

Ledipasvir/Sofosbuvir (Harvoni): Improving Options for Hepatitis C Virus Infection

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INTRODUCTION

Hepatitis C is an infectious liver disease caused by the hepatitis C virus (HCV), a single-stranded RNA virus.¹ Those infected usually develop acute hepatitis C, which spontaneously clears in 15% to 45% of infected persons. The incubation period for acute hepatitis is anywhere from two weeks to six months, and most patients remain asymptomatic. Early diagnosis of HCV infection is rare, and the disease may go unnoticed until patients have already developed serious liver damage. Those who do not spontaneously clear the infection develop chronic hepatitis C.² In the United States, approximately 3.2 million people have chronic HCV infection. Of patients who are chronically infected, 5% to 20% will eventually develop cirrhosis, and 1% to 5% will die from cirrhosis or hepatocellular carcinoma.³

HCV is categorized into nine distinct genotypes, although some experts believe there are as many as 11. The most common genotype infection in the United States is genotype 1 (72%), followed by genotype 2 (16% to 19%) and genotype 3 (8% to 19%). The rest of the genotypes make up 1% to 2% of the HCV-infected population.¹

In the past five years, treatment for HCV has evolved rapidly, especially for genotype 1 infections. Previously, the recommended treatment was pegylated interferon (alfa-2a or alfa-2b) weekly injections plus a weight-based dose of

oral ribavirin, both for 48 weeks, which yielded a sustained virological response (SVR) rate of 45% to 50%. In 2011, the first-generation protease inhibitors came to market—telaprevir (Incivek, Vertex Pharmaceuticals), which was discontinued in 2014, and boceprevir (Victrelis, Merck Sharp & Dohme).⁴ The combination of either protease inhibitor with pegylated interferon alfa-2a (Pegasys, Genentech) and ribavirin increased the SVR rates in treatment-naïve HCV genotype 1 infected patients to 67% to 75%.^{5,6} This was followed by the approval of the second-generation protease inhibitor simeprevir (Olysio, Janssen) and the RNA-dependent RNA polymerase nonstructural protein 5B (NS5B) inhibitor sofosbuvir (Sovaldi, Gilead Sciences) in 2013.⁴

On October 10, 2014, the FDA approved the use of ledipasvir/sofosbuvir (Harvoni, Gilead Sciences) for the treatment of HCV genotype 1 infections.⁷ Shortly afterward, on December 19, 2014, the FDA approved another oral interferon-free regimen, ombitasvir/paritaprevir/ritonavir plus dasabuvir (Viekira Pak, AbbVie).⁸ This regimen, used for the treatment of HCV genotype 1 infections, is a copackaged product that contains ombitasvir, paritaprevir, and ritonavir as a fixed-dose combination tablet and dasabuvir as an individual tablet. Depending on the patient's HCV genotype (1a versus 1b) and the presence of cirrhosis, concomitant administration with weight-based ribavirin may be necessary.⁹ Although Viekira Pak has similar efficacy, the advantage of ledipasvir/sofosbuvir lies in its once-daily fixed-dose regimen that does not require the coadministration of ribavirin.^{7,9}

PHARMACOLOGY

Ledipasvir and sofosbuvir are both direct-acting antiviral agents.¹⁰ Sofosbuvir is a liver-targeted nucleotide prodrug of the active triphosphate GS-461203, which has been approved for use in HCV genotypes 1–4. It works as an inhibitor of the HCV NS5B RNA-dependent RNA poly-

merase, which acts as a chain terminator.^{11,12} Ledipasvir is an NS5A inhibitor that is effective against genotypes 1a, 1b, 4a, and 5a and (with lower activity) against genotypes 2a and 3a. Its exact mechanism of action is unknown, but one suggested mechanism is its inhibition of hyperphosphorylation of NS5A, which seems to be required for viral production. NS5A inhibitors may also cause faulty viral assembly by redistributing the subcellular localization of the protein. The NS5A and NS5B inhibitors demonstrate an additive or synergistic effect when used in combination.¹⁰

PHARMACOKINETICS/ PHARMACODYNAMICS

Once administered, sofosbuvir is absorbed quickly; a peak concentration in the plasma occurs 0.8 to 1 hour post-dose.¹³ Sofosbuvir is 61% to 65% protein-bound and undergoes extrahepatic metabolism. Here it is converted to the primary circulating inactive nucleoside metabolite GS-331007, which is eliminated renally.¹⁴ Consumption of a moderate- or high-fat meal with sofosbuvir increases the area under the curve twofold while only increasing sofosbuvir's peak concentration (C_{max}) 1.3-fold. However, these increases in sofosbuvir levels are not considered to be clinically meaningful.¹⁵

After administration of ledipasvir/sofosbuvir, the concentration of ledipasvir reaches its C_{max} 4 to 4.5 hours post-dose.¹³ Unlike sofosbuvir, ledipasvir concentrations are not affected by food.¹⁵ Ledipasvir is minimally metabolized by the liver, is highly protein-bound (more than 98%), and is primarily eliminated in the feces.¹⁴

Resistance

Due to the multiple proposed mechanisms of action and high potency of NS5A inhibitors, multiple mutations in HCV replicons (genetic units of replication) may be necessary to cause significant resistance.⁴ In general, HCV genotype 1b strains have a higher barrier of resistance

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than HCV genotype 1a strains. A single amino acid substitution such as L31V for genotype 1b gave the HCV replicon a less-than-100-fold increase in resistance to NS5A inhibitors. The Y39H replicon variant increased resistance by 1,319-fold. However, a double amino acid substitution (L31V/Y39H) for HCV genotype 1b or a single amino acid substitution (i.e., Q30E or Y39H/N) conferred a more-than-1,000-fold level of resistance.¹⁶

In sofosbuvir, only the single amino acid substitution S282T conferred resistance and decreased the activity of the NS5B inhibitor.¹⁷ This substitution gave a twofold to 18-fold decrease in susceptibility of the virus to sofosbuvir.¹³

In all three large, multicenter, randomized studies to follow (the ION trials), there were only 29 HCV genotype 1a and eight HCV genotype 1b virological failures out of a total of 1,952 subjects.^{13,18–20} No cross-resistance was seen in the trials, as sofosbuvir was fully active against ledipasvir-resistance-associated substitutions and vice versa.¹³

CLINICAL TRIALS

ION I Trial¹⁸

This phase 3, open-label, multicenter, randomized trial included treatment-naïve patients with chronic HCV genotype 1 infection. The 865 patients were randomized in a 1:1:1:1 ratio into one of four treatment arms: ledipasvir/sofosbuvir for 12 weeks, ledipasvir/sofosbuvir plus ribavirin for 12 weeks, ledipasvir/sofosbuvir for 24 weeks, or ledipasvir/sofosbuvir plus ribavirin for 24 weeks. Randomization was stratified according to patients' HCV genotype 1 subtype (1a versus 1b) and the presence or absence of cirrhosis. The study protocol allowed for cirrhotic patients to account for 20% of the study population. All patients received a fixed daily dose of ledipasvir/sofosbuvir 90/400 mg (Harvoni), while ribavirin was dosed conventionally based on body weight (1,000 mg daily if the patient's body weight was less than 75 kg and 1,200 mg daily if it was 75 kg or more).

The primary endpoint of this study was to achieve an SVR 12 weeks after the end of treatment. The rate of SVR for each treatment arm was compared with an adjusted historical rate of 60%, which was based on the SVR rate (65%) of telaprevir and boceprevir in a separate phase 3 trial (the 5% margin was allowed in exchange

for a shorter duration of therapy and an expected better side-effect profile).

All treatment arms had an SVR superior ($P < 0.001$) to the 60% historical rate, with rates of 99% (95% confidence interval [CI], 96–100%) for 12 weeks of ledipasvir/sofosbuvir, 97% (95% CI, 94–99%) for 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 98% (95% CI, 95–99%) for 24 weeks of ledipasvir/sofosbuvir, and 99% (95% CI, 97–100%) for 24 weeks of ledipasvir/sofosbuvir and ribavirin. Only three patients out of the 865 in the trial had virological failure; one of them was suspected of nonadherence to the study protocol.

The authors concluded that the rate of SVR in all treatment arms was 97% or greater and the discontinuation rates were higher for 24 weeks of treatment versus 12 weeks and in groups that received ribavirin versus those that did not. The study demonstrated that 12 weeks of ledipasvir/sofosbuvir without ribavirin is an effective treatment for patients with HCV genotype 1 infection.

ION II Trial¹⁹

The ION II trial was a phase 3, randomized, open-label study that included HCV genotype 1 patients who had previously been treated with interferon-based therapy but had not achieved an SVR. Similar to the ION I trial, patients were randomized in a 1:1:1:1 ratio into either 12 weeks of ledipasvir/sofosbuvir, 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 24 weeks of ledipasvir/sofosbuvir, or 24 weeks of ledipasvir/sofosbuvir plus ribavirin. Ledipasvir/sofosbuvir and ribavirin dosing was the same as in the ION I trial. In the ION II trial, the primary endpoint was also SVR 12 weeks after the end of treatment.

Patients who were eligible to enroll in the study had to have received peginterferon and ribavirin, with or without a protease inhibitor, and failed to achieve an SVR. Patients were ineligible if they had discontinued their previous treatment due to an adverse event. The study hypothesized that the rate of SVR in the four treatment regimens would be higher than an adjusted historical rate of 25% for this patient population.

Each of the four treatment arms had a higher SVR rate compared with the adjusted historical rate ($P < 0.001$). The rates of SVR were 94% (95% CI, 87–97%) for 12 weeks of ledipasvir/sofosbuvir, 96%

(95% CI, 91–99%) for 12 weeks of ledipasvir/sofosbuvir plus ribavirin, 99% (95% CI, 95–100%) for 24 weeks of ledipasvir/sofosbuvir, and 99% (95% CI, 95–100%) for 24 weeks of ledipasvir/sofosbuvir plus ribavirin. Eleven of 440 patients had a virological relapse after the end of treatment. Seven of those patients came from the 12-week ledipasvir/sofosbuvir arm and four came from the 12-week ledipasvir/sofosbuvir plus ribavirin arm. No patients in the 24-week treatment arms had a virological relapse. Only two patients did not achieve an SVR; one withdrew consent after post-treatment week four and the other had a virological rebound due to nonadherence to the treatment regimen.

Even though this study was not sufficiently powered to compare SVRs between regimens with or without ribavirin for 12 weeks versus 24 weeks, the authors concluded that 12 weeks of ledipasvir/sofosbuvir therapy achieved high rates of SVR in patients with HCV genotype 1 who had not responded to prior interferon-based therapy.

ION III Trial²⁰

The objective of this phase 3, multicenter, randomized, open-label study was to determine if the treatment duration for ledipasvir/sofosbuvir could be shortened from the previously explored 12-week regimen. The 647 patients enrolled were randomized in a 1:1:1 ratio to ledipasvir/sofosbuvir for eight weeks, ledipasvir/sofosbuvir plus ribavirin for eight weeks, or ledipasvir/sofosbuvir for 12 weeks. Ledipasvir/sofosbuvir and ribavirin dosing was the same as in the ION I and ION II trials. Patients were included in the study if they were 18 years of age or older, had chronic HCV genotype 1 infection without cirrhosis, and were treatment-naïve.

The primary endpoint was an SVR 12 weeks after the end of treatment defined as an HCV RNA level of less than 25 IU/mL. The rate of SVR in each arm was compared with the historical response rate of 60%. A secondary endpoint was the noninferiority of eight weeks of ledipasvir/sofosbuvir to the other treatment arms. All three treatment regimens were superior to the historical response rate ($P < 0.001$). The SVR was 94% (95% CI, 90–97%) for eight weeks of ledipasvir/sofosbuvir, 93% (95% CI, 89–96%) for eight weeks of ledipasvir/sofosbuvir plus ribavirin, and 95% (95%

Table 1 Brief Summary of HCV Treatment Guidelines in Patients Who Are HCV Genotype 1–Positive and Treatment-Naïve²⁵

Treatment of HCV Genotype 1a			
	LDV/SOF	OBV/PTV/r + DSV + RBV	SOF + SMV ± RBV
Treatment duration	12 weeks	12 weeks (no cirrhosis) or 24 weeks (cirrhosis)	12 weeks (no cirrhosis) or 24 weeks (cirrhosis)
Recommendation level	Class I, level A	Class I, level A	Class IIa, level B
Treatment of HCV Genotype 1b			
	LDV/SOF	OBV/PTV/r + DSV*	SOF + SMV
Treatment duration	12 weeks	12 weeks (no cirrhosis)	12 weeks (no cirrhosis) or 24 weeks (cirrhosis)
Recommendation level	Class I, level A	Class I, level A	Class IIa, level B

DSV = dasabuvir; HCV = hepatitis C virus; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; r = ritonavir; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir

* The addition of ribavirin is recommended in patients with cirrhosis.

Table 2 Brief Summary of HCV Treatment Guidelines in Patients Who Are HCV Genotype 1–Positive And Failed Prior PEG/RBV Therapy²⁵

Recommended Treatment in Patients Without Cirrhosis				
	LDV/SOF	OBV/PTV/r + DSV*	SOF + SMV ± RBV	
Treatment duration	12 weeks	12 weeks	12 weeks	
Recommendation level	Class I, level A	Class I, level A	Class IIa, level B	
Recommended Treatment in Patients With Compensated Cirrhosis				
	LDV/SOF	OBV/PTV/r + DSV + RBV	LDV/SOF + RBV	SOF + SMV ± RBV
Treatment duration	24 weeks	24 weeks	12 weeks	24 weeks
Recommendation level	Class I, level A	Class I, level A	Class I, level B	Class IIa, level B

DSV = dasabuvir; HCV = hepatitis C virus; LDV = ledipasvir; OBV = ombitasvir; PEG = pegylated interferon; PTV = paritaprevir; r = ritonavir; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir

* The addition of ribavirin is recommended in patients with genotype 1a HCV infection.

CI, 92–98%) for 12 weeks of ledipasvir/sofosbuvir. All three treatment arms were within the prespecified noninferiority margin of 12 percentage points.

No patients had virological breakthroughs during treatment; however, 23 patients (3.5%) had a virological relapse after the end of therapy. Eleven of those patients were from the group that received eight weeks of ledipasvir/sofosbuvir. The authors concluded that there was no improvement in SVR rates by extending the treatment duration from eight weeks to 12 weeks with ledipasvir/sofosbuvir.

ELECTRON Trial²¹

This study was conducted in New Zealand and aimed to assess the effectiveness of an all-oral regimen of sofosbuvir plus ledipasvir. The treatment arms were ledipasvir/sofosbuvir plus ribavirin for 12 weeks in treatment-naïve patients (n = 25) versus ledipasvir/sofosbuvir

plus ribavirin for six weeks in treatment-naïve patients (n = 25). The primary endpoint was achievement of SVR 12 weeks after the end of therapy. The results of the study showed a 100% SVR rate in patients after 12 weeks of therapy versus a 68% SVR rate in patients who received treatment for six weeks. The rest of the patients in the six-week arm had a virological relapse at the end of therapy. This study suggests that eight weeks might be the shortest effective duration of treatment for this regimen.

ADVERSE EFFECTS

In the ION trials, a total of 13 patients discontinued their treatment regimens due to adverse events; two had received 12 weeks of ledipasvir/sofosbuvir alone and four had received 24 weeks of ledipasvir/sofosbuvir alone. The most common adverse events reported by patients were fatigue, headache, nausea, and insomnia.

The use of ledipasvir/sofosbuvir for 8, 12, or 24 weeks resulted in some laboratory abnormalities. Across the phase 3 trials, select patients experienced mild-to-moderate hyperbilirubinemia, transient and asymptomatic lipase elevations, and a mean hemoglobin change of -0.2 g/dL to -0.6 g/dL from baseline.^{18–20}

DRUG INTERACTIONS

Ledipasvir and sofosbuvir are substrates for the drug transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Their intestinal absorption may be decreased by inducers of these transporters (e.g., rifampin and St. John’s wort). Ledipasvir, but not sofosbuvir, also acts as an inhibitor of intestinal P-gp and BCRP, so it may increase the plasma concentrations of these transporter substrates. Neither sofosbuvir nor ledipasvir are substrates for cytochrome P450 isoenzymes or UGT1A1.¹⁴

Table 3 Comparison of Class I, Level A Recommendations: Harvoni and Viekira Pak^{18–20,26–28}

Trial Name	Harvoni (LDV/SOF)			Viekira Pak (OBV/PTV/r + DSV ± RBV)			
	ION I	ION II	ION III	SAPPHIRE I	PEARL III	PEARL IV	TURQUOISE II
Study population	Treatment-naïve	GT 1 null-responders	Treatment-naïve with no cirrhosis	Treatment-naïve with no cirrhosis	GT 1b treatment-naïve with no cirrhosis	GT 1a treatment-naïve with no cirrhosis	Compensated cirrhosis
Treatment regimen	LDV/SOF ± RBV	LDV/SOF ± RBV	LDV/SOF ± RBV	OBV/PTV/r + DSV + RBV	OBV/PTV/r + DSV ± RBV	OBV/PTV/r + DSV ± RBV	OBV/PTV/r + DSV + RBV
Number of patients enrolled	865	440	647	631	419	305	380
Treatment duration	12 or 24 weeks	12 or 24 weeks	8 or 12 weeks	12 weeks	12 weeks	12 weeks	12 or 24 weeks
SVR12	97%–99%	94%–99%	93%–95%	96.2%	99.5%–99.0%	90.2%–97%	91.8%–95.9%
Relapse	2	11	23	7	1	11	13
Breakthrough	0	1	0	1	0	7	4
Discontinuation due to adverse events	0	0	3	4	0	2	8

DSV = dasabuvir; GT = genotype; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; r = ritonavir; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virological response 12 weeks after treatment

Studies conducted on the impact of acid-suppression therapies on ledipasvir/sofosbuvir determined that the H₂-receptor antagonist famotidine and the proton pump inhibitor omeprazole can decrease the concentration of ledipasvir. Ledipasvir's solubility is pH-dependent and is higher under acidic conditions. It is advised that patients not take an H₂-receptor antagonist at a dose greater than the equivalent of famotidine 40 mg twice daily. A proton pump inhibitor can be taken with or two hours after ledipasvir/sofosbuvir if the dose is equivalent to or less than omeprazole 20 mg daily.¹⁵

Coadministration of anticonvulsants (e.g., phenytoin, carbamazepine), antimycobacterials (e.g., rifabutin, rifapentine), and tipranavir/ritonavir is not recommended as these agents can decrease the concentration of ledipasvir/sofosbuvir through P-gp induction. Simeprevir coadministration is not recommended because it can increase ledipasvir/sofosbuvir's concentration.¹³

DOSAGE AND ADMINISTRATION

Harvoni is a fixed-dose combination tablet containing ledipasvir 90 mg and sofosbuvir 400 mg that is administered once daily.^{18–20} The medication can be taken with or without food and patients can follow the usual missed-dose instructions.¹³

COST

As of March 2015, the average wholesale price (AWP) for Harvoni is \$37,800 for 28 tablets, which constitutes a four-week supply of the medication. The AWP for Viekira Pak, on the other hand, is estimated to be \$33,328 for four weeks of treatment. For the typical 12-week course as outlined in the ION I and ION II trials, the AWP for Harvoni will be \$113,400 versus \$99,983 for 12 weeks of Viekira Pak.²² Depending on the patient's genotype and presence of cirrhosis, the patient on Viekira Pak will require the addition of ribavirin to the regimen, which can decrease the price gap between the two treatments.

Currently, Gilead Sciences and AbbVie, the makers of Harvoni and Viekira Pak, respectively, are offering significant price discounts as they compete for contracts with pharmacy benefit managers (PBMs). So far, CVS Health Corp., Anthem Inc., Humana, and Harvard Pilgrim are among those who have signed contracts with Gilead to make Harvoni the preferred agent on their formularies. AbbVie has signed with Express Scripts to gain exclusive coverage. Not all PBMs have chosen to pick one drug over the other. Prime Therapeutics LLC, which covers 25 million patients in 23 states, has given both drugs preferred status due to substantial discounts offered by the companies. The price of the hepatitis C

drugs might drop further in coming years as more competitors enter the market.^{23,24}

CONCLUSION

In the past decade, there have been many changes in the treatment of HCV with the addition of new and more effective agents. Harvoni is the first once-daily, fixed-dose oral combination therapy that has been approved for HCV genotype 1. It is unique in that it does not require the coadministration of interferon and/or ribavirin and has demonstrated superior SVR rates at the end of post-treatment week 12 compared to historical controls. As of December 19, 2014, Harvoni had earned a place in the HCV treatment guidelines, along with Viekira Pak (Tables 1, 2, and 3).

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