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META-ANALYSIS

Hepatitis C virus genotype 3: Meta-analysis on sustained virologic response rates with currently available treatment options

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Abstract

AIM: To address the therapeutic efficacy of various treatment regimens in genotype 3 selecting randomized clinical trials and prospective National Cohort Studies.

METHODS: (1) PEG-INF-based therapy including sofosbuvir (SOF) + RBV for 12 wk *vs* SOF + RBV 24 wk; (2) SOF + RBV therapy 12 wk/16 wk *vs* 24 wk; and (3) the role of RBV in SOF + daclatasvir (DCV) and SOF + ledipasvir (LDV) combinations. This meta-analysis provides robust information with the intention of addressing treatment strategy for hepatitis C virus genotype 3.

RESULTS: A combination treatment including SOF + RBV + PEG-IFN for 12 wk notes better SVR than with only SOF + RBV for 12 wk, although its association with more frequent adverse effects may be a limiting factor. Longer duration therapy with SOF + RBV (24 wk) has achieved higher SVR rates than shorter durations (12 or 16 wk). SOF + LDV are not an ideal treatment for genotype 3.

CONCLUSION: Lastly, SOF + DCV combination is probably the best oral therapy option and the addition of RBV does not appear to be needed to increase SVR rates substantially.

Key words: Hepatitis C; Genotype 3; Sofosbuvir; Daclatasvir; Ledipasvir

Core tip: The landscape of therapy for hepatitis C virus infection is changing rapidly. In genotype 3, the improvement in SVR rates has not been hugely spectacular, being considered the most difficult genotype to treat and representing a major challenge. The advent of direct acting antivirals has not solved all questions about the treatment, while challenges remain such as the use of RBV, the duration of PEG-IFN-free treatment and whether PEG-IFN still plays an important role. These questions are difficult to elucidate with the current data because of the small number of patients included in clinical trials (particularly, those with cirrhosis) and their different designs.

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INTRODUCTION

The landscape of therapy for hepatitis C virus (HCV) infection is changing rapidly[1]. Ideally, new drugs should be all-oral regimen (once-daily, single pill) with pangenotypic activity, and have short treatment course (no more than 12 wk), and with high sustained virological response (at least 90%-95%). A multitude of direct acting antivirals (DAAs) have been developed with or without pegylated interferon (PEG-IFN) and ribavirin (RBV)[2], and others are being tested in promising clinical trials[3]. In genotype 3, the improvement in SVR rates has not relatively suboptimal and is being considered the most difficult genotype to treat and thus representing a major challenge[4]. Unique clinical features of genotype 3 and possible reasons for suboptimal response are: (1) a close relationship with insulin resistance and disturbances in lipid metabolism[5]; and (2) fibrosis progression[6] and higher incidence of hepatocellular carcinoma[7].

The advent of DAAs has not solved all questions regarding the treatment in genotype 3, and with emerging new challenges such as RBV use[8], duration of PEG-IFN-free treatment and whether PEG-IFN still plays an important role[9]. These questions are difficult to elucidate with the current data because of the small number of patients included in clinical trials (particularly, those with cirrhosis) and their different designs. In fact, more valuable data have been derived from prospective observational studies (clinical practice), and beyond randomized clinical trials. In this study, we aimed to address key questions on treatment outcomes through a meta-analysis.

MATERIALS AND METHODS

Data sources and search

The search strategy was in accordance with the recommendations of meta-analysis of clinical trials and observational studies. We searched in MEDLINE, EMBASE and Cochrane Library databases (to November 2015), as well as abstracts published and presented at EASL and AASLD (to November 2015) to identify potentially relevant publications in English language. We included FDA-approved DAA therapies that included SVR as a primary end point. Search terms were: "hepatitis C", "genotype 3", "HCV treatment", "sofosbuvir", "ledipasvir", "daclatasvir", "ribavirin", "interferon". The preceding terms were combined with appropriate Boolean logic. Manual search of cited bibliographies was also performed. Duplicated publications were deleted. Two researchers independently performed the literature search and data abstraction with regard to the inclusion and exclusion criteria by reading titles and abstracts. When reading titles and abstracts did not allow identification of eligible studies, articles were read in full. Relevant reviews and letters to the editor were excluded from the analysis, but read in full to identify potential relevant original studies. Disagreements between two observers were resolved by discussion.

Study selection criteria and data extraction

We selected randomized clinical trials (preferably) and prospective National Cohort Studies in which therapies were administrated in different arms. Therefore, studies including only a combination testing different doses or being administrated to different subset of patients were excluded. Inclusion and exclusion criteria (studies involving genotypes other than 3) were defined prior to initiation of the literature search. Twelve studies were included and classified according to the aims (Figure 1). The following data were extracted: (1) Study: year of publication, number of patients, location, design; (2) Patients: stage of liver disease (cirrhosis or chronic hepatitis), previous HCV treatment (naïve or treatment-experienced); (3) HCV treatment regimen and duration; and (4) SVR rates.

Objectives

We aimed to address the therapeutic efficacy of various treatment regimens in genotype 3. Firstly, we compared a PEG-INF-based therapy including sofosbuvir (SOF) + RBV during 12 wk with SOF + RBV 24 wk. Secondly, we assessed the importance of extending the course of SOF + RBV therapy (12 wk/16 wk *vs* 24 wk). Thirdly, we analyzed the role of RBV in SOF + daclatasvir (DCV) and SOF + ledipasvir (LDV) combinations.

Statistical analysis

Statistical analysis was performed using the Meta-Disc

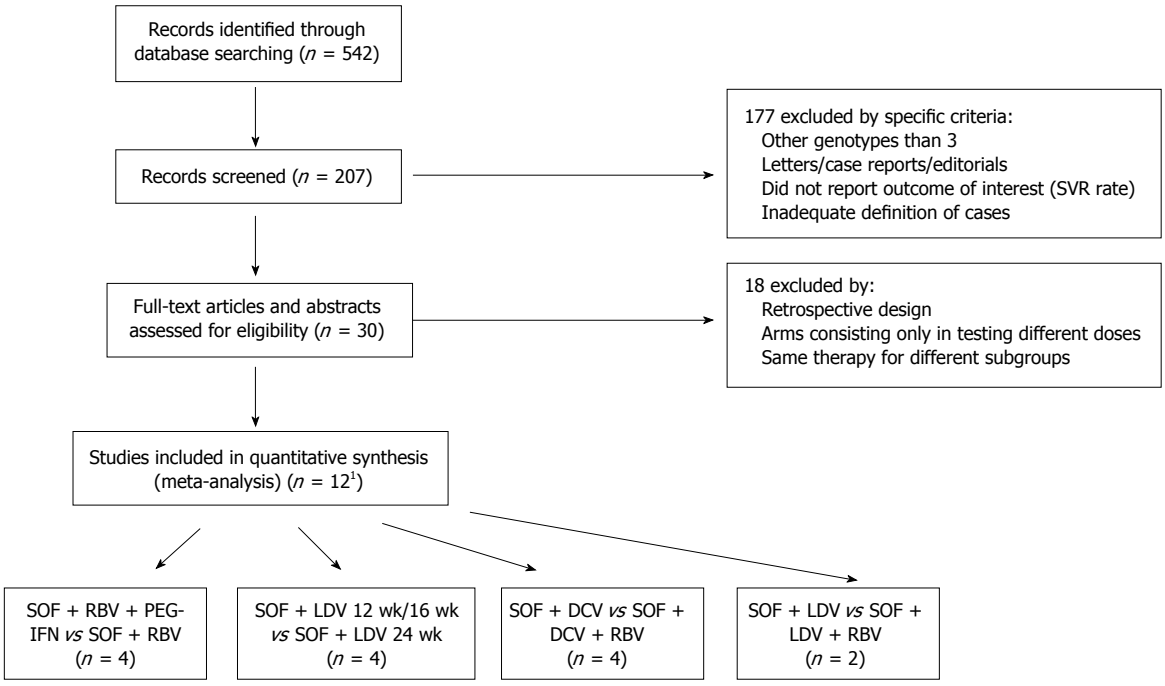

Figure 1 Flow chart of studies screened and included in meta-analysis. [1]Two studies included in two different sub-meta-analysis. SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; PEG-IFN: Polyethylene glycol interferon.

software 1.4[10], considering: (1) a summary of data from individual studies; (2) an investigation of the studies homogeneity, graphically and statistically; (3) calculation of clustered indexes; and (4) exploration of heterogeneity. Our assumption of heterogeneity was tested for each planned analysis using the Cochran-*Q* heterogeneity and I^2 statistics (low, moderate, and high heterogeneity according to I^2 values of 25%, 50%, and 75%, respectively)[11]. Random effects model using Der Simonian and Laird method and fixed effects model were used according to the presence of heterogeneity. To check for publication bias, we used the Begg and Egger tests. Only two-sided tests with a significance level of 0.05 were used. Confidence intervals (CIs) of individual studies were determined or approximated from the available data. Further, we assessed the quality of the studies using the "Quality Assessment of Diagnostic Accuracy Studies" (QUADAS) tool for observational studies ($\geqslant$ 10 were considered as high-quality studies[12]) and Jadad scale for randomized clinical trials ($\geqslant$ 3 were considered as high-quality ones[13]).

RESULTS

Comparison between INF-based and IFN-free regimens

We evaluated four studies that met the selection criteria and that were identified using the search strategy described. Studies characteristics are shown in Table 1. Pooled data included 807 patients. The meta-analysis demonstrated that triple therapy including SOF + RBV + PEG-IFN was able to achieve higher SVR rates (92.5%; 236/255) than SOF + RBV (75.2%; 415/552), using fixed effects model [OR = 3.51 (95%CI: 2.08-5.92)] (Figure 2A). We found neither heterogeneity between these studies [(Cochran-*Q* = 0.94; *df* = 3, *P* = 0.8157); inconsistency I^2 = 0%, and τ^2 = 0.0000)] nor publication bias [(Begg test: Kendall' s tau 1.70, *P* = 0.1); (Egger test: -1.14, *P* = 0.37)].

Course of SOF + RBV treatment

We included four studies involving 850 patients. The meta-analysis demonstrated that a 24 wk-course of SOF + RBV (85.5%; 501/586) combination was better than 12 wk-16 wk (70%; 185/264) in terms of SVR rates, using random effects model [OR = 3.51 (95%CI: 1.59-7.70)] (Figure 2B). We found a moderate heterogeneity between these studies [(Cochran-Q = 7.77, *df* = 3, *P* = 0.0511); inconsistency I^2 = 61%, and τ^2 = 0.3718], but no publication bias [(Begg test: Kendall's tau 0.34, *P* = 0.73); (Egger test: 0.81, *P* = 0.50)]. Three of these studies evaluated SVR rates according to the presence of cirrhosis. In non-cirrhotic patients, longer therapy of SOF + RBV (89.7%; 218/243) achieved higher SVR rates than shorter one (78.2%; 144/184) using random effects model (OR 2.44 (95%CI: 1.41-4.23). We did find a moderate heterogeneity between these studies [(Cochran-*Q* = 4.42; *df* = 2, *P* = 0.11); inconsistency I^2 = 55%, and τ^2 = 0.3987], with no publication bias. Similarly, this effect was observed in cirrhotic population (78.5%; 73/93 *vs* 55%; 38/69) using the random effects model [OR = 2.79 (95%CI: 1.34-5.78)].

Role of RBV in SOF + DCV and SOF + LDV combinations

Additionally, we assessed the role of adding RBV in

Table 1 Overall characteristics of studies included in meta-analysis

Ref.	Year	Patients characteristics	Study design	Outcome (SVR %)
Alqahtani *et al*[31]	2015	HCV mono-infected patients TARGET cohort Randomized by cirrhosis and previous treatment 50% Treatment naïve 51% Cirrhosis	a) SOF + RBV + PEG-IFN (n = 18) b) SOF + RBV (n = 133)	a) 89% b) 65%
Chulanov *et al*[32]	2014	HCV mono-infected patients Russian multicenter cohort Randomized by cirrhosis 100% Treatment naïve 18% Cirrhosis	a) SOF + RBV 16 wk (n = 30) b) SOF + RBV 24 wk (n = 31)	a) 87% b) 90%
Dalgard *et al*[33]	2015	HCV mono-infected patients Scandinavian cohort study 51% Treatment naïve 82% Cirrhosis	a) SOF + RBV + PEG-IFN 12 wk (n = 25) b) SOF + RBV 24 wk (n = 33)	a) 92% b) 79%
Foster *et al*[17](BOSON)	2015	HCV mono-infected patients Randomized study 51% Treatment naïve 31% Cirrhosis	a) SOF + RBV + PEG-IFN 12 wk (n = 181) b) SOF + RBV 16 wk (n = 181) c) SOF + RBV 24 wk (n = 182)	a) 93% b) 71% c) 84%
Foster *et al*[27]	2015	HCV mono-infected patients NHS England Early Access Program 100% Decompensated Cirrhosis	a) SOF + DCV 12 wk (n = 7) b) SOF + DCV + RBV 12 wk (n = 113) c) SOF + LDV 12 wk (n = 7) d) SOF + LDV + RBV 12 wk (n = 61)	a) 71% b) 81% c) 57% d) 72%
Gane *et al*[29] (ELECTRON-2)	2015	HCV mono-infected patients Randomized study 50% Treatment naïve 32% Cirrhosis	a) SOF + LDV 12 wk (n = 25) b) SOF + LDV + RBV 12 wk (n = 26) c) SOF + LDV + RBV 12 wk (n = 50)	a) 64% b) 100% c) 82%
Hezode *et al*[34]	2015	HCV mono-infected patients French Compassionate Use Program 27% Treatment naïve 94% Cirrhosis	a) SOF + DCV 12 wk (n = 26) b) SOF + DCV + RBV 12 wk (n = 4) c) SOF + DCV 24 wk (n = 35) d) SOF + DCV + RBV 24 wk (n = 13)	a) 85% b) 100% c) 91% d) 92%
Ingiliz *et al*[35]	2015	HCV-HIV co-infected patients German multicenter cohort study 50% Treatment naïve38% Cirrhosis	a) SOF + RBV + PEG-IFN 12 wk (n = 31) b) SOF + RBV 24 wk (n = 23)	a) 94% b) 91%
Sulkowski *et al*[22](PHOTON)	2014	HCV-HIV co-infected patients International multicenter cohort 25% Treatment naïve	a) SOF + RBV 12 wk (n = 42) b) SOF + RBV 24 wk (n = 123)	a) 67% b) 89%
Sulkowski *et al*[36]	2014	HCV mono-infected patients Randomized study 100% Treatment naïve 14% Cirrhosis	a) SOF + DCV 24 wk (n = 13) b) SOF + DCV + RBV 24 wk (n = 5)	a) 92% b) 80%
Welzel *et al*[28]	2015	HCV mono-infected patients European Compassionate Use Program 72% Cirrhosis	a) SOF + DCV 24 wk (n = 11) b) SOF + DCV + RBV 24 wk (n = 13)	a) 100% b) 85%
Zeuzem *et al*[37] (VALENCE)	2014	HCV mono-infected patients Randomized study 41% Treatment naïve 24% Cirrhosis	a) SOF + RBV 12 wk (n = 11) b) SOF + RBV 24 wk n = 250)	a) 27% b) 84%

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; PEG-IFN: Polyethylene glycol interferon.

IFN-free regimens. Four studies have evaluated this point regarding the combination treatment of SOF + DCV. Pooled data included 502 patients. The meta-analysis demonstrated that adding RBV was not essential to achieve optimal SVR rates (83%; 173/209 *vs* 86.3%; 253/293), using fixed effects model [OR = 1.09 (95%CI: 0.35-3.40)] (Figure 2C). We did not find heterogeneity between these studies [(Cochran-Q = 2.38; df = 3, P = 0.4981); inconsistency I^2 = 0%, and τ^2 = 0.0000], and did not seem to have publication bias. On the other hand, two studies have evaluated the role of adding RBV in SOF + LDV combination. Pooled data included 169 patients. The meta-analysis demonstrated that adding RBV was important to achieve better SVR rates (81%; 111/137 *vs* 62.5%; 20/32), using fixed effects model [OR = 3.30 (95%CI: 1.35-8.04)] (Figure 2D). We did not find heterogeneity between these studies [(Cochran-Q = 0.61, df = 1, P = 0.4335); inconsistency I^2 = 0%, and τ^2 = 0.0000], and no publication bias was found [(Begg test: Kendall's tau 0.01, P = 0.99)].

DISCUSSION

New challenges have emerged in the evolving era of HCV therapy, particularly with genotype 3, and these

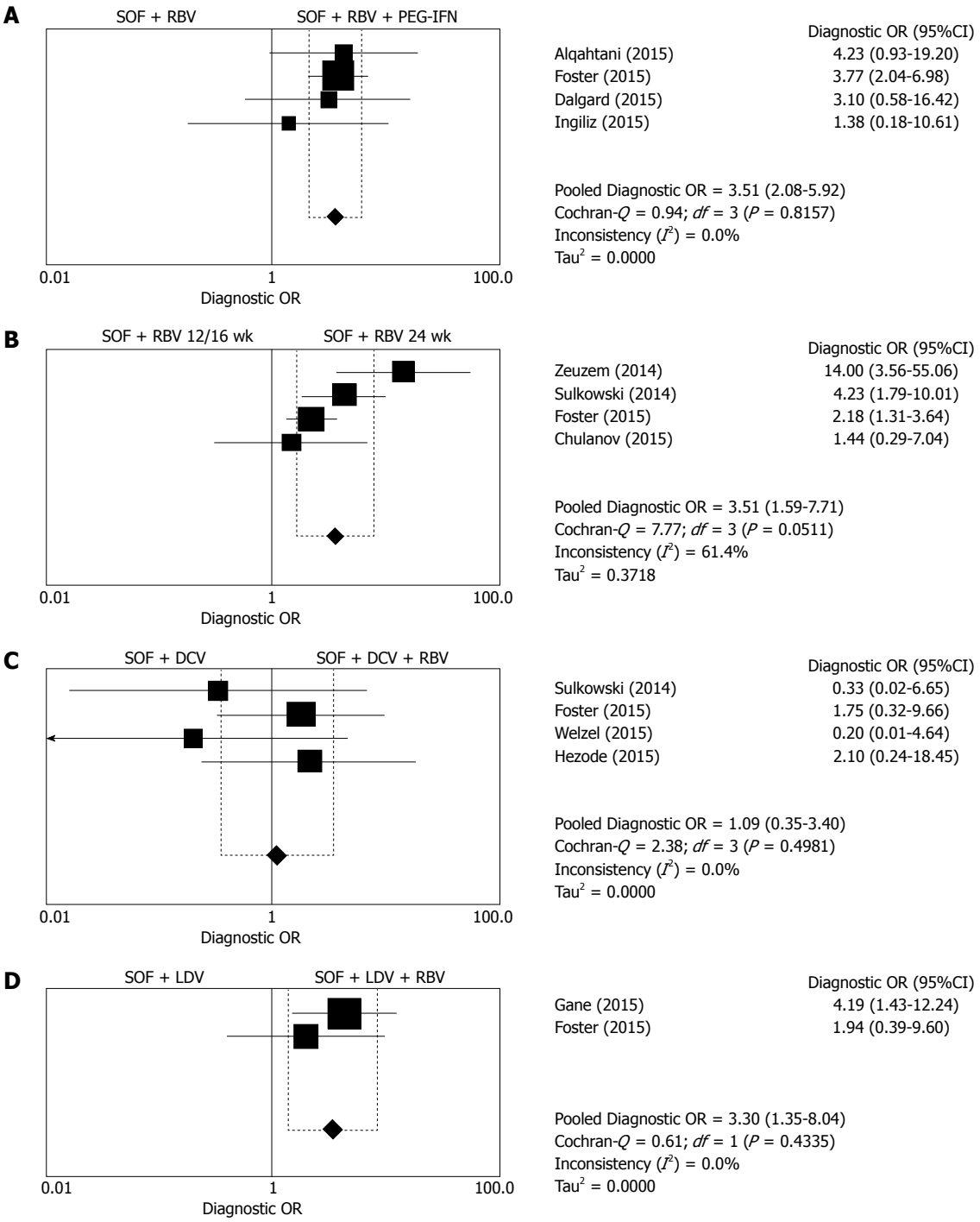

Figure 2 Odds ratio (95%CI) and Forest plot for SVR rates. A: SOF + RBV + PEG-IFN *vs* SOF + RBV combinations; B: SOF + RBV 12 wk/16 wk *vs* SOF + RBV 24 wk combinations; C: SOF + RBV 12 wk/16 wk *vs* SOF + RBV 24 wk combinations; D: SOF + LDV *vs* SOF + LDV + RBV combinations.

include the ongoing role of PEG-IFN, the addition of RBV and the adequate duration of the therapy[13]. The rapid development and use of DAAs in several heterogeneous studies including small number of patients has made robust guideline development and recommendation rather challenging. Thus, a meta-analysis is needed pooling all patients to address these questions.

In this new era, PEG-IFN is being abandoned as part of standard HCV therapy because of the association with serious adverse effects (and the parenteral administration)[14]. From now on, PEG-IFN will not be used for genotypes 1, 2 or 4 anymore. For genotype 3, there are only two DAAs (SOF and DCV) with a significant inhibitory activity *in vitro*[15]. In this context, PEG-IFN could potentially play a role in HCV treatment and could be the last such indication for its use. We demonstrated that the addition of PEG-IFN to SOF + RBV 12 wk was superior to only SOF + RBV combination (92% *vs* 75%, OR = 3.51). BOSON study

represents the main study evaluating this comparison, and it included nearly two hundred patients per arm[16]. Additionally, DCV has been evaluated in combination with PEG-IFN + RBV, although SVR rates were not higher than those patients treated with dual standard therapy (65% *vs* 59%)[17]. Both EASL and AASLD recommend SOF + RBV + PEG-IFN as a good alternative in non-cirrhotic and compensated-cirrhotic patients[18]. On the other hand, no data is available evaluating SOF + RBV + PEG-IFN *vs* SOF + DCV.

We analyzed the combination of SOF + RBV, in terms of duration of therapy. To date, this combination has been evaluated for 12, 16 and 24 wk duration. We compared SOF + RBV 12 wk/16 wk *vs* SOF + RBV 24 wk, and the latter achieved higher SVR rates (89% *vs* 70%, OR = 3.51). Furthermore, SOF + RBV 12 wk (56%) was associated with poorer SVR rates than dual standard therapy with PEG-IFN + RBV 24 wk (63%) in FISSION study[19], and showing similar results than POSITRON study (61%)[20]. Both studies demonstrated that SOF + RBV combination 12 wk was suboptimal, especially in the cirrhotic population. In FISSION study, a longer course of therapy (16 wk) with SOF + RBV showed better results than a shorter one (62% *vs* 30%)[21]. Overall SVR rates with SOF + RBV 12/16 wk were about 60%, which is considered suboptimal in the evolving era of hepatitis C therapy where response rates far below 90% are considered suboptimal. We included four studies that evaluated the course of 24 wk of SOF + RBV and noted an overall SVR rate around 90%. In addition, PHOTON study confirmed the extrapolation of these results in HIV-co-infected patients[22]. Taking into account all of these results, EASL and AASLD guidelines recommend extending SOF + RBV treatment to 24 wk (especially indicated in non-cirrhotic population).

In this meta-analysis, we demonstrated that SOF + LDV combination needs the addition of RBV to achieve optimal SVR rates in patients with genotype 3 (81% *vs* 62%, OR = 3.30). In contrast, RBV did not play any role in the combination of SOF + DCV because it did not improve SVR rates. DCV and LDV are HCV NS5A inhibitors[23], although DCV shows a pangenotypic activity[24] while LDV has a low activity in genotypes 2 and 3[25]. Currently, SOF + DCV combination is the first option to treat patients with genotype 3 in EASL guidelines, 12 wk in non-cirrhotic and 24 wk (with RBV) in cirrhotic patients. This recommendation is mainly based on ALLY-3 study in which SOF + DCV 12 wk achieved 97% and only 58% SVR in non-cirrhotic and cirrhotic population respectively[26]. The UK Early Access Program did not show any impact of adding RBV to SOF + DCV 24 wk in cirrhotic patients (70% *vs* 71%)[27], as well as the European Compassionate Use Program in patients at high risk of hepatic decompensation or death within 12 mo (100% *vs* 85%, *P* = NS)[28]. In a relatively small study, ELECTRON-2 trial, SOF + LDV for 12 wk achieved suboptimal SVR rates while the addition of RBV substantially increased it (100% in non-cirrhotic naïve patients, and 89% in non-cirrhotic and 73% in cirrhotic treatment-experienced patients)[29]. However, this trial should be interpreted with caution because it has very limited data from a phase Ⅱ single-center study and comprising a homogenous population which could limit the generalizability of the results. This, together with the high EC50 of LDV for genotype 3[30], has lead EASL and AASLD to not recommend SOF + LDV±RBV combination for genotype 3.

Recommendations made by EASL and AASLD guidelines were based on few data derived from randomized clinical trials and, due to the rapid and wide use in clinical practice, modified by prospective national cohorts. This meta-analysis provides solid and robust information to address several important questions, regarding the treatment of HCV genotype 3. First, combination including SOF + RBV + PEG-IFN shows better results than only SOF + RBV, although its association with adverse effects may limit the use (*i.e.,* cirrhotic population). Second, longer therapies including SOF + RBV (24 wk) have higher SVR rates than shorter ones (12 or 16 wk). Therefore, SOF + RBV for 24 wk are ideal. Third, SOF + LDV should not be used in genotype 3 and, if so, necessarily with RBV. Lastly, SOF + DCV combination is probably the best option and the addition of RBV does not appear to be needed to increase substantially the SVR rates.

COMMENTS

Background

The advent of direct acting antivirals has not solved all questions of successfully and effectively treating all hepatitis C virus (HCV) genotypes. Genotype 3, a common genotype globally, remains the last challenge.

Research frontiers

Nowadays, it remains unclear if Peg-IFN and RBV are still required to treat HCV genotype 3 effectively. The worldwide research is directed towards a more suitable combination of DAA.

Innovations and breakthroughs

In the present study, the authors investigated the SVR rates of different DAA combinations. This is the first report of a meta-analysis including sofosbuvir, daclatasvir, ledipasvir, peginterferon and ribavirin showing the eradication of the HCV infection.

Applications

The present report allows understanding the role of DAAs in the treatment of HCV genotype 3.

Peer-review

This systematic review and meta-analysis adds useful information for clinical practice and research.

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