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Sofosbuvir + velpatasvir + voxilaprevir for the treatment of hepatitis C infection

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Abstract

Introduction—Hepatitis C is a disease with a significant global impact. Over the last several years, the treatment of the disease has been revolutionized. Therapy has transformed over the last several years with the approval of second generation direct acting antivirals, and currently utilized medications for the treatment of hepatitis C are significantly more efficacious with better safety profiles than previously approved treatments. Treatment for individuals who have failed therapy on direct acting antivirals has, until recently, been complex and difficult to treat, but the approval of sofosbuvir/velpatasvir/voxilaprevir represents a new therapeutic option for these individuals.

Areas covered—Sofosbuvir/velpatasvir/voxilaprevir is a recently approved therapeutic combination for the treatment of hepatitis C. This article reviews the studies leading to the approval of the combination, and its efficacy and safety profile.

Expert opinion—Sofosbuvir/velpatasvir/voxilaprevir fills one of the previously unfilled niches for the treatment of hepatitis C, that of the treatment of individuals who have failed therapy with resistant virus. With the filling of this niche, there appears to be a general slowing of the development of new therapeutics. Although understandable, in the long term, there are considerable risks associated with the decreased development of new drugs to treat hepatitis C.

Keywords

Hepatitis C; NS3 protease inhibitor; NS5A inhibitor; NS5B polymerase inhibitor; sofosbuvir; velpatasvir; voxilaprevir

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Declaration of interest

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1. Introduction

Hepatitis C (HCV) is a disease with a large public health impact, both globally and in the United States. Global HCV prevalence in 2015 has been estimated at 71.1 million infections [1]. Since the identification of the virus in 1989, considerable efforts have been exerted to attempt to cure the virus. Early treatment regimens with interferon-based products were characterized by long treatment courses, significant side effects, and poor therapeutic responses.

Due to the poor efficacy and broad side effect profile of these early drugs, considerable time and effort was dedicated toward developing new drugs which could effectively prevent replication of HCV, eventually leading to the elimination of the virus from infected individuals. This research led to the development of three classes of drugs, which are largely categorized as direct-acting antivirals (DAAs). First, protease inhibitors (PIs) target the NS3 protease, a requirement for the generation of critical viral proteins [2]. Next, nonstructural protein 5B (NS5B) polymerase inhibitors target a polymerase necessary for the production of viral RNA [3]. Finally, the nonstructural protein 5A (NS5A) inhibitors target a protein which is involved with numerous processes in the viral life cycle, including replication and assembly and how the virus interacts with host cell processes [4]. Similar to the treatment of HIV-1, these drugs are exclusively used in combinations of at least two drugs covering two or more classes of medications. Indeed the response rates of current regimens can exceed 95%, after 8–12 weeks of therapy for adherent individuals without cirrhosis who have not previously been treated with DAAs.

2. Overview of the market

When the first DAAs were approved in 2011, they largely revolutionized care for patients with HCV. Telaprevir and boceprevir, an NS3/4A protease and an NS3A PI, were approved, and in combination with pegylated (PEG) interferon/ribavirin (RBV) therapy led to significantly higher responses, with up to 75% of patients with genotype 1 achieving a sustained virologic response (SVR), a key marker for clearance of the body [5]. The approval of the second-generation DAAs in 2013 further revolutionized care, with combination therapies providing shorter time courses, higher therapeutic responses, better side effect profiles, and, in some cases, pan-genotypic coverage of HCV as compared to earlier drugs.

While the drug combinations that have been approved can be extremely efficacious, not all patients have a therapeutic response. This can occur for multiple reasons, notably (1) poor or incomplete adherence to the prescribed drugs; (2) preexisting resistance to prescribed medications, which has been reported to occur with 10–15% of patients even when treated with new medications; and (3) drug–drug interactions [6]. There was thus an unmet need to develop strategies to treat HCV in patients previously treated with other medications.

3. Introduction to the compounds

Sofosbuvir (SOF) is a nucleotide analog inhibitor of NS5B. In addition to Vosevi[®], SOF is commercially available as a single entity, and in other therapeutic combinations. Velpatasvir

(VEL) is an HCV NS5A inhibitor. Voxilaprevir (VOX) is an HCV NS3/4A PI and is a new molecular entity that is only available in SOF/VOX/VEL (Box 1) [7].

Box 1

Drug summary

Drug name	Sofosbuvir	Velpatasvir	Voxilaprevir
Phase	Launched		
Indication	HCV infection		
Pharmacology description/mechanism of action	NS5B protease inhibitor	NS5A protease inhibitor	NS3/4A protease inhibitor
Route of administration		Oral	
Chemical structure
Pivotal trials		[31–33]	

3.1. Chemistry

SOF, also known as PSI-7977 and GS-7977, is a prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate. It is activated in the liver [8]. The active form of SOF, especially the 2'-C-methyl group, is a very potent inhibitor of HCV protease NS5B, causing chain termination and disruption during viral replication [9]. SOF has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45 g/mol. SOF is a weak acid with pK_a of 9.3. It has low solubility in water (pH 2–7.7) [7].

VEL, previously known as GS-5816, is a multifunctional NS5A inhibitor that can interfere with the NS5A protein function at multiple stages of the HCV life cycle [10]. VEL contains a central aromatic scaffold flanked by two dipeptidic moieties. This structure can suppress RNA replication by preventing NS5A dimer formation and RNA binding [11,12]. VEL has a molecular formula of $C_{49}H_{54}N_8O_8$ and a molecular weight of 883.0 g/mol. It is a weak base with pH-dependent solubility. It is soluble at pH 1.2, sparingly soluble at pH 2, and practically insoluble at pH > 5 [7].

VOX, previously known as GS-9857, is a macrocyclic, reversible NS3/4A PI. It can bind reversibly to the NS3/4A active site and interfere the self-cleavage of the HCV polyprotein [10]. Compared with other classes of HCV PIs, VOX has the unique macrocyclic structure that connects quinoxaline substituent of proline core to cycloalkyl substituent of C-terminal

carbamate, which provides an improved resistance profile [13]. It has a molecular formula of $C_{40}H_{52}F_4N_6O_9S$ and a molecular weight of 868.94 g/mol. It is practically insoluble in aqueous media across the physiological pH [7].

3.2. Pharmacodynamics

SOF inhibits HCV genotype 1b wild-type and S282T replicons with EC_{90} values of 0.42 and 7.8 μM [14]. In addition, SOF shows a broad activity across other HCV genotypes. In addition to its broad activity, SOF also displays an excellent resistance profile. The common mutant S282T only shows a very modest shift in EC_{50} for SOF in genotype 2a (JFH-1) replicons [15]. Overall, SOF demonstrates the EC_{50} values ranged from 0.015 to 0.11 μM in genotypes 1a, 1b, 2a, 3a, 4a, 4d, and chimeric 1b replicons encoding NS5B in genotypes 2b, 5a, or 6a [7].

VEL has potent activity against all six major HCV genotypes in preclinical studies. The EC_{50} ranges from 0.02 to 0.13 nM. Phenotypic analysis in Huh7 cells shows that VEL has a low-to-mid resistance in the HCV genotype 1a replicon. Although high levels of resistance have been observed in Y93H/N/R/W and double mutants, the majority of the HCV genotypes 2a, 3a, and 4a single mutants show no or low levels of resistance to VEL [16].

Compared with other HCV PIs, VOX has broader coverage of NS3/4A protease polymorphisms, and an improved resistance profile against NS3 resistance-associated substitutions [7,17]. These characteristics are commonly encountered in HCV genotypes 1a and 1b *in vitro* [18]. In HCV replicon assays, VOX demonstrates a similar antiviral activity of EC_{50} of 0.2–6.6 nM against laboratory and clinical isolates from genotypes 1 to 6 [7].

Overall, the combination of SOF, VEL, and VOX is currently indicated for the treatment of HCV genotypes 1–6. The combination of SOF, VEL, and VOX shows no antagonistic effect in reducing HCV RNA levels in replicon cells. Median EC_{50} values for SOF is 15–110 nM in clinical isolates. VEL has median EC_{50} values of 0.002–0.13 nM in clinical isolates. VOX has median EC_{50} values of 0.2–6.6 nM in clinical isolates [7].

3.3. Pharmacokinetics (PK) and metabolism

3.3.1. Sofosbuvir—SOF exhibits excellent bioavailability. SOF is rapidly absorbed after oral administration, and the median time to reach the peak plasma concentration (C_{max}) is approximately 0.5–2 h post-dose. Approximately 65% of the drug is bound to plasma proteins, with a blood-to-plasma ratio of approximately 0.7. SOF is metabolized in the liver by cathepsin A or carboxylesterase 1, in which the phosphoramidate cleavage occurs by histidine triad nucleotide-binding protein 1. Its metabolism produces a pharmacologically active nucleoside analog triphosphate, GS-461203, which is not detectable in plasma. GS-461203 is further dephosphorylated to GS-331007, a predominant circulating metabolite [8]. A majority of the drug (80%) is eliminated in urine. Approximately 15% of the drug is excreted in feces and 2.5% in expired air. The median elimination $t_{1/2}$ of SOF and GS-331007 is 0.4 and 27 h, respectively [7].

3.3.2. Velpatasvir—In a phase I study, the oral bioavailability of VEL was demonstrated to be 25–30%. After single or multiple dosing, the maximal concentration of VEL in plasma

($C_{\max}$) is reached in 1.5–3.5 h. More than 99.5% of the drug is bound to plasma proteins. The drug is metabolized by CYP2B6, CYP2C8, and CYP3A4 enzymes. VEL is majorly eliminated by biliary route, and its median elimination half-life ($t_{1/2}$) ranges from 11.2 to 16.2 h. Approximately 95% of the drug is excreted in feces with 77% as parent compound, and 0.4% is excreted in urine [19].

3.3.3. Voxilaprevir—VOX is absorbed quickly into systemic circulation, with maximum concentration achieved in 2–5 h post-dosing. Across the multiple doses tested, median steady-state half-life of VOX was 28–41 h. The drug is >99% plasma protein bound and it is metabolized by CYP3A4. Therefore, drug levels may vary when coadministered with CYP3A4 inhibitors/inducers. The drug is eliminated by biliary route and terminal elimination $t_{1/2}$ is 33 h. Approximately 95%, with 40% as parent drug, is excreted in feces [7].

3.3.4. Sofosbuvir/velpatasvir/voxilaprevir— AUC_{0-24} and $C_{\max}$ of SOF are similar in healthy adults and patients with active HCV. Compared to healthy subjects ($N=137$), VEL AUC_{0-24} and $C_{\max}$ are 41% and 39%, respectively, are decreased in HCV-infected subjects. In HCV patients, VOX AUC_{0-24} and $C_{\max}$ are both 260% higher than healthy subjects ($N=63$) [20].

4. Clinical efficacy

4.1. Phase I studies

A phase I study of SOF, which was given along with RBV, was done to test the safety and efficacy profile of SOF in HCV patients. This phase I study was done in eight chronic HCV genotype 1-infected patients, seven of whom had an SVR (ClinicalTrials.gov number NCT01441180) [21].

A second trial assessed SOF with weight-based RBV for 24 weeks. The HCV RNA level of all 55 patients treated with SOF in the combination with RBV was lower than the lower limit of detection, but only 38 of them achieved an SVR 12 weeks after the end of therapy (SVR12). Adverse events (AEs) were graded from 1 (mild) to 4 (severe) and only seven patients reported a grade 3 AE in the entire study. The combination of SOF and RBV was safe and well tolerated with no death or discontinuation of treatment [22].

SOF was also tested in HIV-1-infected individuals with HCV. Naggie et al. studied an open-label phase I trial of a 12-week SOF-RBV regimen in HIV-1-coinfected individuals who has acute HCV infection or HCV reinfection (ClinicalTrials.gov number NCT02128217). A total of 17 male patients were enrolled. All the participants achieved on-treatment undetectable HCV RNA. A total of 10 participants (59%) achieved the primary outcome of SVR12 [23].

Rodriguez-Torres et al. reported results of an open-label phase I study of SOF in combination with commonly used antiretroviral drugs in patients coinfecting with HCV/HIV (ClinicalTrials.gov number NCT01565889). A total of 38 patients were enrolled. A majority of patients were male, Caucasian/Hispanic/Latino, and had HCV genotype 1a infection. No

deaths or serious AEs were reported. No clinically significant drug interactions were observed after coadministration of SOF with commonly used antiretroviral drugs in HCV/HIV-coinfected participants [24].

Lawitz et al. reported a randomized, double-blind, dose-ranging phase I study of VEL in patients with chronic HCV infection, conducted at 10 sites in the United States and Puerto Rico (ClinicalTrials.gov number NCT01740791). A total of 120 patients were enrolled in this study to evaluate the safety, PK, and antiviral activity of once-daily administration of VEL at doses ranging from 5 to 150 mg for 3 days in patients with genotypes 1–4 HCV infection [25,26].

Mogalian et al. reported a first-in-human phase I study with VEL to evaluate safety, tolerability, and PK of VEL in healthy human subjects. Single and multiple once-daily administration of VEL were administered in the presence and absence of food. The PK of VEL was not significantly affected by food. A total of 84 healthy human subjects were enrolled into six cohorts, with 72 subjects receiving VEL and 12 subjects receiving placebo. VEL showed a safe and well-tolerated side effect profile in this study, with no serious AEs. The PK parameters of VEL in human were similar with those during preclinical study [19].

Rodriguez-Torres et al. reported a randomized, double-blind, multicenter, dose-ranging phase I study with VOX (ClinicalTrials.gov number: NCT02185794). This study evaluated the safety, tolerability, antiviral activity, and PK of VOX in chronic HCV-infected patients. A total of 67 patients enrolled in this study received placebo or once-daily VOX at doses ranging from 50 to 300 mg for 3 days. All AEs were mild or moderate in severity. VOX demonstrated a potent antiviral activity with median maximum reductions in HCV RNA of 3 log₁₀ IU/mL following administration of a 100-mg dose. It also has an improved resistance profile against commonly encountered genotype 1 NS3 RAS [20].

There is only one open-label phase I study with the combination of SOF, VEL, and VOX to evaluate the fixed-dose combination on the PK of a representative hormonal contraceptive medication [27]. However, results are not available for public. Table 1 outlines the main phase I clinical trials.

4.2. Phase II trials

A total of four phase II trials have been published in the literature pertaining to the efficacy and safety of SOF-VEL + GS-9857 therapy in patients with HCV infection [26–29].

In the first study, Lawitz et al. enrolled 197 patients in two cohorts. Cohort 1 had treatment-naïve patients belonging to four groups: (1) patients without cirrhosis, who received SOF-VEL + GS-9857 for 6 weeks; (2) patients with cirrhosis, who received SOF-VEL + GS-9857 for 8 weeks; (3) patients without cirrhosis, who received 8 weeks of SOF-VEL + GS-9857; and (4) patients with cirrhosis, who received 8 weeks of SOF-VEL + GS-9857 with RBV.

Cohort 2 had two groups of DAA-experienced patients: those with and without cirrhosis. Both groups received 12 weeks of SOF-VEL + GS-9857. All patients received a fixed-dose combination tablet of 400 mg SOF and VEL (100 mg) once daily, along with a 100 mg tablet of GS-9857 once daily. RBV was administered 1000–1200 mg/day. The primary

efficacy outcome was an SVR12. The secondary efficacy outcome was virologic failure. The primary efficacy outcome was achieved in all patients who received at least 8 weeks of treatment in subjects without cirrhosis. Administration of RBV to Group 4 patients did not have any impact on viral load. In the DAA-experienced patients group, 12 weeks of treatment achieved 100% SVR. A total of 18 patients in the treatment-naïve group had virologic relapse. The most common AEs observed were headache, diarrhea, nausea, and fatigue. Among all the study subjects, only one patient from Group 4 discontinued the treatment due to increased ALT levels (grade 3) [26]. This study suggested the utility of SOF/VOX/VEL in individuals who had failed other therapies [30,26].

In another study, Lawitz et al. enrolled 49 HCV patients who were previously treated with a regimen containing at least one DAA for 6 weeks, and were randomized to two groups. Groups 1 and 2 received a fixed-dose combination of the study drug with or without RBV (1000 or 1200 mg/day), respectively, for 12 weeks. Efficacy (i.e. primary or secondary outcomes, or emerging resistance to the study drug), safety, and tolerability of the study drug were assessed. All patients in both groups achieved SVR12, except for one individual who received RBV who relapsed after the end of treatment [29].

Gane et al. also evaluated the efficacy and safety of SOF-VEL + GS-9857 on different HCV genotypes. In one study, they enrolled 161 treatment-naïve or previously treated patients infected with HCV genotypes 1 or 3, with or without cirrhosis. Cohort 1 consisted of HCV genotype 1 patients who have been assigned to seven groups: Groups 1 and 2 – treatment-naïve without cirrhosis, treated for 4 ($n = 15$) and 6 ($n = 15$) weeks; Group 3 – treatment-naïve with cirrhosis received the study drug 6 weeks ($n = 15$); Groups 4 and 5 – DAA-experienced $\pm$ cirrhosis, 6 weeks ($n = 30$); Group 6 –PEG interferon + RBV-experienced with cirrhosis, 8 weeks ($n = 17$); Group 7 – PI-experienced $\pm$ cirrhosis, 8 weeks ($n = 28$). Cohort 2 consisted of HCV genotype 3 patients, assigned to three groups: Group 1 – treatment-naïve with cirrhosis, received the treatment for 6 weeks ($n = 18$); Group 2 – PEG + RBV-experienced with cirrhosis, 8 weeks ($n = 19$); and Group 3 – DAA-experienced $\pm$ cirrhosis, 8 weeks ($n = 4$). All patients in Cohorts 1 and 2 received SOF (400 mg)-VEL (100 mg) + GS-9857(100 mg) once daily. The study findings suggest that treatment of HCV patients' genotype 1 or 3 with SOF-VEL + GS-9857 for 8 weeks produced SVR12 in most treatment-naïve or prior HCV treatment-experienced patients including those with compensated cirrhosis [27].

Gane et al. aimed to test the efficacy, safety, and feasibility of shortening the duration of SOF/VEL + GS-9857 treatment in patients with HCV genotypes 2, 3, 4, or 6 infections who failed to respond to antiviral therapy. The 8- and 12-week treatment regimens were safe and effective in treatment-naïve and pre-treated HCV patients, respectively. Of the entire study population, only two treatment-naïve and one treatment-experienced patients with cirrhosis discontinued the treatment due to AEs [28]. Table 2 summarizes the main phase II clinical trials.

4.3. Phase III trials

The study duration of the POLARIS-2 and POLARIS-3 was 8 weeks, and 12 weeks in the POLARIS-1 and POLARIS-4 studies. The SVR was utilized as the primary efficacy end

point. The enrolled patients were older than 18 years, predominantly white men. Patients enrolled had HCV RNA 10^{-4} IU/ml. For patients who were previously treated with DAAs, treatment must not been discontinued due to adverse drug reactions, and the patients could not have had a virologic failure as a result of nonadherence [31].

In the POLARIS-1 trial, patients with or without cirrhosis were treated with DAAs including NS5A inhibitor (4-week duration). SOF/VOX/VEL was given once daily for 12 weeks. Ninety-six percent of patients had SVR12 response after the treatment. For patients with cirrhosis, the SVR was 93% compared to 99% for patients who did not have cirrhosis. For the most challenging patients who were infected with type 3 virus and with cirrhosis, 52 out of 56 had SVR. None of the patients in the placebo group achieved an SVR. Among the 10 patients who did not have SVR, 7 had a virologic failure with 1 patient experienced a virologic breakthrough during the treatment and 6 had virologic relapses after the end of treatment. The SOF-VEL-VOX for a 12-week treatment resulted in higher SVR rates than the performance goal of 85% ($p < 0.001$) [31,32].

The POLARIS-2 study was performed in patients who were not exposed to DAAs with or without compensated cirrhosis. Enrolled patients were infected with HCV genotypes 1–6. Patients were randomized to receive either 8 weeks of SOF/VOX/VEL or 12 weeks of SOF/VEL. The overall SVR for 8 weeks of SOF/VOX/VEL treatment group was 95% with 91% of the SVR was observed in patients with cirrhosis compared to 96% for patients without cirrhosis in the same treatment group. A higher overall SVR, 98%, was observed in the SOF-VEL treatment group compared to the SOF-VEL-VOX treatment group. The specific SVR for each genotype was 99% for genotype 1a, 97% for genotype 1b, 100% for genotype 2, 97% for genotype 3, 98% for genotype 4, and 100% for genotype 6. In this group, the SVR for patients who had any type of HCV infection and cirrhosis was 99% while 98% was observed in the patients without cirrhosis. For the virologic relapse rate, the SOF/VOX/VEL group maintained a higher rate which was 4% compared with the other treatment group which was 1%. No virologic breakthroughs were observed. No virologic failure occurred in genotype 3 patients. For patients who were not exposed to DAAs, infected with any HCV genotype with or without compensated cirrhosis, this trial failed to show that 8 weeks of SOF/VOX/VEL treatment was non-inferior to 12 weeks of treatment of SOF/VOX, and was a key factor in SOF/VOX/VEL only being approved for individuals who have previously failed therapy in the United States [31,33].

In the POLARIS-3 study, patients who were infected with chronic genotype 3 HCV with cirrhosis but not treated with DAAs before were enrolled. Genotype 3 infection with cirrhosis is the most challenging type of infection. Patients were randomized to receive either 8 weeks of SOF/VOX/VEL or 12 weeks of SOF/VEL. A 96% SVR was observed in both treatment groups by the week of 12. Two (2%) patients in the SOF-VEL treatment group had virologic failure: one patient had virologic relapse at posttreatment week 4, another patient had a virologic rebound at the week of 8. The predominant metabolite of SOF and VEL was detected at low levels in the two patients, suggesting failures to the adherence of study dosing. This trial demonstrated that SOF/VOX/VEL treatment for 8 weeks was comparable to SOF/VEL treatment for 12 weeks in patients who had cirrhosis and HCV genotype 3 infection while not exposed to DAAs previously [31,33].

POLARIS-4 enrolled patients who were treated with any DAAs other than an NS5A inhibitor. Patients had HCV genotypes 1, 2, 3, or 4 infection with or without compensated cirrhosis. In the treatment group, 46% of patients had cirrhosis, 25% of the patients had received treatment with an NS5B inhibitor plus an NS3/4A inhibitor, 74% received an NS5B inhibitor only, and 1% received NS3/4A inhibitor. Patients were randomized to receive either SOF/VOX/VEL or SOF/VEL for 12 weeks. With the overall SVR of 98% in the SOF-VEL-VOX treatment group, the SVR for each specific genotype was 98% for genotype 1a, 96% for genotype 1b, 100% for genotype 2, 96% for genotype 3, and 100% for genotype 4. A 98% SVR was observed for patients with any genotype who had cirrhosis ($n = 84$). For the SOF-VEL treatment group, 29% had genotype 1a, 15% had genotype 1b, 22% had genotype 2, and 34% had genotype 3. Forty-six percent of the patients in this treatment group had cirrhosis, 25% were treated with an NS5B inhibitor plus an NS3/4A inhibitor previously, 72% had prior treatment with an NS5B inhibitor alone, and 2% were treated with an NS3/4A inhibitor previously. The SVR rates for each genotype were 89% for genotype 1a, 95% for genotype 1b, 97% for genotype 2, and 85% for genotype 3. The SVR for patients with any genotype who had cirrhosis was 86%. Out of 182 patients, 4 in the SOF-VEL-VOX treatment group did not have SVR. For the SOF-VEL treatment group, 15 out of 151 patients failed to have SVR: 14 had a relapse and 1 had virologic breakthrough. Among the 14 relapsed patients, 8 had genotype 3a infection, 5 had genotype 1a infection, and 1 had genotype 1b infection. The trial suggested that 12 weeks of SOF-VEL-VOX treatment resulted in high SVR in patients who were exposed to DAAs previously. The trial suggested that 12 weeks of SOF/VOX/VEL treatment resulted in high SVR in patients who were exposed to DAAs previously [31,33]. Table 3 outlines the main phase III clinical trials.

5. Safety

None of the patients in the SOF/VOX/VEL group in both POLARIS-2 and POLARIS-3 discontinued the treatment due to serious AEs. In the POLARIS-2 study, 72% of patients had AEs and 3% patients had serious AEs in the SOF/VOX/VEL group. A single patient experienced only one serious AE. Pyelonephritis was the only serious AE observed in both treatment groups in the POLARIS-2 study. Other AEs observed in the SOF/VOX/VEL treatment group were headache (27%), fatigue (20%), diarrhea (18%), and nausea (16%) compared to headache (23%), fatigue (21%), diarrhea (7%), and nausea (9%) in the SOF/VEL treatment group. In the POLARIS-3 study, 75% of SOF/VOX/VEL-treated patients had AEs. Out of 110 patients, 2 experienced four serious AEs. The rate of AEs in the SOF/VOX/VEL treatment group was comparable to SOF/VEL 12 weeks of treatment group except for mild nausea and diarrhea which has been observed with prior NS3/4A protease inhibitors [3].

It has been reported that in HCV- and hepatitis B virus (HBV)-coinfected patients who were going through or had completed HCV treatment with DAAs, HBV can be reactivated. Cases like fulminant hepatitis, hepatic failure, and death have been reported. The risk of reactivation may be increased in patients who were on HCV DAAs treatment receiving certain immunosuppressant or chemotherapeutic agents, in patients who are HBsAg positive and in patients with serologic evidence of resolved HBV [7].

6. Tolerability

None of the patients who received SOF/VOX/VEL for 8 weeks discontinued the treatment due to the serious AEs in both POLARIS-2 and POLARIS-3 studies compared to 0.5% for patients who received SOF/VEL for 12 weeks in the POLARIS-2 study. None in the 12 weeks of SOF/VOX/VEL treatment group compared to one in the 12 weeks of SOF/VEL treatment group discontinued treatment in the POLARIS-4 study. For mild or moderate renal impaired patients, no dosage adjustment is needed for SOF/VOX/VEL. The therapy is thus well tolerated in patients.

7. Regulatory affairs

Vosevi was approved in the United States 2017 for two indications: individuals who were previously treated with an NS5A inhibitor, regardless of genotype, or individuals with either genotype 1a or 3 who were previously treated with SOF, but without an NS5A inhibitor. The European Medicines Agency approved the drug for the treatment of HCV in 2017, with an 8-week course of action for DAA-naïve patients without cirrhosis, 12 weeks for naïve patients with cirrhosis, and 12 weeks for DAA-experienced patients, regardless of cirrhosis status [34].

8. Conclusions

The therapeutic combination of SOF/VOX/VEL represents a well-tolerated and effective therapy for individuals who have been unsuccessfully treated with other drugs used for HCV. Additionally, it offers a valuable treatment for all major genotypes of HCV. While there are side effects associated with the drug, it is in general very well tolerated with only one individual discontinuing treatment with SOF/VOX/VEL in the phase III trials. Especially compared to the previous generations of treatments for HCV, the side effects that are observed are in many cases minor. The high rate of SVR in individuals treated with SOF/VOX/VEL, even in individuals who have failed therapy with a different therapeutic option will ensure that SOF/VOX/VEL will be a valuable addition to HCV treatment in the years to come.

9. Expert opinion

Over the last 7 years, the revolutions in the approval of drugs and treatment of HCV have radically altered the landscape of anti-HCV agents, even to the point where drugs approved in 2011 are, in many cases, now largely obsolete. With these remarkable changes, the rate of approval and development of new drugs to fight HCV has slowed. Indeed, it appears that many of the niches for the treatment of HCV have been filled with efficacious and well-tolerated treatment regimens for all major HCV genotypes. While individuals who had failed on pre-DAA regimens can be treated with the drugs which had already been approved, until the approval of SOF/VOX/VEL there were inadequate treatment options for individuals who had failed treatment with the newer DAAs.

Within this niche, SOF/VOX/VEL is likely to be able to become a significant player for the treatment of HCV, and represents an important new therapeutic combination for the

treatment of resistant HCV. It is also of high importance to fully evaluate the effectiveness of SOF/VOX/VEL in individuals who have failed newer regimens, including SOF/VEL and glecaprevir/pibrentasvir. While it has not been approved for treatment-naïve patients in the United States, due to the results of the POLARIS-2 trial, there is a critical need for effective therapy in individuals who have failed first-line regimens. The high rate of SVR with SOF/VOX/VEL even in individuals with virus resistant to approved DAAs will likely ensure that SOF/VOX/VEL will have a critical place in therapy for individuals with HCV going forward. As SOF/VOX/VEL contains agents from all three major classes of DAAs, even if partial resistance existed to one of the agents, it is still likely that a successful response will occur. In our opinion, with the high SVR rates for the vast majority of regimens approved for treatment-naïve patients, especially with regimens that can be taken for only 8 weeks, differences in cost and insurance coverage may be one of the major deciding factors for therapeutic decisions. The relatively recent approval of glecaprevir/pibrentasvir, which combines an 8-week time course for treatment-naïve patients, high SVR, and comparatively low cost may limit the utility of SOF/VOX/VEL use in treatment-naïve patients, should SOF/VOX/VEL be approved for use in the United States for that indication. One interesting development that has been observed with the treatment of HCV is that over time we have seen an incredible improvement in durations of therapy and side effect profiles. Even with newer DAAs, durations of therapy have been improved for many regimens from 12 to 8 weeks. The question remains, however, if even shorter courses could be effective. A 2016 study investigated a 6-week time course with ledipasvir/SOF for genotype 1 infection, showing a high SVR [35]. This contrasts to other previous trials with DAAs showing low efficacy with 6 weeks of therapy. Whether this can be extended to other genotypes or other treatment regimens remains an important question.

The rate of development and research into novel DAAs also reflects how available niches for anti-HCV agents have been filled. A number of pharmaceutical companies have refocused their research and development away from HCV and toward HBV, among other disease states. Currently, it appears that the next major steps in the fight against HCV will be vaccine development, and not additional pharmacologic interventions.

While the shift away from the development of novel anti-HCV agents toward other diseases is understandable from a financial standpoint, it is not without risks. While the agents that are currently used are highly efficacious, with a relatively low risk of resistance, resistance to most DAAs can still occur, with reported rates for some agents in the range of 10–15%. As has been seen with antimicrobials, over time resistance to even these newer agents is likely to occur. With the slower rate of new DAA development, there is an increased risk of the development of resistance for these agents.

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Table 1

Phase I trials of sofosbuvir, velpatasvir, and voxilaprevir in HCV.

Author (year)	Population	N	Treatment groups and duration	Overall SVR (N)	Outcomes
Meissner et al. (2014) [21]	HCV patients with genotype 1	8	Sofosbuvir with weight-based ribavirin	7	Safe and well tolerated with no death or discontinuation of treatment.
Naggie et al. (2015) [23]	HIV-1 and HCV-coinfected individuals	17	Sofosbuvir with ribavirin	10	59% achieved SVR12. Safe and well tolerated.
Lawitz et al. (2016) [16]	HCV patients with genotypes 1–4	120	Velpatasvir at doses ranging from 5 to 150 mg	N/A (only 3 days of treatment)	Well tolerated and resulted in rapid declines in HCV RNA that were sustained over the dosing period of 3 days.
Mogalian et al. (2017) [19]	Healthy human subjects	84	72 subjects receiving velpatasvir and 12 subjects receiving placebo	N/A	Safe and well tolerated. No serious adverse effects were reported.
Rodriguez-Torres et al. (2016) [20]	HCV patients with genotypes 1–4	67	Placebo or once-daily voxilaprevir at doses ranging from 50 to 300 mg.	N/A (only 3 days of treatment)	Voxilaprevir demonstrated a potent antiviral activity for a 3-day dosing period and an improved resistance profile against commonly encountered genotype 1 NS3 RAS. All adverse events were mild or moderate in severity.

HCV: hepatitis C virus; N/A: not applicable; SVR: sustained virologic response.

Table 2

Phase II trials of sofosbuvir–velpatasvir + voxilaprevir in patients with hepatitis C virus infection.

Author (year)	Population	N	Drug (dose)	Treatment groups and duration	Overall SVR	Outcome
Lawitz et al. (2016) [26]	Genotype 1 HCV-infected	197	SOF (400 mg) and VEL (100 mg) + GS-9857 (100 mg) once daily, RBV (1000–1200 mg/day).	All patients received SOF-VEL + GS-9857. Rx-naïve patients without cirrhosis: 6 ($n = 34$) and 8 ($n = 36$) weeks. Rx-naïve patients with cirrhosis: With ($n = 31$) or without RBV ($n = 33$) for 8 weeks. Rx-experienced patients with ($n = 32$) or without ($n = 31$) cirrhosis for 12 weeks.	No Cirrhosis 6 weeks: 71% 12 weeks: 100% Cirrhosis 8 weeks no RBV: 94% 8 weeks with RBV: 81% 12 weeks: 100%	8–12 weeks of Rx with SOF-VEL + GS-9857 was safe and effective in achieving SVR12 in patients with HCV regardless of their cirrhosis state. RBV did not have any impact on HCV viral kinetics.
Lawitz et al. (2017) [29]	Genotype 1 HCV-infected patients who failed to achieve SVR on a DAA-based regimen	49	A fixed-dose combination of SOF-VEL-VOX (400, 100 and 100 mg, respectively) once daily. RBV (1000–1200 mg/day).	All patients received SOF-VEL-VOX. DAA-experienced patients with ($n = 25$) or without RBV ($n = 24$) for 12 weeks. All patients received SOF-VEL-VOX.	No RBV: 100% With RBV: 96%	A fixed-dose combination of SOF-VEL-VOX was well tolerated and effective in patients who failed to achieve SVR on a DAA-based regimen.
Gane et al. (2016) [28]	HCV genotype 1 or 3 infected	161	A fixed-dose combination of SOF (400 mg) and VEL (100 mg) + GS-9857 (100 mg) once daily.	All patients received SOF-VEL + GS-9857. HCV-1 genotype: Rx-naïve without cirrhosis received for 4 ($n = 15$) and 6 ($n = 15$) weeks. Rx-naïve with cirrhosis 6 weeks ($n = 15$); DAA-experienced ± cirrhosis, 6 weeks ($n = 30$); PEG + RBV-experienced with cirrhosis, 8 weeks ($n = 17$); PL-experienced ± cirrhosis, 8 weeks ($n = 28$). HCV genotype 3: treatment-naïve with cirrhosis, 6 weeks ($n = 18$); PEG + RBV-experienced with cirrhosis, 8 weeks ($n = 19$); DAA-experienced ± cirrhosis, 8 weeks ($n = 4$).	Genotype 1: Range from 27% to 100% Genotype 3: 6 weeks with cirrhosis: 83% 8 weeks with past treatment: 100%	8 weeks of treatment with the combination of SOF-VEL + GS-9857 achieved SVR12 in most Rx-naïve or previously treated patients including those with compensated cirrhosis.
Gane et al. (2016) [27]	Patients with HCV genotypes 2, 3, 4, or 6 infections whose prior course of antiviral therapy has failed	128	A fixed-dose combination of SOF (400 mg)-VEL (100 mg) and GS-9857 (100 mg) once daily	All patients received SOF-VEL + GS-9857. Rx-naïve with ($n = 30$) cirrhosis without cirrhosis ($n = 33$) received the drug for 8 and 6 weeks, respectively. Rx-experienced patients with ($n = 29$) or without cirrhosis ($n = 36$) received for 12 weeks.	6 weeks no cirrhosis: 88% 8 weeks with cirrhosis: 93% 12 weeks no cirrhosis: 100% 12 weeks cirrhosis: 97%	SOF-VEL + GS-9857 (8 weeks in Rx-naïve patients or 12 weeks in treatment-experienced patients) safe and effective for patients with HCV genotypes 2, 3, 4, or 6 infections regardless of cirrhosis status.

DAA: direct-acting antiviral; PEG: pegylated interferon; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; HCV: hepatitis C virus; SVR: sustained virologic response; RBV: ribavirin; Rx: treatment. N: total number of patients; n : number of patients in that particular group.

Primary outcomes assessed were efficacy and safety.

Efficacy: achieving SVR 12 weeks after the treatment; safety: permanent discontinuation of treatment.

Table 3

Phase III trials of SOF/VOX/VEL in HCV.

Study	Study population	N	Overall SVR (%)	Outcomes
POLARIS-1 [32] 12 weeks of SOF/VOX/VEL	With or without compensated cirrhosis treated with DAAs including NS5A inhibitor chronic hepatitis C genotypes 1, 2, 3, 4, 5, and 6 infection	263	96	12 weeks of SOF/VOX/VEL treatment led to high SVR rate among patients across HCV genotypes who previously failed DAA treatment.
POLARIS-1 [32] placebo		152	0	
POLARIS-2 [33] 8 weeks of SOF/VOX/VEL	With or without compensated cirrhosis not exposed to DAAs chronic hepatitis C genotypes 1, 2, 3, 4, 5, and 6 infection	501	95	8 weeks of SOF/VOX/VEL treatment was not non-inferior to 12 weeks of SOF-VEL.
POLARIS-2 [33] 12 weeks of SOF/VEL		440	98	
POLARIS-3 [33] 8 weeks of SOF/VOX/VEL	With compensated cirrhosis not treated with DAAs chronic hepatitis C genotype 3 infection	110	96	8 weeks of SOF/VOX/VEL treatment was comparable to 12 weeks of SOF/VEL in treating patients had genotype 3 infection and cirrhosis.
POLARIS-3 [33] 12 weeks of SOF/VEL		109	96	
POLARIS-4 [32] 12 weeks of SOF/VOX/VEL	With or without compensated cirrhosis treated with any DAA but an NS5A inhibitor chronic hepatitis C genotypes 1, 2, 3, or 4 infection	182	98	12 weeks of SOF/VOX/VEL treatment led to high SVR rate among patients across HCV genotypes who previously failed DAA treatment.
POLARIS-4 [32] 12 weeks of SOF/VEL		151	90	

SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; HCV: hepatitis C virus; SVR: sustained virologic response; DAA: direct-acting antiviral; NS5A: nonstructural protein 5A.