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Efficacy and safety of sofosbuvir/velpatasvir with or without ribavirin in hepatitis C genotype 3 compensated cirrhosis: A meta-analysis

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Abstract

BACKGROUND

Hepatitis C virus (HCV) is a leading cause of liver cirrhosis and hepatocellular carcinoma globally. Sofosbuvir/velpatasvir (SOF/VEL) is an effective pangenotypic direct-acting antiviral for the treatment of chronic HCV infection. While the addition of ribavirin (RBV) to SOF/VEL improved sustained virological response (SVR12) in genotype 3 (GT3) decompensated cirrhosis patients, the benefits of RBV in GT3 compensated cirrhosis patients receiving SOF/VEL remains unclear.

AIM

To evaluate the efficacy and safety of SOF/VEL, with or without RBV in GT3 compensated cirrhosis patients.

METHODS

We searched four electronic databases (PubMed/MEDLINE, EMBASE, Cochrane Library and Web of Science) from inception up to June 2021 using both free text and MeSH terms. There was no restriction on language, geography, publication dates and

publication status (full-text or abstracts). All GT3 compensated cirrhosis patients treated with 12 wk of SOF/VEL, with or without RBV, were included, regardless of age, gender or prior treatment experience. The primary outcome was the SVR12. The secondary outcome was treatment-related adverse events, as defined by symptomatic anaemia requiring transfusion or a drop in haemoglobin beyond 2 g/dL. The pooled relative risk (RR), 95%CI and heterogeneity (I^2) were estimated using Review Manager Version 5.3.

RESULTS

From 1752 citations, a total of 7 studies (2 randomized controlled trials, 5 cohort studies) with 1088 subjects were identified. The SVR12 was similar in GT3 compensated cirrhosis patients, regardless of the use of RBV, for both the intention-to-treat (RR: 1.03, 95%CI: 0.99-1.07; I^2 = 0%) and the per-protocol analysis (RR: 1.03, 95%CI: 0.99-1.07; I^2 = 48%). The overall pooled rate of treatment-related adverse events was 7.2%. Addition of RBV increased the pooled risk of treatment-related adverse events in GT3 compensated cirrhosis patients receiving SOF/VEL (RR: 4.20, 95%CI: 1.29-13.68; I^2 = 0%). Subgroup analysis showed that RBV was associated with a higher SVR12 in GT3 compensated cirrhosis patients with baseline resistance-associated substitutions. However, addition of RBV did not significantly increase the SVR12 among treatment-experienced GT3 compensated cirrhosis patients.

CONCLUSION

Ribavirin was not associated with higher SVR12 in GT3 compensated cirrhosis patients receiving SOF/VEL. Our findings suggest limited role for RBV as routine add-on therapy to SOF/VEL in these patients.

Key Words: Direct-acting antiviral; Hepatitis C; Cirrhosis

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Core Tip: Ribavirin as routine add-on therapy was not associated with higher sustained virological response in genotype 3 (GT3) compensated cirrhosis patients receiving sofosbuvir/velpatasvir (SOF/VEL), except in the subgroup of patients with baseline resistance associated substitutions mutation. As ribavirin is associated with a higher risk of treatment-related adverse event, ribavirin as routine add-on therapy to SOF/VEL should be reconsidered among compensated GT3 cirrhosis patients.

INTRODUCTION

Hepatitis C virus (HCV) is an important cause of liver cirrhosis and hepatocellular carcinoma, affecting 71 million people globally[1]. Genotype 3 (GT3) is the second most common HCV genotype worldwide and is responsible for up to 30% of global HCV infections, especially in the south and central Asia region[2,3]. GT3 HCV is associated with a higher incidence of liver steatosis[4], fibrosis progression[5] and liver cirrhosis[6]. Besides, GT3 HCV infection was also associated with a poorer prognosis with an 80% increased risk of hepatocellular carcinoma[6] and 17% increased risk of all-cause mortality compared to other HCV genotypes[7].

The introduction of direct-acting antiviral (DAA) therapy has significantly improved the treatment success for HCV infection, thus providing a simplified approach for global HCV elimination. The improvement in treatment outcome was observed since the first generation of DAA, albeit to a lesser degree among GT3 HCV patients with cirrhosis or prior treatment experience[8,9]. Because of the poorer treatment response among GT3 HCV patients treated with DAA, GT3 HCV infection was considered the "difficult-to-treat" population. Currently, there are two approved pangenotypic DAA regimen available, namely sofosbuvir and velpatasvir (SOF/VEL), as well as glecaprevir and pibrentasvir. While both regiments are highly efficacious with sustained virological response 12-wk post-treatment (SVR12) rates beyond 95% in most scenarios, only SOF/VEL is approved to treat decompensated HCV cirrhosis patients[10,11].

The potential of ribavirin (RBV) as add-on therapy to SOF/VEL to improve SVR12 in HCV patients remains an area of interest. Ribavirin, a guanosine nucleoside analogue, has been used in HCV treatment regimens since the pre-DAA era. It is postulated that RBV interferes with viral replication by direct and indirect means. It inhibits viral mRNA polymerase by binding to the nucleotide binding site of the enzyme and indirectly, by inducing error prone mutagenesis and promoting T helper type-1 mediated immune responses[12]. The addition of RBV to a SOF/VEL regime improves SVR rates where there is pre-existing baseline NS5A Y93H resistance associated

substitutions (RAS). The ASTRAL-3 study reported an SVR of 97% *vs* 84% in patients with or without baseline RAS[13]. Indeed, American Associated for the Study of Liver Disease (AASLD) guidelines recommend adding RBV for compensated GT3 cirrhosis with baseline RAS or decompensated HCV cirrhosis, regardless of genotype[14]. While the use of RBV significantly increases the SVR12 in decompensated cirrhosis receiving SOF/VEL[15], the benefit of RBV remains controversial among GT3 compensated cirrhosis patients. A Spanish randomized controlled trial had demonstrated a comparable SVR12 among GT3 compensated cirrhosis patients treated with SOF/VEL, regardless of the use of RBV[16].

In routine clinical practice, the application of pre-treatment RAS testing for patients with GT3 compensated cirrhosis is often limited by their cost and availability. Moreover, such strategy should be balanced with the need for closer monitoring for adverse events from RBV such as anaemia[17]. In order to address these gaps, we performed a systematic review and meta-analysis to compare the efficacy and safety of RBV in GT3 compensated cirrhosis patients treated with SOF/VEL.

MATERIALS AND METHODS

Eligibility and search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for data extraction and reporting[18]. All potential literature were identified from a comprehensive search of four electronic databases, namely PubMed/MEDLINE, EMBASE, Cochrane and Web of Science, from the beginning of record up to 1st June 2021, with the help of a medical librarian. There was no restriction on language, geography, publication dates and publication status (full text and abstract). The search keywords included a combination of "sofosbuvir", "velpatasvir", "ribavirin", and "Hepatitis C" using both the free text and MeSH terms as detailed in Supplementary Table 1.

All GT3 compensated cirrhosis patients treated with 12 wk of SOF/VEL, with or without RBV, were included, regardless of age, gender or prior treatment experience.

References of all included studies were manually searched for additional studies. We also included grey literature from abstracts published in major conferences from 2015 to 2020.

Study selection

In this meta-analysis, we included all studies that met the following inclusion criteria: (1) studies that evaluated patients with hepatitis C genotype 3 compensated cirrhosis; (2) studies that evaluated the efficacy or safety of SOF/VEL, with or without RBV; and (3) reported SVR12, and/or treatment-related adverse events as study outcomes. We excluded case reports, case series, review articles, editorials, guidelines, and animal or paediatric studies. Two authors independently performed the initial screening of titles and abstracts during the primary search. The full texts of all relevant studies were extracted and reviewed. Any discrepancy in the article selection was resolved by consensus and discussion with a third co-author.

Data extraction

The data from each study were independently extracted by two authors from the included studies using a predefined standardized form. The data extracted included study design, sample size, demographic of study participants, genotype 3 subtypes, co-infection with human immunodeficiency virus (HIV), baseline RAS, history of prior treatment, the SVR12 as well as the treatment-related adverse events. Treatment-related adverse event was defined as symptomatic anaemia requiring transfusion or a drop in haemoglobin > 2 g/dL due to RBV. Corresponding authors were contacted in the event of any missing information.

Data synthesis and analysis

We used Review Manager Software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to perform our meta-analysis. The effect measures were presented as relative risk ratio (RR) and their respective 95%CI. The meta-analysis was

analysed using the random-effects model as the a priori model. A *P* value of less than 0.05 was considered to be statistically significant. The statistical heterogeneity was evaluated using the Cochran's Q test and I^2 statistics[19]. We defined substantial heterogeneity across the study when the p-value is less than 0.10 in Cochran Q test and I^2 beyond 50%. Publication bias of the primary outcome was assessed based on funnel plot symmetry.

Pre-specified subgroup analyses were performed based on study design [randomized controlled trial (RCT) *vs* non-RCT study] and publication status (full text *vs* abstracts). Because non-RCT and abstracts are more susceptible to selection and recall bias, we also performed sensitivity analyses to estimate the effect size by the serial exclusion of individual studies and using a fixed-effect model to assess the reliability of our findings.

Risk of bias assessment

We used the Cochrane Risk of Bias (ROB) 2.0 tool to assess randomized studies based on sequence generation, allocation concealment, performance bias, detection bias and reporting bias[20]. The Newcastle-Ottawa Scale was used to assess cohort studies based on selection, comparability and exposure[21]. Based on a total score of 7 or above, 4 to 6 and less than or equal to 3, each cohort study were classified as low, moderate and high risk of bias, respectively. Two authors independently assessed the risk of bias of all included studies. All discrepancy in risk of bias assessment was resolved by consensus with a third co-author.

RESULTS

Search results and population characteristics

A total of 1752 citations were identified using our search strategy (Supplementary Figure 1). After removing duplicates and the title screen, we included a total of 69 studies for full-text review. Sixty-two studies were excluded for the following reasons: decompensated cirrhosis as study population (n = 6), intervention does not involve SOF/VEL and RBV (n = 42), no comparison of outcomes by genotype (n = 14). Finally, a

total of 7 studies fit our inclusion criteria, as shown in the PRISMA flowchart (Supplementary Figure 1).

Characteristics and quality of studies

A total of 7 studies, including 1088 subjects (506 in the SOF/VEL with RBV group and 582 in the SOF/VEL without RBV group), were included in the final analysis. Five studies were published as full manuscripts[16,22-25], and two studies were published as abstracts[26,27]. The patient characteristics of all included studies are summarized in Table 1. The proportion of patients with GT3a and GT3b subtype was 99.5% and 0.5%, respectively[15]. The pooled rate of HIV co-infection was 13.0% (35/269)[16,23]. Overall, the proportion of subjects with baseline NS5A RASs mutation and prior treatment history was 6.4% (17/264) and 39.6% (127/321), respectively. The proportion of patients with baseline RAS mutation and prior treatment were comparable between the intervention and control groups[16,23]. Four studies had a low risk of bias (Supplementary Figure 2, Supplementary Table 2). Three studies have a moderate risk of bias due to concerns over the severity of liver disease between intervention and control groups[24,26,27].

SVR12

All seven studies (1088 subjects) reported SVR12 in GT3 compensated cirrhosis patients treated with SOF/VEL. The overall pooled rate of SVR12 based on ITT and PP analysis was 95.5% (462/484) and 95.4% (974/1021), respectively. The SVR12 was similar regardless to the use of RBV in GT3 compensated cirrhosis based on both the ITT (RR: 1.03, 95%CI: 0.99-1.07; I^2 = 0%) (Figure 1) and PP analysis (RR: 1.03, 95%CI: 0.99-1.07; I^2 = 48%) (Figure 2), respectively. The SVR12 remained comparable when subgroup analysis was performed based on study design, with less heterogeneity observed among RCTs (RR: 1.06, 95%CI: 1.00-1.13; I^2 = 0%) (Table 2).

Treatment-related adverse events

The overall pooled rate of treatment-related adverse events was 7.2% (95%CI: 4.4%-11.0%)[16,24]. Treatment with SOF/VEL plus RBV increases the pooled risk of treatment-related adverse events compared to SOV/VEL without RBV (RR: 4.20, 95%CI: 1.29-13.68; I^2 = 0%) (Figure 3).

Subgroup analysis

Treatment-experienced: The overall SVR12 among treatment-experienced GT3 compensated cirrhosis patients was 96.4%[16]. The use of RBV did not result in a higher SVR12 among treatment-experienced GT3 compensated cirrhosis patients (96% *vs* 96%).

Baseline RAS mutation: Baseline RAS testing was performed in 17.0% of total subjects, from 2 studies[16,22]. Among those with baseline RAS mutation, the addition of RBV was associated with a higher SVR12 in patients treated with SOF/VEL (96% *vs* 87%, P = 0.12).

Validation of meta-analysis results

We performed sensitivity analysis to assess whether an individual study had a dominant effect on the overall pooled results. No individual study with dominant effect was detected after serial exclusion of individual study. Our findings remained consistent when analysis was performed using a fixed-effect model and odd's ratio as the effect measure (Table 2).

Based on I^2 analysis for heterogeneity, significant statistical heterogeneity was noted with the analysis for SVR12 for per-protocol cohorts, which was reduced when only RCTs were considered. The funnel plot did not reveal significant publication bias for our primary outcome (Supplementary Figure 3).

DISCUSSION

GT3 HCV cirrhosis is considered the last frontier of HCV micro elimination in the era of DAA use. Not only is genotype 3 the second most common genotype globally, affecting

45 million HCV patients worldwide[28], it has also been associated with significantly poorer outcomes–higher risk of steatosis, faster progression to cirrhosis, and accelerated progression to hepatocellular carcinoma[29]. The benefit of RBV among GT3 compensated cirrhosis receiving SOF/VEL remained controversial. While the European Association for the Study of the Liver guideline recommends routine RBV use, the AASLD guideline recommends RBV only when baseline RAS mutation was present.

In this meta-analysis, we found that RBV has a limited role as a routine add-on therapy in GT3 compensated cirrhosis treated with SOF/VEL. The overall SVR12 was similar, regardless of the use of RBV. This finding remained robust when subgroup analysis was performed based on study design and prior treatment experience. In terms of safety, the addition of RBV increased the pooled risk of treatment-related adverse events, defined as symptomatic anaemia requiring transfusion or a drop in haemoglobin more than 2 g/dL. Five studies reported severe adverse events (SAE), defined as the need for hospitalization, intensive care unit, permanent disability, death and treatment cessation[16,22-25]. Overall, treatment-related SAEs were rare (0.8%) and was comparable regardless to the use of RBV. The most common minor adverse event was asthenia followed by headache[16,24].

Our findings suggest that the routine use of RBV in GT3 compensated cirrhosis patients treated with SOF/VEL should be reconsidered. Similar findings were observed in real-world studies demonstrating high SVR12 of around 95% in GT3 compensated cirrhosis patients, regardless the use of RBV[25,30]. Given the limited benefit yet a higher risk of treatment-related adverse event with RBV use, 12 wk of SOF/VEL among GT3 compensated cirrhosis patients provides a simplified approach to safely omit the need for routine genotype and resistance testing, thus allowing rapid treatment upscale[31]. Meanwhile, retreatment using the combination of SOF, VEL, and voxilaprevir has also been shown to be an efficacious strategy, both in clinical trials and real-world settings[32,33].

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There are several strengths in our meta-analysis. First, we conducted a comprehensive search of 4 electronic databases, including grey literature, with the help

of a medical librarian. All relevant data were extracted independently using a predefined template to compare both the efficacy and safety of RBV and SOF/VEL in GT3 compensated cirrhosis patients. All corresponding authors were contacted for any missing data through emails. All included studies were homogeneous in terms of patient characteristics, intervention, and outcome measures. Finally, our findings remained robust under various permutations of sensitivity analysis. To our best knowledge, this is also the first meta-analysis evaluating the safety and efficacy of adding RBV to SOF/VEL, specifically among GT3 compensated cirrhosis patients.

We acknowledged that there are limitations to this study. First, The number of subjects with baseline RAS mutations tested were small and only derived from two studies[16,22]. Although the SVR12 was numerically higher in RBV group, it did not achieve statistical significance. Moreover, few papers reported the specific side effects during the treatment period, thus it is not possible to investigate the dose-dependent effect of RBV in this study. We are unable to exclude indication bias among the non-randomized-randomized trials. Although the decision to initiate RBV may be confounded by indication bias, our findings were consistent between RCTs and non-RCTs. Finally, more studies are needed to investigate the treatment outcome among GT3b patients because GT3b are under-represented from the existing literature[34].

CONCLUSION

Among GT3 compensated cirrhosis patients, adding RBV to 12-wk of SOF/VEL did not significantly increase the SVR12. As RBV was associated with a higher risk of treatment-related adverse events, routine addition of RBV among GT3 compensated cirrhosis patients receiving SOF/VEL should be reconsidered.

ARTICLE HIGHLIGHTS

Research perspectives

Sofosbuvir/velpatasvir (SOF/VEL) is an effective pangenotypic direct-acting antiviral for the treatment of chronic hepatitis C virus (HCV) infection. While the addition of

ribavirin to SOF/VEL improved sustained virological response (SVR12) in genotype 3 (GT3) decompensated cirrhosis patients, the benefits of ribavirin in GT3 compensated cirrhosis patients receiving SOF/VEL remains unclear.

Research conclusions

In routine clinical practice, the application of pre-treatment resistance associated substitutions testing for patients with GT3 compensated cirrhosis is often limited by their cost and availability. Moreover, such strategy should be balanced with the need for closer monitoring for adverse events from ribavirin such as anaemia[17]. In order to address these gaps, we performed a systematic review and meta-analysis to compare the efficacy and safety of ribavirin in genotype 3 compensated cirrhosis patients treated with SOF/VEL.

Research results

Our study aim to evaluate the efficacy and safety of SOF/VEL, with or without ribavirin in GT3 compensated cirrhosis patients.

Research methods

Systematic review and meta-analysis.

Research objectives

Ribavirin as routine add-on therapy was not associated with higher SVR12 in GT3 compensated cirrhosis patients receiving SOF/VEL.

Research motivation

As ribavirin is associated with a higher risk of treatment-related adverse event, ribavirin as routine add-on therapy to SOF/VEL should be reconsidered among compensated GT3 cirrhosis patients.

Research background

With direct acting antiviral that is safe, effective and simple to use, future research should address linkage of care of HCV to achieve elimination.

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4	Jing Hong Loo, Yao Hui Lim, Hwee Ling Seah, Andrew Zhi Quan Chong, Kon Voi Tay. "Intragastric Balloon as Bridging Therapy Prior to Bariatric Surgery for Patients with Severe Obesity (BMI ≥ 50 kg/m2): a Systematic Review and Meta-analysis", Obesity Surgery, 2021 Crossref	82 words — 2%

5	"Abstracts of the 26th Annual Conference of APASL, February 15–19, 2017, Shanghai, China", Hepatology International, 2017 Crossref	35 words — 1%
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7	Rafael Esteban, Juan A. Pineda, Jose Luis Calleja, Marta Casado et al. "Efficacy of Sofosbuvir and Velpatasvir, With and Without Ribavirin, in Patients With Hepatitis C Virus Genotype 3 Infection and Cirrhosis", Gastroenterology, 2018 Crossref	30 words — 1%
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23 J. von Felden, J. Vermehren, P. Ingiliz, S. Mauss et al. "High efficacy of sofosbuvir/velpatasvir and impact of baseline resistance-associated substitutions in hepatitis C genotype 3 infection", Alimentary Pharmacology & Therapeutics, 2018

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