Original Article

Efficacy and Safety of All-oral Emitasvir and Sofosbuvir in Patients with Genotype 1b HCV Infections without Cirrhosis

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Keywords: Hepatitis C virus; Genotype 1; Direct acting antivirals; Emitasvir; Sofosbuvir; Combination treatment.

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DAA, direct-acting antiviral; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; LSM, liver stiffness modulus; NS5A, nonstructural protein 5A; RASs, resistance-associated substitutions; SAEs, serious AEs; SD, standard deviation; SVR, sustained virologic response; ULN, upper limit of normal.

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Abstract

Background and Aims: Emitasvir is a new type of hepatitis C virus (HCV) nonstructural protein 5A (NS5A) inhibitor, and the data of phase 2 trial has shown emitasvir-sofosbuvir to have good safety and tolerance. We conducted this phase 3 trial to further verify the efficacy and safety. ***Methods:*** We evaluated the antiviral activity and safety of a 12-week regimen of emitasvir phosphate (100 mg) combined with sofosbuvir (400 mg) once daily in non-cirrhotic patients with genotype 1 HCV infection. The primary endpoint was a sustained virological response at 12 weeks (SVR12) after the end of treatment. ***Results:*** Of the 362 patients enrolled in the trial, 39.8% were male, 99.2% had HCV genotype 1b, 0.8% had genotype 1a and 79.8% were treatment-naïve. The average age was 47.2 years. All patients completed the treatment and follow-up. All 3 patients with genotype 1a achieved SVR. Two genotype 1b treatment-naïve patients experienced virologic relapse. The rate of SVR12 was 99.7% (358/359), and SVR24 was 99.4% (357/359) in genotype 1b. Overall, 36.2% had resistance-associated substitutions (RASs) in NS5A and 98.3% had RASs in NS5B at baseline. The RASs at baseline had no effect on the rates of response. Serious adverse events were reported in 16 patients and were not related to emitasvir-sofosbuvir. Most adverse events did not require therapy. ***Conclusions:*** The 12 weeks of treatment with emitasvir-sofosbuvir was a highly efficient and safe treatment for a wide range of patients with HCV genotype 1b infection without cirrhosis, who had not been treated or who had been treated with interferon-based regimen previously.

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Introduction

Hepatitis C is a global epidemic, and people of different sex, age and race are susceptible to infection with the hepatitis C virus (HCV). The World Health Organization estimates that 71 million people worldwide had chronic HCV infection in 2015 and that 399,000 people died of liver cirrhosis or hepatocellular carcinoma caused by HCV infection in 2015.[1] In 2006, the positive rate for anti-HCV antibodies was 0.43% in the Chinese population of individuals ages 1-59 years-old.[2] From this, it was estimated that there are 5.6 million people infected with HCV in the general population in China. However, when including the high-risk groups and high-risk areas of HCV infection, China is expected to have a total of about 10 million cases of HCV infection.[2]

In China, genotypes 1b and 2a are common, with the former being the most common, accounting for 56.8%, while genotype 1a accounts for only 1.4%. Genotypes 4 and 5 are very rare, and type 6 is relatively rare.[3,4] The sustained virologic response (SVR) rate of pegylated-interferon combined with ribavirin in HCV genotype 1 patients without cirrhosis is reportedly about 75%.[5] The application of all-oral direct-acting antiviral (DAA) therapy in China starting in 2017 has led to improvements in both treatment options and outcomes for patients with HCV infection, and the SVR rate has reached more than 95%.[6–9] Patients with genotype 1 can be treated with either pangenotypic DAAs or genotype-specific DAAs.

Emitasvir phosphate is a new type of HCV nonstructural protein 5A (NS5A) inhibitor independently developed in China. Preclinical studies showed that the compound has strong antiviral activity against genotype 1 HCV. The data of phase 1 and phase 2 clinical trials showed that the combination regimen of emitasvir-sofosbuvir has good safety and tolerance.[10] In the phase 3 clinical trial described herein, we evaluated the antiviral activity and safety of a 12-week regimen of emitasvir phosphate combined with sofosbuvir in non-cirrhotic patients with genotype 1 HCV infection, who were treatment-naïve (defined as patients who had never been treated for their HCV infection) or treatment-experienced (defined as patients who were previously treated with an interferon-based regimen).

Methods

Study design and treatment

This phase 3, single arm, open-label, multicenter study involved treatment-naïve or treatment-experienced, non-cirrhotic patients with chronic HCV genotype 1 infections, and was conducted at 36 study sites in mainland China between April 2018 and June 2019 (funded by Sunshine Lake Pharma Co., Ltd.; ClinicalTrials.gov number, NCT 03487107). All patients were treated by 100 mg emitasvir capsule (Yichang HEC Changjiang Pharmaceutical Co., Ltd, China) plus 400 mg sofosbuvir tablet (Gilead, USA), and administered orally once daily. The duration of treatment was a consecutive 12 weeks, after which all study participants entered a 24-week treatment-free follow-up period.

This clinical trial was approved by each participating center's independent ethics review board and conducted in accordance with the principles of the Declaration of Helsinki, good clinical practice, and Chinese legal and regulatory requirements. Prior to the beginning of the trial, the subject's written informed consent was obtained.

Patients

The study population included male and female patients aged over 18 years old, body mass index (BMI) between 18 and 32 kg/m^2, and body weight ≥40 kg. For study participation, all female patients had to indicate they had no plans to become pregnant during the screening period, and from the beginning of treatment to 90 days after treatment, the patients had to agree to use of effective contraception. The patients had chronic HCV infection of genotype 1 without cirrhosis, and had an HCV RNA level ≥10,000 IU/mL at the time of screening. The treatment-naïve patients were defined as having no prior exposure to any interferon, ribavirin, or other approved or experimental DAAs. The treatment-experienced patients were defined as having received interferon-based regimen therapy, with completion being at least 2 months before the screening visit. Patients had FibroScan® liver stiffness modulus (LSM) that did not exceed 12.5 kPa at 6 months prior to enrollment or had no cirrhosis confirmed by liver biopsy at 24 months prior to enrollment. Liver biopsy results were preferred to FibroScan® LSM.

Key exclusion criteria included the following: clinical hepatic decompensation or a history of hepatic decompensation, such as ascites, hepatic encephalopathy, or esophageal or gastric varices bleeding; the existence of primary liver diseases not caused by HCV; receipt of any DAAs before

screening; cardiovascular events that had occurred in the 6 months prior to screening; gastrointestinal diseases or post-operative status affecting drug absorption; history of mental illness or related diseases; malignancy within 5 years prior to signing of the informed consent; solid organ transplantation; hepatitis B virus surface antigen or anti-human immunodeficiency virus serological test result positivity; confirmed primary liver cancer; alpha-fetoprotein >100 ng/mL (if 20 ng/mL ≤ alpha-fetoprotein ≤100 ng/mL, ultrasound liver examination was required to exclude primary hepatocellular carcinoma); serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >10 upper limit of normal; total bilirubin >1.5 upper limit of normal; albumin <3.5 g/dL; international normalized ratio >1.5; absolute neutrophil count $<1.5\times10^9$/L; platelet count $<90\times10^9$/L; hemoglobin <110 g/L (for females) or 120 g/L (for males); HbA1c >8.5%; creatinine clearance rate <50 mL/min, as calculated by the Cockcroft-Gault formula; in the absence of effective control, any heart, respiratory, gastrointestinal tract, blood, nerve or other diseases, or diseases whose treatment may interfere with the participants ability to obey the research plan or assessment of the study investigators; a woman or man whose partner was pregnant; and any other conditions the investigator considered inappropriate for exclusion.

Study assessments

HCV RNA was determined using the COBAS AmpliPrep/ COBAS Taqman HCV Test Version 2.0 Virus Quantitative Detection Kit (Roche Molecular System, Inc., USA), with a lower limit of quantification (LLOQ) of 15 IU/mL. HCV genotyping was directly sequenced by reverse transcription PCR (sensitivity 20%). HCV RNA and genotyping were evaluated in the clinical laboratory of Guangzhou Kingmed Center (China). Other clinical laboratory assessments were mainly conducted in local hospital laboratories. Blood samples were collected to determine serum levels of HCV RNA before the initiation of emitasvir- sofosbuvir and at weeks 1, 2, 4, 6, 8, 10 and 12 during treatment and at weeks 4, 12 and 24 after treatment.

Resistance testing was conducted in the clinical laboratory of Guangzhou Kingmed Center, using Sanger sequencing of the NS5A and NS5B regions (threshold ≥20% of the viral population) in samples of all patients at baseline and at the time of treatment failure. The amino acid sites at 24, 28, 30, 31, 32, 58, 92 and 93 of HCV NS5A, and 61, 62, 159, 202, 282, 316, 320, 321 and 440 of HCV NS5B were analyzed based on Sanger sequencing results.

Adverse events (AEs), mainly those occurring during treatment, as well as physical examination, vital signs, and findings from 12-lead electrocardiogram, laboratory examination, and abdominal ultrasound were included in safety assessments. AEs were coded using the MedDRA 22.0 dictionary.

Study endpoints

The primary outcome endpoint was the percentage of subjects who achieved HCV RNA <LLOQ or HCV RNA at undetectable level at 12 weeks after the end of treatment (SVR12). The secondary outcome endpoints were the percentage of subjects who achieved HCV RNA <LLOQ or HCV RNA at undetectable level at 4 and 24 weeks after the end of treatment (SVR4 and SVR24), the percentage of subjects with virological failure during treatment or relapse after treatment, and HCV virus resistance monitored at baseline, during and after treatment.

Safety endpoints included AEs during treatment and serious AEs (SAEs), vital signs, findings from physical examinations, 12-lead electrocardiogram, laboratory tests and abdominal ultrasound, and other safety indicators.

Statistical analyses

Statistical analysis of data was performed using the statistical analysis software SAS Version 9.4 (SAS Institute Inc., USA). Continuous data were analyzed using descriptive statistical

Table 1. Baseline demographics and disease characteristics

Characteristic	Genotype 1a, *n*=3	Genotype 1b, *n*=359	Overall, *n*=362
Mean age (range), years	35.7 (24-46)	47.3 (20-78)	47.2 (20-78)
Age ≥65 years, *n* (%)	0	31 (8.6)	31 (8.6)
Male, *n* (%)	2 (66.7)	142 (39.6)	144 (39.8)
Mean BMI (range), kg/m^2	23.10 (18.2-27.7)	23.44 (18.0-32.0)	23.44 (18.0-32.0)
Prior treatment history			
Treatment-naïve, *n* (%)	2 (66.7)	287 (79.9)	289 (79.8)
Treatment-experienced, *n* (%)	1 (33.3)	72 (20.1)	73 (20.2)
FibroScan® LSM, mean (SD), kPa	6.23 (2.627)	6.81 (2.619)	6.80 (2.616)
HCV RNA			
Mean (SD), Log10 IU/mL	6.43 (0.404)	6.19 (0.781)	6.20 (0.779)
≥ 800,000 IU/mL, *n* (%)	3 (100.0)	261 (72.7)	264 (72.9)
ALT			
Mean (SD), IU/L	50.93 (29.029)	63.04 (54.341)	62.94 (54.169)
> 1.5ULN, *n* (%)	0	117 (32.6)	117 (32.3)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; LSM, liver stiffness modulus; SD, standard deviation; ULN, upper limit of normal.

methods, such as case number, mean, standard deviation, minimum, and maximum. The frequency and classification data were analyzed using frequency and percentage. All subjects enrolled and taking at least one dose of the study drug were included in the full analysis set. The SVR12 point estimate and the bilateral 95% confidence interval (CI) were based on the full analysis set. All enrolled subjects taking at least one dose of the study drug were included in the safety set. All security analysis was based on safety set.

Results

Demographics and baseline characteristics

Of the 440 screened patients, 362 were enrolled. Among them, 3 patients had HCV genotype 1a and 359 patients had HCV genotype 1b. All 362 subjects completed the 12-week treatment period. One treatment-naïve patient with genotype 1b experienced a virologic relapse during the follow-up at 12 weeks after treatment. The other 361 patients completed the follow-up 24 weeks after treatment. As shown in Table 1, the mean age of the patients was 47.2 years, mean weight was 62.26 kg, and mean BMI was 23.44 kg/m^2. Among the patients, 144 (39.8%) were male and 218 (60.2%) were female, 353 (97.5%) were Han nationality and 9 (2.5%) were other nationalities.

Of 362 subjects, 289 (79.8%) were treatment-naïve, including 2 cases of genotype 1a and 287 cases of genotype 1b. There were 73 (20.2%) who were treatment-experienced, including 1 of genotype 1a and 72 cases of genotype 1b. Mean baseline HCV RNA was 6.20 (±0.779) Log10 IU/mL, and 264 patients (72.9%) had a baseline HCV RNA ≥800,000 IU/mL. Mean baseline ALT was 62.94 (±54.169) U/L, and mean baseline FibroScan® LSM was 6.80 (±2.616) kPa.

Baseline resistance-associated substitutions (RASs)

As shown in Table 2, among the 3 subjects with genotype 1a, 1 (33.3%) had M28V mutation in NS5A at baseline. Three (100%) subjects had RASs in NS5B at baseline, of which two (66.7%) had mutations in S62N and one (33.3%) had mutation in S62D. Among the 359 subjects with genotype 1b, 130 (36.2%) subjects had RASs in NS5A at baseline. The mutation rates of R30Q, Y93Y/H and Y93H were more than 5%, and were 11.1% (40/359), 8.4% (30/359) and 5.6% (20/359) respectively with no P32 site mutation. A total of 353 (98.3%) subjects had RASs in NS5B at baseline. The mutation rates of C316N, E440E/G and E440G were 97.5% (350/359), 5.8% (21/359) and 5.6% (20/359) respectively. No mutations were found at D61, S282, L320 and V321 sites.

Table 2. Baseline resistance-associated substitutions in genotype 1

	Genotype 1a, *n*=3	Genotype 1b, *n*=359
HCV NS5A		
RASs	1 (33.3)	130 (36.2)
R30Q		40 (11.1)
Y93Y/H		30 (8.4)
Y93H		20 (5.6)
P58S		14 (3.9)
R30Q/R		12 (3.3)
L28M		5 (1.4)
M28V	1 (33.3)	
No RASs	2 (66.7)	229 (63.8)
HCV NS5B		
RASs	3 (100)	353 (98.3)
C316N		350 (97.5)
E440E/G		21 (5.8)
E440G		20 (5.6)
C316N, E440G		18 (5.0)
C316N, E440E/G		17 (4.7)
D62N		14 (3.9)
D62D/N		13 (3.6)
D62N, C316N		13 (3.6)
D62D/N, C316N		10 (2.8)
E202D		5 (1.4)
L159F		5 (1.4)
E202D, C316N		5 (1.4)
L159F, C316N		5 (1.4)
S62N	2 (66.7)	
S62D	1 (33.3)	
No RASs	0	6 (1.7)

Data are presented as *n* (%).

Abbreviations: HCV, hepatitis C virus; NS5A, nonstructural protein 5A; NS5B, nonstructural protein 5B; RASs, resistance-associated substitutions.

Efficacy

All subjects had good adherence to drug exposure time and dose, ranging from 80-120%. All 362 subjects achieved HCV RNA <LLOQ at 4 weeks after treatment. Except for 1 treatment-naïve patient with genotype 1b who was confirmed to have a virological relapse at 12 weeks after treatment; the other 361 subjects all had lower HCV RNA than LLOQ at 12 weeks after treatment, with SVR12 reaching 99.7% (95%CI: 98.47-99.99%). Another genotype 1b treatment-naïve patient developed virological relapse at 24 weeks after treatment, with SVR24 at 99.4% (360/362). Both SVR4, SVR12 and SVR24 of HCV genotype 1a subjects were 100.0% (3/3), while SVR4, SVR12 and SVR24 of HCV genotype 1b subjects were 100.0% (359/359), 99.7% (358/359), and 99.4% (357/359) respectively.

In this study, very high SVR12 was obtained in all subgroups (Table 3), including treatment-naïve vs. treatment-experienced, <65 years vs. ≥65 years, and male vs. female, as well as subdivisions based on baseline BMI level, baseline HCV RNA level and baseline ALT level. For example, the SVR12 of the treatment-naïve and treatment-experienced subjects was 99.7% (288/289) and 100.0% (73/73) respectively. The efficacy of each subgroup is shown in

Table 3. Efficacy of treatment by subgroup

	Genotype 1a, *n*=3		Genotype 1b, *n*=359		Overall, *n*=362	
	n (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI
Prior treatment history						
Treatment-naïve	2 (100.0)	15.81 - 100.00	286 (99.7)	98.07 - 99.99	288 (99.7)	98.09 - 99.99
Treatment-experienced	1 (100.0)	2.50 - 100.00	72 (100.0)	95.01 - 100.00	73 (100.0)	95.07 - 100.00
Sex						
Male	2 (100.0)	15.81 - 100.00	142 (100.0)	97.44 - 100.00	144 (100.0)	97.47 - 100.00
Female	1 (100.0)	2.50 - 100.00	216 (99.5)	97.46 - 99.99	217 (99.5)	97.47 - 99.99
Age						
<65 years	3 (100.0)	29.24 - 100.00	327 (99.7)	98.31 - 99.99	330 (99.7)	98.33 - 99.99
≥65 years	0	NA	31 (100.0)	88.78 - 100.00	31 (100.0)	88.78 - 100.00
Baseline BMI, kg/m^2						
<30 kg/m^2	3 (100.0)	29.24 - 100.00	349 (99.7)	98.42 - 99.99	352 (99.7)	98.43 - 99.99
≥ 30 kg/m^2	0	NA	9 (100.0)	66.37 - 100.00	9 (100.0)	66.37 - 100.00
Baseline HCV RNA						
<800,000 IU/mL	0	NA	98 (100.0)	96.31 - 100.00	98 (100.0)	96.31 - 100.00
≥800,000 IU/mL	3 (100.0)	29.24 - 100.00	260 (99.6)	97.88 - 99.99	263 (99.6)	97.91 - 99.99
Baseline ALT						
≤1.5 ULN	3 (100.0)	29.24 - 100.00	241 (99.6)	97.72 - 99.99	244 (99.6)	97.75 - 99.99
>1.5 ULN	0	NA	117 (100.0)	96.90 - 100.00	117 (100.0)	96.90 - 100.00

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; BMI, body mass index; ULN, upper limit of normal.

Table 3. SVR12 in the genotype 1a subjects was 100% (3/3, 95% CI 29.24-100.00%), and in genotype 1b subjects SVR12 was 99.7% (358/359, 95% CI 98.46-99.99%).

Effect of HCV NS5A and NS5B RASs on SVR12

This study analyzed the influence of baseline mutations at amino acid sites 24, 28, 30, 31, 32, 58, 92, 93 in HCV NS5A and at amino acid sites 61, 62, 159, 202, 282, 316, 320, 321, 440 in HCV NS5B on SVR12. SVR12 in patients with NS5A RASs at baseline was 99.2% (130/131) and 100% (231/231) in patients without NS5A RAS. SVR12 in patients with NS5B RASs at baseline was 99.7% (355/356) and 100% (6/6) in patients without NS5B RAS. It was found that despite the presence of NS5A RASs or NS5B RASs at baseline, there was no effect on the treatment efficacy on SVR12.

The genotypes of the 2 subjects who failed treatment were all genotype 1b. One subject had no NS5A RASs but NS5B RASs (site 316) at baseline, then NS5A RASs (site 28) and NS5B RASs (site 316) at the time of relapse. Another subject had NS5A RASs (sites 28, 31, 93) and NS5B RASs (site 316) at baseline, then NS5A RASs (sites 28, 31, 93) and NS5B RASs (sites 282, 316) at the time of relapse. In 2 subjects with treatment failure, the main NS5A RASs were L28M, L31V and Y93H, and the main NS5B RASs were S282T and C316N. RASs in L28M and C316N were detected in both 2 subjects.

Safety

A total of 279 subjects (77.1%) experienced AEs during the trial (Table 4). The main AEs reported for ≥5% of patients were upper respiratory tract infection, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, and elevated serum creatine phosphokinase. One hundred and twenty-nine subjects (35.6%) had drug-related AEs. The highest incidence of drug-related AEs was found to involve metabolic and nutritional diseases (18.2%), followed by those detected through various examinations (17.7%) and involving gastrointestinal diseases (5.2%), kidney and urinary diseases (2.5%), general disorders and administration site conditions (2.5%), and diseases of the skin and subcutaneous tissues (2.2%). The main treatment drugs-related symptoms reported for ≥2% of patients were hypercholesterolemia, hypertriglyceridemia, hyperuricemia, elevated serum creatine phosphokinase, elevated lipase, elevated serum lactate dehydrogenase, and elevated amylase.

Thirty SAEs occurred in 16 subjects, including all kinds of injuries, poisoning and surgical complications (contusion, ligament rupture, hand fracture and so on), nervous system diseases (thalamus hemorrhage, ruptured cerebral aneurysm and cerebral infarction), lung infection, appendicitis, dermal sinus, skin mass, thyroid papillary carcinoma, histiocytic necrotizing lymphadenitis, fetal abnormalities, bronchiectasis, and sudden hearing loss. All SAEs were assessed as independent of the study treatment. Most AEs were mild or moderate in severity, and did not require therapy and resolved by themselves (Table 4). No AEs lead to death, and no AEs lead to the premature discontinuation or interruption of the study drug.

Discussion

In this multicenter, single arm, open-label, phase 3 study, the rates of SVR12 were 99.7%. This trial showed that a 12-week

Table 4. Adverse events frequency and severity

AEs, *n* (%)	Overall, *n*=362
Any AEs	279 (77.1)
AEs reported for ≥5% of patients	
Upper respiratory tract infection	51 (14.1)
Hypercholesterolemia	49 (13.5)
Hypertriglyceridemia	35 (9.7)
Hyperuricemia	22 (6.1)
Elevated serum creatine phosphokinase	19 (5.2)
Treatment drugs-related AEs	129 (35.6)
Grade 1	99 (27.3)
Grade 2	22 (6.1)
Grade 3	6 (1.7)
Grade 4	2 (0.6)
Grade 5	0
Treatment drugs-related AEs reported for ≥2% of patients	
Hypercholesterolemia	30 (8.3)
Hypertriglyceridemia	19 (5.2)
Hyperuricemia	17 (4.7)
Elevated serum creatine phosphokinase	14 (3.9)
Elevated lipase	12 (3.3)
Elevated serum lactate dehydrogenase	10 (2.8)
Elevated amylase	8 (2.2)
SAEs	16 (4.4)
AEs leading to premature discontinuation of study drug	0
AEs leading to interruption of study drug	0
Death	0

Abbreviations: AEs, adverse events; SAEs, serious adverse events.

regimen of emitasvir-sofosbuvir, without ribavirin, constitutes a very effective treatment for HCV genotype 1 infection patients without cirrhosis. The response to interferon-based regimens for HCV infection with genotype 1 was lower than other genotypes;[5] however, genotype 1 patients treated with DAAs can achieve very high rates of SVR, as the SVR12 rate in this study was as high as 99.7%. In the era of DAAs, genotype 1 patients became easily curable. Gower *et al.*[11] analyzed 2320 studies on the prevalence of HCV genotypes in PubMed and EMBASE databases, including epidemiological data from 98 countries. The analysis showed that genotype 1 was the dominant genotype (in 46% of HCV infections), followed by genotype 3 (22%), type 2 (13%), type 4 (13%), type 6 (2%), and type 5 (1%). Genotype 1b is the most common subtype, accounting for 22%, but there are significant national and regional variations in distribution. In China, genotype 1 accounted for 58.4%, wherein genotype 1b accounted for 56.8% and genotype 1a was very rare, accounting for only 1.4%. Because genotype 1a was very rare in China, only 3 patients with genotype 1a were included in this study but all obtained SVR12. This 12-week regimen of emitasvir-sofosbuvir for genotype 1b was suitable for more than 20% hepatitis C patients globally and more than one-half hepatitis C patients in China.

The response to an interferon-based regimen for HCV infection varies greatly based on certain characteristics of the patient, such as baseline viral load, ethnicity, HCV genotype, IL28B genotype, and degree of fibrosis, and whether there is an early response during treatment.[12] In the era of antiviral therapy with DAAs, except for individual DAAs, baseline viral load or baseline RASs can affect efficacy, the effectiveness of many DAAs treatments is not affected by the baseline characteristics of the patient.[13,14] In this trial, response rates were generally consistent, regardless of patient characteristics at baseline. For all genotype 1 patients without cirrhosis, the rates of response to a 12-week regimen of emitasvir-sofosbuvir is the same (high), regardless of baseline prior treatment history, sex, age, baseline BMI, baseline HCV RNA level, and baseline ALT level.

This study showed that HCV genotype 1 patients already had some RASs at baseline, such as R30Q and Y93H in the NS5A region, C316N, E440G, and L159F in the NS5B region. The study from Wei L *et al.*[15] showed that in HCV genotype 1b patients, the prevalence of NS3 RASs was 22% in China, lower than in North America (28%) and in Europe (40%). The prevalence of NS5A RASs (including Y93H) was 18-21% in Asian countries, similar in North America (15%) and Europe (19%). The prevalence of NS5B RASs (including L159F) was 1-5% in Asian countries, lower than in North America (4%) or Europe (20%). RASs can reduce the efficacy of some DAA regimens, such as daclatasvir plus asunaprevir. SVR12 was lower among patients with NS5A RASs (at L31 or Y93H) than those without NS5A RASs at baseline (53% vs. 96%).[16] However, there is no standard kit available to detect HCV resistance to approved drugs. Resistance detection mainly relies on in-house techniques based on Sanger sequencing or deep sequencing.[17] In our study, only 2 of the 362 patients showed virologic failure, both of whom were genotype 1b patients, one with C316N RASs and the other with L28M and C316N RASs at baseline. However, the results showed that even with RASs at baseline, there was no effect on the efficacy of emitasvir-sofosbuvir. Therefore, RASs detection at baseline is not required for the treatment of genotype 1 patients with emitasvir-sofosbuvir. Virologic failure was very rare in this study's subjects, occurring in only 0.55% of patients (2 of 362); we did not identify clinical or virologic predictors of treatment failure in these 2 patients. Because both patients had RASs to NS5A inhibitors or NS5B inhibitors at baseline or at the time of relapse, a sofosbuvir-based regimen with a NS5A inhibitor and a protease inhibitor would be an option for retreatment of these 2 patients.

The most common adverse events (≥5%) included upper respiratory tract infection, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, and elevated serum creatine phosphokinase. Most AEs did not require special treatment and were self-limiting or self-resolving. In this trial, no AEs resulted in premature discontinuation or interruption of the study drug, and no deaths occurred. No occurrence of SAEs was related to the study drugs. The emitasvir-sofosbuvir regimen was safe and well tolerated in our Chinese patient population. This treatment regimen does not require a combination with ribavirin, which has significant blood toxicity.

Several DAAs have been approved in China, including pangenotypic DAAs with high efficacy, such as glecaprevir/pibrentasvir and sofosbuvir/velpatasvir. This combo of domestic NS5A inhibitors-emitasvir and sofosbuvir is expected to be less costly than the regimens that have been approved in China. It would be available to the patients with genotype 1b, which accounts for more than half of hepatitis C patients in China, and also including those who have failed a previous interferon-based regimen.

In conclusion, our study showed that the 12 weeks of treatment with emitasvir-sofosbuvir was a highly efficient and safe treatment for a wide range of patients with HCV genotype 1b infection without cirrhosis, who had either not been treated or who had been previously treated with interferon-based regimen. This regimen would be ideal for populations where genotype 1b is predominant such as northern, central and eastern China, and Europe.

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Conflict of interest

Huiying Rao has received speaking fees from Bristol-Myers Squibb, Gilead, and AbbVie. Hongming Xie, Lin Luo, Qingyun Ren, and Yingjun Zhang are employees of Sunshine Lake Pharma Co., Ltd. Lai Wei has received research support and/or consulting fees from Bristol-Myers Squibb, Roche, and Novartis. The other authors have no conflict of interests related to this publication.

Author contributions

Conception and design (HYR, YJZ, LW), data collection (HYR, XXY, YWT, QN, DY, JFW, YFY, SZ, DLY, JLH, QX, CYZ, LLZ, XRM, TS, LB, FCZ, JLJ, YGZ, MRW, WX, YJM, JQ, ZBY, PA, FL, JDJ, XXH, ZJG, JW, YPC, ZSJ, MHL, GQW, YYZ, RH), data analysis and interpretation (HYR, HMX, LL, QYR, YJZ, LW), manuscript writing (HYR, LW).

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