ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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A Fixed-Dose Combination of Sofosbuvir and Ledipasvir for Hepatitis C Virus Genotype 1

Nezam H. Afdhal, MD
Director of Hepatology
Beth Israel Deaconess Medical Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

G&H What is the traditional treatment approach for patients with hepatitis C virus genotype 1?

NA For the past 20 years, treatment of hepatitis C virus (HCV) has consisted of interferon as a backbone, plus ribavirin. Since 2011, the protease inhibitors telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck) could be added to the regimen for HCV genotype 1 patients. The duration of therapy ranged from 24 to 48 weeks, depending on the genotype and response.

G&H What are the newer treatments?

NA In 2014, we were fortunate to see the introduction of the first interferon-free therapies. For HCV genotype 2 and HCV genotype 3, this approach consisted of the nucleotide inhibitor sofosbuvir (Sovaldi, Gilead) plus ribavirin. For HCV genotype 1, the regimen consisted of the combination of sofosbuvir and the protease inhibitor simeprevir (Olysio, Janssen), with or without ribavirin. There are several advantages to these regimens; they enable shorter, simpler, safer, and more effective treatment.

G&H What was the design of the ION trials?

NA The ION trials examined the use of a fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg), with or without ribavirin, in patients with HCV genotype 1. The combination tablet (Harvoni, Gilead) was approved in October 2014. Sofosbuvir is an NS5B nucleotide polymerase inhibitor, whereas ledipasvir is an NS5A inhibitor. Together, the combination provides a high barrier to resistance and high efficacy, which results in an ability to suppress HCV so that it can be cured.

The ION trials were designed to evaluate 3 aspects of treatment: the optimum duration of therapy, whether there is a need for ribavirin, and the magnitude of efficacy. There were 3 ION trials, which enrolled different HCV genotype 1 populations. The phase 3 ION-1 (A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination [FDC] +/- Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects With Chronic Genotype 1 HCV Infection) trial enrolled treatment-naive patients (N=865). The phase 3 ION-2 (Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV) trial enrolled treatment-experienced patients (N=440). ION-1 and ION-2 followed the same 4-arm study design: Patients were randomized to receive the sofosbuvir/ledipasvir tablet with or without ribavirin for 12 or 24 weeks. The phase 2 ION-3 (Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV) trial enrolled treatment-naive, noncirrhotic patients (N=647), who were randomized to receive 8 weeks of the sofosbuvir/ledipasvir tablet with or without ribavirin or 12 weeks of sofosbuvir/ledipasvir alone.

G&H What were the results of these trials?

NA Results were presented at the 2014 Digestive Disease Week and the 2014 meeting of the European Association for the Study of the Liver, as well as published in *The New England Journal of Medicine*. In ION-1, nearly 100% of patients were cured, regardless of the treatment arm. Rates

Table. Response During and After Treatment in ION-2

	12-Week Regimen		24-Week Regimen	
	LDV-SOF (n=109)	**LDV-SOF + RBV (n=111)**	**LDV-SOF (n=109)**	**LDV-SOF + RBV (n=111)**
HCV RNA <25 IU/mL				
During treatment				
At 2 weeks	89 (82%)	92 (83%)	89 (82%)	93 (84%)
At 4 weeks	109 (100%)	110 (99%)	108 (99%)	110 (99%)
At the end of treatment	108 (99%)[a]	111 (100%)	109 (100%)	110 (99%)
After the end of treatment				
At 4 weeks	103 (94%)	107 (96%)	109 (100%)	110 (99%)
At 12 weeks	102 (94%)	107 (96%)	108 (99%)[b]	110 (99%)
Virologic breakthrough during treatment	0	0	0	1 (1%)[c]
Relapse	7 (6%)	4 (4%)	0	0

HCV, hepatitis C virus; ION-2, Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

[a]One of the 109 patients who received 12 weeks of ledipasvir/sofosbuvir had an HCV RNA level of 42 IU/mL at the week 12 visit but had an undetectable HCV RNA level at the visits occurring at 4, 12, and 24 weeks after the end of treatment.

[b]Among the 109 patients who received 24 weeks of ledipasvir/sofosbuvir, 1 patient withdrew consent after the posttreatment week 4 visit; at this visit, the patient's HCV RNA level was less than 25 IU/mL.

[c]This patient did not adhere to the study treatment, as shown by plasma concentrations of ledipasvir and GS-331007 (the predominant circulating metabolite of sofosbuvir) that were below or near the lower level of quantification at weeks 2, 4, and 6 of treatment.

of sustained virologic response at week 12 (SVR12) among patients receiving sofosbuvir/ledipasvir plus ribavirin were equivalent after 12 weeks and 24 weeks of treatment (97% vs 99%, respectively). The regimen that excluded ribavirin also showed similar rates of response at 12 weeks and 24 weeks of treatment (99% vs 98%, respectively).

Similar results were seen in ION-2. All patients showed high rates of SVR12, regardless of the treatment arm (Table). Among patients who received sofosbuvir/ledipasvir plus ribavirin, SVR12 rates were 96% with 12 weeks of treatment and 99% with 24 weeks of treatment. Among patients who did not receive ribavirin, SVR12 rates were 94% with 12 weeks of treatment and 99% with 24 weeks of treatment. In ION-3, SVR12 rates were 94% for 8 weeks of sofosbuvir/ledipasvir, 93% for 8 weeks of sofosbuvir/ledipasvir plus ribavirin, and 95% for 12 weeks of sofosbuvir/ledipasvir without ribavirin.

G&H What is the take-home message of the ION trials?

NA The ION trials showed that ribavirin is not needed for patients with HCV genotype 1, which is an important finding. No patient subgroups appeared to benefit from the addition of ribavirin. The trial also showed that a treatment duration of 12 weeks is suitable for all HCV genotype 1 patients; ION-3 suggested that a shorter duration may be adequate for patients without cirrhosis. Lastly, the efficacy rate was high for the sofosbuvir/ledipasvir combination tablet.

G&H How does the safety profile of sofosbuvir plus ledipasvir compare with that of standard therapy?

NA The safety profile was excellent. In ION-1, the most frequent adverse events associated with sofosbuvir plus ledipasvir were mild and included headache (25%), fatigue (23%), and nausea (12%). Severe treatment-emergent adverse events were reported in 32 patients (4%). In ION-2, the most common adverse events throughout the 4 arms were fatigue (21%-45%), headache (23%-32%), and nausea (6%-23%). Among the patients who received 24 weeks of treatment, serious adverse events were reported in 9 (2%). Across the 4 arms, no patients discontinued treatment owing to an adverse event. In ION-3, adverse events were more common among patients treated with ribavirin. No patients

who received the 8-week regimen without ribavirin discontinued treatment owing to an adverse event.

G&H Will protease inhibitors continue to have a role in the management of HCV?

NA The protease inhibitors telaprevir and boceprevir will likely no longer be used in this setting, and certainly not in combination with interferon. Several new regimens incorporating a protease inhibitor have shown good response rates. They will be available soon.

G&H Now that the sofosbuvir/ledipasvir combination regimen is approved, is it likely that sofosbuvir will be prescribed in this form rather than as a single agent?

NA It is likely that sofosbuvir will be used in combination with ledipasvir for HCV genotype 1. Sofosbuvir alone is pan-genotypic in combination with other drugs such as ribavirin, and the sofosbuvir-plus-ribavirin combination will be needed for patients with HCV genotype 2 or HCV genotype 3.

G&H What impact will this regimen have?

NA The sofosbuvir/ledipasvir combination is an important breakthrough. There are many categories of patients who were previously ineligible for treatment. For example, patients who are not candidates for therapy with interferon or ribavirin are now eligible for treatment. Such patients include those with neuropsychiatric disorders and cardiovascular disease, as well as those who are intolerant of interferon.

G&H Are any other regimens under development in HCV?

NA There are multiple regimens containing different compounds under development. Excellent results were recently reported with a regimen consisting of the protease inhibitor ABT-450 with ritonavir (Norvir, AbbVie), the NS5A inhibitor ombitasvir (ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (ABT-333), and ribavirin. In HCV genotype 1B patients, this regimen can be used without ribavirin, but in HCV genotype 1A patients, ribavirin is still needed. In a phase 3 trial, the cure rate was 95.9% with 12 weeks of therapy.

G&H There is still a large population of people with undiagnosed HCV. What kind of advocacy regarding screening and treatment is needed?

NA Screening should take place in the primary care setting. It is hoped that the introduction of highly safe and effective medications will increase interest in screening among both patients and primary care physicians. The population that should be screened is the baby boomers, who were born between 1945 and 1965. In these patients, HCV disease is likely to be significant or advanced, and therefore screening to enable diagnosis and subsequent referral for treatment is important, regardless of the presence of risk factors.

Dr Afdhal has received research support within the past 2 years for HCV studies from Merck, Vertex, Gilead, AbbVie, and BMS. He is a consultant and/or a member of the advisory boards of Merck, Gilead, Echosens, GlaxoSmithKline, Vertex, Novartis, Boehringer Ingelheim, Ligand, Spring Bank, Medgenics, Kadmon, Janssen, AbbVie, and Achillion. He holds stock options in Spring Bank.

Suggested Reading

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