ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of Patients Who Have Achieved Sustained Virologic Response for Hepatitis C Virus Infection

Paul J. Pockros, MD
Director, Liver Disease Center and SC Liver Research Consortium, Scripps Clinic
Clinical Director of Research, Scripps Translational Science Institute
La Jolla, California

G&H How often is sustained virologic response achieved with the current hepatitis C virus treatment options?

PP There are multiple direct-acting antiviral (DAA) regimens currently approved by the US Food and Drug Administration. Most of these hepatitis C virus (HCV) regimens are effective in treatment-naive patients after 8 weeks of use, although patients who are treatment-experienced or who have cirrhosis need 12 weeks of treatment. Sustained virologic response (SVR), or cure, occurs in roughly 98% of patients with compensated liver disease. However, there are still 2 patient subgroups that have lower SVR rates: patients with decompensated cirrhosis (ie, Child-Pugh B or C cirrhosis) and patients with HCV genotype 3 infection. SVR rates are approximately 85% in the former group and 85% to 95% in the latter group (with treatment-naive patients at the higher end of that range and treatment-experienced patients at the lower end).

G&H Once a patient achieves SVR, is periodic confirmation ever needed later on?

PP According to the current American Association for the Study of Liver Diseases (AASLD) guidelines, once SVR12 or 24 is achieved (ie, HCV RNA below the lower level of quantification 12 or 24 weeks after therapy), no verification is needed at later time points unless the patient's liver test results become abnormal. There are some data suggesting that 1 or 2 in 1000 patients do not maintain SVR for more than a year (ie, late relapse), but this is such an unusual event that it does not need to be tested for unless liver test results become abnormal. Thus, the risk of losing SVR is very remote. There is a greater risk of becoming reinfected with HCV, especially for patients who are intravenous drug users. Such patients should undergo periodic monitoring of their HCV RNA levels. Other patients do not need periodic testing for HCV reinfection.

G&H Is routine follow-up needed for screening of esophageal varices in all patients who have achieved SVR?

PP A number of gastroenterologists think that once patients achieve SVR, they do not require any monitoring and can be discharged from physician care. However, this is not necessarily true. For example, according to the AASLD practice guidelines for esophageal varices that were published at the end of 2017, patients who have achieved SVR should undergo endoscopic monitoring for esophageal varices if their liver stiffness (or transient elastography) measurement exceeds 20 kPa or their platelet count is below 150,000. However, this screening is not needed if the platelet count is—or increases to—150,000 or higher and the liver stiffness measurement is—or decreases to—less than 20 kPa after achieving SVR, regardless of whether cirrhosis is present. If the patient has small varices and ongoing liver injury, he or she should undergo endoscopic monitoring annually. However, if the patient has small varices but no ongoing liver injury—for example, the patient has HCV infection and is cured—then endoscopy can be repeated in 2 years. Endoscopy should also be repeated in 2 years if the patient has no varices but ongoing liver injury. Finally, if the patient has no varices as well as no ongoing liver injury, endoscopic monitoring for esophageal varices can be performed every 3 years.

G&H Should patients who have achieved SVR and had less-than-advanced fibrosis undergo screening for hepatocellular carcinoma?

PP According to the current guidelines published by the American Gastroenterological Association, patients with less-than-advanced fibrosis (ie, F0-F2 fibrosis) who have a platelet count over 150,000 and a liver stiffness measurement less than 9.5 kPa do not need to continue undergoing imaging endoscopies to screen for hepatocellular carcinoma (HCC). In other words, if patients do not have cirrhosis or advanced fibrosis, HCC monitoring is not required unless they develop risk factors from a different cause, such as nonalcoholic steatohepatitis or alcoholic liver disease.

G&H Is HCC screening needed in patients who experience regression of advanced fibrosis or cirrhosis after achieving SVR?

PP Currently, there is no clear guidance on this issue. The AASLD guidelines, as well as the guidelines from the European Association for the Study of the Liver, are very cautious, stating that there is no clear indication if the risk for HCC is eliminated when there is regression of fibrosis or cirrhosis, and if the risk does go away, when screening can be stopped. Thus, based upon an abundance of caution, for now doctors should not use liver stiffness measurement or noninvasive markers such as the Aspartate Transaminase–to-Platelet-Ratio Index to determine whether to stop screening for HCC.

My colleagues and I have been interested in this issue and, for a number of years, have been following a cohort of 240 patients who had advanced fibrosis or cirrhosis before they were cured of HCV infection. Follow-up has consisted of liver stiffness measurement, noninvasive laboratory tests, endoscopy, and screening for HCC, as well as liver biopsies in a subgroup of these patients, and these data have been compiled and submitted for publication. My colleagues and I had hoped that reversal of fibrosis (seen via liver stiffness measurement) could determine whether a patient no longer has to be screened for HCC. In an abstract by Crissien and colleagues, we documented liver stiffness reversal in approximately 60% of patients with cirrhosis within 2 years of being cured. In addition, multiple published studies have confirmed that liver stiffness measurement can show reversal of advanced fibrosis or cirrhosis by at least 1 stage over 1 year or more after cure using DAA therapies. My colleagues and I have been able to biopsy a subgroup of that population and analyze those biopsies with histology and morphometry. Morphometry, a quantitative measure of collagen in liver biopsies, is also a quantitative measure of fibrosis and confirmed that fibrosis regression does occur after SVR via DAA therapies in our study population. However, when routine histology is used as the measure, it is not possible to correctly classify which patients have gone below F3 and F4 fibrosis based upon liver stiffness results. In other words, liver stiffness will overestimate the reversal of fibrosis as assessed by pathologists examining liver biopsies. Thus, a doctor may think that patients have no fibrosis or minimal fibrosis, but many of them actually still have F3 or F4 fibrosis based upon their liver biopsy. According to interim results of our ongoing trial (ie, the first 84 patients being followed), liver stiffness cannot be used to safely determine when a patient is finished with HCC screening.

G&H What is the current understanding of the association between DAA use and HCC (recurrent or de novo)?

PP The possible relationship between DAA agents and the occurrence or recurrence of HCC has been debated for the past year and a half. There have been a number of publications during this time period indicating that there may not actually be a higher risk of HCC recurrence, but that doctors are actually observing what seems to be a higher rate because the patients being treated are at a high risk for HCC in the first place. This issue has not been completely resolved yet. Nevertheless, most centers are now treating patients without fear of HCC recurrence after confirming that complete response to initial HCC treatment is sustained for at least 6 months.

In contrast, multiple studies have confirmed that there is actually a lower risk of de-novo occurrence of HCC after DAA use. The largest study reported to date, conducted by Kanwal and colleagues, showed a markedly decreased rate of HCC in 22,500 HCV-infected veterans who were treated with DAA agents and were monitored carefully for over 2 years after cure. A number of smaller studies from different parts of the world have confirmed this important finding, suggesting that cancer rates are being reduced by curing these patients.

G&H Should patients who have achieved SVR be monitored for reactivation of their hepatitis B virus infection?

PP Hepatitis B virus (HBV) reactivation is a risk during and after DAA therapy in patients who are coinfected with HBV and HCV. Thus, monitoring for HBV reactivation should be performed in any patients who are hepatitis B surface antigen–positive, have HCV infection, and are treated with DAA agents. In addition, the US Food and Drug Administration has recently called

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for monitoring any patients who have positive hepatitis B core antibodies, indicating prior exposure to HBV. The liver enzyme levels of all of these patients should be monitored during therapy and up to 6 months after therapy, according to the current guidelines. This information is now included in black box labelling of all DAA agents. In practical terms, doctors should usually just check liver enzyme levels at week 4 or 8 during therapy and then at SVR12. This is not a trivial issue, as roughly half of all HCV-infected patients in the United States, especially in the Baby Boomer generation, are hepatitis B core antibody–positive.

G&H Do patients who have achieved SVR require monitoring for any other conditions?

PP It is now known that advanced fibrosis or cirrhosis does not reverse after SVR in patients who are developing nonalcoholic fatty liver disease (ie, gaining weight, becoming obese, and developing diabetes), as well as in patients who become alcoholic. In fact, some of these patients can develop subsequent decompensation and worsening liver disease. Because their advanced liver disease is not regressing, ongoing monitoring is required.

G&H Are there any other recommendations or guidelines in terms of following patients after SVR?

PP My colleagues and I typically make sure that these patients have been immunized for hepatitis A and B virus infections. (This is supposed to occur before the initiation of therapy but often does not.) If patients are using β-blockers, there are specific guidelines that should be followed regarding when therapy should be stopped. After achieving SVR, patients still require standard colorectal cancer screening, as with any patients over the age of 50 years. I normally refer patients back to their primary care provider for their other health care needs.

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Suggested Reading

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