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A systematic review with meta-analysis: Is ribavirin necessary in sofosbuvir-based direct-acting antiviral therapies for patients with HCV recurrence after liver transplantation?

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ABSTRACT

Objectives: With the appearance of direct-acting antiviral agents (DAAs), sofosbuvir (SOF)-based DAAs are recommended for patients with hepatitis C virus (HCV) recurrence after liver transplantation (LT). Whether ribavirin (RBV) is needed by patients after LT in combination with SOF-based DAAs remains to be determined. This meta-analysis was conducted to evaluate the necessity of RBV with SOF-based DAAs for post-LT patients.

Methods: PubMed, Web of Science, Cochrane Library and EMBASE databases were systematically searched for eligible studies from the databases' inceptions until November 2018. We accepted the studies that included HCV recurrence in post-LT patients who were treated with SOF-based DAAs ± RBV, and evaluated the rate of sustained virological response 12 weeks (SVR12) after the end of treatment.

Results: Twelve studies, comprising a total of 1466 LT recipients, were included in this study. The pooled SVR12 of these patients was 91% (95% CI: 84% to 95%). There was no statistical difference of SVR12 in the patients treated with SOF-based DAAs + RBV versus –RBV group (risk ratio [RR] = 0.97; 95% CI: 0.92 to 1.03; P = 0.35) by different therapy duration (P = 0.26), with different targets of DAAs (P = 0.13) and in different regions (P = 0.34) but a tendency for a higher incidence of anemia in the +RBV group than in the −RBV group (RR = 5.18; 95% CI: 3.41 to 7.86; p < 0.00001).

Conclusion: The addition of RBV may not contribute to a higher SVR rate and could increase the incidence of anemia, so RBV is not necessary in SOF-based DAAs for patients with HCV recurrence after LT.

Introduction

The global prevalence of viraemia hepatitis C virus (HCV) is 1.0%, corresponding to 71.1 million chronic viraemic infections. In addition, chronic HCV infection is associated with many liver-related complications, including cirrhosis, liver failure and hepatocellular carcinoma (HCC) (Blach et al., 2017). Liver transplantation (LT) has become the preferred treatment for end-stage liver disease caused by HCV (Somerville and Doucette, 2018). Recurrent HCV infection is common in patients who undergo LT for chronic HCV disease (Wiesner et al., 2003), and viral clearance after LT is the most important independent factor that influences the prognosis of patients (Berenguer, 2008).

Recurrence of HCV not only accelerates inflammation and fibrosis of allografts, but also leads to rapidly progressive liver failure, which is often difficult to treat with standard antiviral therapy (Narang et al., 2010; Verna et al., 2013). A previous regimen of peginterferon (peg-IFN) combined with ribavirin (RBV) administered to LT recipients achieved only a modest sustained virological response (SVR) rate of 10%–50% (McCarty and Lim,

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2017; Selzner et al., 2011; Sharma et al., 2013). This regimen is poorly tolerated and carries a risk of significant adverse events (AEs) (Angelico et al., 2007; Chalasani et al., 2005; Dumortier et al., 2004; Moreno Planas et al., 2005; Neumann et al., 2006; Rodriguez-Luna et al., 2004). Especially in patients after LT with advanced graft disease, IFN-based treatment is not recommended because of its risk of worsening liver function (Chung et al., 2018). Compared to previous IFN-based therapies, the all-oral DAA treatment is well tolerated and highly effective. DAAs could be used with RBV, which is expected to increase SVR. The addition of RBV in SOF-based treatment improved SVR12 when tolerated and at reduced dosage in post-LT patients in a study by Lionetti et al. (2018). However, Faisal et al. (2016) concluded that the addition of RBV had no impact on sustained virological response 12 weeks (SVR12) after the end of treatment in sofosbuvir (SOF)-based treatment, and Fontana et al. (2016) did not determine whether RBV was necessary when daclatasvir (DCV) was combined with SOF or simeprevir (SMV) in their study.

The use of high-risk organ donors has increased over the past decade. With the use of DAAs, hepatitis C–positive donors offer new options for patients awaiting liver transplantation (Gonzalez and Trotter, 2018). Therefore, more attention is due to the treatment of HCV after LT. Currently, the Hepatitis C Guidance 2018 from the American Association for the Study of Liver Diseases-Infectious Diseases Society of America (AASLD-IDSA) recommends that patients with HCV recurrence after LT be treated with SOF-based DAAs in combination with RBV (Chung et al., 2018). However, it is known that RBV may cause several kinds of AEs, especially anemia (Koh and Liang, 2014). A decreased glomerular filtration rate due to toxicity of calcineurin inhibitors and myelosuppressive effects of immunosuppressive drugs could increase the risk of RBV-induced anemia in liver transplant recipients (Nair et al., 2017). Up to now, whether RBV is needed by patients with HCV recurrence after LT in combination with SOF-based DAAs is still controversial (Pawlotsky et al., 2018). Therefore, this meta-analysis was performed to compare the efficacy of SOF-based DAA treatment, with RBV and without RBV, in patients with HCV recurrence after LT and to assess the necessity of RBV.

Materials and methods

Data sources and searches

We searched the PubMed, Web of Science, Cochrane Library and Embase databases for relevant studies published from the databases' inception to November 2018, without language restrictions. The following searches, their medical subject heading (MeSH) terms, Emtree terms, free text words, plural forms and variations were used: hepatitis C, sofosbuvir, ribavirin, liver transplantation (see Supplementary data for details). Figure 1 shows a schematic of the literature retrieval process.

Inclusion and exclusion criteria

Two reviewers independently scanned the titles and abstracts, assessed the eligible trials according to the pre-specified criteria, and assessed the methodological quality of the included trials. Trials that were potentially suitable for inclusion were retrieved for a full-text review. Any disagreements regarding study inclusion were resolved by discussion. The inclusion criteria were as follows: (a) at least 20 post-LT patients with HCV recurrence; (b) non-pregnant adults who were at least 18 years of age; (c) the regimens of SOF-based DAAs with or without RBV were used in the studies simultaneously. Primary outcomes were sustained virological response 12 weeks after the end of treatment by different regimens (with or without RBV), and drug-related adverse

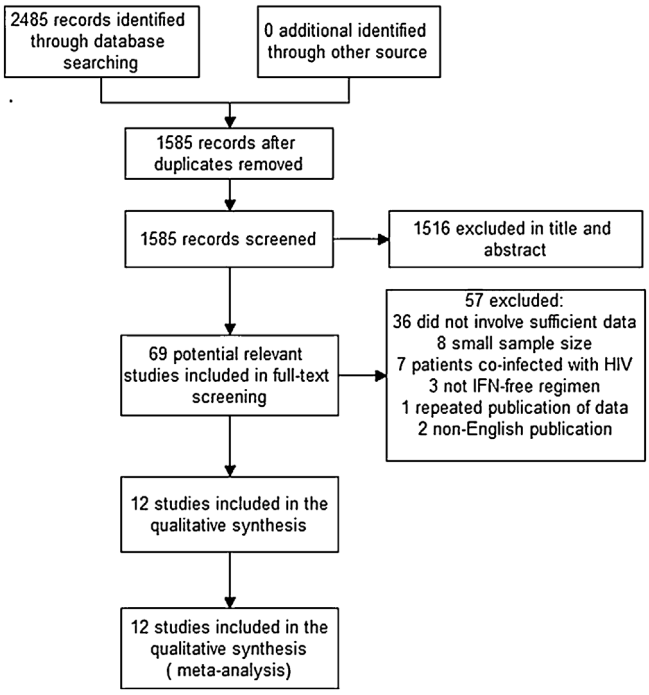

Figure 1. Search strategy: Flow diagram of included studies.

reactions. Some other outcomes, considering that each study had different interventions, which were also evaluated at the same time, could be listed as follows: SVR12 of patients with different HCV genotypes, SVR12 of different drug targets of DAAs (NS3/4 A, NS5A or NS5B) and the SVR12 of different durations of treatment with DAAs ± RBV. The exclusion criteria were as follows: (a) non-English publications; (b) patients involved with human immunodeficiency virus (HIV); (c) studies that did not provide available data.

Risk of bias

Risk of bias for randomised controlled trials was assessed with the Cochrane Collaboration's risk-of-bias tool. The Newcastle-Ottawa scale was used to assess the quality of observational studies (Supplemental Figure S1; Supplemental Table S1). For observational studies, only the studies with a score of at least 5 can be used for analysis.

Statistical analyses

The dichotomous outcomes were expressed as risk ratio (RR) with 95% confidence intervals (CIs). To calculate the pooled event rates, a double arcsine transformation was employed to stabilise variances among original incidence rates. Chi-square test ($\alpha = 0.1$) and I^2 statistics (low heterogeneity: 25%, moderate heterogeneity: 50%, and high heterogeneity: 75%) were used to analyse the heterogeneity of the included studies. Significant heterogeneity was indicated when $P < 0.1$ (Q-test) or $I^2 \geq 50\%$. In this study, the random-effects model was used to integrate the results.

All statistical tests were two-sided, with a P value <0.05 considered statistically significant. The Egger regression test and Begg funnel plot were used to detect publication bias. Review Manager software, version 5.3 (version 5.3; The Cochrane Collaboration, Oxford, UK), Stata software (version 12.0; StataCorp, College Station, Texas, USA) and R 3.5.1 (the R Foundation for Statistical Computing, Vienna, Austria) were used to perform all statistical analyses.

Results

Search results

As shown in Figure 1, after removing 900 duplicates, the remaining 1585 articles were initially screened. Sixty-nine articles were further evaluated for eligibility, and 57 studies were then excluded, 36 of which did not have available data, seven involved patients co-infected with HIV and two were non-English publications. Finally, 12 studies (Abaalkhail et al., 2017; Brown et al., 2016; Ciesek et al., 2016; Crittenden et al., 2016; Herzer et al., 2017; Houssel-Debry et al., 2018; Mucenic et al., 2018; Nair et al., 2017; O'Leary et al., 2017; Pillai et al., 2016; Saab et al., 2017; Saxena et al., 2017) were eligible for meta-analysis from 2485 articles, following the previously described search strategy.

Study description

The specific characteristics of these patients are shown in Table 1. A total of 12 articles, published in the latest three years, comprising 1466 LT recipients, were included for this meta-analysis. All these studies were about sofosbuvir (SOF)-based treatment regimens. Seven of 12 studies were multicentre studies and five were single-centre studies. Seven of the 12 studies were from the United States, three were from Europe, one was from Brazil and one was from the Middle East. Most of the patients in these studies were male (73%), and most patients were infected with HCV genotype 1 (81%). About 58% of the patients in these 12 studies had prior treatment. Nine of the 12 included articles in this study provided available SVR12 rates for different genotypes, and all patients included for meta-analysis were treated with DAA-based treatment for at least 12 weeks.

Pooled rate of SVR12 of SOF-based DAAs ± RBV in post-LT patients

The rate of SVR12 of patients treated with DAAs with or without RBV was offered by all studies. There was high heterogeneity among the studies (Q-statistic = 90.91; $I^2 = 88\%$; $p < 0.01$). The pooled rate of SVR12 was 91% (95% CI: 84% to 95%) in 1466 patients treated with SOF-based DAAs, with or without RBV, post-LT (Figure 2). Funnel plot visual inspection did not reveal significant evidence of publication bias (Supplemental Figure S2). The Egger regression test (P = 0.72) confirmed that. Nine articles provided available SVR12 rates for different genotypes, and the pooled SVR12 of genotype 1, 3 and other genotypes (genotype 2,4 and 5) were 92% (95% CI: 88% to 95%), 92% (95% CI: 74% to 98%) and 91% (95% CI: 77% to 97%), respectively (Supplemental Figure S3). Four of the 12 included articles provided available SVR12 data to analyse the impact of different durations of treatment with SOF-based DAAs ± RBV. Twenty-four weeks of treatment did not do better than 12 weeks (RR = 1.04; 95% CI: 0.90 to 1.21, p = 0.58 (Supplemental Figure S4).

SVR12 for SOF-based DAAs + RBV versus SOF-based DAAs

All studies compared the SVR12 rate of SOF-based DAAs + RBV and that of SOF-based DAAs. In total, 502 patients were treated with SOF-based DAAs + RBV (SVR12: 90%), and 964 patients were treated with SOF-based DAAs (SVR12: 94%). Obviously, there was no statistical difference in SVR12 between the patients treated with SOF-based DAAs + RBV and those treated with SOF-based DAAs (RR = 0.97; 95% CI: 0.92 to 1.03; P = 0.35; $I^2 = 46\%$) (Figure 3). There was moderate heterogeneity among these studies. Sensitivity analysis was performed and showed that the results of our analysis had good stability (Supplemental Figure S5). Some

Table 1
Baseline Demographic and Disease Characteristics.

Author	Year	Collaboration	Regions	Sample size, n	Mean age, year, median (range) or mean ± standard deviation	Male, n (%)	Interval between LT and antiviral therapy, year median (range) or mean ± standard deviation	HCV Genotype1, n (%)	Prior treatment history, n (%)	Regimen
Mucenic et al.	2018	single-centre	Brazil	39	63.5 (49–68)	26 (66.7)	5.2 (0.3–21.1)	13 (33.3)	29 (74.4)	SOF + DCV ± RBV
O'Leary et al.	2016	multicentre	USA	46	60 (49–68)	34 (73.9)	4.5 (0.8–14.3)	46 (100.0)	0 (0.0)	SOF + SMV ± RBV
Ciesek et al.	2016	multicentre	Germany	30	60[a] (50–73)	19 (63.3)	6.6[a] (0.3–28)	26 (86.7)	21 (70.0)	SOF + LDV ± RBV
Brown et al.	2016	multicentre	USA	151	61[a] (46–78)	112 (74.2)	5[a] (0–23)	151 (100.0)	85 (56.3)	SOF + SMV ± RBV
Herzer et al.	2016	multicentre	Europe	87	58 (39–75)	61 (70.1)	3.7 (0.3–22)	76 (87.4)	60 (69.0)	SOF + DCV ± RBV
Crittenden et al.	2016	multicentre	USA	56	61 (7[b])	42 (75.0)	4.58 (6.17[b])	56 (100.0)	41 (73.2)	SOF + SMV ± RBV
Nair et al.	2017	single-centre	USA	53	56 ± 7[c]	34 (64.2)	1.2 ± 0.9	53 (100.0)	30 (56.6)	SOF + SMV ± RBV
Abaalkhail et al.	2016	single-centre	Middle East	50	63[d]	26 (52.0)	3.5 (0.08–7)	7 (14.0)	6 (12.0)	SOF + LDV ± RBV
Houssel-Debry et al.	2018	multicentre	Europe	512	60.3 ± 8.6	395 (77.1)	7.08 ± 6.0	359 (70.1)	336 (65.6)	SOF + DCV ± RBV; SOF+LDV ± RBV
Saab et al.	2017	single-centre	USA	85	63.1 ± 8.6	57 (67.1)	5.7 ± 5.9	85 (100.0)	39 (45.9)	SOF + LDV ± RBV
Saxena et al.	2017	multicentre	USA	347	62 (21–85)	259 (74.6)	not mentioned	299 (86.2)	202 (58.2)	SOF + DCV ± RBV ; SOF+LDV ± RBV
Pillai et al.	2016	single-centre	USA	57	58.1 ± 6.1	43 (75.4)	2.08 (2.33[b])	57 (100.0)	24 (42.1)	SOF + SMV ± RBV

Abbreviations: RBV, ribavirin; DAAs, direct-acting antiviral agents; DCV: daclatasvir; SOF: sofosbuvir; SMV: simeprevir; LDV: ledipasvir.
[a] Mean.
[b] Interquartile range.
[c] Mean ± standard error.
[d] Median.

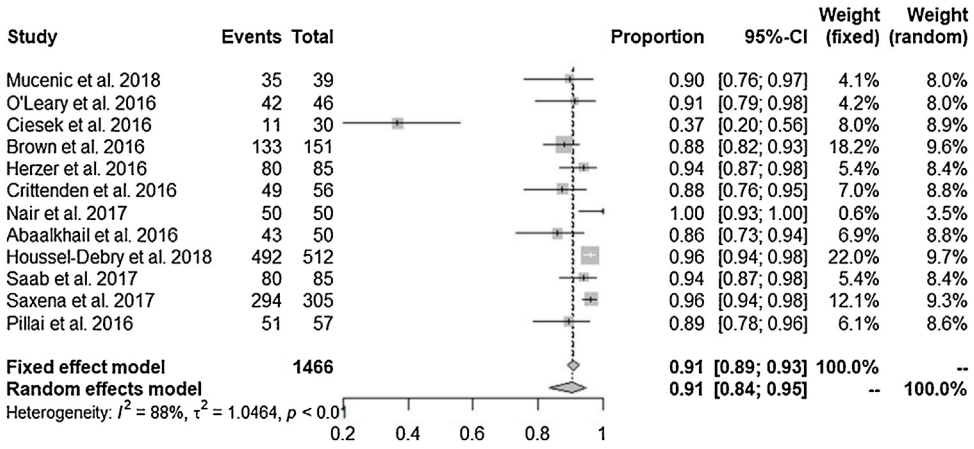

Figure 2. Pooled rate of sustained virological response 12 weeks (SVR12) after the end of treatment of sofosbuvir (SOF)-based, direct-acting antiviral agents (DAAs) with or without ribavirin (RBV) in post-liver transplantation patients.
Events: the number of patients who reached SVR12; total: the number of patients with available SVR12 data.

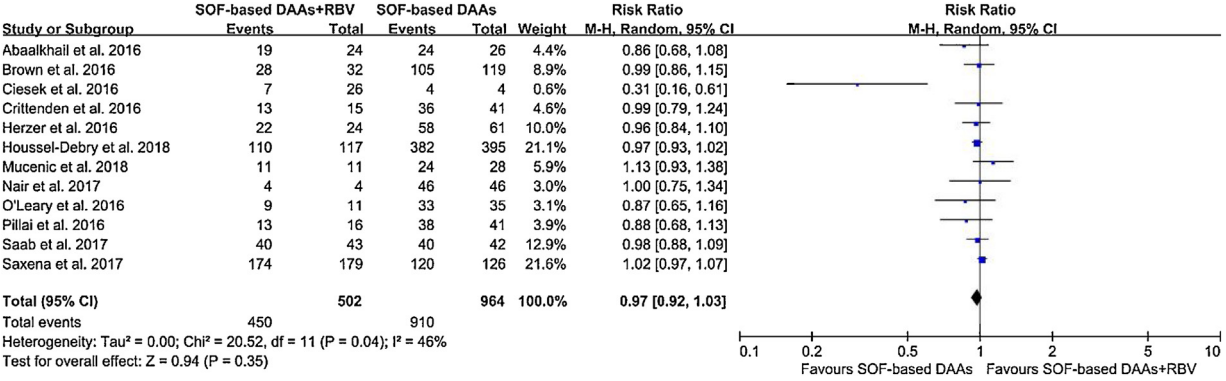

Figure 3. Risk ratio of sustained virological response 12 weeks (SVR12) after the end of treatment in patients with post-liver transplantation treated with sofosbuvir (SOF)-based, direct-acting antiviral agents (DAAs) plus ribavirin (RBV) versus SOF-based DAAs.
Events: the number of patients who reached SVR12; total: the number of patients with available SVR12 data.

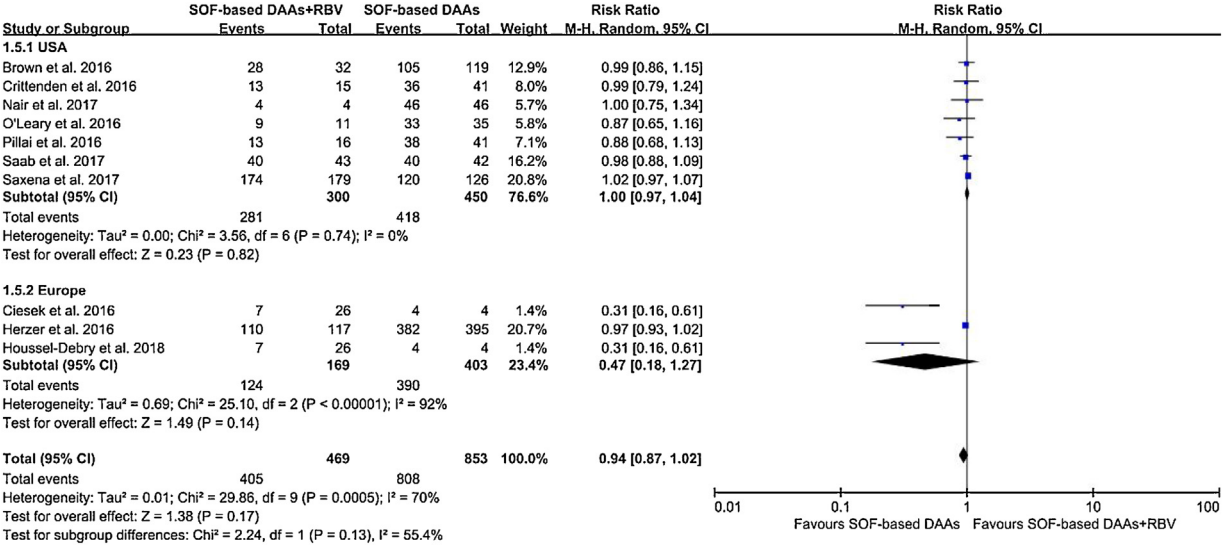

Figure 4. Risk ratio of sustained virological response 12 weeks (SVR12) after the end of treatment in patients with post-liver transplantation in different regions.
Events: the number of patients who reached SVR12; total: the number of patients with available SVR12 data.

subgroup analyses were then conducted. No obvious publication bias in these trials was observed (Supplemental Figure S6), which was confirmed by using the Egger regression test (P = 0.12).

Subgroup analysis by studies in different regions

Seven of the 12 studies were from the United States, three were from Europe, one was from Brazil and one was from the Middle East. Therefore, a subgroup analysis of SVR12 in the United States and Europe was conducted. In the studies from the United States, there was no statistical difference of SVR12 between the patients treated with SOF-based DAAs + RBV and those treated with SOF-based DAAs (RR = 1.00; 95% CI: 0.97 to 1.04; P = 0.82; I^2 = 0%), nor was there in Europe (RR = 0.47; 95% CI: 0.18 to 1.27; P = 0.14; I^2 = 92%). And there was no statistical significance of SVR12 in patients treated with SOF-based DAAs + RBV or SOF-based DAAs between the USA and Europe (Test for subgroup differences: P = 0.13) (Figure 4).

Subgroup analysis by DAA with different targets

A subgroup analysis was then performed based on DAAs with different targets (NS3/4 A + NS5B and NS5 A + NS5B). For the targets of NS3/4 A + NS5B inhibitors, there was no statistical difference of SVR12 between the patients treated with SOF-based DAAs + RBV and those treated with SOF-based DAAs alone (RR = 0.98; 95% CI: 0.91 to 1.05; P = 0.52; I^2 = 67%); similarly, no statistical difference was observed for the NS5 A + NS5B inhibitors (RR = 0.96; 95% CI: 0.87 to 1.06; P = 0.40; I^2 = 0%) (Figure 5). In comparing the targets of NS3/4 A + NS5B inhibitors and NS5 A + NS5B inhibitors, there was no statistical significance in SVR12 on different targets (test for subgroup differences: P = 0.76).

Subgroup analysis by different therapy duration

The pooled results of subgroup analysis by therapy duration suggested there was no difference in SVR12 between SOF-based DAAs + RBV group and SOF-based DAAs group (test for subgroup differences: P = 0.26) for 12 weeks (RR = 1.01; 95% CI: 0.98 to 1.05; P = 0.46; I^2 = 0%) and 24 weeks (RR = 0.91; 95% CI: 0.76 to 1.09; P = 0.31; I^2 = 76%) (Figure 6).

Higher incidence of anemia in DAA + RBV regimen than in DAA regimen

It is undeniable that RBV plays an important role in the treatment of HCV. Among these twelve studies, six showed incidence of anemia with or without RBV. Anemia occurred in 103 of 243 patients (42%) who used SOF-based DAAs + RBV and in 66 of 694 patients (10%) treated with SOF-based DAAs. The pooled analysis showed a significant difference between the SOF-based DAAs + RBV group and the SOF-based DAAs group (RR = 5.18; 95% CI: 3.41 to 7.86; p < 0.00001, I^2 = 26%) (Figure 7). The addition of RBV resulted in a significantly increased incidence of anemia.

Discussion

RBV is a synthetic triazole analogue of guanosine against both RNA and DNA viruses. It was added to interferon-based therapies in hopes of achieving higher SVR rates (Testoni et al., 2014), but the recurrence of HCV after LT was once a serious problem in the era of interferon (IFN)-based therapy, due to the less-than-ideal SVR obtained from treatment. DAAs make the treatment of HCV recurrence after LT easier and more effective, and the SVR rate is very high (Forns et al., 2015; Kwo et al., 2014). Although IFN may be eliminated from most future treatment options, RBV may be beneficial for many new DAAs to exert their full clinical benefit (Welsch et al., 2012). Now the specific mechanism of RBV antiviral is not clear (Testoni et al., 2014), and the use of RBV in patients with HCV recurrence after LT remains controversial (Nair et al., 2017).

Several meta-analyses have discussed the effectiveness and safety of different DAA-based regimens for post-LT patients. The ledipasvir-sofosbuvir-based (LDV-SOF-based) regimen had excellent antiviral performance, and its SVR12 could reach 96% (95% CI: 94.9%–97.5%) (Liao et al., 2017b). The SVR12 of patients treated with DCV + SOF ± RBV was 93.3% (95% CI: 83.3% to 99.4%) (Liao et al., 2017b). The pooled rate of SVR12 was 88% (95% CI: 83.4% to 91.5%) in the Nguyen and colleagues study (Nguyen et al., 2016)

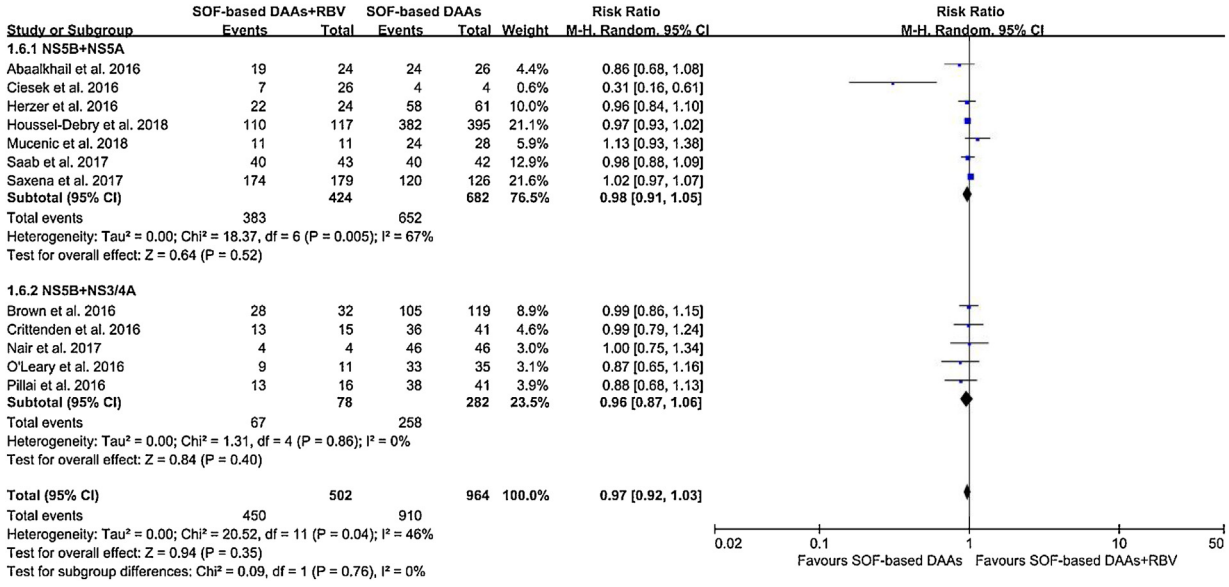

Figure 5. Risk ratio of sustained virological response 12 weeks (SVR12) after the end of treatment in post–liver transplantation patients treated with different targets DAAs (NS3/4A + NS5B, NS5A + NS5B).
Events: the number of patients who reached SVR12; total: the number of patients with available SVR12 data.

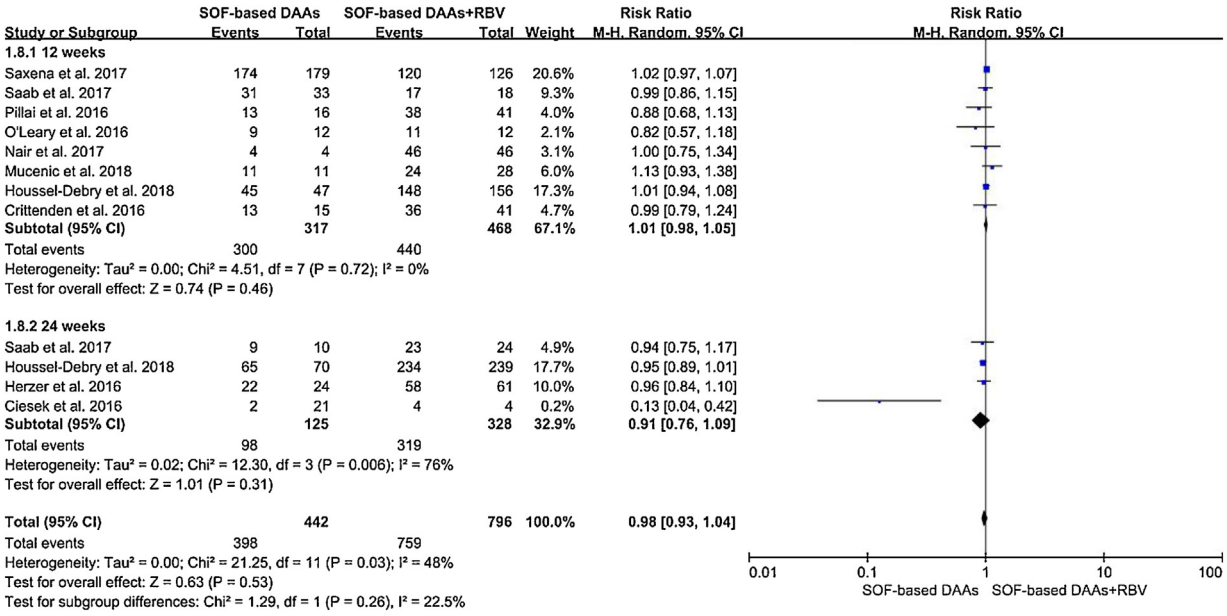

Figure 6. Risk ratio of sustained virological response 12 weeks (SVR12) after the end of treatment in LT patients on different treatment durations. Events: the number of patients who reached SVR12; total: the number of patients with available SVR12 data.

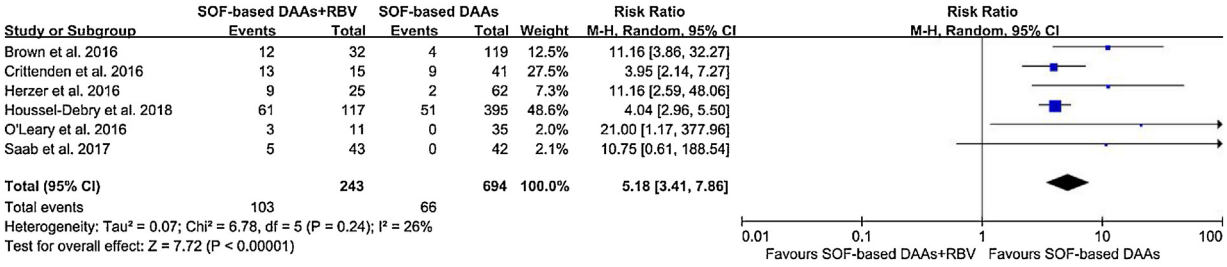

Figure 7. Risk ratio of the incidence of anemia with or without ribavirin (RBV).

with 325 patients after LT. The articles included in this study are all about the SOF-based DAA treatment regimens. The pooled rate of SVR12 in post-LT patients treated with SOF-based DAAs ± RBV was 91% (95% CI: 84% to 95%), and the pooled SVR12 of genotype 1, 3 and other genotypes (genotype 2,4 and 5) were 92%, 92% and 91%, respectively. Clearly, regardless of genotype, SOF-based treatment regimens are very effective in patients with recurrent HCV after LT.

A multicentre clinical study showed that the addition of RBV did not affect the SVR12 rate of treatment in patients with recurrent HCV infection after LT (p = 1.0) (Pungpapong et al., 2015). By comparing the efficacy of SOF/SMV + RBV (n = 32) and SOF/SMV (n = 119) in patients with recurrent hepatitis C after LT in HCV-TARGET, RBV showed no therapeutic advantage (Brown et al., 2016). Interestingly, Liao et al. (2017a) showed that patients receiving DCV + SOF had a higher SVR12 rate than DCV + SOF + RBV (OR: 0.33, 95% CI: 0.12–0.87; P = 0.02). In our study, we compared the rates of SVR12 in SOF-based DAAs combined with RBV and SOF-based DAAs without RBV. There was no statistically significant difference in the post-LT patients treated with SOF-based DAAs + RBV versus SOF-based DAAs (RR = 0.97; 95% CI: 0.92 to 1.03; P = 0.35; I^2 = 46%) by different therapy duration (P = 0.26), with different targets of DAAs (P = 0.13) and in different regions (P = 0.34). This seems to indicate that RBV does not contribute to a higher SVR. Due to the existence of some heterogeneity, sensitivity analysis was performed on these studies by removing each of the included studies one by one and observing the stability of the combined results. After eliminating the Ciesek and colleagues' study, I^2 decreased to 0, indicating that a study may be the source of heterogeneity. It showed that the result of the meta-analysis was robust and credible (Supplemental Figure S5).

Many adverse events (AEs) occur in patients after the addition of RBV, the most relevant of which is anemia (Nair et al., 2017). A clinical research study by Globke et al. (2017) indicated that 43.1% of the patients with HCV recurrence after LT who received RBV developed anemia in the DAA era, which was statistically significant (P < 0.001). Two meta-analyses by Liao et al. (Liao et al., 2017a; Liao et al., 2017) suggested that anemia is the most common adverse event associated with RBV in the patients with HCV recurrence after LT. In our study, the pooled analysis showed a significant difference of anemia between the SOF-based DAAs + RBV group and the SOF-based DAAs group (RR = 5.18; 95% CI: 3.41 to 7.86; p < 0.00001, I^2 = 26%). Obviously, the use of RBV increases the incidence of anemia in patients. In addition to anemia, some other common complications also occur (Supplemental Table S2).

In addition, we also analysed the SVR rates of patients in different stages of liver fibrosis. Four of the 12 included articles provided the SVR of the patients with different stages of liver fibrosis at the beginning of the treatment (Brown et al., 2016; Crittenden et al., 2016; Saab et al., 2017; Saxena et al., 2017) There was no statistically significant difference in SVR rates after patients with different stages of liver fibrosis received SOF-based DAAs treatment (RR: 1.04; 95% CI: 0.99 to 1.08; P = 0.10; I^2 = 0%) (Supplemental Figure S7). However, the results we got were different from the results of a meta-analysis done by Liao et al. that

indicated a trend for a higher SVR12 in patients with no cirrhosis than in those with a more severe degree of fibrosis ($p < 0.05$) (Liao et al., 2017b). As for the effect of previous treatment on the patient's SVR rate, four articles provided SVR12 data of patients with prior treatment or not (Brown et al., 2016; Crittenden et al., 2016; Houssel-Debry et al., 2018; Pillai et al., 2016). It suggested that previous treatments did not contribute to higher SVR rates (RR: 1.02; 95% CI: 0.98 to 1.06; $P = 0.33$; $I^2 = 0\%$) (Supplemental Figure S8). Regarding the impact of different duration of treatment, it seems that 24 weeks of treatment might not be better than 12 weeks (12 weeks versus 24 weeks: RR = 1.04; 95% CI: 0.90 to 1.21, $p = 0.58$, $I^2 = 28\%$) on SVR12.

Of course, there were some limitations in our study. First, the articles we included had only one randomised controlled trial. Meta-analysis based on randomised controlled trials has a higher level of evidence. However, the study subjects were patients with HCV recurrence after LT. The basic condition of the patients was unstable, and randomised controlled trials were difficult to achieve. Therefore, after screening, most of the articles included in this study were observational studies, and most of them were multicentre studies, and most of them were real-world studies; they had practical guidance to some extent. Second, because the addition of RBV in some of the studies included in this study was determined by the doctors, there might be some degree of bias in the results. We tried to conduct a more comprehensive analysis of our systematic reviews by conducting some subgroup analyses. Last, the therapeutic effects of different genotypes have always received much attention, but we did not have enough data available for more analysis. In this regard, we look forward to updating this meta-analysis in the future.

These analyses demonstrated that RBV may not be necessary in the treatment of HCV recurrence after LT with all-oral, direct-acting antiviral agents. On the one hand, our study shows that DAA-based antiviral therapy is effective in patients with recurrent HCV after LT, but the addition of RBV does not contribute to a higher SVR rate. On the other hand, the addition of RBV significantly increased the incidence of anemia in patients. The physical condition of post-LT patients was not very good, so the occurrence of anemia might make the situation more difficult to control. Twelve weeks of SOF-based DAAs without RBV should be enough for post-LT patients with HCV recurrence. In the era of all-oral DAAs, hepatitis C–positive liver donors are increasing. The treatment of hepatitis C after liver transplantation deserves more exploration. All-oral DAAs without IFN-RBV might be the main treatment regimen.

Conclusion

RBV did not contribute to a higher SVR rate. On the contrary, it increased the incidence of anemia in post-LT patients with HCV recurrence. We could try to treat patients with recurrent HCV after LT by SOF-based DAAs without adding RBV. It might be a better treatment strategy.

Conflict of interest

We declare that we have no conflict of interest.

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Ethical approval

Ethical approval was not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.03.038.

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