Sofosbuvir–velpatasvir for treatment of chronic hepatitis C virus infection in Asia: a single-arm, open-label, phase 3 trial

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Summary

Background Treatment with combined sofosbuvir and velpatasvir has resulted in high sustained virological response rates in patients chronically infected with hepatitis C virus (HCV) with genotypes 1–6 in clinical trials and real-world settings, but its efficacy and safety has not been assessed in Asia, a region with diverse HCV genotypes.

Methods In this single-arm, open-label, phase 3 trial, we recruited patients from 38 sites across China, Thailand, Vietnam, Singapore, and Malaysia, who were chronically infected with HCV genotypes 1–6, and were HCV treatment-naive or treatment-experienced, either without cirrhosis or with compensated cirrhosis. Patients self-administered a combined sofosbuvir (400 mg) and velpatasvir (100 mg) tablet once daily for 12 weeks. The primary efficacy endpoint was sustained virological response, defined as HCV RNA less than 15 IU/mL at 12 weeks after completion of treatment (SVR12), assessed in all patients who received at least one dose of study drug. The primary safety endpoint was the proportion of adverse events leading to premature discontinuation of study drug. This trial is registered with ClinicalTrials.gov, number NCT02671500, and is completed.

Findings Between April 14, 2016, and June 30, 2017, 375 patients were enrolled in the study, of whom 374 completed the full treatment course and one discontinued treatment. Overall, 362 (97% [95% CI 94–98]) of 375 patients achieved SVR12. Among 42 patients with HCV genotype 3b, all of whom had baseline resistance-associated substitutions in NS5A, 25 (89% [95% CI 72–98]) of 28 patients without cirrhosis and seven (50% [23–77]) of 14 patients with cirrhosis achieved SVR12. The most common adverse events were upper respiratory tract infection (36 [10%] patients) and headache (18 [5%] patients). There were no discontinuations due to adverse events. Serious adverse events were reported in three (1%) patients, none of which was judged to be related to sofosbuvir–velpatasvir treatment.

Interpretation Consistent with data from other phase 3 studies, single-tablet sofosbuvir–velpatasvir for 12 weeks is an efficacious and safe treatment for Asian patients with chronic HCV infection, but might have lower efficacy in those infected with HCV genotype 3b and with cirrhosis.

Funding Gilead Sciences.

Introduction

Chronic hepatitis C virus (HCV) infection remains a major health threat in Asia, affecting more than 10 million people. The prevalence of HCV ranges from 0·1% to 1·1% in China and southeast Asia, including Malaysia, Thailand, Vietnam, and Singapore, with varying regional distribution of HCV genotypes.[1] HCV genotype 1 (1a or 1b) is the most common genotype in China (57%), and genotype 3b is specific to this area, accounting for around 7% of HCV infections. In Singapore, the most common genotypes are genotypes 1 (41%) and 3 (46%); in Malaysia, almost all patients with HCV have genotypes 1 (36%) or 3 (62%); in Thailand, the predominant genotypes are 3 (48%) and 6 (35%); and in Vietnam, the most common genotypes are 1 (47%) and 6 (51%).[1–7] The diversity of genotypes in these regions necessitates a potent pangenotypic treatment regimen. In addition, a regimen that is simple and safe, with minimal drug–drug interactions and no need for laboratory monitoring, would facilitate a broad treatment approach consistent with the goal of HCV elimination set by WHO.[8]

Sofosbuvir and velpatasvir, two HCV-specific direct-acting antiviral agents for the treatment of chronic genotype 1–6 HCV infection, are available as a fixed-dose combination tablet. Sofosbuvir is a nucleotide analogue that is a potent and selective pangenotypic inhibitor of non-structural protein 5B (NS5B), a protein that directs HCV replication. Velpatasvir is a potent, pangenotypic, second-generation inhibitor of HCV non-structural protein 5A (NS5A), which is also necessary for HCV replication. Global registrational clinical studies of sofosbuvir and velpatasvir have shown that 12 weeks of treatment is well tolerated and results in high rates of sustained virological

Lancet Gastroenterol Hepatol 2018

Published Online December 13, 2018 http://dx.doi.org/10.1016/S2468-1253(18)30343-1

See Online/Comment http://dx.doi.org/10.1016/S2468-1253(18)30417-5

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Research in context

Evidence before this study

In Asia, chronic hepatitis C virus (HCV) infection is a major health concern. With distinct genotypic distributions across countries and regions, a simple, safe, and effective pangenotypic treatment regimen is needed. The safety and efficacy of the fixed-dose combination of sofosbuvir–velpatasvir for 12 weeks were established in the phase 3 registrational trials ASTRAL-1, ASTRAL-2, and ASTRAL-3, which were conducted in North America, Europe, Australia, New Zealand, and Hong Kong. Among patients with genotype 1–6 HCV infection, with and without compensated cirrhosis, 1015 (98%) of 1035 achieved a sustained virological response at 12 weeks after the end of treatment (SVR12). However, no prospective, large-scale studies of sofosbuvir–velpatasvir have been done in Asia. We searched PubMed using the term "velpatasvir" along with "Asia", "China", "Thailand", "Vietnam", "Singapore", and "Malaysia", for clinical trials published before Sept 11, 2018, without language restrictions. The search yielded only one study in Taiwan, in which 67 (97%) of 69 patients co-infected with HIV and HCV, and 156 (98%) of 159 HCV-monoinfected patients achieved a sustained virological response after 12 weeks of generic sofosbuvir–velpatasvir with or without ribavirin.

Added value of this study

In our single-arm, phase 3 trial, patients from China, Malaysia, Thailand, Vietnam, and Singapore with chronic infection with HCV genotypes 1–6, with or without compensated cirrhosis, who were HCV treatment-naive or treatment-experienced, were treated with open-label sofosbuvir–velpatasvir for 12 weeks, and were assessed for efficacy and safety. Overall, 362 (97%) of 375 patients achieved SVR12, consistent with data from the phase 3 ASTRAL studies of mostly non-Asian patients. Among patients with HCV genotype 3b—a globally rare subtype that is more prevalent in Asia—25 (89%) of 28 patients without cirrhosis and seven (50%) of 14 patients with cirrhosis achieved SVR12.

Implications of all the available evidence

These overall results support the use of sofosbuvir–velpatasvir in Asian patients with chronic HCV infection, but suggest that those with HCV genotype 3b and cirrhosis might have lower response rates.

response in patients infected with HCV genotypes 1–6, with or without compensated cirrhosis, regardless of previous treatment experience.[9,10] Sofosbuvir–velpatasvir was initially approved in the countries and regions in which the phase 3 studies were conducted, including the USA and the EU.[11,12] In 2017 and 2018, on the basis of global data, sofosbuvir–velpatasvir was approved in several Asian countries, including China, Thailand, Hong Kong, Singapore, and Malaysia.

The objective of this phase 3 study was to assess the efficacy and safety of 12 weeks of combined sofosbuvir (400 mg) and velpatasvir (100 mg) treatment in adults with chronic HCV infection and diverse HCV genotypes in Asia.

Methods

Study design and participants

This single-arm, open-label, phase 3 study was done at 38 clinical sites in the Asia-Pacific region (25 in China, five in Thailand, four in Vietnam, two in Malaysia, and two in Singapore). Eligible patients were at least 18 years old, were chronically infected with HCV genotypes 1–6 or indeterminate genotype, and had serum HCV RNA of 10^4 IU/mL or more. Patients were HCV treatment-naive or had previously received an interferon-based regimen either with or without ribavirin (prespecified proportion of patients ≤20%; previous use of NS5A or NS5B inhibitors was exclusionary), and were without cirrhosis or with compensated cirrhosis (≤20% of patients; ie, Metavir score of 4 or Ishak score ≥5, FibroTest >0·75 with an aspartate aminotransferase-to-platelet ratio index >2, or Fibroscan >12·5 kPa). Patients with alanine aminotransferase or aspartate aminotransferase more than ten times the upper limit of normal (ULN), direct bilirubin more than 1·5 times the ULN, platelets more than 50 000/μL, glycated haemoglobin (HbA_{1c}) more than 8·5%, creatinine clearance less than 60 mL/min by the Cockcroft-Gault equation, albumin less than 3 g/dL, or international normalised ratio more than 1·5 times the ULN, and those with hepatitis B virus or HIV co-infection were excluded. Detailed inclusion and exclusion criteria are provided in the appendix.

Before enrolment and before any study procedures were done, written informed consent was obtained from all patients. The study was approved by the independent ethics committees at all participating sites, and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Procedures

Patients self-administered one fixed-dose combination tablet consisting of 400 mg sofosbuvir and 100 mg velpatasvir daily for 12 weeks.

Efficacy and safety were monitored at baseline (day 1 of treatment), at treatment weeks 1, 2, 4, 6, 8, 10, and 12, and at post-treatment weeks 4, 12, and 24 (for patients who achieved a sustained virological response 12 weeks after completion of treatment [SVR12]). HCV genotype and subtype were assessed with the VERSANT HCV Genotype 2.0 assay (INNOLiPA; Siemens, Erlangen, Germany). The COBAS AmpliPrep/COBAS TaqMan HCV quantitative test v2·0 (Roche Molecular Systems, Pleasanton, CA,

USA) was used to quantify HCV RNA (lower limit of quantitation 15 IU/mL).

Plasma samples for viral sequencing were collected at baseline and at all on-treatment and post-treatment study visits. HCV NS5A and NS5B coding regions were deep-sequenced from samples obtained from all patients at baseline, and from patients with virological failure at the time of failure. Sequences obtained at the time of virological failure were compared with sequences from baseline to detect treatment-emergent resistance-associated substitutions. Resistance-associated substitutions were reported at a 15% assay cutoff.

Safety was monitored at every study visit up to and including post-treatment week 4 and included adverse events, concomitant medications, vital signs, clinical laboratory measurements, and physical examinations. Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 20.1.

Outcomes

Efficacy and safety were assessed in all patients who received at least one dose of study drug. The primary efficacy endpoint was SVR12, defined as HCV RNA less than the lower limit of quantitation of the assay (15 IU/mL) 12 weeks after completion or discontinuation of treatment. The primary safety endpoint was the proportion of patients who prematurely discontinued treatment because of adverse events. Secondary endpoints were the proportion of patients with on-treatment HCV RNA less than the lower limit of quantitation, change in HCV RNA concentration from day 1, sustained virological response at 4 weeks and at 24 weeks (SVR24) after completion or discontinuation of treatment with study drug, proportion of patients who had virological failure (defined as either confirmed HCV RNA ≥15 IU/mL after two consecutive measurements showing HCV RNA <15 IU/mL, or an increase in HCV RNA concentration of >$\log_{10}$ from the nadir during the treatment period), and the emergence of viral resistance.

Statistical analysis

Efficacy data were analysed by region for the primary endpoint, and by region and genotype for all other analyses. Specifically, point estimates and two-sided exact 95% CIs using the binomial distribution were generated for SVR12 rates for the study population overall, for participating patients in China, and for those in the other Asian countries.[13] In China, a sample size of 260 patients (80 patients with HCV genotype 1, 60 with genotype 2, 60 with genotype 3, and 60 with genotypes 4, 5, or 6) was selected to provide more than 80% power to detect an improvement of at least 6 percentage points in the SVR12 rate from the performance goal of 85%, using a two-sided exact one-sample binomial test at the 0·05 significance level. With a sample size of 100 patients from Malaysia, Thailand, Vietnam, and Singapore, resulting in a total study population of 360 patients, two-sided 95% exact CIs were calculated for these 100 patients and overall. Safety results and secondary outcomes were summarised descriptively. All statistical summaries and analyses were done using SAS software version 9.4. This trial is registered with ClinicalTrials.gov, number NCT02671500, and is completed.

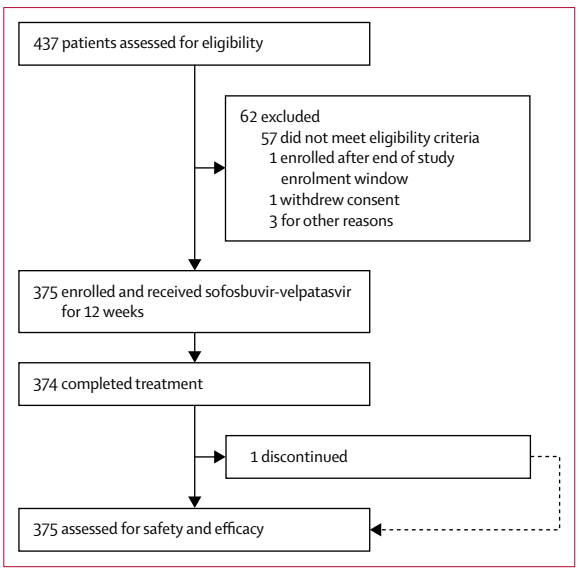

***Figure*: Trial profile**

Role of the funding source

Gilead Sciences oversaw trial management, data collection, statistical analyses, and the writing and review of this manuscript. All authors had access to the study data and reviewed and approved the final manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 14, 2016, and June 30, 2017, we screened 437 patients, 62 of whom were excluded, most due to not meeting eligibility criteria. 375 patients were enrolled in the study and treated with sofosbuvir and velpatasvir (figure).

Overall, there were similar proportions of men and women (53% *vs* 47%), with a median age of 45 years (IQR 36–54; table 1). Per the study design, most patients were Chinese (264 [70%] of 375). Most patients had HCV genotype 1 (34%), 3 (22%), or 6 (26%). Of the 84 patients with genotype 3 HCV infection, 42 (50%) had genotype 3b, of whom 37 (88%) were enrolled in China. Most patients (82%) were HCV treatment-naive. Of the 68 patients who had previously received treatment, 52 (76%) had been treated with an interferon-based regimen without a direct-acting antiviral.

All patients had HCV RNA less than the lower limit of quantitation by treatment week 8 (table 2; appendix). HCV

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See Online for appendix

	Patients (n=375)
Age, years; median (IQR)	45 (36–54)
Sex	
Male	197 (53%)
Female	178 (47%)
Country of enrolment	
China	264 (70%)
Thailand	41 (11%)
Vietnam	36 (10%)
Singapore	22 (6%)
Malaysia	12 (3%)
Body mass index, kg/m^2; median (range)	23 (16–37)
HCV genotype*	
1	129 (34%)
1a	22 (6%)
1b	107 (29%)
2	64 (17%)
2 (no confirmed subtype)	41 (11%)
2a	1 (<1%)
2a/2c	22 (6%)
3	84 (22%)
3 (no confirmed subtype)	1 (<1%)
3a	41 (11%)
3b	42 (11%)
6	98 (26%)
6 (no confirmed subtype)	1 (<1%)
6a	3 (1%)
6a/6b	63 (17%)
6c-l	26 (7%)
6f	4 (1%)
6v	1 (<1%)
IL28B genotype	
CC	320 (85%)
Other	55 (15%)
HCV RNA, $\log_{10}$ IU/mL; mean (SD)	6·2 (0·9)
Compensated cirrhosis	
No	308 (82%)
Yes	67 (18%)
Previous HCV treatment	
No	307 (82%)
Yes	68 (18%)
Direct-acting antiviral* plus pegylated-interferon and ribavirin	3 (1%)
Interferon plus ribavirin	14 (4%)
Pegylated interferon plus ribavirin	38 (10%)
Other	13 (3%)

(Table 1 continues in next column)

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	Patients (n=375)
Response to previous HCV treatment	
Non-responder	15 (4%)
Relapse or breakthrough	46 (12%)
Early treatment discontinuation	4 (1%)
Met a virological stopping rule	2 (1%)
Unknown	1 (<1%)

Data are n (%) unless otherwise specified. HCV=hepatitis C virus. *All three patients received boceprevir.

Table 1: **Patient demographics and baseline characteristics**

	Patients
Response	
Treatment week 2	276/374 (74% [69–78])
Treatment week 4	357/374 (95% [93–97])
Treatment week 8	374/374 (100% [99–100])
Treatment week 12	374/374 (100%[99–100])
Post-treatment week 4	364/375 (97% [95–99])
Post-treatment week 12 (all genotypes)	362/375 (97% [94–98])
Genotype 1a	22/22 (100% [85–100])
Genotype 1b	107/107 (100% [97–100])
Genotype 2	64/64 (100% [94–100])
Genotype 3a and no confirmed subtype	40/42 (95% [84–99])
Genotype 3b	32/42 (76% [61–88])
Genotype 6	97/98 (99% [94–100])
Relapse before post-treatment week 12	12/375 (3%)
Lost to follow-up	1/375 (<1%)

Data are n/N (% [95% CI]). Response was defined as hepatitis C virus RNA <15 IU/mL.

Table 2: **Responses during and after treatment**

RNA concentrations and the change from baseline by treatment visit are shown in the appendix. Of the 375 treated patients, 362 (97% [95% CI 94–98]) achieved the primary endpoint of SVR12 (table 2). Of the 264 patients enrolled in China, 254 achieved SVR12 (96% [93–98]). The proportion of patients who achieved SVR12 for patients in China was significantly greater than the prespecified 85% performance goal ($p<0·0001$), meeting the primary efficacy endpoint for the study. Of the 111 patients enrolled in Thailand, Vietnam, Singapore, and Malaysia, 108 (97% [92–99]) achieved SVR12.

All 193 (100%) patients with HCV genotype 1a, 1b, or 2 and 97 (99%) of the 98 patients with genotype 6 achieved SVR12 (table 2). SVR12 was achieved in 86% (95% CI 76–92) of patients with genotype 3, 95% (84–99) of those with genotype 3a, and 76% (61–88) of those with genotype 3b. 60 (90% [80–96]) of 67 patients with cirrhosis achieved SVR12, and all seven patients with cirrhosis who did not achieve SVR12 had genotype 3b HCV infection. SVR12 was achieved in seven (50% [23–77]) of 14 patients with genotype 3b and cirrhosis, versus 25 (89% [72–98]) of 28 patients with genotype 3b without cirrhosis (appendix).

13 (3%) of 375 patients did not achieve SVR12: one patient with genotype 3a and without cirrhosis was lost to follow-up after 8 days of treatment with study drug; and the other 12 patients (ten patients with genotype 3b, seven of whom had cirrhosis; one patient with genotype 3a without cirrhosis; and one patient with genotype 6f

	Patients with NS5A RASs	NS5A RASs*	Patients achieving SVR12		
			With NS5A RASs	Without NS5A RASs	Overall
Genotype 1a	5/22 (23%)	Lys24Arg, Met28Thr, Gln30His, Tyr93Asn/Phe	5/5 (100%)	17/17 (100%)	22/22 (100%)
Genotype 1b	37/106 (35%)	Arg30Gln, Tyr93His	37/37 (100%)	69/69 (100%)	106/106 (100%)
Genotype 2	56/62 (90%)	Leu31Met and others	56/56 (100%)	6/6 (100%)	62/62 (100%)
Genotype 3a	6/41 (15%)	Ala30Lys, Ala30Val+Tyr93His	5/6 (83%)	35/35 (100%)	40/41 (98%)
Genotype 3b	40/40 (100%)	Ala30Lys+Leu31Met, Leu31Met	30/40 (75%)	..	30/40 (75%)
Genotype 6	30/96 (31%)	Phe28Met/Val, Phe28Val+Thr93Ser, Thr93Ser, others	30/30 (100%)	65/66 (98%)	95/96 (99%)

Data are n/N (%). Only patients with available sequencing data and known virological outcome are included. NS5A=non-structural protein 5A. RASs=resistance-associated substitutions. SVR12=sustained virological response 12 weeks after completion of treatment. *RASs reported were observed either alone or in combination.

Table 3: **Prevalence and effect of baseline NS5A RASs on treatment outcome**

without cirrhosis) had virological relapse (relapse rate 3%). No patients had on-treatment virological failure.

Of the 361 patients who achieved SVR12 and returned for a study visit 24 weeks after completion of treatment with study drug, 100% achieved SVR24 and none had late relapse.

174 (47%) of 367 patients with NS5A sequencing data had NS5A resistance-associated substitutions at baseline (table 3). The prevalence of baseline NS5A resistance-associated substitutions varied across HCV genotypes, from 15% of patients with genotype 3a to 100% of patients with genotype 3b (table 3). Among the 40 patients with genotype 3b, 38 (95%) had both Ala30Lys and Leu31Met, and two (5%) had Leu31Met only. All patients with HCV genotype 1a, 1b, 2, or 6 with NS5A resistance-associated substitutions at baseline achieved SVR12. SVR12 was achieved in five (83%) of six patients with genotype 3a and 30 (75%) of 40 patients with genotype 3b with NS5A resistance-associated substitutions at baseline.

28 (8%) of 365 patients with NS5B sequencing data had baseline NS5B substitutions associated with nucleoside inhibitor resistance (data not shown). The most common substitution was Met289Leu, which was observed in 21 patients with HCV genotype 6. The substitutions Leu159Phe and Glu237Gly (or both) were observed in six patients with genotype 1a, 1b, 3a, or 3b. With the exception of two patients (one with HCV genotype 6f and Met289Leu, and one with genotype 3b and Leu159Phe and the NS5A resistance-associated substitutions Ala30Lys and Leu31Met), SVR12 was achieved in all patients with NS5B substitutions associated with nucleoside inhibitor resistance.

Three of 12 patients who had virological relapse had treatment-emergent resistance-associated substitutions: NS5A Tyr93His emerged in one patient with HCV genotype 3a infection, and NS5B Ser282Thr (associated with nucleoside inhibitor resistance) emerged in two patients with genotype 3b, both of whom had resistance-associated substitutions in Ala30Lys and Leu31Met of NS5A at baseline (appendix).

	Patients (n=375)
Any adverse event	189 (50%)
Any grade 3 or 4 adverse event	0
Any serious adverse event	3 (1%)
Any adverse event leading to discontinuation of study drug	0
Death	0
Adverse events that occurred in ≥5% of patients	
Upper respiratory tract infection	36 (10%)
Headache	18 (5%)
Grade 3 or 4 laboratory abnormalities that occurred in >1 patient	10 (3%)
Platelets <140 × 10^3/μL	2 (1%)
Lipase >100 U/L	2 (1%)

Data are n (%).

Table 4: **Adverse events and laboratory abnormalities**

Adverse events were reported for 189 (50%) of 375 patients (table 4). No patients discontinued or interrupted sofosbuvir–velpatasvir because of adverse events. Three patients had one serious adverse event each (diabetes-related foot infection, pneumonia, and ligament rupture); none of these was considered to be related to treatment with sofosbuvir–velpatasvir, and all resolved during the study follow-up period. No patients died.

Eight (2%) of 375 patients had a grade 3 laboratory abnormality. The only grade 3 laboratory abnormalities that occurred in more than one patient were decreased platelets (two [1%] patients) and elevated lipase (two [1%] patients). Both patients with decreased platelets had graded decreased platelets at screening or baseline and at all other study visits. Grade 3 lipase elevations were transient and asymptomatic.

Two (1%) of 375 patients had a grade 4 laboratory abnormality: one had isolated, asymptomatic elevated potassium at treatment week 8 that was normal on repeat testing 5 days later and at all other visits; and one had isolated, asymptomatic, elevated creatine kinase at

treatment week 4, which was grade 1 on repeat testing 3 days later and normal at all other study visits.

One patient with a medical history of palpitations had two abnormalities on electrocardiogram at post-treatment day 1 that were considered clinically significant by the investigator: one old anteroseptal myocardial infarction, and one short-term atrial tachycardia were reported as a treatment-related adverse event of atrial tachycardia that had resolved at the post-treatment week 4 visit.

Discussion

This study evaluated the efficacy and safety of sofosbuvir–velpatasvir for patients with chronic HCV infection of any genotype in China, Thailand, Vietnam, Singapore, and Malaysia. After treatment with sofosbuvir–velpatasvir for 12 weeks, SVR12 was achieved in 97% of patients overall, and in more than 99% of patients with HCV genotypes 1, 2, or 6, with and without cirrhosis. Among patients infected with HCV genotype 3, SVR12 was achieved in 86%. This lower efficacy was driven by patients with genotype 3b HCV infection and cirrhosis, who were primarily enrolled in China; for patients with HCV genotype 3b, the proportion achieving SVR12 was 76% overall, and was 50% in those with cirrhosis, with almost all patients having baseline resistance-associated substitutions.

Among the 71 million patients infected with HCV globally, there is more genotypic heterogeneity in Asia than is seen in North America and Europe, with genotype 1 HCV infection accounting for only 47% of patients. Furthermore, the availability of advanced health-care services including genotype testing is not universally available throughout this region. A single-tablet regimen that is effective at a single duration for all HCV-infected patients, irrespective of genotype or degree of fibrosis, would simplify therapy and enable delivery of care in resource-limited settings. The cost savings and reduction in complexity of not requiring genotyping or on-treatment laboratory monitoring could be substantial.

The response to HCV therapy depended on both viral and patient factors, although, in the current era of all-oral, highly potent direct-acting antiviral regimens, high rates of sustained virological response are generally expected, regardless of patient demographics or other characteristics. The efficacy results observed in this study are consistent with those observed in the global sofosbuvir–velpatasvir development programme.[9,10,14] In the phase 3 ASTRAL-1,[9] ASTRAL-2,[10] and ASTRAL-3[10] studies, the SVR12 after 12 weeks of treatment with sofosbuvir–velpatasvir in patients chronically infected with HCV genotypes 1–6, with or without compensated cirrhosis, was 98% (1015 of 1035 patients). The phase 3 ASTRAL-3 study, which was conducted in the USA, the UK, France, Australia, Germany, Canada, Italy, and New Zealand, assessed the safety and efficacy of sofosbuvir–velpatasvir for 12 weeks in patients chronically infected with HCV genotype 3, with or without cirrhosis. Overall, 95% of patients with HCV genotype 3 achieved SVR12 (97% for those without cirrhosis and 91% for those with cirrhosis). Consistent with the global distribution of HCV genotype 3 subtypes, 96% of the patients enrolled in ASTRAL-3 who received sofosbuvir–velpatasvir for 12 weeks had subtype 3a, 96% (253 of 265 patients) of whom achieved SVR12; 0·7% (two patients) had subtype 3b, both of whom achieved SVR12. Findings from a real-world study in Asia suggest that Asian patients with HCV genotype 3 might have better responses to direct-acting antiviral therapy than do other patients.[15]

In the current study, substitutions associated with resistance to NS5A and nucleoside inhibitors were detected in NS5A in 47% and in NS5B in 8% of patients at baseline, with the prevalence of resistance-associated substitutions varying between HCV genotypes and subtypes and region. For patients with HCV genotypes 1a, 1b, 2, 3a, or 6, baseline NS5A resistance-associated substitutions did not affect SVR12. All patients infected with HCV genotype 3b had NS5A resistance-associated substitutions, and most had both Ala30Lys and Leu31Met substitutions in NS5A at baseline, consistent with previous observations.[16] The combination of Ala30Lys and Leu31Met in a genotype 3b replicon confers high-level (>100-fold) resistance to velpatasvir (unpublished data). Three of the ten patients with virological failure had treatment-emergent resistance-associated substitutions at relapse, two of whom had genotype 3b HCV infection, baseline Ala30Lys and Leu31Met in NS5A, and developed the sofosbuvir signature mutation Ser282Thr in NS5B.

Although HCV genotype 3b (mostly with HCV Ala30Lys and Leu31Met) is more common in Asia than in other regions, it accounts for a small proportion of the total HCV-infected population in that region.[16] In China, the most common HCV subtypes are 1b (52%) and 2a (29%), and the prevalence of genotype 3b is 7%.[3] Furthermore, among those with genotype 3b in China, only about 1% have cirrhosis.[17] Thus, patients with HCV genotype 3b and cirrhosis were over-represented in this study because of enrolment targets that enriched for these patients (5%), compared with the estimated prevalence of these patients in China (about 0·7%).[3,17] The prevalence of HCV genotype 3b in Asia outside of China is not well described, and the clinical and real-world studies that have evaluated all-oral direct-acting antiviral regimens in patients with HCV genotype 3 have been conducted in North America and Europe, and are likely to have enrolled patients with HCV genotype 3a.[10,18–21] Moreover, the high frequency of NS5A resistance-associated substitutions at baseline in the small selected group of patients with HCV genotype 3b in our study might not be representative, and warrants further study.

The clinical effect of the lower sustained virological response rates observed in patients with HCV genotype 3b infection and cirrhosis is anticipated to be small from an elimination perspective. The addition of ribavirin to sofosbuvir–velpatasvir for patients with HCV genotype 3b

and cirrhosis, who are highly likely to have the NS5A Ala30Lys and Leu31Met resistance-associated substitutions, might increase response rates, as has been observed in patients with cirrhosis who are infected with HCV genotype 3.[18,22] In a Spanish study of 12-week sofosbuvir–velpatasvir treatment in patients with compensated cirrhosis and genotype 3 HCV infection, 94% of whom had genotype 3a, the addition of ribavirin decreased the relapse rate from 5% to 2%, and the benefit was greatest for patients with pretreatment NS5A resistance-associated substitutions.[18] The lower rates of sustained virological response for patients with genotype 3b HCV and cirrhosis in this study make the addition of ribavirin a reasonable option for this patient population.

Asia is a large geographical region that comprises genetically and ethnically diverse populations, and the generalisability of the results of this study might thus be limited because of the enrolment of patients from five selected countries.

The development of direct-acting antivirals has dramatically improved the globally available treatment options for HCV-infected patients. Compared with historical interferon-based regimens, current direct-acting antiviral options consist of all-oral regimens that are shorter, safer, more easily tolerated, and more efficacious for treatment of all HCV genotypes, regardless of previous treatment experience or cirrhosis status.[23,24] Many of these regimens are recognised as being important for the treatment of HCV in the Asia-Pacific region, where they have been recommended for use in region-specific guidelines.[25] The Asian Pacific Association for the Study of the Liver recommends several all-oral, interferon-free, combination direct-acting antiviral regimens, and the selection and duration of these regimens, as well as the need to include ribavirin, are determined by patient characteristics (eg, HCV genotype, presence or absence of cirrhosis, or presence of resistance-associated substitutions). Sofosbuvir–velpatasvir addresses unmet medical needs in China and southeast Asia by providing a simple, highly effective, well tolerated, interferon-free and ribavirin-free, pangenotypic treatment, which will facilitate the WHO goal of HCV elimination.[8]

Contributors

LW, SGL, and DMB contributed to the study design. LW, SGL, QX, KNV, TP, YH, SW, MX, HT, JC, HLM, YG, ZM, AS, XD, ST, YN, CKT, QN, HPT, YM, Y-FY, LD, G-QW, TT, PH, PT, LZ, ZLG, FL, TTPL, JS, GG, JL, MS, ZD, RM, JLH, and JJ served as study investigators and collected data. SL, HD-S, HM, and LMS analysed and interpreted the data. All authors provided critical revision and approval of the manuscript.

Declaration of interests

LW has received research funding from AbbVie, Bristol-Myers Squibb, and Roche. SGL has served on the advisory boards for Gilead, AbbVie, Roche, and Abbott, and has received research funding from Gilead, MSD, Abbott, and Roche. TP has served on advisory boards for Bristol-Myers Squibb, Bayer, and Mylan, has served as a speaker for Bristol-Myers Squibb, MSD, Bayer, and Mylan, and has received research funding from Bristol-Myers Squibb, Gilead, MSD, Fibrogen, and Bayer. C-KT has served on advisory boards and as a speaker for Gilead. LMS, SL, HD-S, HM, and DMB are employees of, and hold stock in, Gilead. All other authors declare no competing interests.

Data sharing statement

Data collected for the study can be made available by request. Please contact the corresponding author with all requests.

Acknowledgments

Writing and editorial assistance was provided by Roberta Kelly of Gilead Sciences. Sandra Chen of Gilead Sciences also provided editorial assistance.

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