Editorials

Family Physicians Can Manage Adults with Hepatitis C

Richard R. Andrews, MD, MPH
HOPE Clinic, Houston, Texas

Hepatitis C virus (HCV) causes the only chronic viral disease that is consistently curable with medication. However, it causes more deaths in the United States than the next 60 reportable infections combined, including human immunodeficiency virus (HIV), tuberculosis, and pneumococcal disease.[1]

The epidemiology of HCV infection is complex and differs in key ways from hepatitis B and HIV infections. HCV is not commonly transmitted through sex, but it is far more infectious than hepatitis B virus and HIV when transmitted via injection and intranasal drug use.[2] Despite effective treatments, the incidence of HCV infection is increasing in the United States. High-risk groups include persons born between 1945 and 1965, those who use certain illicit drugs, and those who are incarcerated.[2]

Sustained viral response (SVR), defined as the persistent absence of detectable virus in the blood, is the goal of hepatitis C treatment. The term SVR12 is used when SVR occurs 12 weeks or more after completion of antiviral treatment. SVR12 is widely accepted as reflecting the eradication of HCV from the body, as opposed to mere suppression. Medications can eliminate HCV because the virus does not have a hidden reservoir in the body, unlike hepatitis B virus.[3]

SVR was first achieved in 1986 using interferon; ribavirin (Virazole) was added in later regimens. Complex treatment protocols often caused severe adverse effects and were less effective against certain viral genotypes.[4] Currently recommended treatments use direct-acting antivirals. When used for the specified durations, these medications consistently achieve SVR12 rates at or above 90%, and the newest agents are effective against all HCV genotypes[5-10] *(Table 1[11])*.

SVR can reverse liver fibrosis, and even cirrhosis can start to reverse after viral hepatitis is cured.[12] It is not known whether SVR achieved with direct-acting antivirals reduces the occurrence of hepatocellular carcinoma, but recent evidence is encouraging.[13,14] Reflecting the systemic nature of chronic hepatitis C, persons who achieve SVR have a lower incidence of diabetes mellitus, glomerulonephritis, non-Hodgkin lymphoma, stroke, and other conditions.[15]

It is not clear whether the high cost of direct-acting antivirals is offset by long-term savings related to reduced morbidity and mortality from hepatitis C. Economic estimates vary by health system and by type of study analysis (e.g., whether the study end point is focused on achieving SVR or on post-SVR improvements in HCV-related extrahepatic disease).[16-19] A typical treatment course is one to three pills per day for eight to 12 weeks, and is usually well tolerated. Viral counts are obtained at four weeks to assess effectiveness. A final test is performed 12 weeks or more after the last pill is taken. Guidelines recommend that patients with pretreatment evidence of cirrhosis have lifelong surveillance for hepatocellular carcinoma using liver imaging and α-fetoprotein testing at six-month intervals.[20] Prior HCV infection and treatment do not confer immunity, so patients at high risk of reinfection (e.g., those with active injection or intranasal drug use, sex partners of infected persons) should be screened periodically.[21]

The Centers for Disease Control and Prevention encourages family physicians to treat hepatitis C.[22] Outcomes when primary care physicians prescribe direct-acting antivirals to patients with uncomplicated hepatitis C are comparable to those of subspecialists.[23] Patients with hepatitis C who do not have cirrhosis, or who have compensated cirrhosis, typically respond well to management by primary care physicians. Treatment in patients with decompensated cirrhosis (characterized by the presence of ascites, esophageal varices, or hepatic encephalopathy) is complex. Family physicians should be able to identify these patients and refer them to a gastroenterologist or hepatologist.

Additional content at https://www.aafp.org/afp/2018/1001/p413.html.

Author disclosure: In 2016, Dr. Andrews received compensation for travel expenses to attend a meeting on hepatitis B from Gilead Sciences, Inc., which manufactures drugs used to treat hepatitis C. Dr. Andrews declined an honorarium from Gilead.

TABLE 1

Direct-Acting Antiviral Agents for Hepatitis C Treatment–Naive Patients Without Cirrhosis

Drug	HCV genotypes	Dosage	Treatment duration	Cost*†
Elbasvir/grazoprevir (Zepatier)	1 and 4	One 50-mg/100-mg tablet daily with or without food	12 weeks	$54,000
Glecaprevir/pibrentasvir (Mavyret)	All	Three 100-mg/40-mg tablets once daily with food	Eight weeks	$26,000
Ledipasvir/sofosbuvir (Harvoni)	1a, 1b, 4, 5, and 6	One 90-mg/400-mg tablet daily with or without food	Genotype 1a or 1b: eight weeks in nonblack patients who do not have human immunodeficiency virus infection if HCV RNA < 6 million IU per mL; 12 weeks in black patients or if HCV RNA ≥ 6 million IU per mL Genotypes 4 to 6: 12 weeks	$62,000 to $93,000 depending on treatment duration
Sofosbuvir/velpatasvir (Epclusa)	All	One 400-mg/100-mg tablet daily with or without food	12 weeks	$74,000

HCV = hepatitis C virus.

*—Estimated retail price for full treatment course based on information obtained at http://www.goodrx.com (accessed June 12, 2018).
†—See eTable B for information about pharmaceutical assistance programs for uninsured and underinsured patients.

Information from reference 11.

Training and support are available for family physicians who wish to treat patients with hepatitis C. A reasonable initial approach would be to complete one or more self-paced online study courses *(eTable A)*. Because some insurers require consultation with a subspecialist before they will cover a direct-acting antiviral, use of a telehealth program such as Project ECHO (Extension for Community Healthcare Outcomes) can be helpful. These resources provide real-time affordable access to subspecialist consultation using a case presentation format.

By reducing the prevalence of HCV infection, direct-acting antivirals are a key tool in the treatment-as-prevention approach.[24] They are a necessary—but not sufficient—component of any worldwide program to eliminate HCV. As with many treatments, these medications are most effective when combined with evidence-based public health measures, such as accessibility of clean needles in exchange for used needles among persons who inject drugs.[25]

Although the new direct-acting antivirals to treat hepatitis C are expensive, especially in the United States, there are multiple pharmaceutical assistance programs to ensure access to therapy for all patients, regardless of their ability to pay *(eTable B)*. By participating in treatment programs and advocating for effective policy decisions, such as needle exchanges, family physicians can have a major impact on the hepatitis C epidemic.

Address correspondence to Richard R. Andrews, MD, MPH, at randrews@hopechc.org. Reprints are not available from the author.

References

1. Ly KN, Hughes EM, Jiles RB, Holmberg SD. Rising mortality associated with hepatitis C virus in the United States, 2003-2013. *Clin Infect Dis*. 2016;62(10):1287-1288.
2. Hall EW, Rosenberg ES, Sullivan PS. Estimates of state-level chronic hepatitis C virus infection, stratified by race and sex, United States, 2010. *BMC Infect Dis*. 2018;18(1):224.
3. Kim CW, Chang KM. Hepatitis C virus: virology and life cycle. *Clin Mol Hepatol*. 2013;19(1):17-25.
4. Strader DB, Seeff LB. A brief history of the treatment of viral hepatitis C. *Clin Liver Dis*. 2012;1(1):6-11.
5. Geddawy A, Ibrahim YF, Elbahie NM, Ibrahim MA. Direct acting anti-hepatitis C virus drugs: clinical pharmacology and future direction. *J Transl Int Med*. 2017;5(1):8-17.

6. Sulejmani N, Jafri SM. Grazoprevir/elbasvir for the treatment of adults with chronic hepatitis C: a short review on the clinical evidence and place in therapy. *Hepat Med*. 2018;10:33-42.
7. Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol*. 2017;67(2):263-271.
8. 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;65(4):1094-1103.
9. Gayam V, Khalid M, Mandal AK, et al. Direct-acting antivirals in chronic hepatitis C genotype 4 infection in community care setting. *Gastroenterology Res*. 2018;11(2):130-137.
10. Liu CH, Sun HY, Liu CJ, et al. Generic velpatasvir plus sofosbuvir for hepatitis C virus infection in patients with or without human immunodeficiency virus coinfection. *Aliment Pharmacol Ther*. 2018;47(12):1690-1698.
11. American Association for the Study of Liver Diseases; Infectious Diseases Society of America. Testing, evaluation, and monitoring of hepatitis C. September 21, 2017. http://www.hcvguidance.org. Accessed June 11, 2018.
12. Hytiroglou P, Theise ND. Regression of human cirrhosis: an update, 18 years after the pioneering article by Wanless et al. [published online ahead of print March 27, 2018]. *Virchows Arch*. https://link.springer.com/article/10.1007%2Fs00428-018-2340-2. Accessed June 12, 2018.
13. Calvaruso V, Cabibbo G, Cacciola I, et al. Incidence of hepatocellular carcinoma in patients with HCV-associated cirrhosis treated with direct-acting antiviral agents [published online ahead of print April 12, 2018]. *Gastroenterology*. https://www.gastrojournal.org/article/S0016-5085(18)30441-4/pdf. Accessed June 12, 2018.
14. Konjeti VR, John BV. Interaction between hepatocellular carcinoma and hepatitis C eradication with direct-acting antiviral therapy. *Curr Treat Options Gastroenterol*. 2018;16(2):203-214.
15. Mahale P, Engels EA, Li R, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. *Gut*. 2018;67(3):553-561.
16. Linas BP, Nolen S. A guide to the economics of hepatitis C virus cure in 2017. *Infect Dis Clin North Am*. 2018;32(2):447-459.
17. Maier MM, Zhou XH, Chapko M, Leipertz SL, Wang X, Beste LA. Hepatitis C cure is associated with decreased healthcare costs in cirrhotics in retrospective Veterans Affairs cohort. *Dig Dis Sci*. 2018;63(6):1454-1462.
18. Younossi ZM, Park H, Dieterich D, Saab S, Ahmed A, Gordon SC. The value of cure associated with treating treatment-naïve chronic hepatitis C genotype 1: are the new all-oral regimens good value to society? *Liver Int*. 2017;37(5):662-668.
19. Cacoub P, Buggisch P, Carrión JA, et al. Direct medical costs associated with the extrahepatic manifestations of hepatitis C infection in Europe [published online ahead of print February 24, 2018]. *J Viral Hepat*. https://onlinelibrary.wiley.com/doi/abs/10.1111/jvh.12881. Accessed June 12, 2018.
20. Costentin C, Layese R, Bourcier V, et al.; ANRS CO12 CirVir group. Compliance with hepatocellular carcinoma surveillance guidelines associated with increased lead-time adjusted survival of patients with compensated viral cirrhosis [published online ahead of print May 2, 2018]. *Gastroenterology*. https://www.gastrojournal.org/article/S0016-5085(18)30488-8/pdf. Accessed June 12, 2018.
21. Falade-Nwulia O, Sulkowski MS, Merkow A, Latkin C, Mehta SH. Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. *J Viral Hepat*. 2018;25(3):220-227.
22. Mitruka K, Thornton K, Cusick S, et al.; Centers for Disease Control and Prevention. Expanding primary care capacity to treat hepatitis C virus infection through an evidence-based model – Arizona and Utah, 2012-2014. *MMWR Morb Mortal Wkly Rep*. 2014;63(18):393-398.
23. Tran TT. Hepatitis C: who should treat hepatitis C virus? The role of the primary care provider. *Clin Liver Dis*. 2018;11(3):66-68.
24. Olafsson S, Tyrfingsson T, Runarsdottir V, et al. Treatment as prevention for hepatitis C (TraP Hep C) - a nationwide elimination programme in Iceland using direct-acting antiviral agents. *J Intern Med*. 2018;283(5):500-507.
25. Bixler D, Corby-Lee G, Proescholdbell S, et al. Access to syringe services programs - Kentucky, North Carolina, and West Virginia, 2013-2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(18):529-532. ■

eTABLE A

Selected Hepatitis C Resources for Physicians

Website	Comments
HCVGuidelines.org (https://www.hcvguidelines.org)	Online, free, self-paced guidance from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America
Hepatitis C Online (https://www.hepatitisc.uw.edu/go/evaluation-treatment/cost-access-medications/core-concept/all)	Free, self-paced online courses with available continuing medical education from the University of Washington and University of Alabama–Birmingham, funded by a grant from the Centers for Disease Control and Prevention
Project ECHO (Extension for Community Healthcare Outcomes; https://echo.unm.edu/)	Free scheduled videoconferences and optional case presentations with subspecialist feedback and continuing medical education from the University of New Mexico, funded by multiple federal, state, and private entities, including the Centers for Disease Control and Prevention
UpToDate (https://www.uptodate.com/home)	Online subscription service with continuing medical education

eTABLE B

Selected Resources for Improving Access to Hepatitis C Medications for Uninsured and Underinsured Patients

AbbVie Patient Support (patient assistance program for Mavyret)

https://www.mavyret.com/hcp/patient-support or (877) 628-9738

Gilead Sciences Support Path (patient assistance program for Epclusa and Harvoni)

http://gilead.com/responsibility/us-patient-access

HepMag: Paying for Hepatitis Treatment (overview and contact information for multiple patient assistance programs)

https://www.hepmag.com/basics/hepatitis-c-basics/paying-hepatitis-c-treatment

Merck Access and Support (patient assistance program for Zepatier)

https://www.merckaccessprogram-zepatier.com

Specialty pharmacies (staff members are familiar with patient assistance programs for acquiring direct-acting antivirals and typically will do most of the required paperwork on behalf of the patient and physician, and arrange delivery and tracking)

Note: One or more office staff members can be assigned to process applications for the programs listed above. Approval can take several weeks, but the paperwork is less cumbersome than might be expected, especially for pharmaceutical patient assistance programs.