Sofosbuvir-Velpatasvir-Voxilaprevir for Chronic Hepatitis C - A Review

Abstract

Hepatitis C virus (HCV) infection affects as many as 185 million people worldwide. Since the emergence of new direct-acting agents (DAAs), interferon-free therapy has become the cornerstone of treatment. These combination therapies result in more effective treatment, shorter duration of therapy, and better tolerability compared to older therapies. However, there remain subgroups of patients that are more difficult to treat such as those with cirrhosis, those infected with HCV genotype 3, and those who have failed previous treatment—particularly those who failed an NS5A inhibitor combination. Furthermore, a minimum of 12 weeks of therapy is typically required for these patients. This review will summarize the evidence for the newly available combination therapy of sofosbuvir, velpatasvir, and voxilaprevir for the treatment of chronic HCV.

Keywords: Direct acting antiretroviral agents; HCV; Hepatitis C; Voxilaprevir; Sofosbuvir; Velpatasvir; Vosevi

Abbreviations: HCV: Hepatitis C; DAA: Direct-Acting Antiretroviral Agent; HBV: Hepatitis B Virus; HIV: Human Immunodeficiency Virus; RNA: Ribonucleic Acid; SVR: Sustained Virologic Response; SOF: Sofosbuvir; VEL: Velpatasvir; VOX: Voxilaprevir; RAS: Resistance-Associated Substitution; IDSA: Infectious Diseases Society of America; AASLD: American Association for the Study of Liver Diseases; BCRP: Breast Cancer Resistance Protein; CYP: Cytochrome P450; OATP: Organic Anion-Transporting

Introduction

Hepatitis C virus is associated with a substantial disease burden in the western world. It is the leading cause of chronic hepatitis, cirrhosis, and liver cancer; and is a primary indication for liver transplantation [1]. As many as 185 million persons worldwide, including 3.4 to 4.4 million in the United States, are chronically infected with HCV; 3 to 4 million individuals are estimated to be newly infected each year [2,3]. Acute infection develops within 2 to 26 weeks after HCV exposure [4,5]. Some of these acutely infected patients may spontaneously clear HCV, but the majority will progress to chronic infection [6]. Approximately 25% of chronically infected persons will develop cirrhosis. Progression to cirrhosis was thought to occur gradually over 25 to 30 years; however, some data suggest that this progression can occur over 5 to 10 years in some individuals, especially in those over 58 years of age [7]. Other factors that accelerate progression to cirrhosis include coinfection with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV) [8,9]. Once cirrhosis develops, 25% of patients will develop hepatocellular carcinoma and/or decompensated liver disease, and eventually death [7]. Upwards of 350,000 people worldwide die from HCV-related complications each year [10].

HCV is an enveloped positive-sense viral ribonucleic acid (RNA) [11]. The viral RNA uses the host’s hepatocyte ribosomes for translation into a polyprotein that is processed into ten polypeptides with their own distinct functions [12]. The replication machinery lacks proof-reading, resulting in viral mutations and a high level of variation [13]. The variations differ greatly based on geographic origin, leading to seven major HCV genotypes [2,14]. Each genotype is grouped into a number of subtypes denoted by the letters a, b, etc [15,16]. The most prevalent HCV genotype in the United States is genotype 1, constituting about 75% of all infections; the remaining 25% is comprised of genotypes 2 and 3 [2]. The HCV lifecycle begins when the virion enters hepatocytes and is translated into a polyepitope consisting of ten structural and non-structural proteins. The structural proteins include capsid protein C and the envelope glycoproteins E1 and E2. The non-structural proteins include porin p7, autoprotease and assembly factor NS2, serine protease and RNA helicase NS3, NS3 protease co-factor NS4A, the organizer of replication complex and membranous web NS4B, the regulator of replication and viral assembly NS5A, and RNA-dependent RNA polymerase NS5B. The resulting HCV polypeptide is cleaved by cellular proteases and viral NS2/3 and NS3/4A proteases to release the ten HCV proteins [15]. The replication complex is formed next. NSSA plays an important role in the formation of this replication complex [12,17]. The HCV RNA template binds to NSSA in the complex [18]. Lipid biosynthesis also plays a central role in the HCV lifecycle. Lastly, the mature virus is released from cells as lipoviral particles [12].

Treatment of HCV

The primary outcome in HCV clinical trials is sustained virologic response 12 weeks after the end of treatment (SVR12), defined as undetectable HCV RNA serum levels. Analyses of
studies using interferon-based treatment have shown that an SVR is associated with lower all-cause mortality in patients with HCV infection and advanced hepatic fibrosis and in patients with HCV-HIV coinfection, including both liver-related and non-liver-related mortality [19-22]. The combination of peginterferon and ribavirin was considered the standard of care for patients with HCV for many years [23]. The introduction of direct-acting agents in 2011, specifically first-generation NS3/4A protease inhibitors, led to interferon-sparing combinations resulting in a shorter duration of therapy with a higher rate of virologic cure [24]. As more classes of DAAs were introduced, agents from two or more classes could be combined to eliminate the need for peginterferon, which was previously needed to reduce the emergence of resistance to protease inhibitors [25]. Disease association is largely similar across all HCV genotypes, but treatment response varies [15]. Genotype 3, for example, has improved rates of SVR with peginterferon and ribavirin compared to genotypes 1 or 4. However, it also had diminished clinical benefits in response to the first-generation HCV protease inhibitors telaprevir and boceprevir. The results of clinical trials have confirmed that the non-CC IL28B genotype, which is associated with poor response to peginterferon-containing regimens, is not associated with poor response to interferon-free treatments [26-29]. However, patients with cirrhosis and/or HCV genotype 3 remain difficult to treat compared to patients without cirrhosis or those with other HCV genotypes [30]. The most promising progress in HCV genotype 3 treatment was in a fixed-dose regimen of sofosbuvir and velpatasvir (SOF/VEL) in June 2016, resulting in 95% SVR after 12 weeks of treatment [31]. Until recently, there was no approved regimen for patients who had failed an HCV regimen containing an NS5A inhibitor.

### Sofosbuvir-Velpatasvir-Voxilaprevir (SOF-VEL-VOX)

The combination of sofosbuvir, velpatasvir, and voxilaprevir (SOF-VEL-VOX) has been evaluated for the treatment of HCV genotype 1 through 6 in clinical trials and was approved by the U.S. Food and Drug Administration July 18, 2017. These three DAAs are manufactured by Gilead Sciences. Their pharmacokinetic properties can be found in Table 1. Sofosbuvir, an HCV NS5B polymerase inhibitor, is currently indicated for the treatment of HCV genotypes 1 through 4 [32]. It also has *in vitro* activity against HCV genotypes 1 through 6 [33]. Sofosbuvir is a prodrug that must be converted to its active metabolite GS-461203 within hepatocytes [34]. It can be taken without regard to food [33]. Since 80% of sofosbuvir is eliminated via urine, it is not recommended for patients with a glomerular filtration rate < 30 mL/min/1.73 m² or with end-stage renal disease. These patients have exhibited 5-fold or greater increases in the serum concentration of sofosbuvir’s active metabolite during pharmacokinetic studies [35]. Additionally, clinical trials have generally excluded patients with creatinine clearance < 60 mL/min. Sofosbuvir is generally well-tolerated when included in interferon-free combination therapies. However, post-marketing surveillance has revealed a risk of serious and potentially fatal bradycardia when sofosbuvir is taken with amiodarone.

### Table 1: Pharmacokinetic Properties of SOF-VEL-VOX

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sofosbuvir [34,53]</th>
<th>Velpatasvir [54]</th>
<th>Voxilaprevir [39-41]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>400 mg once daily</td>
<td>100 mg once daily</td>
<td>100 mg once daily</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>0.5 h (parent drug), 27 h (active metabolite)</td>
<td>16-19 h</td>
<td>29-42 h</td>
</tr>
<tr>
<td><strong>Protein-binding</strong></td>
<td>60%</td>
<td>99%</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Urine (80%), feces (14%)</td>
<td>Feces (99%), urine (1%)</td>
<td>Feces</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>Category B</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Substrate</strong></td>
<td>P-glycoprotein, BCRP</td>
<td>P-glycoprotein</td>
<td>OATP, P-glycoprotein, CYP3A</td>
</tr>
<tr>
<td><strong>Inhibition</strong></td>
<td>Intestinal BCRP, P-glycoprotein</td>
<td>---</td>
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</tr>
</tbody>
</table>

BCRP: Breast Cancer Resistance Protein; CYP: Cytochrome P450; OATP: Organic Anion-Transporting Polypeptides

Velpatasvir is a second-generation HCV NS5A inhibitor. It possesses pan-genotypic antiviral activity *in vitro* [37]. Pharmacology studies have not found any clinically significant drug interactions between velpatasvir and sofosbuvir. Unlike sofosbuvir, velpatasvir is primarily eliminated in the feces, with less than 1% eliminated in the urine [38]. Voxilaprevir is a second-generation HCV NS3/4A inhibitor. It has potent *in vitro* activity against HCV genotypes 1 through 6. It also has an improved resistance profile against commonly encountered genotype 1 NS3 resistance-associated substitutions (RAS) [39,40]. A phase 1 study evaluating drug-drug interactions with the combination of SOF-VLE-VOX found a significant increase in the concentration of rosuvastatin (a breast cancer resistance protein/organic anion-transporting polypeptide substrate) but not pravastatin (an organic anion-transporting polypeptide substrate) [41]. Furthermore, there were no significant interactions with bicitravir, cobicistat, darunavir, elvitegravir, emtricitabine, rilpivirine, or tenofovir. No changes in ethinyl estradiol or norgestrel pharmacokinetics were seen, either. While VOX concentrations were increased when administered with voriconazole, use of CYP3A inhibitors was permitted in phase 3 trials. There was no interaction between VOX and grapefruit juice. Concurrent use of VOX with efavirenz, atazanavir/ritonavir, or potent P-glycoprotein/CYP inducers is not recommended. Concurrent use of VOX with rifampin is contraindicated.

Clinical Trials

The safety and efficacy of SOF-VEL-VOX has been evaluated in several phase 2 studies. There seemed to be a lack of benefit to the addition of ribavirin to SOF-VEL-VOX for treatment-naïve patients with cirrhosis in these studies [40,42]. In addition, a minimum of 8-weeks of treatment appeared to be necessary as shorter treatment durations resulted in low SVR rates [40,43,44]. SOF-VEL-VOX has been evaluated in several phase 3 trials. POLARIS-1 [45] was a double-blind, placebo-controlled, multicenter, phase 3 trial in the United States, Canada, New Zealand, Australia, France, Germany, and the United Kingdom. The study enrolled 415 patients with HCV genotypes 1 through 6 who had previously failed a regimen containing an NSSA inhibitor (i.e. NSSA-experienced), 41% of whom had compensated cirrhosis. Patients were randomized to receive SOF-VEL-VOX 400 mg/100 mg/100 mg once daily or a placebo for 12 weeks. Only patients with HCV genotype 1 were assigned to the placebo group. Patients with creatinine clearance < 50 mL/min as calculated by the Cockcroft-Gault equation and those with decompensated cirrhosis were excluded. Overall, 172 patients had cirrhosis, 218 patients had HCV genotype 1a, and 98% of patients with cirrhosis. The treatment was well-tolerated, with no patient discontinuing SOF-VEL-VOX due to adverse events. Common adverse events included headache (25%), fatigue (21%), diarrhea (18%), and nausea (14%), all of which also occurred in the placebo arm with similar frequencies.

POLARIS-3 [46] was an open-label, active-controlled, multicenter, phase 3 trial in the United States, Canada, New Zealand, Australia, France, Germany, and the United Kingdom. The study enrolled 415 patients with HCV genotypes 1 through 6 who had previously failed a regimen containing a DAA but not an NSSA inhibitor, 46% of whom had compensated cirrhosis. Patients were randomized to receive SOF-VEL-VOX 400 mg/100 mg/100 mg once daily or SOF-VEL 400 mg/100 mg for 12 weeks. Patients with creatinine clearance < 50 mL/min as calculated by the Cockcroft-Gault equation and those with decompensated cirrhosis were excluded. Overall, 174 patients had cirrhosis, 341 patients had HCV genotype 1a, 116 patients had HCV genotype 2, and 181 patients had HCV genotype 3. SVR12 was achieved in 95% and 98% of all patients who received 8 weeks of SOF-VEL-VOX and 12 weeks of SOF-VEL, respectively. Despite a high SVR rate in the SOF-VEL-VOX group, the study failed to show pre-specified non-inferiority to 12 weeks of SOF-VEL. Among patients who received 8 weeks of SOF-VEL-VOX, SVR12 was achieved in 92% of patients with HCV genotype 1a, 97% of patients with HCV genotype 2, 99% of patients with HCV genotype 3, and 91% of patients with cirrhosis. Overall, virologic relapse by post-treatment week 12 occurred in 21 patients (4%) in the SOF-VEL-VOX group and 3 patients (1%) in the SOF-VEL group. The treatment was well-tolerated, with no patient discontinuing SOF-VEL-VOX due to adverse events. Common adverse events included headache (27%), fatigue (21%), diarrhea (18%) and nausea (16%) among patients receiving SOF-VEL-VOX, and headache (23%), fatigue (21%), nausea (9%), and diarrhea (7%) among patients receiving SOF-VEL.

POLARIS-4 [45] was an open-label, active-controlled, multicenter, phase 3 trial in the United States, Canada, New Zealand, Australia, France, Germany, and the United Kingdom. The study enrolled 333 patients with HCV genotypes 1 through 4 who had previously failed a regimen containing a DAA but not an NSSA inhibitor, 46% of whom had compensated cirrhosis. Patients were randomized to receive SOF-VEL-VOX 400 mg/100 mg/100 mg once daily or SOF-VEL 400 mg/100 mg for 12 weeks. Patients with creatinine clearance < 50 mL/min as calculated by the Cockcroft-Gault equation and those with decompensated cirrhosis were excluded. Overall, 153 patients had cirrhosis, 181 patients had HCV genotype 1a, 98 patients had HCV genotype 3. SVR12 was achieved in 92% of patients who received 12 weeks of SOF-VEL-VOX and 12 weeks of SOF-VEL, respectively. Despite a high SVR rate in the SOF-VEL-VOX group, the study failed to show pre-specified non-inferiority to 12 weeks of SOF-VEL. Among patients who received 8 weeks of SOF-VEL-VOX, SVR12 was achieved in 92% of patients with HCV genotype 1a, 97% of patients with HCV genotype 2, 99% of patients with HCV genotype 3, and 91% of patients with cirrhosis. Overall, virologic relapse by post-treatment week 12 occurred in 21 patients (4%) in the SOF-VEL-VOX group and 3 patients (1%) in the SOF-VEL group. The treatment was well-tolerated, with no patient discontinuing SOF-VEL-VOX due to adverse events. Common adverse events included headache (27%), fatigue (21%), diarrhea (18%) and nausea (16%) among patients receiving SOF-VEL-VOX, and headache (23%), fatigue (21%), nausea (9%), and diarrhea (7%) among patients receiving SOF-VEL.

POLARIS-2 [46] was an open-label, active-controlled, multicenter, phase 3 trial in the United States, Canada, New Zealand, Australia, France, Germany, and the United Kingdom. The study enrolled 941 treatment-naïve patients with HCV genotypes 1 through 6, 18% of whom had compensated cirrhosis. Patients were randomized to receive SOF-VEL-VOX 400 mg/100 mg/100 mg once daily for 8 weeks or SOF-VEL 400 mg/100 mg for 12 weeks. Patients with creatinine clearance < 50 mL/min as calculated by the Cockcroft-Gault equation and those with decompensated cirrhosis were excluded. Overall, 174 patients had cirrhosis, 341 patients had HCV genotype 1a, 116 patients had HCV genotype 2, and 181 patients had HCV genotype 3. SVR12 was achieved in 95% and 98% of all patients who received 8 weeks of SOF-VEL-VOX and 12 weeks of SOF-VEL, respectively. Despite a high SVR rate in the SOF-VEL-VOX group, the study failed to show pre-specified non-inferiority to 12 weeks of SOF-VEL. Among patients who received 8 weeks of SOF-VEL-VOX, SVR12 was achieved in 92% of patients with HCV genotype 1a, 97% of patients with HCV genotype 2, 99% of patients with HCV genotype 3, and 91% of patients with cirrhosis. Overall, virologic relapse by post-treatment week 12 occurred in 21 patients (4%) in the SOF-VEL-VOX group and 3 patients (1%) in the SOF-VEL group. The treatment was well-tolerated, with no patient discontinuing SOF-VEL-VOX due to adverse events. Common adverse events included headache (27%), fatigue (21%), diarrhea (18%) and nausea (16%) among patients receiving SOF-VEL-VOX, and headache (23%), fatigue (21%), nausea (9%), and diarrhea (7%) among patients receiving SOF-VEL.

The results of POLARIS-1 and POLARIS-4 confirm that 12 weeks of SOF-VEL-VOX is safe and effective in patients with HCV infection, including those infected with HCV genotype 3 and those who are NS5A-experienced.
Resistence

Sofosbuvir has a high barrier to resistance. No resistant variants have been detected in clinical trials when it was used as part of dual or triple therapy [47,48]. In the ELECTRON [49] trial, however, when sofosbuvir was used as monotherapy to treat HCV genotype 2 or 3, one patient developed the S282T resistance mutation. This mutation has not been isolated in patients with genotype 1. Velpatasvir also has a high barrier to resistance. In ASTRAL-1 [50], two patients exhibited virologic relapse by post-treatment week 4, both of whom had NS5A-resistant variants at baseline. However, 99% of patients with baseline NS5A-resistant variants achieved SVR12. In ASTRAL-2 [31], 134 patients in the SOF-VEL group had NS5A RAS at baseline, most commonly L31M (52%). Despite the presence of pretreatment NS5A and NS5B RAS, no patient receiving SOF-VEL had virologic failure. In ASTRAL-3 [31], 43 patients had a detectable NS5A RAS (A30K, L31M, and Y93H) at baseline. Of these patients, 38 (88%) achieved an SVR. Of the 25 patients with the Y93H RAS at baseline, 21 (84%) achieved an SVR. Of the 231 patients without NS5A RAS at baseline, 225 (97%) had an SVR. All 10 patients with a baseline NS5B RAS (N142T, L159F, E237G, L320I, and V321A/I) achieved an SVR. In ASTRAL-4 [51], a total of 22 patients had virologic failure, 9 of whom had HCV genotype 1. In the 12-week SOF-VEL arm, three patients with genotype 1a and two patients with genotype 1b had relapsed, while one patient with genotype 1a in the arm receiving 12 weeks of sofosbuvir-velpatasvir plus ribavirin had relapsed. In the arm receiving 24 weeks of SOF-VEL, two patients with genotype 1a and one patient with genotype 1b had relapsed. Among patients with HCV genotype 1 and baseline NS5A resistance-associated variants, the rate of SVR12 was 80% and 90% with 12 and 24 weeks of SOF-VEL, respectively, and 100% with the addition of ribavirin. All patients with baseline NS5B resistance-associated variants achieved SVR12.

Voxilaprevir has a high barrier to resistance as well. While the presence of baseline HCV genotype 1 NS5A RASs has been associated with a higher rate of virologic failure with sofosbuvir-ledipasvir, the presence of baseline RASs appears to have no impact on treatment outcomes with SOF-VEL-VOX in a phase 2 trial [40]. In POLARIS-1, 83% (205/248) of patients receiving SOF-VEL-VOX had viral substitutions associated with resistance to NS3 inhibitors or NS5A inhibitors at baseline. Of these patients, 97% (199/205) achieved an SVR. In POLARIS-4, 49% of patients had viral substitutions associated with resistance to NS3 inhibitors or NS5A inhibitors at baseline. The SVR rate was 100% (83/83) among these patients for whom viral sequence data were available. In POLARIS-2, the rates of SVR in patients with and without baseline RAS in HCV genotype 1a were 89% and 95%, respectively. The Q80K RAS was the most commonly observed HCV genotype 1a NS3 variant. Although the Q80K RAS does not confer change to voxilaprevir susceptibility in vitro, it was associated with a reduction in SVR rates in patients with HCV genotype 1a who received 8 weeks of SOF-VEL-VOX. Of the 21 patients who relapsed in the SOF-VEL-VOX group by post-treatment week 12, 1 had treatment-emergent NS5A RAS Q30R and L31M. In POLARIS-3, all 46 patients with baseline RAS achieved an SVR.

Conclusion

Over recent years, we have experienced great advancements in the treatment of HCV with high cure rates in clinical trials. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) guidelines for HCV currently recommend a daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with ribavirin for patients who have baseline NS5A RASs for elbasvir, but offer no recommendations for those patients who have failed other NS5A inhibitors [52]. SOF-VEL-VOX combinations offers effective therapy for NS5A-experienced patients as well as for patients with HCV genotype 3 and cirrhosis who have historically been difficult to treat. However, these patients still require 12 weeks of therapy. While SOF-VEL-VOX seems to be a promising 8-week option for treatment-naive patients, more data are needed due to the lack of non-inferiority established in POLARIS-2. Emerging therapies could potentially eliminate the need for 12 weeks of therapy in the coming years. Cost is also an issue that may limit the accessibility of these regimens. As more regimens become available, there will be more opportunities to decrease the burden of HCV infection and its complications. In the meantime, 12 weeks of SOF-VEL-VOX is effective for treatment of all HCV genotypes, regardless of treatment status [53,54].

Disclosures

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Conflict of Interest

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References

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