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Research Article

A Systematic Review And Meta: Analysis of Ribavirin with Newer Directly Acting Antivirals in the Treatment of HCV

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Abbreviations HCV: Hepatitis-C Virus; RBV: Ribavirin,; DAA: Directly Acting Antiviral; SVR: Sustained Virologic Response; AE: Adverse Event; TW: Treatment Week; SAE: Serious Adverse Event; confidence interval

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Abstract

Background: In the current era of interferon free oral Directly Acting Antivirals (DAAs), Ribavirin (RBV) is widely used. A relevant question in focus is the value of RBV to date, from the accrual of data from all clinical studies and real world data. We aimed to assess the efficacy of DAAs in combination with RBV compared with DAAs without RBV, and discuss pertinent literature.

Methods: We identified studies through a systematic review of PubMed, Embase, Clinical Trials.gov, meeting abstracts and a national HCV database repository (HCV Target). We used cumulative random effects meta-analysis to combine effect estimates from the data.

Findings: We included 19 studies that met the inclusion criteria. The meta-analysis of HCV patients comprised data for 9350 patients (DAAs with RBV=3371, DAAs alone=5979). The baseline characteristics were similar between the two groups. In cumulative meta-analysis adjusted for age, sex, previous treatment failure, IL-28 beta genotype, and male sex no factor was associated with a statistically significant increase in SVR 12.The use of RBV with DAA for HCV was not associated with a significant increase in SVR 12 rates compared with the use of DAA alone in all patients OR of 0.90 (95% CI 0.53-1.53; p=0.7), in the subgroup of cirrhotic patients OR of 0.99 (95% CI 0.53-1.85; p=0.98), in the subgroup of treatment experienced patients OR of 1.19 (95% CI 0.80-1.75; p=0.65) and in the subgroup of G3 patients OR of 0.97 (95% CI 0.25-3.71; p=0.96). The adverse effects of RBV appears to be mostly non-fatal but contributes to significant morbidity.

Interpretation: Although the use of RBV with DAAs is common in the era of IFN free therapy, its synergistic effect with DAAs in clinical studies to achieve superior SVR 12 rates remains inconclusive. Therefore the use of RBV with DAAs needs to cautiously reconsidered in all patients with HCV, especially in those at risk for serious adverse events.

Introduction

Disease burden of chronic HCV is estimated to be well over 150 million patients world-wide [1]. Chronic HCV is a major cause of cirrhosis, decompensated liver disease and hepatocellular carcinoma in the US and globally 2. Research and development of contemporary HCV clinical therapeutics is facing a race against time to develop, optimize, safely apply and make available durable curative therapies, as numbers of cases of cirrhosis and hepatocellular carcinoma from chronically HCV infected patients are projected to peak in 2020 [3].

Successful curative therapy for hepatitis C results in a Sustained Virologic Response (SVR), a reliable surrogate of virologic cure, is expected to benefit nearly all chronically infected patients. Thus the quintessential goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA at least 12 weeks after initiation of therapy and this end point has proven durability, in large prospective studies, in more than 99% of patients followed up for 5 years or longer [4,5].

Ribavirin (RBV) has been used in therapeutic regimens targeting HCV for over a decade.6The strategy to achieve SVR in chronic HCV infected patients has seen a generational change in the last decade from standard IFN and RBV resulting in dismal SVR 12 rates (<25%) to IFN free treatments with all oral, Directly Acting Anti-Viral Agents (DAAs) with RBV demonstrating promising (>90%) SVR 12 rates, thus defining the holy grail of HCV therapeutics [6-8].

There is considerable ongoing debate regarding the value of RBV in an all oral DAA regimen [9]. The overriding scientific rationale favoring the use of RBV with DAA is from studies which demonstrated its utility in IFN free regimen with a protease inhibitor and non-nucleoside inhibitor, in which patients without RBV developed viral breakthrough, in contrast addition of RBV enhanced

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antiviral activity with superior SVR rates and delayed/no resistance [10,11]. However, others have demonstrated that RBV is probably not necessary when 2 drug DAA regimens are used to achieve durable and superior SVR rates and appears to be safe without emergence of resistance [12-14] .

We performed this meta-analysis of prospective cohort studies focusing on the clinically imperative question of the relevance to date, of RBV with DAA in achieving SVR12, compared with DAAs used alone. We supplement published studies identified through systematic reviews with unpublished data from meetings abstract EASL, AASLD and national databases such as HCV Target.

Methods

Search strategy and selection criteria

In compliance with PRISMA guidelines [15] we identified published studies through a systematic review of Pub Med and Embase from inception to September 25th 2015, with the following search terms without restrictions-*"Directly Acting Antivirals", "Ribavirin", "Hepatitis C", "Protease Inhibitor", "Nucleoside Inhibitor", "Treatment Naïve", "Treatment Experienced", "Cirrhotic"*.

After exclusion of duplicate studies, three investigators (MMA, NJ and PB) independently reviewed titles and abstracts of the remaining articles to establish their eligibility on the basis of predefined inclusion and exclusion criteria. We included studies published in English, had a prospective cohort study design and outcome data, examining the effect (SVR12) of RBV with and without DAAs.

Data extraction

We extracted the following information from each eligible article: name of the first author, study randomization and patient allocation to groups, study drugs used in each group, SVR 12 rates achieved, dropout rates, mean age, sex, race, genotype, IL-28B, prior treatment failure, cirrhosis, adverse events.

Unpublished individual-participant data

We supplemented the data from the published studies with unpublished individual level data from HCV TARGET database (http://www.hcvtarget.org/) which is an international Phase III clinical study repository. All the studies with unpublished data were approved by the relevant local or national ethics committee and all participants gave informed consent to participate.

Covariates

Harmonized covariates, including potential confounding factors were age, sex, BMI, HIV status, cirrhosis severity, IL28B genotype, HCV RNA, platelet and ALT.

Additional covariates unavailable for all the studies included only race which was unavailable for 1 study [16].

Quality assessment

Quality control of included studies was carried out using the Cochrane Risk of Bias Tool for cohort studies [17]. The selection of study groups (RBV with DAA *vs* DAA only groups), level of exposure of the study variable i.e. RBV dose and duration of regimen, adjustment of confounding variables, assessment of outcome and adequacy of follow-up. The quality of the study was considered to be of high quality if all domains were assessed favorably.

Statistical analysis

Der Simonian-Laird model with inverse variance weighting was used to generate OR and 95% CI for odds of SVR achievement in the study arms. This method was chosen as the included studies had varying sample sizes and the overall effect was estimated as the weighted mean of the individual effects where each study is weighted as a function of inverse variance. Hence more precise studies (generally studies including more experimental subjects, weighted higher as their results are considered more reliable and less error prone [18] .

Heterogeneity of study specific estimates was evaluated using the I^2 statistic (higher values denote greater heterogeneity) and we present the summary effect of random-effects or fixed effects analysis based on heterogeneity of the studies selected [19]. We examined publication bias in studies included using funnel plot. The statistical analysis was carried out using Rev Man version (5.3) (Cochrane Collaboration Inc), Graph Pad Prism version (6) (La Jolla CA, USA) and Open Meta (AHRQ NIH, USA).

Results

(Figure 1) shows a flow diagram for the study selection process. From 23 published studies, 8 were excluded and similarly from 5 unpublished studies, 1 was excluded. The exclusion criteria being IFN in any of the study arms, co-infection with HBV, liver transplant recipients, discordant trial arms with confounding variables, inadequate follow up and non-adherence to PRISMA guidelines.

(Figure 2) is a funnel plot that demonstrates the low bias risk of the included studies in the sub-analyses groups- cirrhotic patients, treatment experienced and genotype 3.

(Figure 3) Forest Plot: Cumulative meta-analysis of published and unpublished data on all treated patients on achievement of SVR 12 comparing DAAs with DBV *vs* DAAs alone.

(Figure 4) Forest Plot: Cumulative meta-analysis of published and unpublished data on cirrhotic patients on achievement of SVR 12 comparing DAAs with DBV *vs* DAAs alone.

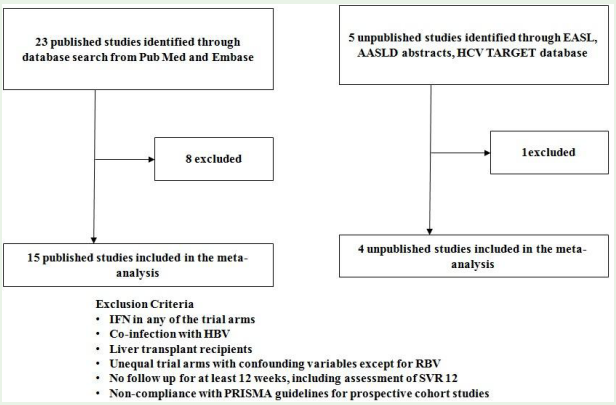

Figure 1: Changes in Mean Facial (± S.E.) Width-to-Height Ratios of Major League Baseball Players Active 1870-1989.

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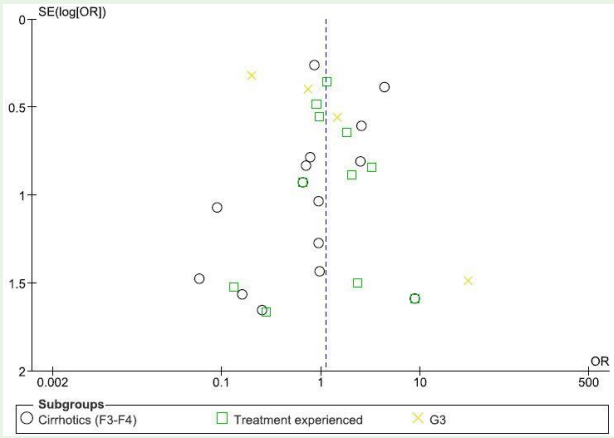

Figure 2: Funnel plot of included studies.

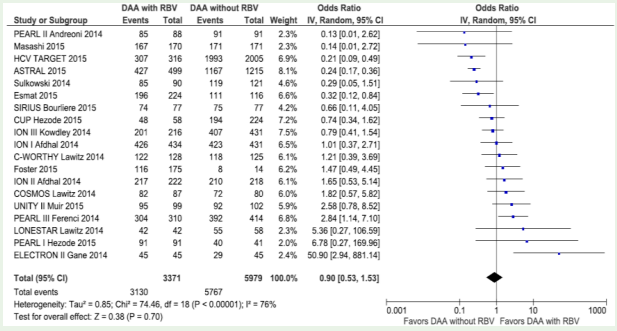

Figure 3: Forest Plot: Cumulative meta-analysis of published and unpublished data on all treated patients on achievement of SVR 12 comparing DAAs with DBV *vs* DAAs alone.

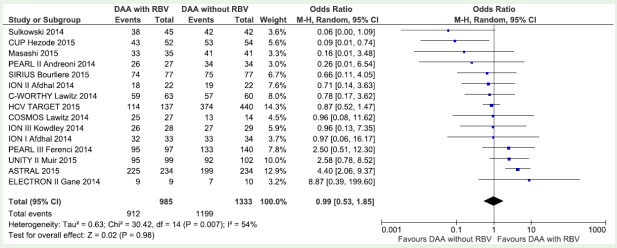

Figure 4: Forest Plot: Cumulative meta-analysis of published and unpublished data on cirrhotic patients on achievement of SVR 12 comparing DAAs with DBV *vs* DAAs alone.

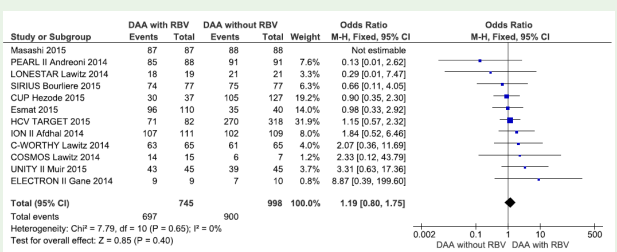

Figure 5: Forest Plot: Cumulative meta-analysis of published and unpublished data on treatment experienced patients on achievement of SVR 12 comparing DAAs with DBV *vs* DAAs alone.

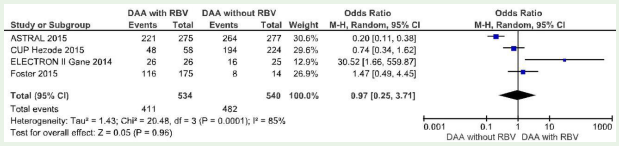

Figure 6: Forest Plot: Cumulative meta-analysis of published and unpublished data on Genotype 3 patients on achievement of SVR 12 comparing DAAs with DBV *vs* DAAs alone.

(Figure 5) Forest Plot: Cumulative meta-analysis of published and unpublished data on treatment experienced patients on achievement of SVR 12 comparing DAAs with DBV *vs* DAAs alone.

(Figure 6) Forest Plot: Cumulative meta-analysis of published and unpublished data on Genotype 3 patients on achievement of SVR 12 comparing DAAs with DBV *vs* DAAs alone.

Discussion

Cornerstone of HCV therapeutics has traditionally included Ribavirin as a sentinel therapeutic agent in combination with IFNα. Ribavirin's debut into HCV therapy was heralded following a study that demonstrated its synergism of doubling the efficacy of standard alfa interferon [20]. Further studies corroborated this finding in PEGylated versions of interferon and ribavirin [21,22]. Ribavirin was also found to favorably reduce the relapses and breakthroughs in IFN containing regimens, although actual SVR rates were still suboptimal, closer to 50% [23]. Its role was therefore indispensable, in the IFN use era.

With the advent of IFN-free regimens (DAAs), several trials have proven SVR efficacies of well over 95% with equivocality in response rates for DAA combinations with or without RBV. Such findings prompted a reconsideration on the role of RBV from several well-constructed trials of DAAs with RBV as compared with DAAs alone. Several trials have underscored this line of investigation with DAAs such as pan-genotypic polymerase inhibitor sofosbuvir associated with NS5A inhibitors ledipasvir or daclatasvir (genotype 1, 3, 4), or with a protease inhibitor simeprevir (genotype 1, 4); triple combination paritaprevir boosted with ritonavir (protease inhibitor), ombitasvir (NS5a inhibitor) and quadruple combination of paritaprevir, ritonavir, ombitasvir and dasabuvir, a polymerase inhibitor for genotype 1, 4 patients.

A meta-analysis of trials in the DAA era, was therefore quintessential to demonstrate the renewed role and value of RBV in all DAA trials (without IFN), effect on SVR in combination with DAAs and to determine its overall risk *vs* benefit analysis.

Non-cirrhotics

As majority of patients in the trials were G1 as with the profile of the majority genotype of HCV in US population, this finding is consistent with previously published evidence [13]. Treatment naïve G1 non-cirrhotics in the ION 3 study, 8-wk ledipasvir-sofosbuvir regimen was non-inferior to the 12-wk regimen with RBV [24]. In the ELECTRON study, among treatment-naive patients who received 6 weeks of sofosbuvir, ledipasvir and ribavirin, only 17 of 25 (68%) achieved SVR12 [13]. In overall analysis of all DAA trials the addition of RBV to DAAs did not demonstrate superiority in achieving SVR 12 in non-cirrhotic patients.

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Cirrhotics and treatment experienced patients

For HCV treatment in both compensated and decompensated cirrhosis recent evidence suggests that the addition of ribavirin allows the treatment duration to be limited to 12 weeks in patients with advanced liver disease, including patients with compensated cirrhosis especially if they are treatment-experienced patients. In a meta-analysis of 7 clinical trials which evaluated the safety and efficacy of fixed-dose combination of ledipasvir and sofosbuvir, with and without RBV in 513 treatment-naive and treatment experienced G1 cirrhotics, receiving 12 weeks of treatment (SVR12 rate of 90% without *vs* 96% with ribavirin) [25]. Although 12 weeks of LDV-SOF was safe and effective for treatment-naive patients with HCV genotype 1 and compensated cirrhosis. The relatively lower SVR in treatment-experienced patients treated with 12 weeks of LDV-SOF raised the question of whether these patients would have benefited from adding RBV. DAA without RBV was found to be statistically non-inferior [25]. Grazoprevir-Elbasvir combination without ribavirin for 12 wk is effective in difficult-to-treat G1 and G4 patients. C-Worthy trial demonstrated superior SVR12 rates regardless of the use of RBV or of the extension of treatment duration from 12 to 18 wk in two cohorts of G1 patients, i.e., cohort 1, naive cirrhotic patients and cohort 2 previous null responders with or without cirrhosis. SVR rates without RBV was 97% and 91% in the two cohorts respectively [26]. G1 treatment naïve cirrhotic patients, DAA combination of daclatasvir NS5A pan-genotypic inhibitor, asunaprevir NS3 protease inhibitor and beclabuvir NS5B non- nucleosidic polymerase inhibitor without ribavirin, achieved high SVR rates in naive patients (93%) [27]. However, in treatment experienced cirrhotics RBV demonstrated slightly better SVR with this DAA combination, which did not reach statistical significance [27].

Overall, all DAAs combinations used alone were statistically non-inferior to DAAs with RBV in cirrhotics and treatment experienced patients in achieving SVR 12.

Genotype 3

In G3 patients treated with sofosbuvir and ribavirin for 24 wk in phase III trials, the response rates were 91% in non- cirrhotics and a dismal 68% in cirrhotics, respectively [28]. Sofosbuvir and Daclatasvir without RBV for 12 wk in G3 cirrhotic patients led to a similar poor 63% SVR [29].

Interestingly, recent ASTRA- 3 results, clearly demonstrated DAA combinations in achieving superior SVR rates to DAA combinations with RBV even in G3 cirrhotics [30]. RBV use in G3 based on this data demonstrated non-inferiority of DAAs in comparison with DAAs with RBV. However to convincingly demonstrate DAA superiority without RBV more phase III/ IV studies are needed.

Adverse effects of RBV in DAA combination therapy:

RBV was cause for frequent (up to 50%) morbidity mostly mild-moderate consisting of anemia, infections, insomnia, nausea, diarrhea, headache and pruritus. However there was no RBV related mortality in any of the studies.

Since RBV is contraindicated in patients with CKD with GFR<30, a recent trial C-SURFER high SVR rates with Grazoprevir-Elbasvir is achievable obviating the need for RBV use in this special population [31].

Conclusion

RBV is likely relegated to clinical trials given lack of efficacy to significantly boost SVR responses with new DAA combinations. On weighing their risks *vs* benefits, frequent mild-moderate morbidity can be avoided by avoiding their use except when benefits outweigh the risks in special groups of patients who have failed treatment with DAAs due to resistance or cirrhotics, in whom more data needs to be accrued before clear recommendations can be made.

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