Systematic Review and Meta-Analysis

Medicine

OPEN

Safety and efficacy of sofosbuvir-velpatasvir
A meta-analysis

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Abstract

Introduction: The sofosbuvir-velpatasvir single-tablet regimen (Epclusa) is a newly FDA-approved inhibitor of hepatitis C virus (HCV). This meta-analysis aimed to investigate the safety and efficacy of velpatasvir-sofosbuvir in the treatment of chronic HCV infection.

Methods: A comprehensive literature search of PubMed, Cochrane CENTRAL, EMBASE and Web of Science was conducted. Data from eligible studies were pooled in a fixed-effect meta-analysis model, using Open-Meta and RevMan software's.

Results: Pooled data showed that velpatasvir-sofosbuvir achieved sustained virological response (SVR12) rates of 94.2% (95% CI 90.7–97.7%, $P < .001$) in 1277 patients. The addition of ribavirin did not significantly increase the SVR12 (RR = 1.03, 95%CI [0.95, 1.11]) in HCV genotype-1 patients and the SVR12 (RR = 1.09, 95%CI [0.86, 1.38]) in HCV genotype-2 patients. However, adding ribavirin significantly increased SVR12 (RR = 1.13, 95% CI [1.04, 1.23]) in genotype-3 patients.

Conclusion: In conclusion, the 12-week regimen of sofosbuvir-velpatasvir was highly effective in HCV patients. Except for genotype-3, adding ribavirin was not associated with significant improvements in SVR12 rates.

Abbreviations: DAAs = direct antiviral agents, GT = genotype, HCV = hepatitis C virus, NS5B = non-structural protein 5B, RCT = randomized controlled trial, SVR = sustained viral response.

Keywords: HCV, ribavirin, sofosbuvir-velpatasvir, SVR12

1. Introduction

Hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease. According to the World Health Organization predication recently, the infection rate of HCV is about 3% globally, which means that about 180 million people are infected with HCV, and about 35,000 new cases of hepatitis C are reported each year.[1] HCV is single-stranded linear RNA virus that belongs to Flaviviridae, with genomic features of high polymorphism and heterogeneity. Based on differences in nucleotide sequences, HCV is divided into 8 genotypes with different geographical distribution, influencing disease progression and treatment response.[2] The most common genotype (GT) is GT1, which accounts for more than half of all HCV-infected patients worldwide, another common genotypes are GT3 and GT4.[3]

Failure to provide antiviral treatment timely and effectively will lead to HCV progression, even leading to the most serious complications, including cirrhosis, liver function damage, hepatocellular carcinoma, etc. Therefore, eradication of HCV effectively is crucial.[4]

A combination of two or three agents working at a different site of the replication process is required for successful treatment, which is defined as sustained virological response 12 weeks after therapy completion (SVR12).[5,6]

The non-structural protein 5B (NS5B) nucleotide inhibitor sofosbuvir is approved to treat HCV infection in combination with other agents. Velpatasvir (formerly known as GS-5816, Gilead Sciences) is an investigational inhibitor of the HCV non-structural protein 5A protein with antiviral activity against all HCV genotypes. Sofosbuvir is the nucleoside analogue inhibitor of NS5B polymerase, an unstructured protein of HCV RNA. SOF can phosphorylate to active ATP in host hepatocytes, then compete with NS5B polymerase and result in termination of HCV gene replication. In many nations, the sofosbuvir-velpatasvir single-tablet regimen (Epclusa) has been approved to treat all HCV genotypes and patients with or without compensated cirrhosis.[7–9]

Recently, some different randomized controlled trials (RCTs) have explored the efficacy of the combination (sofosbuvir-velpatasvir) to treat different HCV genotypes. Therefore,

The study did not involve the human participant and thus not required to obtained the informed consent.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The current study is a meta-analysis and the study are extracted from the previous studies. We have cited those studies with in the manuscript. Furthermore, the data analysis is briefly explained with the manuscript. Further data and analysis details can be requested.

Ethical approval are not required for the current study due to the nature of the current study.

Supplemental Digital Content is available for this article.

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How to cite this article: Ren X-D, Fu X, He Y-Q, Li C-Y, Guo M, Qiao M. Safety and efficacy of sofosbuvir-velpatasvir: A meta-analysis. Medicine 2022;101:42(e31183).

Received: 2 January 2021 / Received in final form: 14 September 2022 / Accepted: 15 September 2022

http://dx.doi.org/10.1097/MD.0000000000031183

we conducted this meta-analysis to evaluate the safety and efficacy of sofosbuvir-velpatasvir regimen in chronic HCV infection and to understand the combined effects of adding ribavirin.

2. Materials and Methods

2.1. Literature search strategy

We searched the PubMed, Cochrane CENTRAL, EMBASE and Web of Science using the following query: "('Hepatitis C' OR 'hepatitis C' OR 'HCV') and ('epclusa' OR 'MyHep All' OR 'sofosbuvir-velpatasvir' OR 'sofosbuvir/velpatasvir')". We searched for relevant studies published from the inception to December 2019. No restrictions by language were applied. Ethical approval is not required for the current study due to the nature of the current study.

2.2. Eligibility criteria and study selection

The inclusion criteria were: population: HCV-infected patients (all genotypes) with or without cirrhosis; intervention: oral sofosbuvir-velpatasvir (400–100 mg) single-tablet with ribavirin; comparator: sofosbuvir-velpatasvir (control group in double-arm analysis); outcomes: the rates of SVR12 as well as the risk of adverse events; and study design: RCTs. We excluded observational studies, trials in which patients were not randomly allocated to the treatment arms or their outcomes were not reported as dichotomous data, and conference abstracts for inability to perform a thorough risk of bias assessment.

2.3. Data extraction

Two authors independently extracted the information using a standardized form for each study, including author's name, year of publication, study type, sample size, onset condition (cirrhosis or not, Naïve or experienced, genotypes), sex, mean age of participants, therapy method, observation time, number of patients with sustained virologic response, number of adverse events, and number of patients with virologic failure. Any discrepancies were resolved by discussion with senior investigators.

2.4. Quality assessment

Two authors independently assessed the risk of bias in each included study, following strict accordance with the Cochrane handbook for systematic reviews of interventions. We used the risk of bias assessment table provided in the same book. The Cochrane risk of bias assessment tool includes the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selection outcome reporting (reporting bias), and other potential sources of bias. The authors' judgment is categorized as "low risk", "high risk" or "unclear risk" of bias.

2.5. Data synthesis

The proportions of SVR12 rates were pooled in a meta-analysis model, using the Mantel–Haenszel method. Statistical analyses were performed by Open Meta [Analyst] and RevMan software. If significant heterogeneity (Chi-Square $P < .1$) was observed, a random-effects model was used; otherwise, the fixed-effect model was adopted. The funnel plot was used to detect publication bias.

3. Results

3.1. Search results and study characteristics

Initially, a total of 969 studies were identified from Medline, Embase, Cochrane Library and the Web of Science databases. Among these studies, we removed 445 duplicate studies. Through careful screening of abstracts and titles, 438 studies were excluded because they did not meet our inclusion criteria by reviewing their titles and abstracts. Among them, 305 articles were non-relevant, 78 were non-RCT studies, 35 were reviews, 15 were conference abstracts and 5 were basic medical studies. Then, 81 studies were excluded by reviewing full-text, including 53 conference abstracts, 3 reviews, and 25 with no eligible control group. Eventually, 5 articles[10–14] were included in the final analysis (Fig. 1).

3.2. Characteristics of included studies

The design and main findings of included studies are shown in Table 1 and baseline characteristics of eligible patients are shown in Table 2. All selected studies were assessed for methodological quality by Cochrane ROB. All included studies were of low risk of bias in terms of random sequence generation, attrition and reporting biases. All included studies were of high risk in terms of performance and detection biases (open-label studies), except for the study performed by Feld et al. Whereas, the included studies were of a low risk of bias in terms of random sequence generation, attrition, and reporting biases. A summary of the risk of bias assessment domains is shown in Figure 2.

3.3. Incidence of efficacy points

The single tablet regimen of sofosbuvir-velpatasvir (Epclusa) for 12 weeks achieved SVR12 rates of 83.3% (95% CI [75.6–91.0%], $P < .001$,90 patients) in Curry's study; 91.1% (95% CI [85.5–96.6%], $P < .001$, 101 patients) in Esteban's study; 96.6 % (95% CI [94.8–98.3%], $P < .001$, 411 patients) in Foster's study; 99.0% (95% CI [98.3–99.8%], $P < .001$, 624 patients) in Feld's study; 92.2% (95% CI [84.8–99.5%], $P < .001$, 51 patients) in Takehara's study; 94.2% (95% CI [90.7–97.7%], $P < .001$, 1277 patients) (Fig. 3). The random effects model was again used.

3.4.1. The role of adding ribavirin to sofosbuvir-velpatasvir

Svr12 Three randomized clinical trials[10,11,14] investigated the effect of adding ribavirin to sofosbuvir-velpatasvir. Fixed effects model was used in this analysis. The overall effect did not favor the 12 weeks' regimen of sofosbuvir-velpatasvir and ribavirin over the 12 weeks' regimen of sofosbuvi-velpatasvir in GT 1 (RR = 1.03, 95%CI [0.95, 1.11], $P = .48$, 216 patients), GT 2 (RR = 1.09, 95% CI [0.86, 1.38], $P = .47$, 29 patients), GT 4 (RR = 1.00, 95% CI [0.56, 1.79], $P = 1.0$, 6 patients). However, the ribavirin containing regimen was superior to the ribavirin free regimen in terms of SVR12 rate in GT 3 patients (RR = 1.10 95% CI: 1.01–1.19], $P = .02$, 232 patients) (Fig. 4). Funnel plot visual inspection did not reveal significant evidence of publication bias (Supplemental Figure S1, http://links.lww.com/MD/H646).

3.4.2. Virologic failure rate (relapse rate or breakthrough)

The estimation of overall effect showed that the 12 weeks' regimen of sofosbuvir-velpatasvir combined with ribavirin presented a lower virologic failure rate compared with the 12 weeks' regimen of sofosbuvir-velpatasvir (RR = 2.52, 95%CI [0.18, 0.80], $P = .01$, 483 patients) (Fig. 5). The fixed-effect model was adopted in this analysis.

3.4.3. Serious adverse events

The overall effect estimate did not favor the 12 weeks' regimen of sofosbuvir-velpatasvir and ribavirin over the 12 weeks' regimen of sofosbuvir-velpatasvir

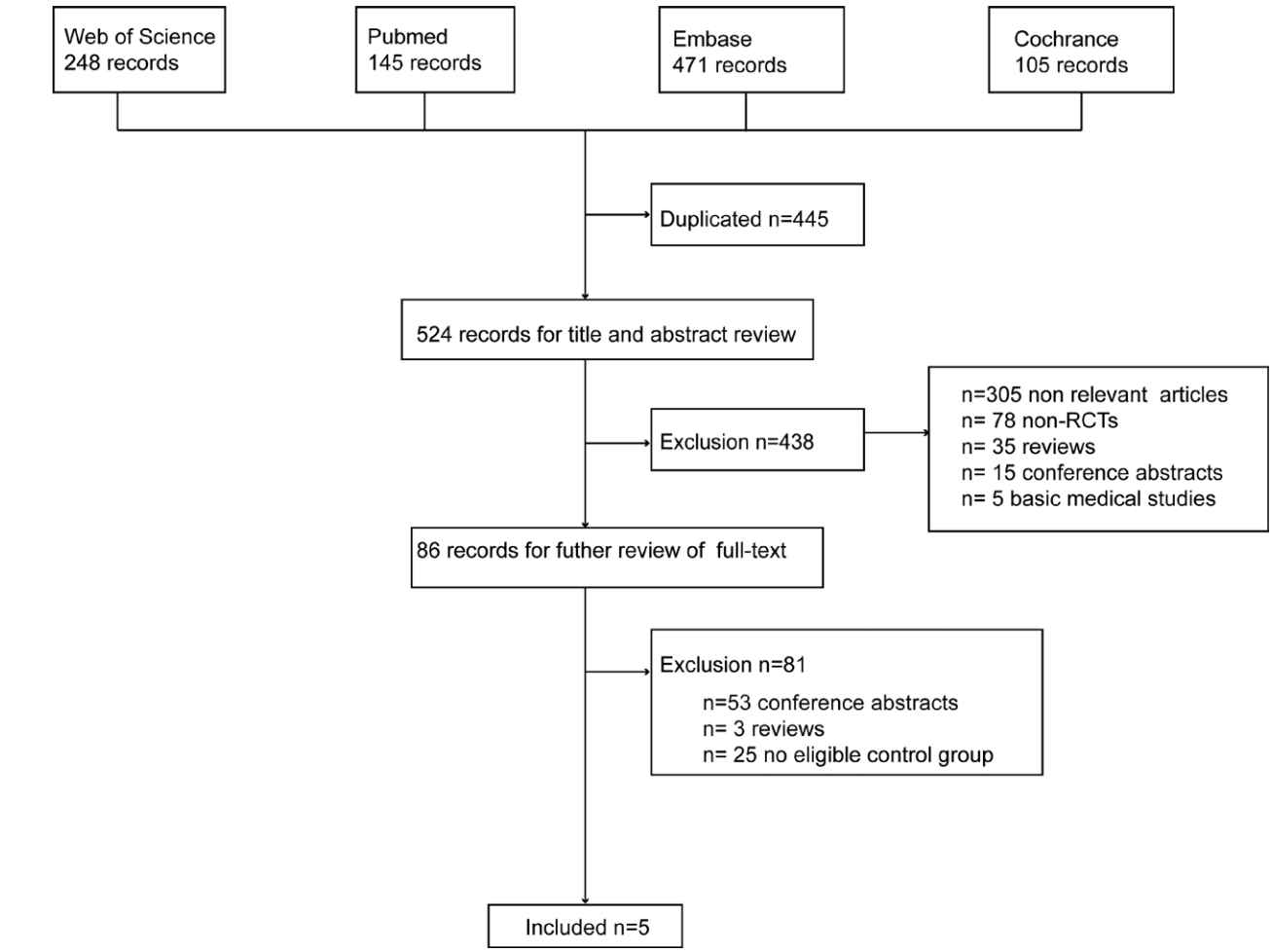

Figure 1. The PRISMA flow diagram of studies' screening and selection.

Table 1

A summary of the design and findings of included studies.

Author	Study type	Sample size	Population	Study arms			Main finding
Curry et al	RCT	267	Naïve or experienced, decompensated cirrhotic patients with HCV (genotypes 1–6).	SOF 400 mg + VEL100 mg + RBV (12 wk)	SOF 400 mg + VEL 100 mg (12 wk)	SOF 400 mg + VEL 100 mg (24 wk)	Sofosbuvir–velpatasvir with or without ribavirin for 12 wk and with sofosbuvir–velpatasvir for 24 wk resulted in high rates of sustained virologic response in patients with HCV infection and decompensated cirrhosis.
Foster et al	RCT	818	Naïve or experienced, compensated cirrhotic and non-cirrhotic patients with HCV (genotypes 2 or 3)	(GT 2, 3) SOF 400 mg/ VEL 100 mg (12 wk)	(GT 2) SOF 400 mg + RBV (12 wk)	(GT 3)SOF 400 mg + RBV (24 wk)	Twelve wk of treatment of sofosbuvir (400 mg) and velpatasvir (100 mg) resulted in high rates of SVR that were superior to those with sofosbuvir and ribavirin
Feld et al	RCT	706	Naïve or experienced, compensated cirrhotic and non-cirrhotic patients with HCV (genotypes 1–6)	SOF400 mg/ VEL 100 mg (12 wk)	Placebo		Sofosbuvir–velpatasvir plus ribavirin for 24 wk was highly effective and well tolerated in Japanese patients with chronic HCV genotype 1 or 2 infection who previously failed treatment with a DAA.
Esteban et al	RCT	204	Naïve or experienced, patients with genotype 3 HCV infection and compensated cirrhosis	SOF 400 mg/ VEL 100 mg (12 wk)	SOF 400 mg + VEL100 mg + RBV (12 wk)		Patients with genotype 3 HCV infection and compensated cirrhosis achieved a high overall SVR12 rate when treated with 12 wk of sofosbuvir and velpatasvir with or without ribavirin.
Takehara et al	RCT	102	Patients with any HCV genotype and decompensated cirrhosis	SOF 400 mg/ VEL 100 mg (12 wk)	SOF 400 mg + VEL100 mg + RBV (12 wk)		Addition of ribavirin to the regimen did not improve efficacy and was associated with more adverse events and laboratory abnormalities.

DAA = direct antiviral agents, GT = genotype, HCV = hepatitis C virus, RCT = randomized controlled trial, RBV = ribavirin, SOF = sofosbuvir, SVR = sustained virological response, VEL = velpatasvir.

Table 2

Baseline characteristics of the population of included studies.

Study	Treatment	No	Duration (wk)	Age mean	BMI mean	Population	Genotypes	HCV RNA – log10 IU/mL (mean ± SD)	HCV RNA ≥ 800.000 log10 IU/mL no. (%)
Curry et al	SOF + VEL	90	12	58 (42–73)	31 (17–56)	Cirrhotic	Genotype 1, 2, 3, 4, and 6	6.0 ± 0.5	59 (66)
	SOF + VEL + RBV	87	12	58 (40–71)	30 (20–55)	Cirrhotic	Genotype 1, 2, 3, 4, and 6	5.8 ± 0.6	45 (52)
	SOF + VEL	90	24	58 (46–72)	30 (18–50)	Cirrhotic	Genotype 1, 2, 3, 4, and 6	5.9 ± 0.6	45 (50)
Foster et al	SOF + VEL	134	12	57 (26–81)	28 (17–45)	Cirrhotic	Genotype 2	6.5 ± 0.78	111 (83)
	SOF + RBV	132	12	57 (23–76)	29 (19–61)		Genotype 2	6.4 ± 0.74	101 (77)
	SOF + VEL	277	12	49 (21–76)	26 (17–48)	Cirrhotic	Genotype 3	6.2 ± 0.72	191 (69)
	SOF + RBV	275	24	50 (19–74)	27 (17–56)	Cirrhotic	Genotype 3	6.3 ± 0.71	194 (71)
Feld et al	Placebo	116	12	53 (25–74)	26 (18–40)	Cirrhotic	Genotype 1, 2, 4, 5, and 6	6.3 ± 0.58	87 (75)
	SOF + VEL	624	12	54 (18–82)	27 (17–57)	Cirrhotic	Genotype 1, 2, 4, 5, and 6	6.3 ± 0.66	461 (74)
Esteban et al	SOF + VEL	101	12	51 (7.3)	27 (5.1)	Cirrhotic	Genotype 3	6.2 ± 0.64	
	SOF + VEL + RBV	103	12	51 (7.6)	27 (4.9)	Cirrhotic	Genotype 3	6.3 ± 0.56	
	SOF + VEL + RBV	60	24	63 (35–79)	23 (18–36)	Cirrhotic	Genotype 1 and 2	6.2 ± 0.58	46 (77)
Takehara et al	SOF + VEL	51	12	66 (43–82)	26.5 (20.4–43.0)	Cirrhotic	Genotype 1, 2, and 3	5.7 (3.7–7.1)	
	SOF + VEL + RBV	51	12	66 (41–83)	25.8 (18.3–58.6)	Cirrhotic	Genotype 1, 2, and 3	5.8 (4.2–7.0)	

GT = genotype, HCV = hepatitis C virus, RBV = ribavirin, SOF = sofosbuvir, SVR = sustained virological response, VEL = velpatasvir.

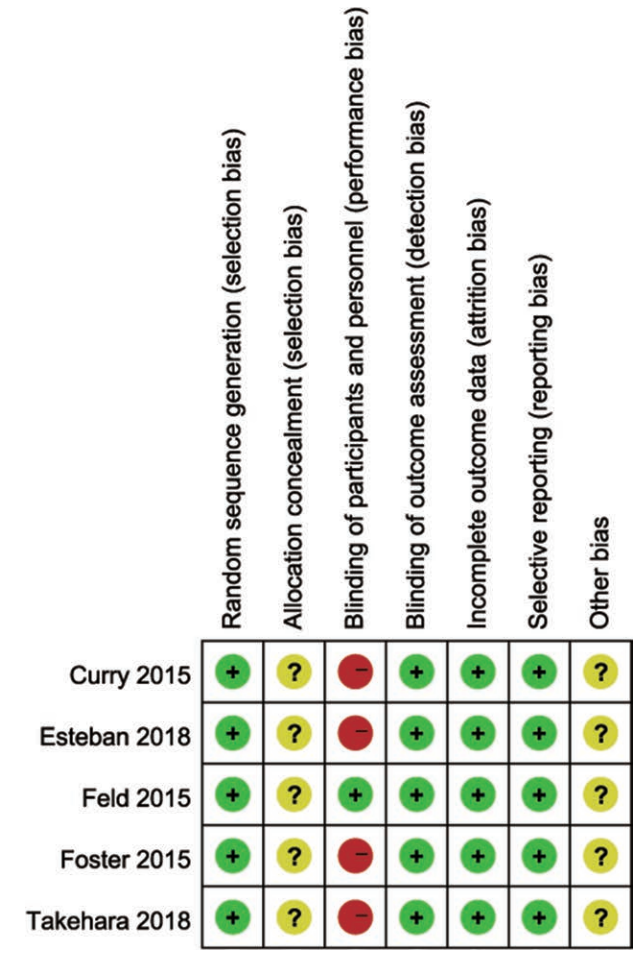

Figure 2. Risk of bias summary according to Cochrane risk of the bias assessment tool.

(RR = 0.94, 95%CI: 0.55–1.59, P = .81, 483 patients) (Fig. 6). The fixed-effect model was adopted in this analysis.

3.5. Safety analysis of sofosbuvir-velpatasvir

The frequency of adverse events was comparable between groups. In the 5 included studies, 1367 patients have the sofosbuvir-velpatasvir. Several common adverse events were reported, such as anemia, arthralgia, asthenia, back pain, cough, diarrhea, dyspnea, dyspepsia, fatigue, headache, insomnia, irritability,muscle spasm, myalgia, nasopharyngitis, nausea, pruritus, reduced hemoglobinlevel, reduced lymphocyte, reduced neutrophil, etc. Among all the common adverse events, headache, fatigue, nausea and nasopharyngitis were the most frequently occurring events (Fig. 7).

3.6. Euromerican patients versus Asia patients

Pooled data from two studies[10,11] showed that compared with the Asian group, treatment of ribavirin containing achieved superior SVR12 rates in Euromerican patients (RR = 2.89, 95%CI [1.30, 6.40], I^2 = 0%, P = .009, 381 patients). On the other hand, one trial[14] suggested that ribavirin-containing treatment did not improve the therapeutic effect of the ribavirin group. The fixed-effect model was adopted in this analysis.

3.7. Cirrhotic versus non-cirrhotic patients

Pooling data from three studies[8,10,15] (283 non-cirrhotic and141 cirrhotic patients) showed that treatment of HCV GT 1 infection with sofosbuvir plus velpatasvir achieved SVR12 rates of 97.5% (95% CI [95–100%], P < .001) in cirrhotic and 98.5% (95% CI [97–99.9%], P < .001) in non-cirrhotic patients.

4. Discussion

The outstanding performance of direct antiviral agents (DAA) makes the antiviral treatment more promising. The therapeutic

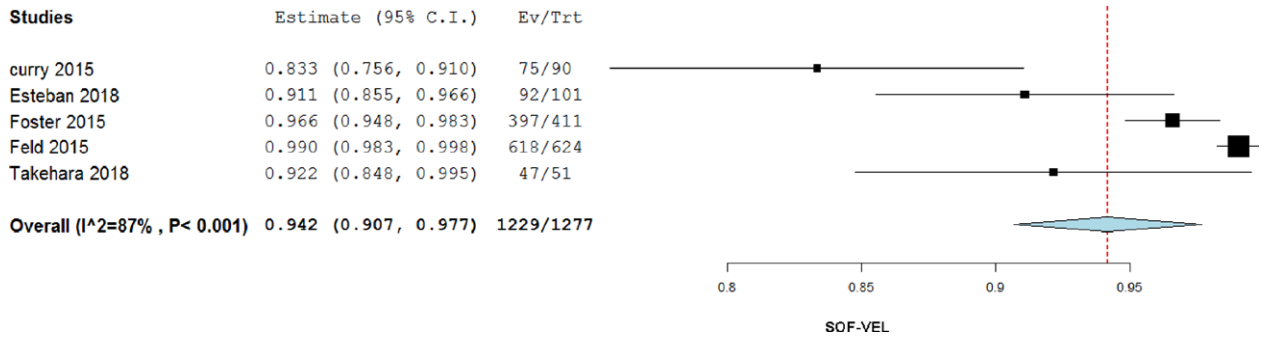

Figure 3. Forest plots of pooled proportions of SRV rates for sofosbuvir-velpatasvir in HCV patients.

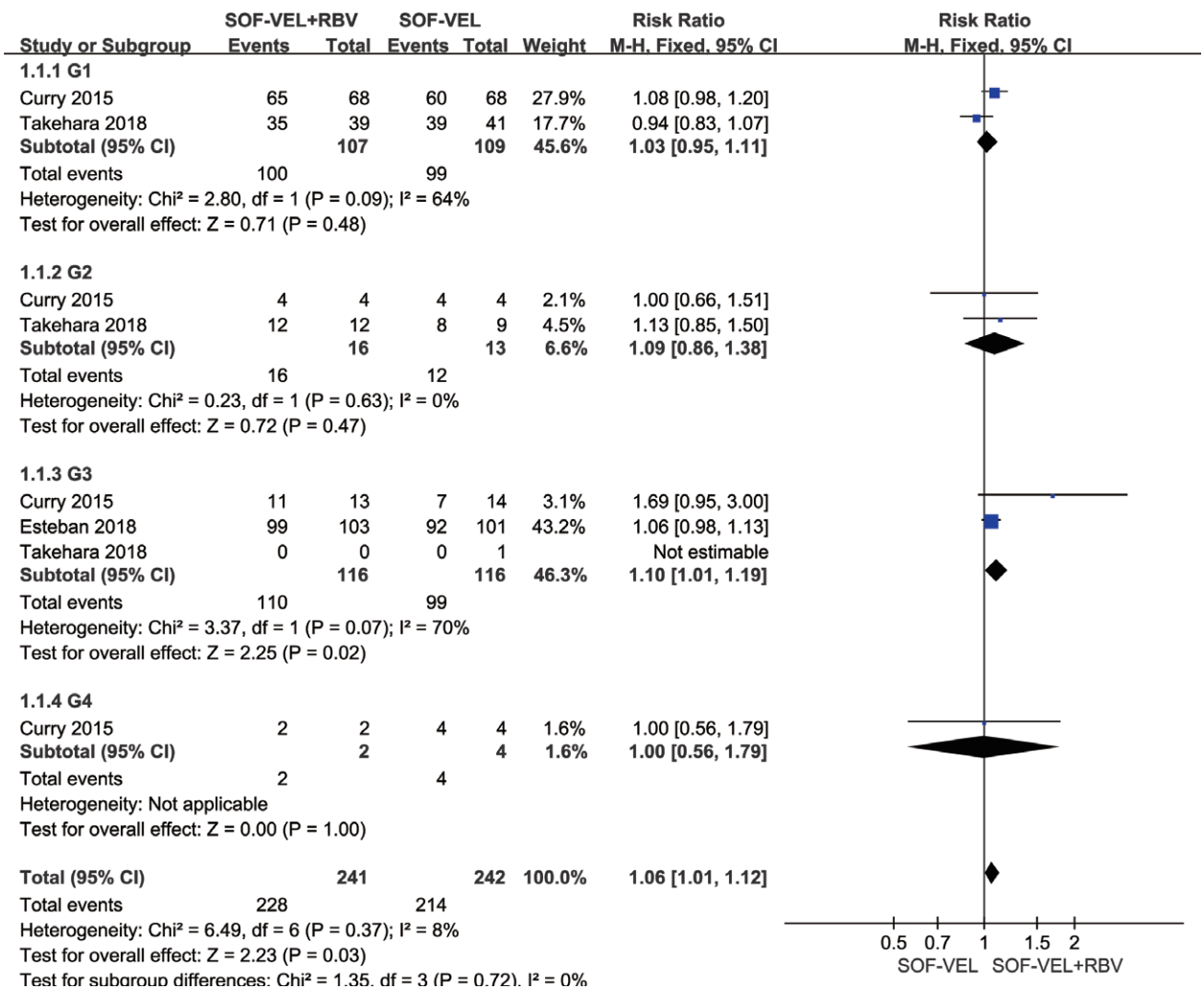

Figure 4. Forest plots of pooled risk ratio comparing sofosbuvir plus velpatasvir with the sofosbuvir-velpatasvir and RBV in terms of SVR 12 rates in different GTs.

effect of sofosbuvir on chronic HCV was significantly improved, compared with the traditional regimen, which is a good choice for intolerant patients or drug-fast to interferon.[16,17]

This meta-analysis study suggests that the single-tablet regimen of sofosbuvir- velpatasvir (Epclusa) is highly effective in chronic HCV (GT–6) patients, with SVR12 rates >94%. Previously, the standard antiviral treatment for chronic HCV in China and many other countries was interferon combined with ribavirin. There are some shortcomings of this regimen, including low sustained virological response rate (about 60%), low cure rate, frequent adverse reactions, inconvenient administration, poor compliance of patients, long course of treatment (general 48 weeks), and so on.[15,17] The appearance of a single-tablet regimen of sofosbuvirs-velpatasvir has changed the therapeutic effect of chronic HCV. Although, another similar meta-analysis conducted by Hussien Ahmed et al[18] demonstrated that the combination of sofosbuvir and velpatasvir got a SVR12 rates >97%, except for chronic HCV (GT 3) patients. However, there are some different points between the two meta-analyses. Firstly, in one primary clinical study[6] included in Ahmed's study, the sofosbuvir and 100 mg of velpatasvir were given, respectively. It was not a real single-tablet regimen of

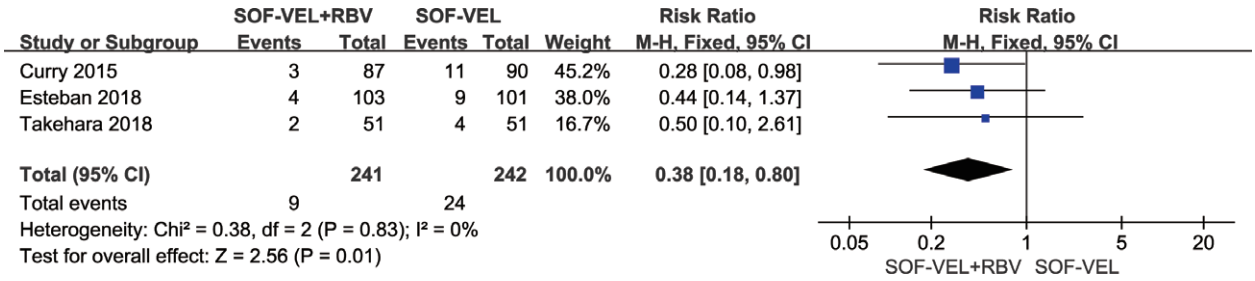

Figure 5. Forest plots of pooled risk ratio comparing sofosbuvir-velpatasvir with the sofosbuvir-velpatasvir and RBV in terms of virologic failure rates with 95% CI. CI = confidence interval, RBV = ribavirin, RR = risk ratio.

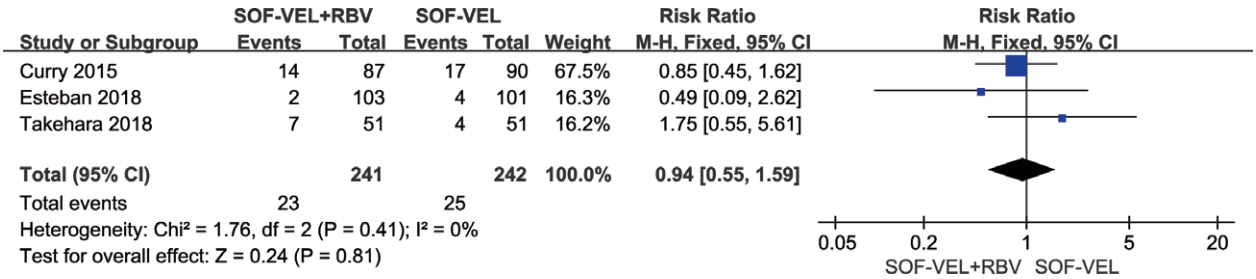

Figure 6. Forest plots of pooled risk ratio comparing sofosbuvir plus velpatasvir with the sofosbuvir-velpatasvir and RBV in terms of serious adverse event rates in HCV patients.

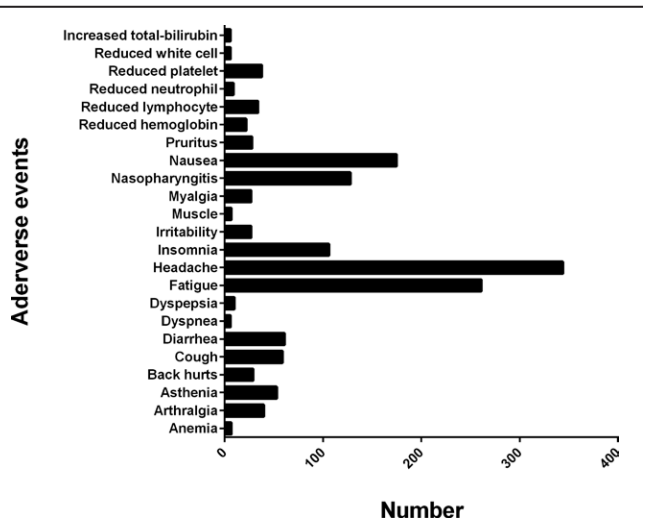

Figure 7. The distribution of common adverse events of sofosbuvir-velpatasvir in HCV patients.

sofosbuvir-velpatasvir. Hence, our study might be a more suitable evaluation for the Epclusa. Secondly, all of the selected clinical studies in the current meta-analysis were published between 2015 and 2018. Whereas, primary clinical trials in Ahmed's study were published in 2015. In contrast, our research is more updated. Lastly, our study reveals that the addition of ribavirin does not increase the SVR12 and the serious adverse event rate. Moreover, in terms of common adverse events for the sofosbuvir-velpatasvir in HCV patients, the headache occurs more frequently.

Sofosbuvir is a sort of nucleoside analogue, which was approved in 2013. The main advantages of sofosbuvir, including a high SVR rate 90% in the patients with HCV1 infection, consistent with the results in this analysis. In terms of SVR12, subgroup analysis shows that the differences between sofosbuvirs-velpatasvir and sofosbuvirs-velpatasvir plus ribavirin are non-significant except for GT 3. This result suggests that the addition of ribavirin to sofosbuvirs- velpatasvir has no additional obvious clinical benefit. However, another subgroup analysis about virologic failure rates showed that the ribavirin-containing group has lower virologic failure rates, such as a breakthrough or a relapse. Thus, DAAs could be used with RBV, which is expected to decrease a relapse or patients with HCV recurrence. For example, in recent years, the HCV Guidance 2018 compiled by the American Association for the Study of Liver Diseases-Infectious Diseases Society of America (AASLD-IDSA) recommends sofosbuvirs -based DAAs in combination with ribavirin for patients HCV recurrence after liver transplantation.[19] Secondly, another subgroup analysis was conducted, which suggests that different Ethnicities may get different therapeutic effects. In all genotype 3 patients who are either cirrhotic or have treatment experience with baseline Y93 substitutions, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend adding ribavirin to sofosbuvir plus velpatasvir.[20] In the United States and the European Union (EU), a single tablet of sofosbuvir plus velpatasvir was recently approved for the treatment of all HCV genotypes in non-cirrhotic and compensated cirrhotic patients (Child-Pugh class A), or combined with ribavirin for the treatment of all HCV genotypes in decompensated cirrhotic patients.[21]Further studies should be designed to investigate the effect of adding ribavirin to this regimen in HCV GT 3 patients or Asia patients with HCV.

In terms of safety, the incidence of severe adverse events was not comparable in the ribavirin-containing and ribavirin-free groups. Nevertheless, according to the selected trials in this meta-analysis, the common adverse events of the sofosbuvir-velpatasvir are numerous, and headache, fatigue, nausea as well as nasopharyngitis occur most frequently.

5. Conclusion

The result of current study showed that the single-tablet regimen of sofosbuvir-velpatasvir is a highly effective treatment in HCV patients with GT 1–6. Ribavirin-containing therapy was

not related to an obvious improvement of SVR12 in the GT3. Ribavirin-containing therapy also did not show superior effects in the Asian population.

6. Limitations

There are several limitations to the current study. Firstly, most of the included studies were open-label and were conducted solely in European and American countries. In addition, some of the included trials only included one or two HCV GT. Taken together, the risk of allocation, performance, and ascertainment bias should be considered, although no significant association between methodological quality and trial results were found. Secondly, the current study did not include appropriate control and replication. Furthermore, the sample size is small. Therefore, further studies need to be conducted with rigorous control and larger sample size. Lastly, we were unable to assess the effectiveness of the velpatasvir combination in several difficult-to-treat patients, such as those with decompensated cirrhosis, resistance-associated substitutions, and HIV co-infection, due to a lack of data. Which remain to be elucidated.

Author contributions

Data curation: Yuan-Qun He.
Formal analysis: Yuan-Qun He.
Methodology: Xue Fu, Yuan-Qun He.
Project administration: Xue Fu, Min Qiao.
Resources: Xiao-Dan Ren.
Software: Chun-Yan Li.
Supervision: Chun-Yan Li.
Validation: Meng Guo.
Writing – original draft: Min Qiao.
Writing – review & editing: Min Qiao.

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