New Treatments for Hepatitis C

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SOFOSBUVIR-BASED THERAPY FOR HEPATITIS C VIRUS

K. Rajender Reddy, MD, University of Pennsylvania, Philadelphia, Pennsylvania, USA, discussed sofosbuvir (SOF)-based therapy for hepatitis C virus (HCV)-infected patients. Direct-acting anti-HCV compounds are categorized concerning activity. Inhibitors of nonstructural (NS) protein 5A include dalatasvir, ledipasvir, and ABT-267. Polymerase inhibitors (ie, non-nucleoside [NUC] NS5 and NUC NS5B inhibitors) include SOF, mericitabine, ALS-2200, ABT-333, ABT-072, VX-222, BMS-731225, deleobuvir, setrobuvir, and filibuvir. NS3 protease inhibitors include ABT-450 in combination with ritonavir, MK-5172, asunaprevir, danoprevir, sovaprevir, simeprevir, faldaprevir, baceprevir, and telaprevir.

The effectiveness of a 12-week SOF plus ribavirin (RBV) regimen in treatment-naïve patients infected with HCV genotype 1 has been chronicled [Gane EJ et al. *N Engl J Med.* 2013]. High sustained virologic response at 24 weeks (SVR24) rates were also obtained using the 12-week regimen in the absence of pegylated interferon (PEG) and with varying durations of interferon treatment. SOF monotherapy was not as effective.

The open-label NEUTRINO trial [NCT1641640] examined SOF plus PEG/RBV in genotype 1, 4, and 6 patients. High SVR12 rates in all genotypes in cirrhotic and noncirrhotic black and nonblack patients were evident [Lawitz et al. *N Engl J Med.* 2013]. SOF was also effective in the POSITRON trial [NCT01542788] for HCV genotype 2 cirrhotic and noncirrhotic patients refractory to other treatments; the response (SVR12) was less pronounced for genotype 3 [Jacobson IM et al. *N Engl J Med.* 2013]. Treatment of prior relapsers or nonresponders with a 12- or 16-week regimen involving SOF plus RBV in the FUSION trial [NCT01604850] was also more effective in genotype 2 noncirrhotic patients, especially with longer treatment [Jacobson IM et al. *N Engl J Med.* 2013]. The FISSION trial [NCT01497366] documented a markedly better response to 12 weeks of SOF plus RBV versus PEG plus RBV in noncirrhotic, treatment-naïve, genotype 2 patients. SVR12 displayed by their cirrhotic counterparts, and cirrhotic and noncirrhotic patients infected with HCV genotype 3, was relatively poor [Lawitz et al. *N Engl J Med.* 2013].

In the VALENCE trial [NCT01682720], SOF plus RBV was offered for 12 or 24 weeks. The extended treatment produced high SVR12 rates in HCV genotype 2 or 3 treatment-naïve and treatment-experienced cirrhotic and noncirrhotic patients [Zeuzem S et al. *N Engl J Med.* 2014].

ION-1 [NCT01701401] and ION-2 [NTC01768286] chronicled the efficacy of 12- or 24-week treatment with a PEG- and RBV-free regimen (SOF + ledipasvir) in HCV genotype 1–infected cirrhotic and noncirrhotic, treatment-naïve and treatment-experienced patients, including patients who failed prior therapy [Afdhal N et al. *N Engl J Med.* 2014a, 2014b]. A shorter duration (8-week) may be effective [Kowdley KV et al. *N Engl J Med.* 2014], with even shorter treatment requiring the addition of a third direct-acting antiviral agent [Gane EJ. *Gastroenterol.* 2014].

The collective findings point to the availability of various treatment options, with the selected platform treatment depending on a number of factors.

NEW INTERFERON- AND RIBAVIRIN-FREE THERAPIES FOR HEPATITIS C VIRUS INFECTION

Gregory Everson, MD, University of Colorado, Denver, Colorado, USA, discussed possible HCV therapies that do not involve PEG and RBV. These focus on the 3 aforementioned targets of HCV replication—NS5A, NUC/non-NUC NS5B, and NS3 protease [Gane EJ, Agarwal K. *Am J Transplant.* 2014].

An approach that may be very effective in HCV control uses a combination of ABT450 (protease inhibitor), ritonavir (enhances ABT450 action), ombitasvir (NS5a inhibitor), dasabuvir (non-NUC

protease inhibitor) ± RBV. Six phase 3 trials have examined this combination.

In noncirrhotic patients, the regimen including RBV produced high SVR12 rates in HCV genotype 1–infected, treatment-naïve [SAPPHIRE I; NCT0716585] or treatment-experienced patients, of whom nearly half were prior nonresponders [SAPPHIRE II; NCT01715415; Feld JJ et al. *N Engl J Med.* 2014a, 2014b]. SVR12 was unaffected by factors that diminish response to interferon-based treatment.

RBV may not be necessary for an anti-HCV effect in noncirrhotic patients, based on results of high SVR12 from the 12-week use of the RBV-free regimen in HCV genotype 1b-infected, treatment-experienced or treatment-naïve patients in the PEARL II [NCT01674725] and PEARL III [NCT01767116] trials, respectively, and HCV genotype 1a–infected, treatment-naïve patients in the PEARL IV trial [NCT01833533; Andreone P et al. *Gastroenterol.* 2014; Ferenci P et al. *N Engl J Med.* 2014]. RBV may be needed for optimal anti-HCV effect in genotype 1a patients.

The influence of cirrhosis was examined in the TURQUOISE II trial [NCT01704755]. The 12- and 24-week regimen included RBV. High SVR12 rates were evident, with prior nonresponders benefiting most from the longer treatment duration [Poordad F et al. *N Engl J Med.* 2014].

Another potentially efficacious regimen uses the protease inhibitor asunaprevir + NS5a protein inhibitor daclatasvir plus non-NUC polymerase inhibitor BMS-791325. Evaluation of fixed doses in HCV genotype 1a and 1b, cirrhotic, and noncirrhotic [Everson GT et al. *Gastroenterol.* 2014] patients demonstrated high SVR12, particularly for genotype 1a. Findings of the HALLMARK-DUEL trial [NCT01581203] indicate that the asunaprevir plus daclatasvir combination may also be useful [Manns M et al. *Lancet* 2014].

The as-yet unpublished C-WORTHY trial of the protease inhibitor MK-5172 and the NS5a protein inhibitor MK-8742 demonstrated high SVR12 rates for HCV noncirrhotic patients with or without RBV and for HCV/HIV coinfected patients in the RBV-containing regimen, with similar patterns evident for patients with cirrhosis and prior nonresponders.

These treatments are expensive. However, the costs of not treating chronic HCV infection are considerable.

PREDICTING DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN HCV-INFECTED PATIENTS

James Trotter, MD, Baylor University Medical Center, Waco, Texas, USA, discussed the use of alpha-fetoprotein (AFP) to predict hepatocellular carcinoma (HCC).

AFP is a serum protein that fulfills much of the functions of albumin in the fetal and postnatal period. It is elevated during hepatic proliferation in development, regeneration, and malignancy. Although easy to measure in blood, AFP is not produced by 25% to 30% of HCCs, producing a substantial false-negative rate. Moreover, AFP can be elevated in cases of hepatitis and cirrhosis, producing false-positive results.

Efforts to find better predictive models of HCC have focused on the analysis of data points from the electronic medical records of thousands of patients to generate predictive models using common lab tests, including aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatise, bilirubin, prothrombin, and platelets. The data mining, which is easier and less expensive to do than actual studies, is based on known associations of advanced age and more severe/longer duration of liver disease with HCC, and the lack of association of ALT with elevated AFP.

The Department of Veterans Affairs database was examined to identify patients with HCV infection. Patients (n = 11 721; median age 52.0 years, 98.1% male, and, limiting generalization of the findings, only 39% non-Hispanic white patients) treated from 1998 to 2005 had antibody to HCV, detectable HCV RNA, cirrhosis, and ≥ 1 measurement of serum AFP after HCV diagnosis. The total number of AFP tests was 35 494. By 2005, 987 (8.4%) of the patients had developed HCC. The median follow-up was 3.5 years.

AFP level, ALT, platelet count, and age were linked with increased frequency of HCC. The probability of HCC was three times higher for normal vs high ALT. The risk of HCC was increased as platelet count decreased; low platelet number was indicative of more severe and prolonged liver disease and worse portal hypertension. Finally, HCC risk increased with age.

The findings offer the possibility that data from common lab tests can be used to compute a score that is predictive of HCC risk. The real-life implications of the level of risk (eg, 10% vs 30%) remain to be clarified.