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REVIEW ARTICLE

Sofosbuvir/velpatasvir: a pangenotypic drug to simplify HCV therapy

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Abstract Treatment for chronic hepatitis C virus (HCV) has evolved rapidly from an interferon based regimen of modest efficacy with significant adverse events to a well-tolerated, highly effective all-oral directly acting antiviral (DAA) therapy. Although significant improvement in sustained virologic responses (SVR) has been reported with new DAAs for genotypes 1 and 4, effective treatments for genotype 3 have been lacking, and a single pill that can yield high SVR rates against HCV genotypes 1–6 has not been available until now. Sofosbuvir (a pangenotypic NS5B inhibitor) and velpatasvir (a pangenotypic NS5A inhibitor) were recently approved in a fixed-dose combination pill. The availability of this pangenotypic pill holds promise for providing highly effective treatment with minimal laboratory testing for chronic HCV worldwide.

Keywords Epclusa · Sofosbuvir · Velpatasvir · FDC · Pangenotypic · ASTRAL

Introduction

The treatment of chronic hepatitis C virus (HCV) infection has undergone rapid and dramatic changes since the introduction of direct acting antivirals (DAAs), proven to be both more effective and better tolerated than previous interferon-based regimens. There has been growing interest in finding a HCV therapy that addresses the virus's numerous genetic variants. Pretreatment stratification, including genotyping and fibrosis staging, are required to optimize currently available DAA therapies. The United States Food and Drug Administration (FDA) recently approved the fixed-dose combination of sofosbuvir (SOF) and velpatasvir (VEL) (brand Name: Epclusa, Gilead Sciences), the next step in DAA combination therapies: a once daily pangenotypic DAA combination tablet that safely and effectively treats all HCV genotypes in patients with all stages of fibrosis, from early disease to decompensated cirrhosis.

Background

The most recent estimates indicate that 110 million individuals worldwide are infected with HCV and 80 million may have chronic infection [1]. With a global health burden of more than 700,000 estimated deaths in 2013, HCV persists as a serious public health concern [1]. Prior to the introduction of DAAs, HCV therapy consisted of pegylated interferon (IFN) and ribavirin (RBV) combination therapy, where sustained virologic response (SVR) remained at about 50% for HCV genotype 1 (GT-1), with poor patient tolerability, resulting in high discontinuation rates [2]. While the initial first generation DAAs, boceprevir and telaprevir, continued to be used in conjunction with IFN and RBV, the second generation DAA sofosbuvir (SOF) was shown to be more effective and safer, with fewer adverse events (AE), beginning a new era of IFN-free therapy [3]. Current DAA combinations have demonstrated SVR rates of greater than 90% in both late-phase clinical trials and real world use, where SVR rates nearly matched those in clinical trials in treatment-naïve GT-1 patients [4, 5]. The new generations of DAA agents have vastly

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improved all areas of previous HCV therapy, including efficacy, safety, and adherence.

DAAs target stages of the HCV life cycle, specifically inhibiting the nonstructural proteins necessary for viral RNA replication [6], shown in Fig. 1. Upon viral entry into the cell, HCV positive-strand RNA is released into the cytoplasm, followed by its translation, post-translational processing, viral replication, assembly, and release [7]. Two important nonstructural proteins are NS5A, involved in viral replication, assembly, and release, and NS5B, RNA-dependent RNA polymerase (RdRp) necessary for viral transcription [4]. The lack of proof-reading ability in the RdRp gives rise to viral variants, which may affect virologic response to HCV treatment [8].

The six major genotypes (although a seventh was recently described [9]) of HCV are globally distributed such that the majority of HCV-infected patients in the United States [8] and 46.2% of those throughout the world [10] are infected with GT-1, more than any other genotype. Genotype 3 (GT-3) is estimated to be the next most common strain of the virus [10] contributing to 30% of global infections and up to 35–80% of infections in regions of India [11]. Of the remaining genotypes, GT-2, -4, and -6 produce the majority of the remaining infections globally, with [10] genotype 4 (GT-4) in Egypt, where 15% of the total population is infected with HCV [11, 12]. Genotyping provides important clinical information, in particular, about GT-3, which is especially prevalent in South and Southeast Asia, has consistently shown to produce lower SVR rates in response to DAA therapy [13], and has been associated with more rapid disease progression and lower rates of response to treatment. It has posed as a challenging subpopulation of HCV-infected patients to treat [14].

Additional challenges are presented by mixed and recombinant infections, which may be addressed by a pangenotypic therapy. Mixed infections occur when a patient is infected with more than one HCV genotype and are enriched in persons infected through intravenous drug use [15]. According to a study of incarcerated injection drug users (IDUs), as many as 25.3% of HCV-infected subjects were infected with two or more HCV variants [15]. Recombinant infections, in which a person is infected

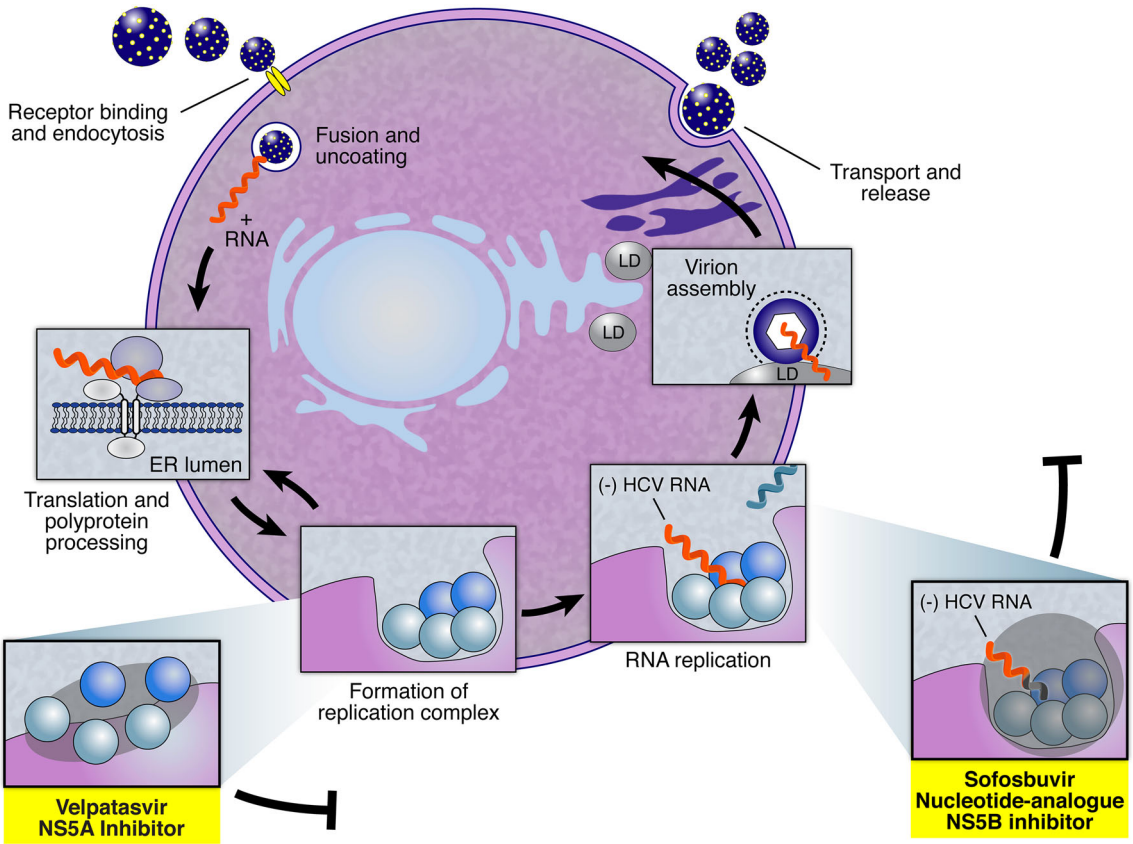

Fig. 1 The HCV replication cycle. The steps of viral replications, including receptor binding and endocytosis, translation and polyprotein processing, formation of the replication complex, RNA replication, and transport and release, are shown. The sites of velpatasvir and sofosbuvir inhibition are indicated. Velpatasvir acts to inhibit and destabilize the replication complex. Sofosbuvir acts as a nucleotide mimic, prematurely terminating the newly replicated RNA strand. *ER* endoplasmic reticulum, *LD* lipid droplet, *NS5A* nonstructural protein 5A, *NS5B* nonstructural protein 5B

with a combined variant produced when the error-prone RdRp combines two different HCV variants into one new viral strand, such as 2k/1b or 2b/1a, also exist as an obstacle for current genotype-specific HCV treatments [9].

Reliable genotyping poses a challenge for populations with limited laboratory access and highlights a need for a pangenotypic therapy. While SOF/VEL obviates the need for the majority of genotyping, relieving the burden in areas with limited laboratory access, genotyping remains an important clinical tool in areas with a high prevalence of GT-3 infection because patients may benefit from the addition of ribavirin to combination DAA treatment.

SOF is a NS5B nucleotide polymerase inhibitor, whose active nucleoside analog triphosphate GS-461203 inhibits HCV replication by incorporating in the primer strand and terminating the chain [16]. The catalytic site of the NS5B RdRp is highly conserved across genotypes 1–6, accounting for its pangenotypic activity [16]. Because of its broad spectrum activity and high barrier to resistance, SOF is considered the most successful NS5B inhibitor in treatment of HCV infection [4, 16]. SOF is metabolized by Cathepsin A, CES1, and HENT1, meaning that it has few interactions for the majority of medications metabolized through the CYP450 pathways [17]. Velpatasvir (VEL) is a novel second-generation NS5A inhibitor whose pangenotypic activity was exhibited in vitro as well as in a phase 1b monotherapy against genotypes 1–6 [11]. It has demonstrated mean 50% effective concentrations (EC_{50}) of 6–120 pM against GT-1-6, while also treating clinically significant GT-1 NS5A resistance-associated substitutions [4]. VEL is metabolized by the following cytochrome p450s: CYP2B6, CYP2C8, and CYP3A4 [17].

There are other successful DAA therapies such as paritaprevir/ritonavir-ombitasvir and dasabuvir (PrOD) with or without ribavirin, which is used to treat GT-1, and paritaprevir ritonavir-ombitasvir (PrO) for GT-4 [18]. However, PrOD is contraindicated in patients with moderate-to-severe hepatic impairment [18] and requires more frequent on-treatment monitoring for those with cirrhosis; it is also not indicated for GT-3. Other DAA combinations include elbasvir/grazoprevir, which treats GT-1 and GT-4, including patients with chronic kidney disease (CKD) [18], but requires routine on-treatment therapeutic monitoring for hepatic decompensation, and may require the addition of RBV for those with GT-1a infection. SOF/VEL may be a preferable alternative DAA combination for patients because it has greater genotypic coverage and has been proved safe in decompensated liver disease in combination with ribavirin. However, these alternative DAA combinations may be more appropriate in patients with CKD or those who are taking high-dose proton pump inhibitors (PPI).

This SOF/VEL fixed-dose combination (FDC), approved by the US FDA in June 2016, has improved the current DAA-based therapies by addressing several challenges to HCV treatment: the existence of a variety of HCV genotypes, prevalence of multiple infections, and different stages of hepatic fibrosis.

Phase 2 clinical trials

Phase 2 trials of SOF/VEL were extremely promising: demonstrating the efficacy and safety of the 100-mg VEL dose.

SOF with VEL in treatment-naive noncirrhotic patients with genotype 1–6 HCV infection

In this phase 2, randomized, open-label, multicenter study by Everson et al., 377 treatment-naive noncirrhotic patients with genotypes 1 through 6 were enrolled and administered SOF with either 25 or 100 mg VEL. Of note, patients with previous HCV treatment experience or creatinine clearance less than 60 mL/min were excluded [19]. This was the first phase 2 trial suggesting that the combination of SOF and VEL (100 mg) is an effective pangenotypic treatment for HCV.

The trial divided 377 patients into two different randomized study arms: in group A, 154 patients infected with HCV genotypes 1 through 6 were treated with 400 mg SOF with either 25 or 100 mg of VEL for 12 weeks. In group A, SVR rates ranged from, at the lowest, 93% for GT-3-infected patients to 96–100% for GT-1 patients who received 400 mg SOF and 25 mg or 100 mg VEL, respectively. In group B, 223 patients with HCV genotypes 1 or 2 were treated with 400 mg SOF and either 25 or 100 mg VEL, with or without ribavirin for 8 weeks. While response rates were lower for 8 weeks of therapy (ranging from 81 to 90% for GT-1 and from 77 to 88% for GT-2), there was no improvement with the addition of RBV. Overall, 337 (89%) of the 377 randomly assigned patients achieved SVR12.

Of the 377 total patients, 262 (69%) reported at least one adverse event, which included fatigue, headache, and nausea, the majority of which were mild. Only one patient discontinued treatment because of an adverse event. There was one death; a patient with preexisting psychiatric disease committed suicide after completion of 12 weeks of treatment. Of note, patients treated with ribavirin had specific adverse events, including a higher incidence of fatigue, insomnia, and rash, a low incidence of decreased hemoglobin (1%), and increased bilirubin levels (2%).

In combination with 400 mg SOF for 12 weeks, the 100-mg dose of VEL appeared to have a clinical advantage over the 25-mg dose. Virologic failure was low and

exhibited in 1/55 patients with GT-1, 3/55 patients with GT-3, and 0/45 patients with genotypes 2, 4, 5 or 6. On-treatment viral failure for one patient with GT-3 receiving the 25-mg dose of VEL and relapse of one patient with GT-1 also receiving the 25-mg dose supported favorability of the 100-mg dose [19]. This study supported the pangenotypic activity of SOF plus VEL (100 mg) and would be followed by studies enrolling patients with prior treatment failure and cirrhosis.

SOF plus VEL combination therapy for treatment-experienced patients with genotype 1 or 3 HCV infection

GT-1 and GT-3 are the two most common HCV genotypes; cirrhotic patients infected with these genotypes and previously unsuccessfully treated tend to have lower rates of SVR. In a phase 2, randomized, open-label multicenter study, Pianko et al. investigated the efficacy of SOF with VEL on patients with genotypes 1 or 3 who had previous treatment experience [20]. Patients with hepatic decompensation or creatinine clearance less than 60 mL/min/1.73 m^3 were excluded [20].

This phase 2 study enrolled 321 previously treated HCV patients with genotypes 1 or 3 infection and administered 12 weeks of 400 mg SOF with either 25 mg VEL, with or without RBV, or 100 mg VEL, with or without RBV. The patients were divided into 3 cohorts: those with GT-3 without cirrhosis, those with GT-3 with compensated cirrhosis, and those with GT-1 unsuccessfully treated previously with a protease inhibitor, pegIFN and RBV [20].

All patients (100%) with GT-1 who received 25 mg or 100 mg VEL attained SVR12, while 97% of those who received 25 mg VEL and RBV and 96% of those who received 100 mg VEL with RBV achieved SVR12. Patients with GT-3 who received 25 mg VEL demonstrated SVR12 rates of 58% without ribavirin and 84% with ribavirin; those who received 100 mg VEL demonstrated 88% without ribavirin and 96% with ribavirin. Addition of ribavirin was seen to improve SVR in patients receiving 25 mg VEL in GT-3 patients, but, in GT-1 patients, neither VEL dose nor the addition of RBV had a significant effect on SVR. Notably, cirrhosis did not predict lower efficacy [20]. In this study, SOF/VEL was demonstrated to be a safe and efficacious therapy for treatment experienced patients infected with the most common genotypes, 1 and 3.

PHASE 3; ASTRAL program

A series of phase 3 trials, named ASTRAL-1 through ASTRAL-5 investigated the efficacy and safety of a combination of SOF/VEL on patients with HCV genotypes 1–6, varying levels of cirrhosis, and HIV coinfection. A summary of the phase 3 studies are shown in Table 1.

ASTRAL-1

ASTRAL-1 was a double-blind, placebo-controlled, phase 3 trial that enrolled 624 patients with genotypes 1, 2, 4, 5, and 6 infection, and, unlike the previously mentioned study, ASTRAL-1 enrolled both treatment naïve and experienced patients. The protocol for ASTRAL-1 specified intended enrollment of about 20% of the patients who had not obtained SVR with an IFN-containing therapy and about 20% of patients who had demonstrated cirrhosis. Patients who had previous experience with any nucleotide analogue NS5B inhibitor or NS5A inhibitor were not eligible for this trial [21].

Patients were randomly assigned in a 5:1 ratio to receive once-daily, fixed-dose SOF/VEL combination pill with 400 mg of SOF and 100 mg of VEL, once daily for 12 weeks, or a placebo control group. Patients in the placebo group received a placebo tablet and were eligible for deferred treatment with SOF/VEL. The overall SVR12 rate was 99%, and the SVR rates remained high in all subgroups. Only 2 (<1%) of patients experienced virologic failure. The difference in incidence of adverse events between the experimental (78%) and placebo group (77%) was not significant [21].

One limitation of the ASTRAL-1 trial was the small number of patients with genotype 5 (GT-5) enrolled in the study. Thirty-five patients were enrolled from the United States, Canada, Europe, and Hong Kong, but patients infected with GT-5 are primarily in South Africa [21, 22]. Because of the low number of patients, the GT-5 group was not randomized and did not have a placebo control.

ASTRAL-2 and ASTRAL-3

Unlike HCV GT-1, which is predominant in the United States, genotypes 2 and 3 are more common in low-income regions globally, in Asia, sub-Saharan Africa, Latin America, and Eastern Europe [8, 11]. A pangenotypic DAA treatment such as the SOF/VEL combination may offer an advantage in countries where access to pretreatment genotyping is limited. For GT-2, the current standard of care consists of 12 weeks of SOF plus ribavirin; for GT-3, it is 24 weeks of SOF plus ribavirin [14].

In these 2 randomized, multicenter, open-label phase 3 trials, the efficacy of combination SOF and VEL was examined in patients with HCV genotype 2 and 3 infection in ASTRAL-2 and ASTRAL-3, respectively, and compared with the current standard of care. Entry criteria for both trials were equivalent, except for enrollment of the respective genotypes. Eligible patients could be treatment-

Table 1 Summary of phase 3 ASTRAL clinical trials

Trial	*n*	Genotypes	Demographics[a]	Dose	Duration (weeks)	SVR (overall) (%)
ASTRAL-1	624	1–6	54-year-old 60% male 8% Black, 79% White, 10% Asian 32% treatment experienced	400 mg SOF 100 mg VEL	12	99
ASTRAL-2	266	2	57-year-old 55% male 9% Black, 84% White, 4% Asian 15% treatment experienced	400 mg SOF 100 mg VEL	12	99
ASTRAL-3	552	3	50-year-old 63% male <1% Black, 87% White, 11% Asian 26% treatment experienced	400 mg SOF 100 mg VEL	12	95
ASTRAL-4	267	1, 2, 3, 4, 6 decompensated cirrhosis	58-year-old 76% male 6% Black, 91% White, 0% Asian 54% treatment experienced	400 mg SOF 100 mg VEL + ribavirin	12	83 94
ASTRAL-5	106	1–4	86% male 45% Black 29% treatment experienced	400 mg SOF 100 mg VEL	12	95

[a] Demographics stratified by mean age, sex, ethnicity, and treatment experience of the experimental group

naïve or -experienced; about 20% had previously received an interferon containing therapy [14]. Additionally, the two studies had intended to enroll about 20% of patients with compensated cirrhosis, but patients with clinical evidence of hepatic decompensation were excluded from both trials [14]; HCV treatment for patients with hepatic decompensation would be better elucidated in ASTRAL-4.

Patients infected with HCV genotype 2 or 3 infection were randomly assigned to treatment with either a 400-mg SOF and a 100-mg VEL FDC pill once daily for 12 weeks or with 400 mg SOF plus ribavirin for 12 weeks (GT-2) or 24 weeks (GT-3). In both trials, patients were primarily white male with a non-CC *IL28B* genotype, which has been associated with reduced response to IFN-based HCV treatment [23]. One limitation of this study was the relative underrepresentation of Black patients, likely because of the decreased population of genotypes 2 and 3 in these patients.

In ASTRAL-2, 266 patients with GT-2 HCV infection were treated and achieved 99% SVR rates in patients who received SOF/VEL for 12 weeks compared to 94% of those who received SOF-ribavirin for 12 weeks. In ASTRAL-3, 552 patients with GT-3 HCV infection were treated. A 95% SVR12 rate was observed in patients who received SOF/VEL for 12 weeks, compared to 80% in those who received SOF-RBV for 24 weeks [14].

ASTRAL-4

In addition to treating all genotypes, SOF/VEL FDC has been shown to treat all fibrosis stages. The ASTRAL-4 phase 3 trial examined the efficacy of SOF/VEL on HCV-infected patients with moderate decompensated cirrhosis, an important subpopulation projected to increase in numbers as chronic HCV-infected patients age [24]. This study was unable to make conclusions about more severe liver decompensation. Decompensated cirrhosis patients were defined as Child–Pugh–Turcotte (CPT) class B, which is measured from a scale of 5 to 10, as well as the Model for End-Stage Liver Disease (MELD) score, which is measured from a scale of 6 to 24. The median baseline CPT score was 8, median baseline MELD score was 10, and median creatinine clearance was 84.7 ml/min. Patients with previous liver transplantation, experience with any nucleotide NS5B inhibitor or NS5A inhibitor, or creatinine clearance less than 50 ml/min were excluded [24].

Of the 267 patients who received treatment, GT-1a was predominant (60%), followed by genotypes 1b (18%), 2

(4%), 3 (15%), 4 (3%), and 6 (1%). Patients were enrolled from the United States and thus primarily had HCV GT-1, a reflection of the US HCV epidemic. Because of the small numbers of patients in these groups, no conclusions could be made about genotypes 2, 4, or 6. More than half, 55%, of patients had received previous treatment for HCV infection [24].

The addition of RBV improved SVR rates in patients with HCV infection with decompensated cirrhosis. Patients who received SOF/VEL for 12 weeks achieved a SVR12 rate of 83%, while patients who received 12 weeks of SOF/VEL with ribavirin had a SVR12 of 94%, and patients who received SOF/VEL for 24 weeks had a SVR24 rate of 86%. Patients received weight-based dosing of RBV: 1000 mg daily for those with body weight less than 75 kg and 1200 mg daily for patients weighing greater than or equal to 75 kg. The addition of RBV was especially important within patients with HCV GT-3, as these patients achieved SVR rates of 50% with SOF/VEL alone and 85% for those who received SOF/VEL dosed with RBV. ASTRAL-4 also revealed early improvements in hepatic function, measured by changes in CPT and MELD scores, for many patients. An ongoing registry study (NCT01457755) will monitor liver disease progression who have achieved SVR for up to 5 years after the end of treatment [24].

Special populations

ASTRAL-5

HCV/HIV-coinfected patients suffer from higher rates of cirrhosis and liver decompensation disease than their monoinfected counterparts, [25] and treatment for these patients is an area that needs to be elucidated. In this phase 3 ASTRAL-5 trial, SOF/VEL was examined in 106 HCV/HIV coinfected patients with genotypes 1–4, treatment-naïve and -experienced, as well as cirrhotic and noncirrhotic, were treated with 400 mg SOF and 100 mg VEL for 12 weeks. The median baseline CD4 count was 598 cells/μL and patients were completely virally suppressed with antiretroviral therapy (ART) [26]. Treatment was highly efficacious with an overall SVR rate of 95% [26].

Treatment experienced patients

The SOF/VEL FDC is a viable treatment option for patients with HCV infection who have failed treatment in the past. Gane et al. presented preliminary data about the administration of SOF/VEL with RBV for 24 weeks in patients who had failed prior NS5A-containing DAA regimens. While results varied significantly by genotype, SVR12 rates were high overall for this difficult to treat population, with SVR rates of 33/34 (97%), 13/14 (91%), and 13/17 (76%) for genotypes 1, 2, and 3, respectively. GT-3 patients characteristically had lower SVR, and an additional third DAA agent was proposed to expand efficacy [27].

Drug limitations

The FDC SOF/VEL is a safe pangenotypic therapy for chronic HCV infection with some notable drug limitations. Per prescribing information provided by Gilead Sciences, EPCLUSA is not recommended for patients taking amiodarone, as it may cause severe symptomatic bradycardia when coadministered. Drug efficiency appears to be reduced with antacids and proton pump inhibitors, which decrease the absorption of VEL, as well as a number of anticonvulsants, antimycobacterials, and the chemotherapy topotecan [17].

SOF/VEL therapy is safe and effective in patients with mild or moderate renal impairment but is not recommended in patients with more severe kidney disease (eGFR <30 mL/min/1.73 m^2). The combination of EPCLUSA and ribavirin is contraindicated in patients in whom ribavirin is contraindicated [17].

Resistance-associated variants

Because of the high error rate of the RdRp, the HCV viral population within one infected individual exhibits tremendous diversity. Some amino acid substitutions exhibit reduced susceptibility to DAAs. These are called resistance-associated variants (RAVs) and may contribute to viral relapse [4], but the clinical utility of RAV testing remains unclear. RAVs may be transmitted or develop during treatment in response to the selective pressure of HCV therapies, depending on the DAA's genetic barrier to resistance, level of drug exposure, and viral fitness of the resistant variant [28]. Though certain combinations of NS5A RAVs have demonstrated as high as >1000-fold reduced susceptibility to the NS5A inhibitor LDV [29], their presence does not seem to be a major obstacle to achieving SVR. In a retreatment study of patients who relapsed after 4–6 weeks of treatment with LDV/SOV plus an investigational NS5B inhibitor GS-9669 with or without GS-9451, Wilson et al. found that 29/34 (85%) of relapsed patients demonstrated NS5A RAVs (K24R, M28T, Q30H/R/L/T, L31M/V/I, and Y93H/N). After LDV/SOF retreatment for 12 weeks, 26/29 (90%) achieved SVR12, despite the presence of, in some cases, high-level (>100-fold reduced susceptibility), baseline RAVs [29]. One possible advantage a combination of SOV/VEL may have over LDV/SOV is an apparent improvement in

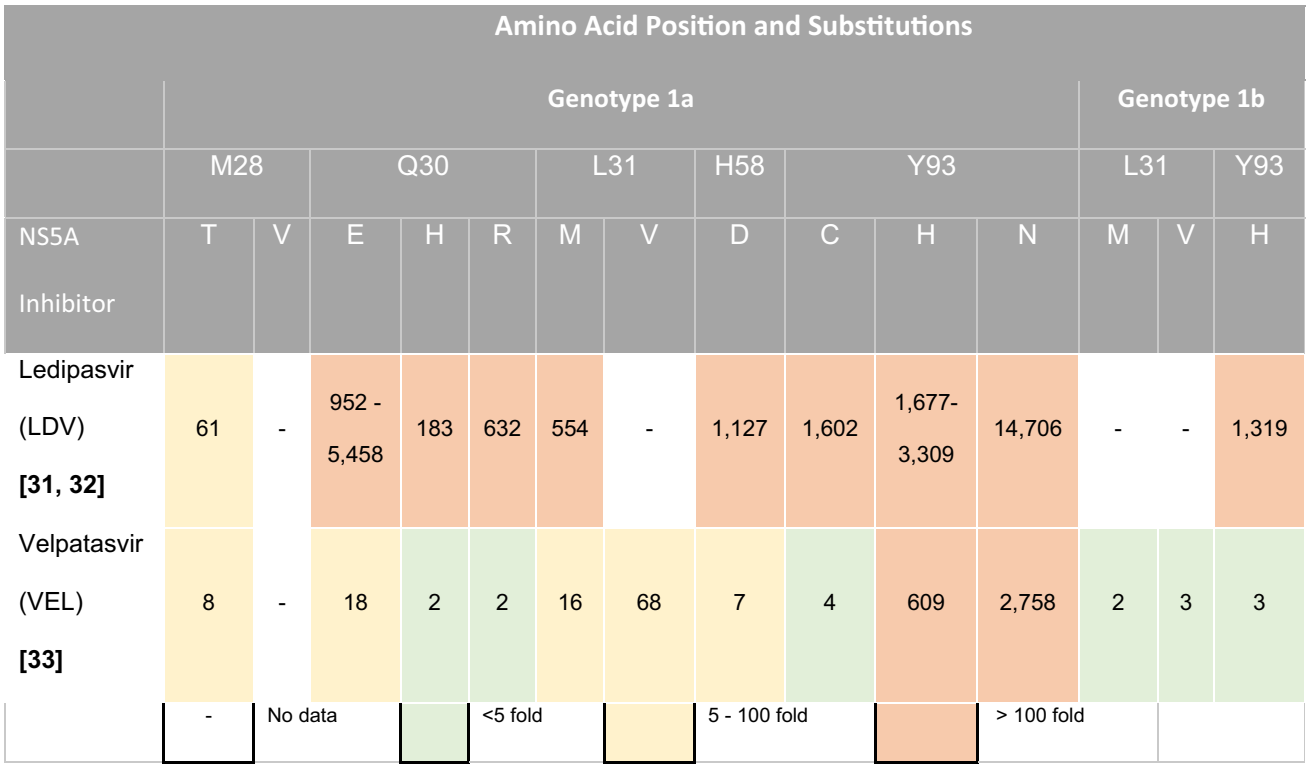

Fig. 2 NS5A inhibitors and NS5A resistance associated variants [30]. *Numbers* denote fold change in reduced susceptibility to the NS5A inhibitor for the indicated amino acid substitution, rounded to the nearest integer

Table 2 Summary of resistance-associated variants in ASTRAL clinical trials

Trial	NS5A RAV (%)	Common substitutions	SVR12 in patients with baseline RAVs (%)
Everson et al.	128/375 (34%)		90
ASTRAL-1	257/616 (42%)		99
ASTRAL-2	79/132 (60%)	L31M (52%)	100
ASTRAL-3	43/216 (16%)	A30K, L31M, Y93H	88
ASTRAL-4	72/255 (28%)		89

Trial	NS5B RAV (%)	Common substitutions	SVR12 in patients with baseline RAVs (%)
Everson et al.	17/372 (5%)		88
ASTRAL-1	54/601 (9%)		100
ASTRAL-2	13/134 (10%)		100
ASTRAL-3	10/274 (4%)	N142T, L159F, E237G, L3201	100
ASTRAL-4	8/251 (3%)	N142T, L159F, E237G, M2891	100

susceptibility to key NS5A RAVs by VEL, with relative fold change for each indicated amino acid substitution shown in Fig. 2 [30].

Clinical trials studying SOF/VEL treatment have also suggested that RAVs do not necessarily impede treatment outcomes for this combination therapy. While patients in these clinical trials who experienced virologic failure did frequently have baseline RAVs, shown in Table 2, the majority of patients with baseline RAVs achieved cure. The phase 2 trial by Everson et al. found 328 (87.4%) of 375 patients with sequencing data had pretreatment NS5A RAVs, and only 4 of those relapsed [19]. Similarly, in the entirety of the ASTRAL trials, all patients with genotypes 2, 4, 5, and 6 who had baseline NS5A RAVs achieved

SVR12. Only 12 patients experienced virologic failure and were tested for RAVs: 1 of the 2 GT-1 subjects and all 10 of the GT-3a subjects exhibited the NS5A resistance substitution Y93H, which confers a 100-fold reduction in velpatasvir susceptibility in GT-1a, GT-1b, GT-3a, and in GT-6 [17].

Neither baseline NS5A nor NS5B RAVs predicted virologic failure for patients in ASTRAL trials 1, 2, and 5 [14, 21, 26]. However, in ASTRAL-3, the rate of SVR was 88% for GT-3 patients with baseline NS5A RAVs, notably lower than the 97% SVR obtained by those without [14]. In ASTRAL-4, 89% of patients with pretreatment NS5A RAVs achieved SVR, compared to 92% without. In the preliminary data from Gane et al., 15, 62, and 81% of patients infected with GT1, 2, or 3 had deep sequencing for NS5A RAVs, respectively. For GT-1 and GT-2, all of those patients with pretreatment NS5A RAVs achieved SVR, but in GT-3, only 77% patients did, while in patients without NS5A RAVs, there were no instances of virologic failure [27]. Despite the extraordinary success of DAA therapy in HCV treatment, RAVs continue to pose a challenge, particularly in GT-3 HCV-infected patients.

Conclusion

The SOF/VEL FDC has been shown in clinical trials to solve many of our current therapeutic challenges in the path to HCV eradication, including the virus's genetic variability, the spectrum of fibrosis, and failed response to prior treatment. As a pangenotypic regimen, whether SOF/VEL will streamline, or perhaps eliminate, the pre-treatment evaluations and on treatment monitoring that can be a barrier to treatment access remains to be seen. Whether the cost will prove prohibitive also remains to be seen. Initial pricing estimates would make this fixed-dose combination cheaper than a comparable course of one of its components, sofosbuvir, but the individual prices negotiated by countries and other stakeholders will likely affect the accessibility of the SOF/VEL FDC. There is clearly a role for this regimen in difficult-to-treat patients, including those with HCV and HIV co-infection and the GT-3-infected populations, and especially those patients with decompensated cirrhosis. Further research must be conducted to explore how to expand access to HCV therapy for patients of special populations, including patients with multiple infections and those with renal disease, where current knowledge is lacking.

Future directions

Pangenotypic SOV/VEL comes with new directions in the effort to seek an ideal cure to HCV. One potential benefit of this combination drug is reduced laboratory monitoring, particularly in areas with a low prevalence of GT3 infection. In addition to their difficult side effects, IFN and ribavirin-based therapies require frequent laboratory monitoring [12]. The SOF/VEL combination therapy requires RBV only for patients with decompensated cirrhosis. A minimal follow-up monitoring study should be conducted to confirm that SOF/VEL is appropriate without continuous laboratory monitoring. Furthermore, SOF is currently contraindicated in patients with severe renal disease, with creatinine clearance <30 mL/min and a safe dosing regimen remains undefined for these patients [34]. Because patients with severe renal disease suffer from higher exposures of the predominant sofosbuvir metabolite [17], they persist as a difficult-to-treat population.

Future directions for SOF/VEL should also be directed towards the treatment of challenging patient populations, such as patients coinfected with HIV and GT-3 HCV-infected patients. As discussed in ASTRAL-5, SOF/VEL is effective in treating HCV/HIV-coinfected patients. However, most clinical trials, including ASTRAL-5, study patients with mean CD4 counts greater than 500 cells/μL with complete HIV viral suppression, [25] which does not necessarily represent the typical patient in this population. A second patient population of concern are those infected with GT-3. The role of the RAVs Y93H and A30K in DAA therapy remain to be elucidated. In the seminal IMPACT study, a combination of simeprevir (SMV), daclatasvir (DCV), and SOF demonstrated 100% SVR12 in patients infected with GT-1 or GT-4 with decompensated cirrhosis [35]. Collaborative studies combining DAAs from different manufacturers may benefit patients, specifically by combining SOF/VEL with a pangenotypic protease inhibitor which may help address this challenging patient group.

A noteworthy limitation in the ASTRAL trials was the limited racial demographics of enrolled patients, who were composed primarily of White patients and fewer Black and Asian patients. Hepatitis C is a global health problem, and though the pangenotypic activity of SOF/VEL provides a wide-ranging therapy, specific populations with variable host genetics may benefit from tailored treatment plans. The high frequency of the favorable IL28B genotype, a single-nucleotide polymorphism (SNP) near the interleukin-28B gene, may contribute to high spontaneous HCV clearance in Asian populations [36]. The IL-28B gene does not appear to significantly alter DAA treatment outcome; however, per The Asian Pacific Association for the Study of the Liver (APASL) guidelines, IL28B genotyping could be clinically useful in interferon-based therapy [36]. The ASTRAL studies provided basic information about SVR obtained by race, and no information was specific for Asian patients. In a phase 2a proof-of-concept study, Lau et al. found that all 18 Chinese patients chronically infected with GT-1b HCV and without cirrhosis, who were able to

achieve ultrarapid response (defined as HCV RNA <500 IU/ml by day 2) after 3 weeks with SOF and other DAA combinations, went on to achieve SVR12 [37]. By carefully selecting this patient population with an easier-to-treat 1b genotype against a favorable host genetic background in Asian patients, a shortened therapy may be possible. Ji et al. conducted a prospective observational cohort study investigating 12 weeks of DAA combinations SOV/DCV or SOF/LDV in 94 Chinese patients infected with GT-1b. The patients had previous treatment experience and 56.4% had liver cirrhosis. All 94 of the patients achieved SVR24 [38]. Since such great promise has been shown in these Chinese patients with success despite shortened duration of therapy, future studies should elucidate variations of treatment regimen in various ethnic populations.

As we pursue increased accessibility of HCV therapies and continue eradication efforts, the next obstacle will be affordability. With ongoing negotiations of the price of SOF/VEL, the hope is that the majority of patients will be able to financially access the therapy. Shortening the duration of treatment is a potential method to decrease the cost of therapy. Future studies may also seek to establish a shorter or more potent therapy with different DAA combinations as was investigated for therapy with SOF/LDV, [39, 40] ultimately seeking a short, effective treatment with a low pill-burden. But for now, with a recommended treatment duration of 12 weeks, single tablet FDC SOF/VEL is an excellent option for patients with HCV GT1-6, requiring RBV only in patients with decompensated cirrhosis. Thus far, the treatment for chronic HCV has made a great deal of progress within the recent few years. SOF/VEL is the next step, bringing us closer to a test-and-treat simplified therapy.

Compliance with ethical standards

Conflict of interest Eleanor Wilson and Shyam Kottilil have received research grants from Gilead Sciences Inc. to their institution. Rebecca Lee declares that she has no conflict of interest.

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