Hepatitis C Virus Standard of Care: A Rapid Evolution and Considerations for Acute Hepatitis C Virus

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Hepatitis C virus (HCV) therapy from the first interferon studies, which were given every day to three times a week to once weekly, evolved slowly over the late 1990s and early 2000s. Treatment was fraught with side effects from both interferon and ribavirin, but clinicians and patients persevered because a cure was a possibility in 30% to 50% of those treated.

The first direct-acting antiviral (DAA) therapies were the protease inhibitors, but again they were combined with interferon and ribavirin, and despite higher sustained virologic responses (SVRs), important lessons were learned about DAA side effects. It was not until sofosbuvir (SOF) was approved in December 2013 that the possibility of all-oral combinations came to fruition, and from that time, the evolution of HCV standard of care (SOC) evolved at a breakneck speed for the next several years. We have now

reached a stage where no further HCV therapeutic developments are on the horizon, and SOC is stable.

Current SOC is highly dependent on availability and resources. With those caveats in mind, the current SOC is efficacy with SVR >95% for treated patients, with minimal side effects. Several all-oral DAA combination therapies are available and can be classified by pan-genotype therapies (SOF/velpatasvir, glecaprevir/pibrentasvir) and non-pan-genotype combinations (elbasvir/grazoprevir, SOF/ledipasvir [LED]). Determination of cirrhosis prior to treatment may be required for some therapies because shorter durations of therapy (8 weeks) may be dependent on non-cirrhosis status. Although other combinations are available (e.g., SOF/daclatasvir) and may be used in some geographies or clinical situations, those therapies listed in this article are first-line recommendations of American Association

Abbreviations: AASLD, American Association for the Study of Liver Diseases; DAA, direct-acting antiviral; HCV, hepatitis C virus; IDSA, Infectious Diseases Society of America; IVDA, intravenous drug abuse; LED, ledipasvir; MSM, men who have sex with men; RAS, resistance-associated substitution; SOC, standard of care; SOF, sofosbuvir; SVR, sustained virologic response. From the Cedars-Sinai Medical Center, Comprehensive Transplant Center, West Hollywood, CA.

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TABLE 1. FIRST-LINE TREATMENT REGIMENS FOR PATIENTS WITHOUT CIRRHOSIS, BOTH ACUTE AND CHRONIC THERAPY

Genotype	Treatment Regimen	Duration
Genotype 1a noncirrhotic	Elbasvir/grazoprevir for patients without baseline NS5A RASs for elbasvir	12 weeks
	Glecaprevir/pibrentasvir	8 weeks
	LED/SOF	12 weeks
	LED/SOF for patients who are not black, without HIV infection, and whose HCV RNA level is <6 million IU/mL	8 weeks
	SOF/velpatasvir	12 weeks
Genotype 1b noncirrhotic	Elbasvir/grazoprevir	12 weeks
	Glecaprevir/pibrentasvir	8 weeks
	LED/SOF	12 weeks
	LED/SOF for patients who are not black, without HIV infection, and whose HCV RNA level is <6 million IU/mL	8 weeks
	SOF/velpatasvir	12 weeks
Genotype 2 noncirrhotic	Glecaprevir/pibrentasvir	8 weeks
	SOF/velpatasvir	12 weeks
Genotype 3 noncirrhotic	Glecaprevir/pibrentasvir	8 weeks
	SOF/velpatasvir	12 weeks
Genotype 4 noncirrhotic	Glecaprevir/pibrentasvir	8 weeks
	SOF/velpatasvir	12 weeks
	Elbasvir/grazoprevir	12 weeks
	LED/SOF	12 weeks
Genotype 5/6 noncirrhotic	Glecaprevir/pibrentasvir	8 weeks
	SOF/velpatasvir	12 weeks
	LED/SOF	12 weeks

for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) HCV guidance (Table 1).¹

NEW INFECTIONS AND ACUTE HEPATITIS C

Patients with previously diagnosed cirrhosis have been prioritized for therapy both by clinicians and payers because of their advanced disease. As therapy has become more widely available, the more common patient being treated going forward is more likely to be younger, noncirrhotic, and have been more recently infected. The incidence of reported HCV cases has tripled since 2010, with 34,000 new infections in the United States in 2015.² People who inject drugs account for a large number of these cases,³ especially young adults (<30 years) and incarcerated individuals.

Other high-risk groups for acute HCV include HIV-positive men who have sex with men (MSM) and those acquiring HCV via unsterile health practices in low- to middle-income countries.⁴

Acute HCV infection has been defined as the time from viral exposure through 6 months. Diagnosis may be challenging because clinical features of acute infection may be nonspecific constitutional symptoms, such as malaise, anorexia, headache, nausea, among others, and may manifest in only 15% of cases. Abnormal blood tests such as transaminitis, with alanine aminotransferase levels that can be as high as 10 times the upper limit of normal, may assist in the diagnosis. If a patient presents with a viral syndrome and HCV antibody is checked, it may be positive as early as 6 weeks after exposure but may also be present much later in those with immune suppression. Therefore, the clinician would have to check the HCV polymerase chain reaction for diagnosis in the early period postexposure and in those with mitigating immune suppression.

Spontaneous clearance of acute HCV occurs in this early 6-month time period in up to 20% to 50% of those infected.⁵ Data exist that in HIV-positive patients acutely infected, rapidly decreasing viral levels (>2 logs IU/mL) in the 4 weeks after diagnosis may suggest a higher rate of spontaneous clearance, whereas persistent viremia at 12 weeks suggests a higher risk for chronicity.⁶ Current AASLD/IDSA guidelines¹ do not recommend treatment of acute HCV earlier than 6 months. This is to avoid unnecessary treatment in those who would have otherwise cleared the virus without therapy, avoiding cost and potential risk. Some special situations are discussed in the guidelines, such as those with ongoing transmission risk (medical personnel, active intravenous drug abuse [IVDA], MSM) or those with short periods of availability for treatment (incarcerated patients) where earlier treatment may outweigh the costs and risks. In these cases, treatment options should be the same as those who have chronic disease, assuming no evidence of cirrhosis (Table 1).

Although the general principle of not treating acute HCV in everyone newly diagnosed may have been relevant in the era of interferon therapy, this may not be as applicable in the era of DAA therapy. Naggie et al.⁷ reported on treatment of 27 individuals with acute HCV (as well as HIV-1 infection) who received 8 weeks of LED/

SOF. Eighty-one percent of these patients were new infections, 18% were reinfections, and all 27 achieved SVR, suggesting high SVR rates are achievable in this population. One recent simulation model of immediate treatment of HCV versus waiting until the chronic phase (6 months) using 8 weeks of theoretical treatment found that early treatment is both cost saving (\$3655) and results in improved outcomes (0.03 quality-adjusted life year) in those at risk for transmitting HCV.⁸ Shorter treatment durations of 4 to 6 weeks have been reported with excellent outcomes, so these data may evolve further.

In conclusion, acute or recently infected HCV due to increasing opioid abuse will lead to an HCV-infected treatment population of younger and perhaps more challenging clinical considerations of diagnosis, linkage to care, treatment access, and reinfection. Fortunately, treatment of acute HCV has excellent SVR rates with current therapies and appears to be cost-effective even at current costs. Future areas of research may be even shorter durations of therapy and better predictors of clearance.

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REFERENCES

- 1) American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA). Recommendations for testing, managing, and treating hepatitis C. Available at: <https://www.hcvguidelines.org>. Accessed September 2018.
- 2) Centers for Disease Control and Prevention (CDC). New Hepatitis C Infections Nearly Tripled Over Five Years. Atlanta, GA: CDC; 2017.
- 3) Page K, Hahn JA, Evans J, et al. Acute hepatitis C virus infection in young adult injection drug users: A prospective study of incident infection, resolution, and reinfection. *J Infect Dis* 2009;200:1216-1226.
- 4) Thursz M, Fontanet A. HCV transmission in industrialized countries and resource-constrained areas. *Nat Rev Gastroenterol Hepatol* 2014;11:28-35.
- 5) Kamal SM. Acute hepatitis C: A systematic review. *Am J Gastroenterol* 2008;103:1283-1297.
- 6) Vogel M, Boesecke C, Rockstroh JK. Acute hepatitis C infection in HIV-positive patients. *Curr Opin Infect Dis* 2011;24:1-6.
- 7) Naggie S, Fierer DS, Hughes M, et al. Sofosbuvir-containing regimens without interferon for treatment of acute hepatitis C virus (HCV) infection (SWIFT-C). Trial data reported for Cohort 2. ClinicalTrials.gov Identifier: NCT02128217. Available at: <https://clinicaltrials.gov/ct2/show/NCT02128217>. Updated April 27, 2018. Accessed September 20, 2018.
- 8) Bethea ED, Chen Q, Hur C, et al. Should we treat acute hepatitis C? A decision and cost effective analysis. *Hepatology* 2018;67:837-846.