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Drug profile

Sofosbuvir, Velpatasvir and Voxilaprevir combination for the treatment of hepatitis C

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Abstract

Introduction

The advent of direct-acting antiviral (DAA) treatments for chronic hepatitis C virus (HCV) infection has dramatically increased rates of cure. However, there remain difficult-to-treat populations, including patients with genotype 3 infection and cirrhosis, and limited salvage treatment options for those that have failed first-line DAA therapy.

Areas covered

This is a review of the preclinical and clinical development of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX), an interferon-free, oral, once daily, pangenotypic treatment for chronic HCV infection. All relevant literature from 2015 through June of 2017 is included.

Expert commentary

Voxilaprevir, a second-generation HCV protease inhibitor, in combination with the already approved combination of sofosbuvir and velpatasvir, was evaluated in the POLARIS trials and found to be a safe and effective regimen. Patients with prior DAA treatment failure, genotype 3, cirrhosis and/or unfavorable resistance profiles all achieved cure rates of 96% or greater. The most distinctive role for this potent regimen may prove to be as a salvage regimen for patients who have failed previous DAA therapy.

Keywords: hepatitis C virus (HCV), direct acting antiviral (DAA), sofosbuvir (SOF), velpatasvir (VEL), voxilaprevir (VOX), NS5A, NS5B, NS3/4A, protease inhibitor

1.Introduction

The hepatitis C virus (HCV) is a flavivirus with 6 major genotypes that currently infects approximately 71-150 million people worldwide [1,2]. Untreated chronic HCV infection often leads to progressive liver fibrosis and cirrhosis with the potential for hepatic decompensation and/or hepatocellular carcinoma (HCC). Globally, nearly half a million people die annually from liver disease related to chronic HCV infection [3].

Fortunately, HCV is curable. The first available treatment regimen was prolonged interferon-based therapy, first without and later with ribavirin, which was associated with substantial side effects and a relatively low rate of cure [4]. The first direct-acting antiviral agents (DAAs) were approved in 2011 in the form of two protease inhibitors, telaprevir and boceprevir, each combined with pegylated interferon and ribavirin for genotype 1 infection [5,6]. Subsequent rapid clinical development of new all-oral DAA regimens has dramatically increased overall cure rates to over 95% and this sustained virologic response (SVR) confers an overall mortality benefit with reduced risk of complications in patients with advanced fibrosis or cirrhosis [7]. Thus, the American Association for the Study of Liver Disease (AASLD) and the Infectious Disease Society of America (IDSA) advocate for early access to treatment in all patients with chronic HCV infection [8].

Despite the successes of currently available pangenotypic DAA regimens, a small percentage of patients do not achieve SVR [9-11]. Certain genotypes have proven more difficult to cure than others, notably genotypes 1a and 3, the latter especially in patients with cirrhosis. The presence and emergence of resistance associated substitutions (RASs) confer additional challenges to treatment. Patients who have failed prior treatment currently have no approved options for salvage therapy. Thus, there is an unmet medical need for patients with DAA failure.

2.Overview of current therapy

As of April, 2017, there were 6 approved and recommended DAA regimens on the market in the United States [8], one of which has garnered approval for use across all HCV genotypes [12]. Overall SVR rates with these regimens are well over 90%, and in some cases have approached 99-100%. There remain, however, subgroups of patients that are, at least in a relative sense, more difficult to cure depending on the regimen, the virus and host factors. Most notably, these groups include patients with HCV genotypes 1a and 3, RASs and/or cirrhosis. Current salvage regimens are limited in number and effectiveness, and, as of April 2017, there are no FDA-approved salvage regimens. The AASLD Guidance document recommends deferring re-treatment in certain populations with unfavorable genotypes, RASs and/or previous treatment exposure(s), particularly when there is no urgent need for treatment. To meet this need, a regimen consisting of the fixed-dose combination of sofosbuvir (SOF) 400 mg, velpatasvir (VEL) 100 mg and a second-generation HCV protease inhibitor, voxilaprevir (VOX, formerly GS-9857) 100 mg, developed by Gilead Sciences (Foster City, California), has completed phase III trials across a broad range of HCV-infected populations, including those with DAA failure, and is the focus of this review. Another regimen in development is a fixed-dose combination of glecaprevir 300mg and pibrentasvir 120 mg (G/P, formerly ABT-493 and ABT-530), a pangenotypic protease and NS5A inhibitor, respectively, which has shown promising results as an eight week regimen for noncirrhotic patients, and 12 weeks for cirrhotic patients, across HCV genotypes, as well as high efficacy rates in HIV/HCV coinfection, liver and renal transplant recipients, patients with renal failure, and many patients with DAA failure [13-15]. Another regimen in development with promising pangenotypic efficacy is the already available protease inhibitor grazoprevir (GZR), ruzasvir (RZR, formerly MK-8408), a second-generation NS5A inhibitor, and MK-3682, a nucleotide polymerase inhibitor. The present review will focus on the triplet regimen of sofosbuvir,

velpatasvir, and voxilaprevir.

3.Introduction to Sofosbuvir, Velpatasvir and Voxilaprevir

Sofosbuvir (SOF) is a once-daily pangenotypic HCV NS5B nucleotide polymerase inhibitor approved in the United States and abroad for the treatment of chronic HCV infection [16]. It is an oral prodrug that undergoes hepatic metabolism into an active nucleotide analog that competitively inhibits the NS5B polymerase, thereby preventing viral replication. Velpatasvir (VEL) is a once-daily pangenotypic HCV NS5A protein inhibitor, including equivalent potency in vitro against genotype 3 compared with other genotypes, approved in the United States and abroad for the treatment of HCV infection in combination with SOF (Epclusa, Gilead Sciences) [12,17]. Inhibition of the NS5A protein disrupts HCV replication, assembly and possibly egress [18]. Voxilaprevir (VOX) is a novel macrocyclic NS3/4A protease inhibitor that has recently completed phase III clinical development in combination with SOF/VEL. It has excellent activity across all HCV genotypes and against most of the RASs associated with first-generation protease inhibitors.

4.Pharmacokinetics

As SOF/VEL is already on the market, the pharmacokinetics (pK) of each individual component and the combination of the two drugs are already well-described in the literature [19]. SOF is rapidly absorbed with peak concentrations at 30-60 minutes. Its active metabolite has a half-life of 25 hours and it is renally excreted. SOF is contraindicated in patients taking amiodarone as there is a risk of serious and even fatal symptomatic bradycardia [12]. VEL reaches peak concentration in 3 hours, has a half-life of 15 hours and is excreted through the biliary system. The absorption of VEL decreases as gastric pH increases, leading to the recommendation of avoidance of proton pump inhibitors while taking VEL and limiting the use

of other antacids when possible [12]. No dose adjustment is needed for SOF/VEL in hepatic or moderate renal impairment, but SOF, and therefore SOF-containing regimens, are not approved or recommended for use in patients with GFR<30 as there is accumulation of the major metabolite of SOF and the safety and efficacy of the medication has not been definitively reported in this population [12].

In preclinical and first-in-human studies [20,21], VOX demonstrated linear pK at a dose range of 30-300 mg after single and multiple dose administrations. It reaches peak concentration at 1.8-5 hours and has a half-life of 28-41 hours, supporting once daily dosing. Evaluation of transporter and cytochrome P450-mediated drug-drug interactions found that hepatic OATP plays a significant role in the pharmacokinetics of VOX, and to a lesser extent that of P-gp and CYP3A [22]. VOX may be co-administered with inhibitors of CYP3A or 2C8 without dose modification. It should be administered with potent P-gp inhibitors with caution. Co-administration of VOX with potent hepatic OATP inhibitors, or potent or moderate inducers of CYPs and P-gp is not recommended.

5.Clinical efficacy

The clinical efficacy of SOF/VEL/VOX has been tested in a series of phase I, II and III clinical trials culminating in the POLARIS series [23,24]. The safety and efficacy of SOF/VEL as the first approved pangenotypic regimen has been previously established [12,17,19].

The first published study of GS-9857 (VOX) in HCV infected individuals was in 2016 [25]. In a randomized, double-blind, placebo controlled multicenter 3-day dosing study conducted in the United States and Puerto Rico, the safety, antiviral efficacy and pK of GS-9857 at doses ranging from 50 to 300 mg were assessed in patients with chronic genotype 1-4 HCV infection. Participants were excluded if they had prior treatment with NS3/4A protease inhibitors or cirrhosis.

There were 12 dosing cohorts based on viral genotype. Patients with genotype 1a, 2 or 3 received GS-9857 (50, 100 or 300mg for genotypes 1a and 3 and 100mg for genotype 2) or placebo once daily. GS-9857 100mg was administered once daily to patients with genotypes 1b and 4.

A total of 67 patients were included in the safety and efficacy analyses and 59 patients that received GS-9857 were included in the pK analyses. GS-9857 was well-tolerated without drug- or dose-related safety concerns. No serious adverse events (SAEs), adverse events (AEs) leading to study drug discontinuation or deaths occurred during the study. All AEs were mild or moderate in severity. The most common AEs were diarrhea, occurring in 5% of patients receiving GS-9857 and in 13% of patients receiving placebo, and headache, occurring in 2% of patients receiving GS-9857 and in 25% of patients treated with placebo. The incidence of AEs was not correlated with the dose of the study drug.

Daily administration of GS-9857 for 3 days resulted in a rapid decline of HCV RNA from pretreatment levels in all doses and across all genotypes (mean and median maximum HCV RNA reduction >3 log10 IU/mL) except among patients with genotype 3 infection who received GS-9857 50 mg. No change in viral RNA was observed in the placebo-treated patients.

At baseline, 24% (16/66) of participants had pre-treatment NS3 RASs. Treatment with GS-9857 resulted in similar mean maximal viral load reduction in patients with or without the presence of NS3 RASs at baseline. Post-baseline emergence of NS3 RASs was detected in 26% (14/53) of patients receiving GS-9857, and only in patients with genotypes 1 and 3.

Progression to phase II trials followed the promising results from phase I investigations of GS-9857. Two phase II trials to assess the safety and efficacy of SOF/VEL plus GS-9857 were performed contemporaneously, one evaluating patients with genotype 1 and the other evaluating patients with genotype non-1 HCV infection [26,27]. Both trials were multi-center,

open-label, 2-cohort studies conducted in the United States and New Zealand. Cohort 1 enrolled treatment-naive patients and cohort 2 enrolled patients previously treated with regimens that contained an NS5A inhibitor alone, or at least 2 classes of DAAs.

The phase II trial of patients with genotype 1 enrolled 197 participants [26]. Of the treatment-naive patients without cirrhosis, sustained virologic response 12 weeks after completing therapy (SVR12, the definition of cure) rates of 71% (24/34; 95%CI, 53 to 85) were achieved in patients receiving 6 weeks of treatment and 100% (36/36; 95%CI, 90 to 100) in patients receiving 8 weeks of treatment. Among treatment-naive patients with cirrhosis, the SVR12 rates were 94% (31/33; 95%CI, 80 to 99) in patients receiving 8 weeks of SOF/VEL plus GS-9857 versus 81% (25/81; 95%CI, 63 to 93) in patients receiving 8 weeks of SOF/VEL plus GS-9857 plus ribavirin. In the cohort of patients previously treated with DAA-containing regimens, SVR12 was 100% (31/31; 95%CI, 89 to 100) in patients without cirrhosis receiving 12 weeks of treatment and 100% (32/32; 95%CI, 89 to 100) in patients with cirrhosis receiving 12 weeks of treatment. Eighteen patients experienced relapse after completing treatment, of which only 3 had treatment-emergent RASs that were all at frequencies less than 2% of the viral population. One treatment-naive patient with cirrhosis receiving SOF/VEL plus GS-9857 with ribavirin discontinued treatment due to the development of abnormally high levels of alanine aminotransferase (grade 3) and aspartate aminotransferase (grade 2). That patient also developed a grade 1 increase in total bilirubin at a single timepoint during the study.

The phase II trial of genotype non-1 patients enrolled 128 participants [27]. Among treatment-naive patients, SVR12 rates were 88% (29/33; 95%CI, 72 to 97) in those without cirrhosis receiving 6 weeks of treatment and 93% (28/30; 95%CI, 78 to 99) in those with cirrhosis receiving 8 weeks of treatment. Of treatment-experienced patients given 12 weeks of SOF/VEL plus GS-9857, rates of SVR12 were 100% (36/36; 95%CI, 90 to 100) in patients

without cirrhosis and 97% (28/29; 95%CI, 82 to 100) in patients with cirrhosis. Seven patients experienced relapse after completing treatment, of which only 1 had a treatment-emergent RAS, Q80R, which does not confer in vitro resistance to GS-9857. Three patients, all with cirrhosis, discontinued treatment due to AEs. One was fatigue, another vomiting and diarrhea and the third gastritis. In both phase II trials, the most common AEs were headache, nausea, fatigue and diarrhea.

The POLARIS studies were a series of four phase III clinical trials evaluating fixed-dose SOF/VEL/VOX (400/100/100mg) that were conducted at total of 117 sites in the United States, Canada, France, Germany, United Kingdom, Australia and New Zealand (Table 1). These trials evaluated patients with chronic HCV of all genotypes, with and without cirrhosis, previous DAA exposure and/or RASs. Patients with chronic hepatitis B virus (HBV) infection, human immunodeficiency virus (HIV) infection, solid organ transplant and/or on chronic immunosuppression (for transplant or otherwise) were excluded.

POLARIS-1 was a double-blind, randomized, placebo-controlled trial of SOF/VEL/VOX in DAA-experienced patients who had previously received an NS5A inhibitor [23]. It enrolled a total of 415 patients with HCV genotypes 1-6. Patients with genotype 1 at screening were randomized equally to SOF/VEL/VOX or matching placebo. All other genotypes were assigned to SOF/VEL/VOX. All genotypes were stratified by the presence of cirrhosis. Compensated cirrhotic patients comprised 46% of the study population. The most common prior NS5A inhibitors were ledipasvir (55%) and daclatasvir (23%).

SVR12 was achieved in 96% (253/263; 95%CI, 93 to 98) of the participants who received SOF/VEL/VOX and none of the placebo-treated patients ($p<0.001$). Rates of SVR12 by intent-to-treat analysis for individual genotypes were 96% (97/101; 95%CI, 90 to 99) for genotype 1a, 100% (45/45; 95%CI, 92 to 100) for genotype 1b, 100% (5/5; 95%CI, 48 to 100) for genotype 2, 95% (74/78; 95%CI, 87 to 99) for genotype 3, 91% (20/22; 95%CI, 71 to 99)

for genotype 4, 100% (1/1) for genotype 5 and 100% (6/6; 95%CI, 54 to 100) for genotype 6. Among all cirrhotic study participants, the SVR12 rate was 93% (113/121; 95%CI, 87 to 97), while in noncirrhotics the SVR12 rate was 99% (140/142; 95%CI, 95 to 100).

Of the 263 patients who received study medication, 10 did not achieve SVR12. Six experienced relapse, 1 on-treatment failure, 2 withdrew consent and 1 was lost to follow up. All of the patients that experienced relapse or on-treatment failure had cirrhosis. A total of 205 of 248 (83%) patients for whom sequencing data was available had baseline NS3 and/or NS5A RASs, of whom 199 (97%) achieved SVR12 (94% in those with NS5A RASs alone, 97% in those with dual class RASs). None of the patients who relapsed had treatment-emergent RASs.

POLARIS-2 was an open-label, randomized, active-comparator trial of SOF/VEL/VOX for 8 weeks versus SOF/VEL for 12 weeks in DAA-naive patients infected with HCV [24]. It enrolled a total of 943 patients and started treatment on 941 patients with genotypes 1-6 with and without compensated cirrhosis, except for genotype 3 patients with cirrhosis (separately enrolled in POLARIS-3). Patients with genotypes 1-4 were randomized in a 1:1 fashion. Patients with other genotypes were intended to be assigned exclusively to SOF/VEL/VOX (a small number of patients were initially classified as genotype 1 patients, assigned to receive SOF/VEL, and on genotype retesting were found to have genotype 6). Participants were stratified by genotype, cirrhosis and prior treatment experience (naive or interferon-experienced).

Overall SVR12 was achieved in 95% (476/501; 95%CI, 93 to 97) of the participants who received SOF/VEL/VOX for 8 weeks and 98% (432/440; 95%CI, 96 to 99) of the participants who received SOF/VEL for 12 weeks. The SVR12 rate for patients receiving treatment with SOF/VEL/VOX for 8 weeks was not statistically non-inferior to the SVR12 rate for patient receiving SOF/VEL for 12 weeks, as the pre-specified noninferiority margin was 5%

and the proportional difference was -3.2 (2-sided 95% CI, -6.0% to -0.4%). Rates of SVR for individual genotypes in the 8-week SOF/VEL/VOX arm were 92% (155/169) for genotype 1a, 97% (61/63) for genotype 1b, 97% (61/63) for genotype 2, 99% (91/92) for genotype 3, 94% (59/63) for genotype 4 (in whom 3 out of 5 failures were nonvirologic), 94% (17/18) for genotype 5, 100% (30/30) for genotype 6 and 100% (2/2) for unknown genotype(s). Rates of SVR for individual genotypes in the 12-week SOF/VEL arm were 99% (170/172) for genotype 1a, 97% (57/59) for genotype 1b, 100% (53/53) for genotype 2, 97% (86/89) for genotype 3, 98% (56/57) for genotype 4 and 100% (9/9) for genotype 6. Notably, among the 181 noncirrhotic genotype 3 patients, none in either arm had virologic failure.

Virologic relapse occurred in 21 of the 501 patients enrolled in the SOF/VEL/VOX arm compared to only 3 of the 440 in the SOF/VEL arm. Of the 21 relapses that occurred in the SOF/VEL/VOX arm, 14 (67%) occurred in patients infected with genotype 1a compared to only 1 genotype 1a relapse in the 12-week SOF/VEL arm. Thus, it was the genotype 1a patient population that drove the failure to attain noninferiority with SOF/VEL/VOX. Further analysis revealed that it was predominantly the genotype 1a patients with the Q80K polymorphism, as occurs in about 50% of U.S. genotype 1a patients, that was associated with lower SVR rates, despite the absence of any change in the susceptibility of this strain of the virus to voxilaprevir in in vitro studies [28]. Across all genotypes, relapse occurred in 3% (14/411) of noncirrhotics versus 8% (7/90) of cirrhotics that received SOF/VEL/VOX. The relapses in the SOF/VEL arm occurred in 1 patient with genotype 1a, 1 patient with genotype 1b and 1 patient with genotype 5.

A total of 250 of 501 (50%) patients in the SOF/VEL/VOX arm for whom sequencing data was available had baseline NS3 and/or NS5A RASs, of whom 234 (94%) achieved SVR12 (91% in those with NS3 alone, 94% in those with NS5A alone and 100% in those with dual class RASs). A total of 220 of 440 (50%) patients in the SOF/VEL arm for whom

sequencing data was available had baseline NS3 and/or NS5A RASs, of whom 217 (99%) achieved SVR12 (100% in those with NS3 alone, 98% in those with NS5A alone and 97% in those with dual class RASs).

Four patients in each arm of the study were lost to follow-up and 2 in the SOF/VEL discontinued due to an AE (described below).

POLARIS-3 was an open-label, randomized, active-comparator trial of SOF/VEL/VOX for 8 weeks versus SOF/VEL for 12 weeks in DAA-naive patients infected with HCV genotype 3 and cirrhosis [24]. It enrolled a total of 220 patients and 219 began treatment. Randomization was 1:1 and participants were stratified by prior treatment experience (naive or interferon-experienced).

SVR12 was achieved in 96% (106/110; 95%CI, 91 to 99) of patients in the SOF/VEL/VOX arm and 96% (105/109; 95%CI, 91 to 99) of patients in the SOF/VEL arm. Superiority was significant compared to the pre-specified 83% performance goal ($p<0.001$). In the SOF/VEL/VOX arm there were 2 relapses, 1 withdrew consent and 1 death (determined to not be related to the study drugs). In the SOF/VEL arm there was 1 breakthrough, 1 relapse, 1 discontinuation due to AE and 1 lost to follow up.

Of the treatment-naive patients, SVR12 was achieved in 96% (72/75) of the SOF/VEL/VOX group and 99% (76/77) of the SOF/VEL. Of those previously treated with interferon, the primary outcome was met in 97% (34/35) of those treated with SOF/VEL/VOX and 91% (29/32) of those treated with SOF/VEL.

Baseline RASs were present in 21% of the SOF/VEL/VOX group and 21% of the SOF/VEL group. There were 6 patients with the Y93H RAS in the SOF/VEL/VOX group and 4 in the SOF/VEL group, all of whom achieved SVR. There were no treatment emergent RASs in the SOF/VEL/VOX group. However, both of the virologic failures in the SOF/VEL group had Y93H at relapse. There were 9 patients with an NS5B RAS at baseline, all of whom achieved

SVR12 except for 1 who did not have the RAS at relapse.

Finally, POLARIS-4 was an open-label, randomized, active-comparator trial of SOF/VEL/VOX for 12 weeks versus SOF/VEL for 12 weeks in DAA-experienced, genotype 1-6 patients without prior NS5A experience [23]. It enrolled a total of 333 patients. Participants with genotypes 1-3 were randomized 1:1 and all other genotypes were assigned to SOF/VEL/VOX. Participants were stratified by genotype and the presence of cirrhosis. Compensated cirrhotic patients comprised 46% of the study population. A majority of participants had failed previous treatment with sofosbuvir, among other DAAs.

The primary endpoint of the study was SVR12 and the independent performance goal was 85% for both arms of the study with a pre-specified p-value of 0.025. SVR12 was achieved in 98% (178/182; 95%CI, 95 to 99) of patients in the SOF/VEL/VOX arm, reaching significant superiority ($p<0.001$). SVR12 was achieved in 90% (136/151; 95%CI, 84 to 94) in the SOF/VEL arm, not achieving superiority ($p=0.09$), 94% in noncirrhotics and 86% in cirrhotics. There were 14 relapses and 1 breakthrough in the SOF/VEL arm compared to 1 relapse, 1 death (not related to study drug) and 2 lost to follow-up in the SOF/VEL/VOX arm.

For genotype 1a, 98% (53/54) achieved SVR12 with SOF/VEL/VOX compared to 89% (39/44) with SOF/VEL. For genotype 1b, 96% (23/24) achieved SVR12 with SOF/VEL/VOX versus 95% (21/22) with SOF/VEL. For genotype 2, SVR12 rates were 100% (31/31) with SOF/VEL/VOX and 97% (32/33) with SOF/VEL. Notably, for genotype 3, 96% (52/54) achieved SVR12 with SOF/VEL/VOX compared to only 85% (44/52) with SOF/VEL.

While SVR12 rates between patients in the SOF/VEL/VOX arm with and without cirrhosis were the same (98%), the SVR12 rates of patients in the SOF/VEL arm with cirrhosis were markedly lower (94% vs 86%).

Baseline RASs to NS3 and/or NS5A were present in 49% of study participants. All patients with baseline RASs in the SOF/VEL/VOX arm achieved SVR. No treatment-emergent

RASs were observed in the subjects who relapsed following SOF/VEL/VOX. Only 90% of patients in the SOF/VEL arm with baseline RASs achieved SVR. Of the 16 patients who failed following SOF/VEL, 11 had treatment-emergent Y93H or Y93C RASs. All 22 subjects with baseline NS5B RASs achieved SVR12.

6.Safety and tolerability

The safety and tolerability of SOF/VEL/VOX was carefully monitored in the POLARIS trials. There were no serious related AEs in any of the trials. The most commonly reported AEs in all of the trials were headache, fatigue, diarrhea and nausea. In POLARIS-1, where SOF/VEL/VOX was compared to placebo, there was an increased incidence of nausea (14% vs 8%) and diarrhea (18% vs 13%). There was also an increased incidence in nausea and diarrhea when comparing SOF/VEL/VOX and SOF/VEL in the other POLARIS trials (POLARIS-2: nausea 16% vs 9%, diarrhea 18% vs 7%; POLARIS-3: nausea 21% vs 9%, diarrhea 15% vs 5%; POLARIS 4: nausea 12% v 8%, diarrhea 20% vs 5%).

In POLARIS-1, SOF/VEL/VOX was well-tolerated with only a single (<1%) treatment discontinuation due to an AE unrelated to study medication (angioedema attributed to ramipril). This compared favorably to the 2% AE discontinuation rate in the placebo arm of the study. Overall, the AE event profile was similar to that of placebo.

In POLARIS-2, both SOF/VEL/VOX and SOF/VEL were well-tolerated with only 2 (<1%) treatment discontinuation due to AEs unrelated to study medication (1 patient discontinued treatment due to upper respiratory tract infection and 1 patient due to *Clostridium difficile* infection; neither was assessed as related to the study medication).

In POLARIS-3, both SOF/VEL/VOX and SOF/VEL were well-tolerated with only 1 (<1%) treatment discontinuation due to an AE and 1 death, both unrelated to the study medication. The discontinuation was in the setting of a pelvic fracture and the death occurred on post-

treatment day 78 and was determined to be due to hypertension unrelated to the study drugs.

In POLARIS-4, both SOF/VEL/VOX and SOF/VEL were well-tolerated with only 1 (<1%) treatment discontinuation in the SOF/VEL arm due to an AE and 1 death in the SOF/VEL/VOX arm. The discontinuation was due to worsening headache, and the death occurred on post-treatment day 2 from an illicit drug overdose.

7.Regulatory considerations

A New Drug Application (NDA) for the once-daily, single tablet regimen of SOF/VEL/VOX (400/100/100mg) was submitted to the US Food and Drug Administration (FDA) on December 8, 2016. A Marketing Authorization Application (MAA) was submitted to the European Medicines Agency (EMA) and was fully validated for assessment on January 20, 2017.

8.Conclusion

SOF/VEL/VOX is a safe and well-tolerated pangenotypic, once-daily, single tablet regimen. Treatment has proven efficacy in curing chronic HCV infection, most notably in difficult to cure populations. Patients with prior DAA treatment failure, noncirrhotic and cirrhotic patients infected with genotype 3, and patients with unfavorable resistance profiles prior to receiving SOF/VEL/VOX all achieved cure rates of 96% or greater in phase III trials. This regimen is an important addition to the armamentarium of curative treatments for chronic HCV infection.

9.Expert commentary

The global demand for simple, highly-effective, pangenotypic HCV treatment remains high [29]. This is particularly important in places where pre-treatment testing for genotype and resistance profiles are prohibitive. An important step towards this goal was the introduction of

SOF/VEL, which represented the first regimen approved across all HCV genotypes. There remain, however, difficult to treat subgroups of patients. This includes patients with HCV genotype 3, baseline RASs, cirrhosis and prior failure of a DAA regimen. The POLARIS trials evaluated the efficacy and safety of a potent, single 3 DAA-class pill in a broad spectrum of HCV-infected patients with a particular focus on the potential to shorten the duration of therapy in DAA naïve patients, those with genotype 3 cirrhosis, and prior DAA failure.

There are limited salvage treatment options for the DAA-experienced patient. The AASLD Guidance document currently recommends deferring retreatment of certain patients that have failed DAA regimens in the hopes of the development of more effective salvage therapies. In an attempt to meet this need, POLARIS-1 and POLARIS-4 evaluated treatment of patients that failed previous DAA therapy either with (POLARIS-1) or without (POLARIS-4) an NS5A inhibitor. The studies demonstrated very high SVR rates of 96% and 97%.

Patients infected with HCV genotype 3 and cirrhosis have proven to be the most difficult to cure since the advent of the DAA era, with even the pangenotypic SOF/VEL regimen yielding SVR in 89% of treatment (IFN)-experienced cirrhotics in the ASTRAL-3 study. In POLARIS-3 this population achieved an SVR rate of 96%, underscoring the efficacy and high barrier to resistance of this regimen. Overall, the results of SOF/VEL/VOX in genotype 3 patients in both POLARIS-2 and POLARIS-3 suggests that this regimen is an excellent option against this most difficult to cure genotype in the DAA era. To be sure, SOF/VEL for 12 weeks performed comparably well in POLARIS-2 and -3, but the results of the ASTRAL-3 study have led to recommendations that ribavirin be added to the double regimen when baseline Y93H is present in treatment-naïve cirrhotics and treatment-experienced noncirrhotics, and that ribavirin be used in general in treatment-experienced cirrhotic patients with genotype 3 [9].

It should be noted that the use of ribavirin was found to have no added benefit in phase

II trials of SOF/VEL/VOX and therefore was not included in any of the phase III trials. It has been difficult to fully eliminate the use of ribavirin in the treatment of chronic HCV infection and this was an important step away from the use of a drug associated with a distinctive side effect profile, including its potential for teratogenicity and the need for corresponding precautions and pregnancy testing.

A notable finding was the failure of the POLARIS-2 to demonstrate noninferiority of SOF/VEL/VOX for 8 weeks compared to SOF/VEL for 12 weeks in DAA-naive patients of all genotypes. It had been hoped that the addition of a potent second-generation protease inhibitor would enable shortening of the regimen to 8 weeks. The outcome of POLARIS-2 in treatment naïve patients, with the demonstrated absence of treatment-emergent RASs in patients with virologic failure after 8 weeks of SOF/VEL/VOX, suggests that, despite the potency of the regimen, an 8-week duration was insufficient to attain optimal viral eradication – with the proviso that this difference was driven by the genotype 1a patients with baseline Q80K polymorphisms despite the absence of any impact of this polymorphism on the in vitro sensitivity to voxilaprevir [28].

No discussion of the POLARIS studies would be complete without noting the high rates of efficacy for the already approved 12-week regimen of SOF/VEL across the populations evaluated in these trials, including cirrhotic patients with genotype 3, with the exception of NS5A-experienced patients in whom SOF/VEL was not evaluated. The one study in which the results of SOF/VEL fell somewhat short was in the DAA-experienced but NS5A-naïve population in POLARIS-4, the majority of whom had been exposed to SOF previously. As we await the anticipated approval of SOF/VEL/VOX, the most distinctive role for this potent combination may prove to be as a salvage regimen for patients who have failed previous DAA therapy. In due course, we will learn whether other next generation regimens being developed or awaiting approval offer comparable efficacy in this population.

10.Five-year view

We continue to make great strides in HCV research. It has been several years since we cast off the burden of interferon-based treatment in the United States and many other countries. We are increasingly free of the need to augment certain regimens with ribavirin, a drug of which we are still unsure the mechanism of action but well-versed in the unwanted side effects. We have several highly potent, safe and well-tolerated DAA regimens prescribed based upon genotype, RASs and the degree of fibrosis. With remarkably high cure rates, we now turn our focus towards simplicity and access. The less complicated our prescribing algorithms, the easier it will become to tackle the burden of chronic HCV infection globally. The coming years promise a great reduction in the burden of chronic HCV infection and the complications of chronic liver disease.

11.Key issues

- Voxilaprevir (VOX) is an investigational, pangenotypic NS3/4A protease inhibitor with a high barrier to resistance developed for use in combination with sofosbuvir (SOF) and velpatasvir (VEL) to treat chronic HCV infection
- The POLARIS studies were 4 phase III trials investigating the safety and efficacy of SOF/VEL/VOX
- The POLARIS-1 and POLARIS-4 studies achieved SVR in 96% and 97% of patients previously treated with DAAs containing or not containing an NS5A inhibitor, respectively. In POLARIS-1, noncirrhotics had an SVR rate of 99% with no virologic failures versus 93% SVR12 in cirrhotics.
- The POLARIS-2 study achieved SVR in 95% of DAA-naive patients with 8 weeks of

SOF/VEL/VOX but failed to meet noninferiority compared to 12 weeks of treatment with SOF/VEL, a difference that was driven by the genotype 1a patient population.

- The POLARIS-3 study achieved SVR in 96% of patients with HCV genotype 3 and cirrhosis treated with 12 weeks of SOF/VEL/VOX.
- Of the 1,056 patients in the POLARIS studies that received SOF/VEL/VOX, only 1 discontinued due to an adverse event considered related to the medication

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IM Jacobson has served as a consultant for AbbVie, Bristol-Myers Squibb, Intercept, Gilead, Merck and Trek. IM Jacobson has conducted research for Genfit, Gilead and Merck. IM Jacobson has served as a speaker for Gilead, Intercept and Merck. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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TABLE 1. Summary of Study Participants and Overall SVR12 Rates of All POLARIS Trials

Study	Population	Genotype	Cirrhosis	Any RAS(s)	Treatment	Duration	SVR 12 Rates
POLARIS-1	NS5A inhibitor-experienced	1, 2, 3, 4, 5, 6	46%	83%	SOF/VEL/VOX	12 Weeks	96% (253/263)
			34%	Not reported	Placebo	12 Weeks	0% (0/152)
POLARIS-2	DAA-naïve	1, 2, 3, 4, 5, 6	18%	50%	SOF/VEL/VOX	8 Weeks	95% (476/501)
			19%	50%	SOF/VEL	12 Weeks	98% (432/440)
POLARIS-3	DAA-naïve	3	100%	21%	SOF/VEL/VOX	8 Weeks	96% (106/110)
			100%	21%	SOF/VEL	12 Weeks	96% (105/109)
POLARIS-4	DAA-experienced (no NS5A inhibitor)	1, 2, 3, 4	46%	49%	SOF/VEL/VOX	12 Weeks	97% (177/182)
			46%	49%	SOF/VEL	12 Weeks	90% (136/151)