued intermittent IDU and presented in October 2018 with a detectable viral load, now with genotype 1a. The patient similarly agreed to undergo an 8-week regimen of ledipasvir/sofosbuvir, considering his de novo infection to be treatment naïve. His viral load at treatment week 3 was quantitatively negative while qualitatively detectable at < 15 U/mL. He completed his treatment course in March 2019 and was determined to have achieved SVR24 in September 2019.

Case 3

A 51-year-old male presented with a history of HCV genotype 1a and a low FibroScan

score (4.9 kPa). The patient was previously infected with genotype 2 and had achieved SVR24 following a 12-week regimen of sofosbuvir/velpatasvir in 2017. The patient subsequently was reinfected with genotype 1a and completed an 8-week course of ledipasvir/sofosbuvir in May 2019. The patient had his SVR12 lab drawn 9 days early and was undetectable at that time. He reported 0 missed doses during treatment and achieved an undetected viral load by treatment week 4.

DISCUSSION

We demonstrate that HCV reinfection after treatment with previous interferon and/or DAA-based regimens can be treated with less costly 8-week treatment regimens. Current guidelines include a statement allowing for reinfected patients to follow initial treatment guidelines, but this statement has previously lacked published evidence and may be overlooked by HCPs who refer to recommendations for treatment-experienced patients. Given the increasing likelihood of HCPs encountering patients who have become reinfected with HCV after achieving SVR from a DAA regimen, further delineation may be needed in the recommendations for treatment-experienced patients to highlight the important nuance of recognizing that reinfections should follow initial treatment guidance.

While all 3 of these cases met criteria for the least costly and simplest 1 pill once daily 8-week regimen of ledipasvir/sofosbuvir, patients requiring retreatment with alternative genotypes or evidence of advanced fibrotic liver disease could benefit from a similar approach of using the least expensive and/or shortest duration regimen for which they meet eligibility. With this approach, coverage could be further expanded to the PWID population to help limit HCV transmission amid the opioid crisis.[1]

Studies have established that PWID are able to achieve similar SVR efficacy rates similar to that of the general population when treated in the setting of an interdisciplinary treatment team that offers collaborative management of complex psychosocial comorbidities and harm reduction strategies.[11,12] These integrative patient-centric strategies may include personalized behavioral health pretreatment evaluations, access to substance use treatment, harm reduction counseling, needle exchange programs, and close follow-up by a case manager.[2,13] Current DAA regimens combined with 1 or more of these strategies have demonstrated SVR12 rates of 90 to 95% for initial treatment regimens.[11] These high SVR12 rates were even achieved in a recent study in which 74% (76/103) of participants had self-reported IDU within 30 days of HCV treatment start and similar IDU rates throughout treatment.[12] A meta-analysis, including real-world studies of DAA treatment outcomes yielded a pooled SVR of 88% (95% CI, 83-92%) for recent PWID and 91% (95% CI, 88-95%) for individuals using opiate substitution therapy (OST).[14] Additionally, linking PWID with OST also reduces risk for reinfection.[14,15]

For any patient with detectable HCV after completing the initial DAA regimen, it is important to distinguish between relapse and reinfection. SVR12 is generally synonymous with a clinical cure. Patients with ongoing risk factors posttreatment should continue to have their HCV viral load monitored for evidence of reinfection. Patients without known risk factors may benefit from repeat viral load only if there is clinical concern for reinfection, for example, a rise in liver enzymes.

We have shown that patients with ongoing risk factors who are reinfected can be treated successfully with cost-effective 8-week regimens. For comparison this 8-week regimen of ledipasvir/sofosbuvir has an average wholesale price (AWP) of $28,800, while alternative regimens approved for treatment-naïve patients vary in AWP from $31,680 to $43,200, and regimens approved for retreatment of DAA failures have an AWP as high as $89,712.

An 8-week treatment regimen for both initial and reinfection regimens affords many advantages in medication adherence and both medication and provider resource cost-effectiveness. First, new HCV reinfections are disproportionally younger individuals often with complex psychosocial issues that impact retention in treatment. An 8-week course of treatment can be initiated concurrently with substance abuse

treatment programs, including intensive outpatient programs and residential treatment programs that are usually at least 28 days. Many of these programs provide aftercare options that would extend the entire course of treatment. These opportunities afford individuals to receive HCV treatment in a setting that supports medication adherence, sobriety efforts, and education on harm reduction to reduce risk for reinfection.

Finally, statistical models indicate eradication of HCV will require scaling up the treatment of PWID in conjunction with harm reduction strategies such as OST and needle exchange programs.[16] In contrast, there are low risks associated with retreatment given these medications are well-tolerated, treatment of PWID lowers the risk of further HCV transmission, and the understanding of these reinfections being treatment naïve disavows concerns of these patients having resistance to regimens that cleared their prior infections. The opportunity to provide retreatment without escalating regimen complexity or cost increases access to care for a vulnerable population while aiding in the eradication of HCV.

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Disclaimer

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