

# Continued Progress Against Hepatitis C Infection

Hari Conjeevaram, MD, MSc

**The worldwide epidemic** of hepatitis C virus (HCV) infection affects more than 130 million people,<sup>1</sup> includes health-related outcomes such as cirrhosis, reduces quality of life, and



Related articles pages 1728 and 1736

poses economic burden on societies. Yet, there has been progress in achieving HCV eradication, reaching sustained virological response (SVR) rates of 90% to 100%, even among patients with characteristics associated with lower response rates (ie, black/African American race, high viral load, HCV 1a subgenotype, presence of cirrhosis, and prior null response to then-available standard therapies). Additional progress has been made in reducing the effect of the epidemic because the majority of the new drug regimens are orally administered and interferon free, and some are ribavirin free as well. The availability of these regimens has resulted in improved tolerability of antiviral therapy, while broadening the potential use of these agents in several settings in which interferon, ribavirin, or both are contraindicated or difficult to administer.

In this issue of *JAMA*, Poordad and colleagues<sup>2</sup> and Muir and colleagues<sup>3</sup> report the results of 2 multinational studies evaluating viral eradication rates with an all-oral interferon (IFN)-free drug combination using daclatasvir (an NS5A inhibitor), asunaprevir (an NS3 protease inhibitor), and beclabuvir (a nonnucleoside NS5B inhibitor) in 415 patients infected with HCV genotype 1 who did not have cirrhosis,<sup>2</sup> and in 202 patients who had compensated cirrhosis.<sup>3</sup> In both studies, treatment duration was for 12 weeks and included patients who were treatment naive (312 patients without cirrhosis<sup>2</sup> and 112 patients with cirrhosis<sup>3</sup>) and patients who failed prior treatment regimens with IFN-based combination therapies. The additional role of ribavirin was also studied among patients with cirrhosis.

As observed in several recently published studies using all-oral regimens with or without ribavirin, Poordad et al<sup>2</sup> report that rates of SVR in patients who were noncirrhotic and using the triple drug oral regimen without ribavirin were high, with an overall SVR<sub>12</sub> rate of 91% (92% in patients in the treatment-naive group and 89% in patients in the treatment-experienced group).<sup>2</sup> Nearly three-quarters of patients had genotype 1a and the SVR<sub>12</sub> rate was lower compared with genotype 1b patients (overall, 89% vs 98%) and especially in patients who were treatment experienced (85% vs 100%). Similar rates of SVR<sub>12</sub> were also reported by Muir et al<sup>3</sup> among patients with compensated cirrhosis. The addition of ribavirin appeared to benefit only those patients who were in the treatment-experienced group. The overall SVR<sub>12</sub> rates among patients whose regimens included ribavirin

were 98% in the treatment-naive group and 93% for those in the treatment-experienced group; and for those without ribavirin, overall SVR<sub>12</sub> rates were 93% in the treatment-naive group and 87% in the treatment-experienced group. Even prior null responders (patients who did not obtain viral suppression) responded very well to the treatment combination with and without ribavirin, although overall numbers of patients were small.

Similar to the patients who were noncirrhotic, SVR<sub>12</sub> rates were lower among patients with genotype 1a, especially among those who were treatment experienced and who did not receive additional ribavirin (86% vs those who did (91%). The majority of treatment failures were related to relapse followed by breakthrough response. The presence of resistance-associated variants to at least 2 drugs predicted relapse, whereas resistance-associated variants to all 3 drugs predicted a breakthrough response. As with other all-oral IFN-free regimens, treatment with the triple drug combination was well tolerated, with few serious adverse events attributed to the antiviral regimens and few adverse events leading to treatment discontinuation (0.7%-1.9%).

These 2 studies<sup>2,3</sup> add to the armamentarium of all-oral IFN-free regimens that have revolutionized management of hepatitis C, not only for patients who are treatment naive with no significant liver disease but also for those who are treatment experienced and those with cirrhosis. Several recent studies have shown high rates of SVR with these regimens in all genotypes and with treatment as short as 8 weeks in some patients with treatment naive HCV genotype 1 infection. Among patients without cirrhosis, rates of SVR have exceeded 90% among patients who are treatment naive as well as treatment experienced, even without ribavirin. Although similar SVR rates have been reported among patients who are treatment naive with cirrhosis with 12 weeks' therapy, the addition of ribavirin or extension of treatment to 24 weeks appears to be warranted with some regimens. The high response rates, especially among patients with cirrhosis, is substantial and important clinically, given that viral eradication has been shown to delay or decrease chance of decompensation of liver disease and also hepatocellular carcinoma.

Despite the progress and the success of viral eradication, numerous questions remain unanswered such as response based on race, still difficult-to-treat situations such as patients with end-stage liver disease or undergoing hemodialysis, access to and affordability of these therapies, improvement in quality of life, and cost-effectiveness. It is time to reflect on these challenges and find solutions because the influence of HCV infection on global society is an ongoing challenge.

Although published information is available about some of these important issues, reaching some populations with certain characteristics remains difficult. For instance, the addition of protease inhibitors to pegylated interferon and ribavirin has decreased the gap in SVR rates between black/African American and white patients and all-oral IFN-free regimens have similar overall SVR rates among black/African American and white patients, even among patients with cirrhosis.<sup>4-11</sup> However, black/African American patients remain underrepresented in the majority of published studies on HCV treatment.

Several studies have demonstrated that chronic HCV infection can significantly affect both the health-related quality of life and productivity in the work place. Factors such as high utilization rate of medical resources and increased absenteeism from work can have negative economic effects on society, but these effects potentially could be reversed with eradication of HCV infection. In a study of patient-reported outcomes among patients with HCV infection and cirrhosis who were treated with sofosbuvir-containing regimens,<sup>12</sup> achieving SVR<sub>12</sub> with the all-oral IFN-free regimen resulted in improvement in some aspects of patient-reported outcomes. In another study,<sup>13</sup> the presence of advanced fibrosis was independently associated with impairment of health-related quality of life and work productivity; there was significant improvement in both outcomes after achieving viral eradication with ledipasvir and sofosbuvir and this improvement was seen regardless of fibrosis stage (in both early and advanced fibrosis). Such improvement in work productivity with viral eradication is considered an important step that may contribute to substantial benefits to society.

One of the most important factors that warrants discussion is the cost that these all-oral regimens bring to society at large—even if the high costs of these drugs were to be covered by insurance companies in countries. In the United States, the cost for a 12-week course is as follows: for sofosbuvir, \$84 000; ledipasvir/sofosbuvir combination, \$94 500; paritaprevir-ritonavir/ombitasvir/dasabuvir combination, \$83 000; and simeprevir/sofosbuvir combination, \$150 000. Equally important is the concern that cost should not limit use of these medications only to patients with more advanced fibrosis, considering that until recently, the practice has been to care for all patients infected with hepatitis C. In 2 studies that addressed cost-effectiveness of HCV oral regimens in the United States from a societal perspective,<sup>14,15</sup> it was reported that even though these novel treatments were cost-effective compared with usual care, the concern remains that increased demand for treatment may create substantial economic challenges to society.

Hepatitis C is a global disease and although substantial progress has been made in HCV eradication, the success of such progress will be defined not just by the SVR rates but by accessibility and affordability of these medications. Differences in SVR rates between the good and poor predictors of outcomes have been significantly narrowed by these all-oral agents (including differences based on race, HCV RNA levels, advanced fibrosis, and prior treatment failure—especially prior null response). However, the disparity between patients who have access to these therapies vs those who do not also should be narrowed to achieve the goal of changing the trajectory of disease progression and its complications, and to move further along the path of global eradication of HCV infection.

#### ARTICLE INFORMATION

**Author Affiliation:** Division of Gastroenterology, University of Michigan, Ann Arbor.

**Corresponding Author:** Hari Conjeevaram, MD, MSc, Division of Gastroenterology, University of Michigan, 1500 E Medical Center Dr, 3912 Taubman Center, Ann Arbor, MI 48109-5362 (omsairam@umich.edu).

**Conflict of Interest Disclosures:** The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

#### REFERENCES

- World Health Organization. Hepatitis C fact sheet No 164. April 2014. <http://www.who.int/mediacentre/factsheets/fs164/en/> Accessed June 9, 2014.
- Poordad F, Sievert W, Mollison L, et al. Fixed-dose combination therapy with daclatasvir, asunaprevir, and beclabuvir for noncirrhotic patients with HCV genotype 1 infection. *JAMA*. doi:10.1001/jama.2015.3860.
- Muir AJ, Poordad F, Lalezari J, et al. Daclatasvir in combination with asunaprevir and beclabuvir for hepatitis C virus genotype 1 infection with compensated cirrhosis. *JAMA*. doi:10.1001/jama.2015.3868.
- Afdhal N, Zeuzem S, Kwo P, et al; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*. 2014;370(20):1889-1898.
- Afdhal N, Reddy KR, Nelson DR, et al; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med*. 2014;370(16):1483-1493.
- Manns M, Pol S, Jacobson IM, et al; HALLMARK-DUAL Study Team. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. *Lancet*. 2014;384(9954):1597-1605.
- Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370(17):1594-1603.
- Kowdley KV, Gordon SC, Reddy KR, et al; ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. 2014;370(20):1879-1888.
- Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370(17):1604-1614.
- Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med*. 2014;370(21):1973-1982.
- Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child's class A cirrhosis. *Gastroenterology*. 2015;148(4):762-770.e2.
- Younossi ZM, Stepanova M, Nader F, et al. Patient-reported outcomes in chronic hepatitis C patients with cirrhosis treated with sofosbuvir-containing regimens. *Hepatology*. 2014;59(6):2161-2169.
- Younossi ZM, Stepanova M, Afdhal N, et al. Improvement of health-related quality of life and work productivity in chronic hepatitis C patients with early and advanced fibrosis treated with ledipasvir and sofosbuvir [published online March 17, 2015]. *J Hepatol*. doi:10.1016/j.jhep.2015.03.014.
- Rein DB, Wittenborn JS, Smith BD, Liffmann DK, Ward JW. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus [published online March 16, 2015]. *Clin Infect Dis*. doi:10.1093/cid/civ220.
- Najafzadeh M, Andersson K, Shrank WH, et al. Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. *Ann Intern Med*. 2015;162(6):407-419.