Care of Patients Following Cure of Hepatitis C Virus Infection

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Abstract: The vast majority of persons with chronic hepatitis C virus (HCV) infection will achieve virologic cure with the current direct-acting antiviral therapies. Prevention of reinfection is an important aspect of postcure management and key to the elimination of HCV infection globally. Equally important aspects of postcure care are the prevention of liver disease progression and the management of complications in patients who have significant fibrosis at the time of achieving cure. Patients with advanced fibrosis need to remain under surveillance for liver complications, including hepatocellular carcinoma. All patients are potentially at risk for liver disease progression if other factors causing liver injury are present, such as harmful levels of alcohol use or risk factors for fatty liver including obesity, diabetes, and other metabolic comorbidities. Fatty liver is a particular threat to the long-term well-being of patients after HCV cure due to the high prevalence of its risk factors in this population. Strong counseling messages and ongoing monitoring are key.

Keywords
Sustained virologic response, reinfection, cirrhosis, hepatocellular carcinoma, decompensation

Since the approval of the first direct-acting antiviral (DAA) agent in late 2014, an increasing number of persons have gained access to hepatitis C virus (HCV) treatment and have achieved cure. Although much needs to be done to achieve elimination of HCV infection within the United States[1] and globally, there is no doubt that the advances in HCV therapeutics have provided substantial health benefits. The HCV care cascade (Figure) highlights important areas of deficiency that need to be improved upon to achieve elimination.[2] First and foremost is the identification of infected persons. There are 2 strategies that need to be implemented: screening persons with risk factors (eg, those with a history of injection drug use or exposures via contaminated blood or injections in health care settings, especially in developing countries), and screening the Baby Boomer cohort (persons born between 1946 and 1964). Once HCV-infected persons are identified, linkage to an HCV health care provider to facilitate additional testing and treatment is paramount. Prior to treatment, this provider will determine the stage of disease,

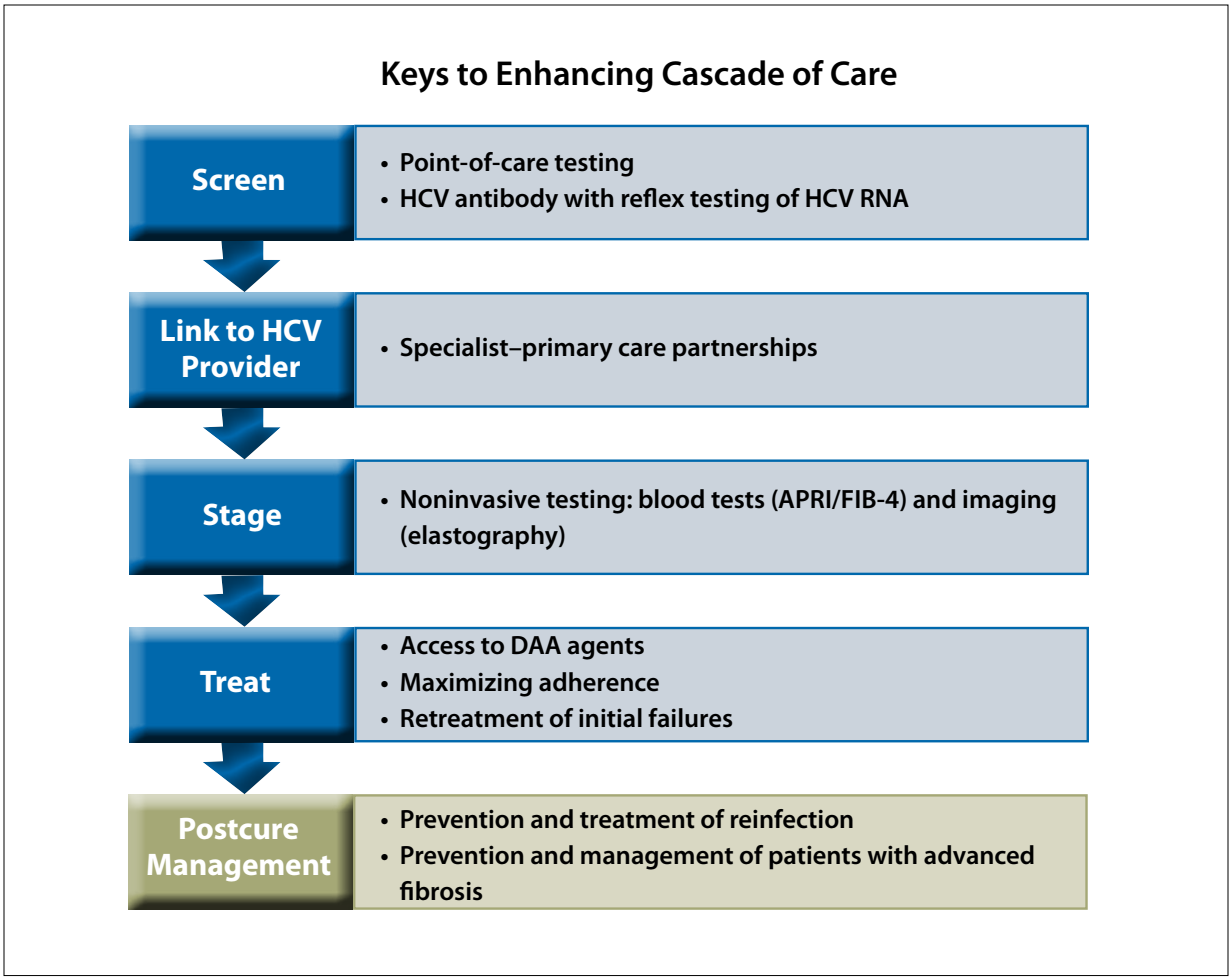

Figure. If the goal of HCV elimination is to be achieved, all persons with HCV infection need to be identified, evaluated, treated, and, if appropriate, managed after cure. For each step in the cascade of care, interventions can be considered to maximize success.

APRI, Aspartate Aminotransferase to Platelet Ratio Index; DAA, direct-acting antiviral; FIB-4, Fibrosis-4 Index; HCV, hepatitis C virus.

the presence of liver comorbidities (eg, alcohol use, metabolic fatty liver), and relevant issues related to HCV treatment (eg, drug interactions, coinfections). Although the achievement of virologic cure may be viewed as the end of the cascade of care, important final steps remain—the prevention of reinfection and the management of liver-related risks after cure—which are the focus of this article.

Defining Cure for Hepatitis C Virus Infection

In the registration trials leading to approval of HCV therapies, an HCV RNA level below the limit of quantitation 12 weeks after completing the therapy defined treatment success—that is, sustained virologic response (SVR) 12. This time point is highly correlated with SVR24.[3] However, because relapses beyond SVR12 have rarely been reported, treatment guidelines recommend confirming cure by testing for HCV RNA at 24 to 48 weeks after the end of treatment (SVR24 or SVR48).[4,5] Late relapse, when it occurs, typically happens between 12 and 24 weeks posttreatment. In a large study evaluating late relapse, 12 of 3004 patients with SVR12 were found to be HCV RNA–positive between weeks 12 and 24. Interestingly, using phylogenetic sequencing, it was determined that 7 of 12 relapses were actually new infections and 5 of 12 were true relapses. Thus, the rate of late relapse (beyond SVR12) was 0.2%.[6] Very late relapse, beyond 24 weeks posttreatment, is exceedingly rare.[7] However, the takeaway point is that the determination of cure requires repeat HCV RNA testing beyond 12 weeks posttreatment. I recommend obtaining both SVR12 and SVR48. If HCV RNA is undetectable at the later time point, the patient can be confidently informed that he or

she is cured, and no further testing is indicated unless the patient is at risk for reinfection.

Risk of Reinfection and Who Needs Serial Hepatitis C Virus RNA Testing Postcure

The presence of antibody does not protect against HCV infection, and persons who have been cured of HCV can become reinfected if reexposed. In a meta-analysis of studies evaluating HCV recurrence after SVR, HCV-monoinfected patients at low risk for recurrence had a 1% rate of HCV RNA positivity at 5 years post-SVR compared with 11% in patients at high risk (eg, injection drug users, prisoners).[8] Studies focusing on persons who inject drugs report reinfection rates of approximately 2% to 3% annually among persons who achieve SVR.[9-11] Another high-risk group is HIV-infected men who have sex with men (MSM), in whom the reported rates of reinfection are 3% per year.[12] For all persons at risk for HCV reinfection, regular monitoring using HCV RNA is needed. For persons who are engaged in injection drug use and for HIV-positive MSM, testing at least annually, or if alanine aminotransferase levels increase, is recommended.[4,5] Another group at risk for HCV infection after cure is MSM on preexposure prophylaxis for HIV, leading experts to recommend regular monitoring for HCV infection in this group as well.[13]

Reinfection is defined as the detection of HCV RNA after SVR12. The presence of a different genotype, or a phylogenetically distant strain if the genotype is the same, confirms reinfection, although the test for the latter scenario is not commercially available. For persons identified as being reinfected based on HCV RNA testing, consideration of DAA therapy is necessary if they do not clear the infection spontaneously (typically evident within 6 months of exposure).[14,15] In clinical scenarios where there is a high risk of transmission to others, it may be prudent to treat the infection immediately rather than wait to see if spontaneous clearance occurs.

Counseling Messages for Patients Who Achieve Hepatitis C Virus Cure

The achievement of HCV cure substantially reduces the risk of liver disease progression, but some patients remain at risk. Moreover, liver injury can occur from other causes before and after cure, specifically related to alcohol use or superimposed metabolic fatty liver. Thus, it is important to provide counseling messages to patients for lifelong liver health.[16] While safe levels of alcohol intake for otherwise healthy men and women are fewer than 4 and 2 drinks per day, respectively, these levels were defined in persons without known preexisting liver disease.[17] Thus, for patients with HCV infection who have underlying fibrosis, these levels cannot be considered safe, and abstinence is recommended.[4] For patients with no or minimal fibrosis, counseling messages should stress safe levels of alcohol use (≤2 drinks per day for men and ≤1 drink per day for women[18]), although a recent study suggests that even lower limits should be adopted.[19] Marijuana may also have profibrogenic potential in patients with fibrosis, so daily use is not recommended.[20] Fatty liver from metabolic causes (obesity, diabetes) is a major concern given the epidemic of these comorbidities in the population. Aiming for the ideal body weight and for control of metabolic cofactors is very important for maintenance of liver health after cure. Finally, avoidance of potentially hepatotoxic medications, herbal products, or over-the-counter medications should be mentioned to patients. Safe levels of acetaminophen are 2 g or less.

Specialist Care After Hepatitis C Virus Cure

Although patients receive HCV treatment from a wide array of providers, from primary care physicians to specialists, patients with or at risk for liver-related complications should be considered for follow-up care by a gastroenterologist or hepatologist. Patients with advanced fibrosis (F3 or F4) on staging tests prior to HCV treatment are at risk for hepatocellular carcinoma (HCC) and decompensation, even with cure.[21] These patients should undergo surveillance with ultrasound and α-fetoprotein every 6 months.[4] Also, for patients with cirrhosis, screening endoscopy is indicated, with the subsequent frequency of endoscopies dictated by the initial findings.[4,5] Additionally, sodium, creatinine, total bilirubin, international normalized ratio, and albumin should be monitored to determine Model for End-Stage Liver Disease (MELD) and Child-Pugh scores, and can be used to monitor serial progression or improvement in patients with cirrhosis.

For patients with intermediate levels of fibrosis (F2), the decision for specialist care vs primary care follow-up should take into consideration the presence of cofactors for liver disease progression. For example, patients with coexisting alcohol-associated liver disease or fatty liver disease may progress to more advanced fibrosis despite HCV cure and may be best kept in specialist care for monitoring and management.

An essential element in triaging patients between primary care and specialty care is knowing the stage of liver disease. To be reliable, noninvasive testing of the fibrosis stage must be performed prior to HCV treatment. Noninvasive tests reflect the combined effects of inflammation and fibrosis, and appropriate cutoffs to define advanced fibrosis, including cirrhosis,

Table. Summary of Recommendations for Persons Who Achieve SVR12

All Persons Who Achieve SVR12	• Recheck HCV RNA at SVR24 or beyond (once).
	• Optimize metabolic profile to avoid development of fatty liver.
	  • Control diabetes.
	  • Strive for ideal body mass index.
	  • Treat hyperlipidemia.
	• Avoid use of daily marijuana.
	• Avoid use of potentially hepatotoxic medications.
	• Alcohol abstinence may be ideal; safe levels for women and men should be used.
	• Avoid repeat HCV RNA testing (unless at risk as stated below).

Persons at Risk for Reinfection[a]	• Perform at least annual HCV RNA testing. • Counsel patients on practices to avoid reinfection.
Additional Recommendations for Persons With Advanced Fibrosis (F3/F4) Pre- or Post-SVR12	• Perform abdominal imaging and AFP testing every 6 months. • Obtain liver function tests/MELD score every 6-12 months. • Perform upper endoscopy if cirrhosis is present. • Conduct clinical evaluation for progression to cirrhosis or decompensation.

[a]Persons who inject drugs and men who have sex with men.

AFP, α-fetoprotein; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; SVR, sustained virologic response.

were developed and validated in untreated patients. After HCV cure, inflammation is reduced, and, thus, most noninvasive tests performed at SVR12 show an improvement. However, these noninvasive measures do not accurately reflect fibrosis levels postcure. Therefore, it is critical to use pretreatment staging information to determine post-SVR follow-up. For patients with discordant pretreatment staging data or for those in whom pretreatment staging information is not available, I recommend initial staging with elastography post-SVR, and if the results meet the criteria for cirrhosis (>12.5 kPa), then the patient should be treated accordingly. If the results are not consistent with cirrhosis, the patient may still have advanced fibrosis (F3 or F4), so liver biopsy may be considered in select patients to exclude an advanced stage. If biopsy is not an option, the conservative approach is to assume that the stage is advanced and continue surveillance for HCC and fibrosis progression.

Assessing Fibrosis Regression Vs Progression After Cure of Hepatitis C Virus Infection

Natural history studies have established that regression of fibrosis can occur if the cause of the chronic liver injury is removed.[22,23] This is true for patients with chronic HCV infection, and even cirrhosis regression has been documented. In a paired biopsy study (approximately 5 years apart) of 38 patients with cirrhosis who achieved SVR, regression was observed in 61%, and collagen content, assessed morphometrically, decreased in 89%.[24] Currently, liver biopsy is rarely used to stage fibrosis, as noninvasive measures such as hepatic elastography are available. Serial measurements of liver stiffness show that values decrease dramatically during treatment and in the early SVR period, but then plateau or decrease more slowly. For example, in a study of 112 patients with serial measurements of liver stiffness, the mean baseline liver stiffness was 12.3 kPa (range, 9.0-17.8 kPa), with the sharpest decline occurring by the end of treatment (-2.5 kPa) and at SVR24 (-3.7 kPa) and then slower thereafter (-1.2 kPa between years 1 and 5 posttreatment).[25] This pattern reflects an initial improvement in stiffness related to reduction in necroinflammation and later a slower decline reflective of fibrosis remodeling and regression.

Although the majority of patients, especially those without cirrhosis at baseline, will show evidence of fibrosis regression as time increases from HCV cure, some patients can progress. This may be related to concurrent alcohol use or the presence of nonalcoholic fatty liver disease. Alternatively, genetic or immunologic factors may contribute to the risk of liver complications after cure.[26] Given this possibility, counseling patients on measures for maintaining good liver health is important (Table). Additionally, periodic assessment of fibrosis severity using elastography may be beneficial. Post-SVR, the absolute value for liver stiffness is difficult to interpret and should not be relied upon to provide accurate staging information, although trends in liver stiffness values are helpful. For example, liver stiffness values that are stable or decreasing would be indicative of stable or reduced fibrosis, whereas an increase in liver stiffness values may reflect increased necroinflammation or fibrosis and promote further investigation into the cause. Importantly, even if post-SVR elastography measures

show reversal of advanced fibrosis to levels indicative of F2 or less, this should not lead to a discontinuation of surveillance for HCC.[4,5]

Risks for Liver Complications in Patients Who Achieve Cure of Hepatitis C Virus Infection

The rationale for keeping cured patients under the care of a specialist is to prevent and manage the complications of liver disease that can occur in spite of cure. The patients at highest risk for liver-related complications are those with cirrhosis at the time of cure. Longitudinal studies of DAA-treated patients with cirrhosis show a significant reduction in the risk of liver-related mortality for decompensation and HCC,[27,28] but risk persists. Patients with decompensated cirrhosis are at a higher risk of future liver complications than those with compensated cirrhosis. For patients with decompensated cirrhosis who achieve cure, approximately 75% will experience an improvement in MELD and Child-Pugh scores, but only 25% will improve to compensated cirrhosis.[29] Thus, most patients with decompensated cirrhosis remain at risk for liver complications and need close monitoring. Consideration of liver transplantation in appropriate patients is critical.

Overall, an approximately 70% reduction in HCC occurs with cure,[27,28] with the rate in patients with compensated cirrhosis who have achieved HCV cure being 2% per year compared with 6% in those who have not achieved HCV cure.[28] Factors associated with the development of HCC after cure are an active area of study, but older age, more advanced cirrhosis, diabetes, and alcohol use have been linked with HCC risk most consistently.[27,28,30] These associations highlight the importance of minimizing cofactors for liver disease progression, such as alcohol use or concurrent metabolic risks for fatty liver. Although there was some initial concern raised regarding whether HCC risk was negatively impacted by DAA therapy, multiple studies have established that DAA therapy has a significant benefit in terms of reducing HCC risk.[31] As previously highlighted, guidelines recommend that patients with advanced fibrosis (F3 or F4) should undergo lifelong surveillance for HCC with biannual abdominal imaging with or without α-fetoprotein monitoring.[4,5]

Summary

As we work toward ensuring that each HCV-infected person is identified and treated, the importance of effective management after cure must not be neglected. The goals are 2-fold: to prevent reinfection and to prevent and treat complications of liver disease. Critical to appropriate triage of patients is accurate staging of liver fibrosis prior to cure. Patients with cirrhosis may develop HCC and other liver-related complications postcure, although the rates are significantly reduced by clearance of HCV. Specialists play a key role in educating nonspecialists regarding appropriate follow-up postcure and in caring for patients with advanced fibrosis and liver-related complications.

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