Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Comparative Effectiveness and Safety of Direct-Acting Antiviral Agents for Treatment-Naive Hepatitis C Genotype 1

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Abstract: All possible direct-acting antiviral agent (DAA) regimens for treatment-naive hepatitis C genotype 1 were evaluated by many randomized controlled trials (RCTs). However, the optimum regimen remains inconclusive. We aim to compare interventions in terms of sustained virological response at 12 (SVR12) and 24 (SVR24) weeks after the end of treatment and adverse effects (AEs) (fatigue, headache, nausea, insomnia).

PubMed, Embase, and the Cochrane Library were searched for RCTs until July 31, 2015. We estimated odds ratios (ORs) between treatments on clinical outcomes.

Twenty-two eligible RCTs were included. Compared with peginterferon-ribavirin (PR), daclatasvir plus PR (OR 8.90, \(P \leq 0.001\)), faldaprevir plus PR (OR 3.72, \(P \leq 0.001\)), simeprevir plus PR (OR 3.59, \(P \leq 0.001\)), sofosbuvir plus PR (OR 4.69, \(P \leq 0.001\)) yield a significant effect in improving SVR12. Consistently, simeprevir plus PR (OR 3.49, \(P \leq 0.001\)), sofosbuvir plus PR (OR 4.51, \(P \leq 0.001\)), daclatasvir plus PR (OR 4.77, \(P \leq 0.001\)) also improved the rates of SVR24 significantly compared with PR. With respect to AEs, compared with PR, ledipasvir plus sofosbuvir plus PR (OR 2.13, \(P \leq 0.001\)) confer a significant AE in nausea, whereas daclatasvir plus PR (OR 0.20, \(P \leq 0.001\) and OR 0.18, \(P \leq 0.001\), respectively) lowered the incidence of fatigue and nausea significantly when compared with ledipasvir plus sofosbuvir plus PR.

Daclatasvir plus PR was the most effective in SVR12 and SVR24, but caused an increased AEs profile (headache and insomnia). Combined ledipasvir with sofosbuvir or combination of PR was associated with higher incidence of fatigue and nausea.

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) affects approximately 170 million people worldwide and is a major cause of cirrhosis and hepatocellular carcinoma.1

Since 2007, HCV-related deaths have exceeded those from human immunodeficiency virus infection in the United States.2–3 HCV is classified into 6 major genotypes. Specifically, genotypes 1, 2, and 3 are found worldwide, with subtype 1a predominating in the United States and subtype 1b predominating in Europe, Japan, and China.4–5

To reduce associated mortality and improve health-related quality of life for HCV patients, achievement of sustained virological response (SVR) is a surrogate endpoint for these goals.6–7 Forty-eight weeks of peginterferon and ribavirin (PR) achieves SVR only about 45% of treatment-naive patients with genotype-1 virus.6–8 Adding these oral, direct-acting antiviral (DAA) agents, boceprevir (BCV) or telaprevir (TLV) has been shown to improve this proportion, with SVR achieved in 68% and 75% of HCV patients, respectively.10 In addition, more and more randomized controlled trials (RCTs) recently have shown DAA regimes, such as simprevir (SMV), beclabuvir (BEC), faldaprevir (FDV), sofosbuvir (SOF), daclatasvir (DCV), asunaprevir (ASV), and ledipasvir (LDV) associated with high rates of SVR among patients infected with HCV genotype 1.11–22 However, the addition of these drugs was associated with more adverse events (AEs), including fatigue, headache, and insomnia, which might reduce tolerability and adherence.
Owing to the lack of direct comparisons obtained in clinical trials, there are still some controversies in determining the optimum direct-acting antiviral agents for patients with treatment-naive hepatitis C genotype 1. Therefore, it may be answered theoretically by conducting a very large clinical trial with multiple comparator arms. However, it is unlikely that any single trial will compare all available treatments. On this occasion, network meta-analysis is a potential solution, as it may permit the integration of direct and indirect evidence, allowing us to simultaneously compare different treatments. In doing so, we aimed to summarize a much broader evidence base and to compare such main clinical outcomes or safety profile with major interventions (SMV plus PR, BEC plus PR, TLV plus PR, FDV plus PR, DCV plus PR, LDV plus SOF, LDV plus SOF plus PR, LDV plus PR, SOF plus PR or PR) for treatment-naive hepatitis C genotype 1 patients.

METHODS

Search Strategy

This systematic review is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (Supporting information 1, http://links.lww.com/MD/A743). We identified RCTs (RCTs) published up to July 31, 2015, comparing different strategies for treatment-naive HCV genotype 1 patients by searching the following databases: PubMed, Embase, and the Cochrane Library without any language or date restrictions. We searched the bibliographies of selected articles in an effort to identify any other relevant articles. Two reviewers (G-QZ, Z-LZ) independently assessed the eligibility of all potential abstracts and titles. The study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Selection Criteria

Studies included, fulfilled the following criteria: randomized design irrespective of blinding; studied patients were treatment-naive HCV genotype 1; interventions: combined DAA with PR, combined dual DAAs with and without PR, or PR alone. DAAs included in this review comprised SMV, BEC, TLV, FDV, SOF, DCV, ASV, and LDV; ≥1 of the following outcomes were assessed: SVR at week 12 (SVR12) or 24 (SVR24) after the end of treatment, AEs (fatigue, nausea, insomnia, or headache). The flow diagram of the studies excluded from this analysis is shown in Figure 1. Eligible studies had to be published as full-length articles in peer-reviewed journals. Studies were excluded when assessing other interventions, nonrandomized design, or no usable data from trials.

Data Extraction and Quality Assessment

Data on study-, patient- and treatment-related characteristics were abstracted into an electronic standardized form, by 2 authors independently: study characteristics—first author, time
of publication, geographic location, and centers where study was conducted, duration of follow-up; patient characteristics—age, sex, male proportion; treatment characteristics—dosing and schedule of interventions; outcome assessment—number of patients in intervention and comparator group, and proportion achieving the outcomes of interest (as dichotomous variable); and adverse events—proportion of patients with fatigue, nausea, insomnia, or headache. Any discrepancies regarding the extraction of data were resolved by an additional investigator (M-HZ). When relevant information on design or outcomes was unclear, or when some needed data were unavailable directly from the study, the original authors were contacted for further clarifications and assistance by email.

We assessed the risk of bias of individual studies in the context of the primary outcomes, using the Cochrane Risk of Bias assessment tool. Studies were deemed to be at high, low, or unclear risk of bias by using this tool, which was based on adequacy of sequence generation, allocation concealment, blinding, method of addressing incomplete data, selective reporting, and other biases.

Outcome Assessed

The primary outcome of interest was the relative efficacy of different DAA interventions for treatment-naïve hepatitis C genotype 1 patients in improving SVR12 or SVR24 after the end of treatment. The secondary outcome of interest was the incidence of most common AEs, including fatigue, nausea, insomnia, or headache.

Data Analysis

Traditional pairwise meta-analysis was performed using the method of DerSimonian and Laird random effects model. We calculated the pooled estimates of odds ratios (ORs) and 95% confidence intervals (CIs) of direct comparisons between 2 strategies according to Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Publication bias was examined with the funnel plot method and Begg regression test from pair-wise meta-analysis. $I^2$ (presented as Q) were represented as markers of heterogeneity. $I^2$ values between 30% and 60% were defined as moderate heterogeneity, 60% to 75% as considerable heterogeneity, and values >75% as substantial heterogeneity. Values <30% were considered unimportant.

To incorporate indirect comparisons, we conducted the network meta-analysis within a Bayesian framework using Markov chain Monte Carlo methods in WinBUGS (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom). A network meta-analysis synthesizes all available evidence within a consistent framework, which accounts for multiple comparisons within a trial when there are more than two treatment groups. Detail information of Bayesian methods can be seen in our previous published network meta-analyses. The pooled ORs from the network meta-analysis were compared with corresponding ORs from pairwise random-effects meta-analysis of direct comparisons to assess whether there was inconsistency between direct and indirect comparisons. We assessed the probability that each treatment was the most effective therapy, the second best, and so on, by counting the proportion of simulations in which each treatment had the smallest ORs, the second smallest, and so on. Even if the differences in effect size among treatments obtained were small, clinical decision-making about the choice of treatments can still be suggested based on the probabilities of treatment ranking. We reported the pooled ORs for dichotomous data in terms of SVR12, SVR24, and AEs (fatigue, insomnia, nausea, or headache) with corresponding 95% CIs, and as well as the probabilities of ranking by treatment. Hence, the bayesian analytical approach increased statistical power by integrating both direct and indirect evidence across all interventions.

RESULTS

Characteristics of Trials and Patients

Figure 1 shows the flow chart of the study and summarizes the process of identifying trials. We identified 1961 studies for review of title and abstract. After the initial screening, we excluded 1939 articles that did not meet inclusion criterion. Overall, we used 22 eligible studies for meta-analysis, with a total of 7709 patients who received 1 of the 8 treatment strategies or PR (Figure 2). The duration of treatment ranged from 8 to 48 weeks and the mean age of trial participants was 52.4 years and range from 45 to 58.5 years. Table 1 presents the
| Author (Year) | Region | Mean Age (Range) | Body Mass Index (Range) | Treatments | Treatment Duration | Study Size | SVR12 Treatment/Control | SVR24 Treatment/Control | Treatment/Control | Treatment/Control | Treatment/Control | Treatment/Control | Treatment/Control | Treatment/Control | Adverse Events |
|--------------|--------|------------------|-------------------------|------------|--------------------|------------|------------------------|------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|------------------|
| Afzal et al11 (2014) | United States and Europe | 52.5 (18–80) | 26.75 (18–48) | LDV plus SOF plus PR vs LDV plus SOF | 12–24 wk 12–24 wk | 865 | 98/98 | NR/NR | NR/NR | NR/NR | 16/12 | 37/23 |
| Fried et al13 (2013) | North America, Europe, and Asia-Pacific regions | 46.4 (18–69) | 25.06 (16.8–42.2) | SMV plus PR vs PR | 12–24 wk/24–48 wk | 48 wk | 386 | 82/66 | 81/65 | NR/NR | 46/52 | 28/27 | 42/48 |
| Hayashi et al14 (2014) | Japan | 55.5 (23–69) | 23.75 (16.9–41) | SMV plus PR vs PR | 12/24–48 wk | 48 wk | 183 | 89/62 | 89/57 | NR/NR | NR/NR | NR/NR | NR/NR |
| Hezode et al15 (2009) | France, Germany, the United Kingdom, and Austria | 45 (18–65) | 22.16 (16.9–33.2) | TLV plus PR02 vs PR | 12 wk/24–48 wk | 48 wk | 323 | 72/43 | 55/46 | NR/NR | NR/NR | NR/NR | NR/NR |
| Jacobson et al17 (2011) | International sites | 49 (19–69) | 26.1 (17–48) | TLV plus PR vs PR | 8–12 wk/24–48 wk | 48 wk | 1088 | NR/NR | 72/44 | NR/NR | 28/31 | 57/57 |
| Kowdley et al18 (2014) | United States | 52.3 (20–75) | 28 (18–56) | LDV plus SOF plus PR vs PR | 8 wk | 647 | 93/95 | NR/NR | 25/15 | 18/9 | 35/22 |
| Kwo et al47 (2010) | USA, Canada, and Europe | 47.3 (18–60) | 25.06 (16.8–42.2) | SMV plus PR vs PR | 24–48 wk/28–48 wk | 48 wk | 520 | 63/38 | 46/33 | 45/43 | 62/55 |
| Lauz et al19 (2013) | USA, Europe, North America, and South America | 46.3 (18–73) | 26 (18–53.5) | SMV plus PR vs PR | 12 wk/24–48 wk | 24–48 wk | 391 | 81/50 | NR/NR | 24/31 | 39/37 | 37/42 |
| Pol et al40 (2012) | USA and France | 51 (28–68) | 49.3 (NR) | DCV plus PR vs PR | 24–44 wk | 48 wk | 1097 | 72/25 | 69/25 | NR/NR | 36/50 | 53/75 |
| Rodriguez-Torres et al22 (2013) | United States and Puerto Rico | 45 (18–65) | 28.2 (19–35.6) | SOF plus PR vs PR | 28 days/48 wk | 48 wk | 63 | 71/50 | 73/43 | NR/NR | 35/36 | 45/43 |
| Szulowski et al15 (2014) | United States | 54.9 (18–70) | 25.06 (16.8–42.2) | DCV plus DFV plus PR vs DCV plus PR | 12–24 wk | 12–24 wk | 126 | 96/100 | 95/96 | 14/14 | NR/NR | NR/NR |
| Tatum et al44 (2015) | USA | 48 (22–63) | 28.2 (19–35.6) | BEC plus PR vs PR | 28–48 wk | 48 wk | 391 | 81/50 | NR/NR | 24/31 | 39/37 | 37/42 |
| Zeuzem et al45 (2013) | Europe, Australia, and New Zealand | 47.8 (18–75) | 26.5 (20–30) | BDV plus DFV plus PR vs DFV plus DLV plus PR | 48 wk | 48 wk | 362 | 56/39 | 54/39 | 35/23 | NR/NR | 25/26 |
| Zhu et al46 (2014) | Argentina, Australia, Austria, Canada, Czech Republic, and United States | 46 (18–65) | 28 (21–35) | FDV plus DFV plus DLV plus PR vs FDV plus PR | 24 wk/48 wk | 48 wk | 17/25 | 46/33 | 35/15 | 46/38 |
| Ferenci et al21 (2015) | European countries and Japan | 47.8 (18–70) | 25 (NR) | FDV plus ASV plus BEC plus PR vs DCV plus ASV plus BEC plus PR | 12–24 wk | 24 wk | 781 | 60/23 | 60/23 | NR/NR | NR/NR | 18/24 |
| Nishiguchi et al22 (2015) | N | 52.3 (NR) | 23 (NR) | FDV plus PR plus PR vs PR | 4 wk/48 wk | 48 wk | 16 | NR/NR | 58/50 | 25/25 | 25/25 | NR/NR |
| Izumi et al44 (2015) | Antivir Ther | 55.7 (28–67) | 48.1 (NR) | DCV plus DFV plus PR vs DCV plus PR | 12–24 wk | 48 wk | 25 | NR/NR | 94/75 | 17/25 | 18/30 | NR/NR |
| Lawitz et al19 (2015) | United States, Canada, France, and Australia | 58.5 (19–76) | 25.06 (16.8–42.2) | DCV plus DFV plus PR vs DFV plus DLV plus PR | 8 wk | 8–12 wk | 60 | 100/95 | 100/95 | 100/95 | 41/25 | 14/5 |
| Suzuki et al45 (2014) | Japan | 52.2 (21–66) | 25 (NR) | FDV plus DFV plus DLV plus PR vs DCV plus PR | 24–48 wk | 48 wk | 27 | NR/NR | 18/24 | NR/NR | 18/24 |

BCV = boceprevir, BEC = beclabuvir, DCV = daclatasvir, FDV = faldaprevir, LDV = ledipasvir, NR = not reported, PR = peginterferon and ribavirin, SMV = simeprevir, SOF = sofosbuvir, SVR = sustained virological response, TLV = telaprevir.
TABLE 2. Quality Assessment of Included Studies

| Study                  | Random Sequence Generation (Selection Bias) | Allocation Concealment (Selection Bias) | Blinding of Participants and Personnel (Performance Bias) | Blinding of Outcome Assessment (Detection Bias) | Incomplete Outcome Data (Attrition Bias) | Selective Reporting (Reporting Bias) | Other Bias |
|------------------------|---------------------------------------------|----------------------------------------|--------------------------------------------------------|------------------------------------------------|----------------------------------------|-------------------------------------|------------|
| Afadh et al11 2014     | 0                                           | 0                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 0          |
| Fried et al13 2015     | 0                                           | 1                                      | 0                                                      | 0                                              | 1                                      | 1                                   | 1          |
| Hayashi et al14 2014   | 0                                           | 1                                      | 0                                                      | 0                                              | 0                                      | 0                                   | 0          |
| Hézode et al15 2009    | 0                                           | 1                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 0          |
| Jacobson et al17 2011  | 0                                           | 1                                      | 0                                                      | 0                                              | 0                                      | 0                                   | 1          |
| Kowdley et al16 2014   | 0                                           | 0                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 1          |
| Kwo et al19 2010       | 0                                           | 0                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 0          |
| Lawitz et al39 2013    | 0                                           | 1                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 0          |
| Manns et al40 2014     | 0                                           | 0                                      | 0                                                      | 0                                              | 0                                      | 0                                   | 0          |
| Pol (2012)             | 0                                           | 0                                      | 0                                                      | 0                                              | 0                                      | 0                                   | 0          |
| Poordad et al10 2011   | 0                                           | 0                                      | 2                                                      | 0                                              | 0                                      | 0                                   | 0          |
| Rodriguez-Torres (2013)| 0                                           | 1                                      | 0                                                      | 0                                              | 2                                      | 1                                   | 1          |
| Sulkowski et al43 2014 | 0                                        | 1                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 1          |
| Tatum et al44 2015     | 0                                           | 1                                      | 0                                                      | 2                                              | 0                                      | 0                                   | 1          |
| Zeuzem et al45 2013    | 0                                           | 1                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 1          |
| Sulkowski et al42 2013 | 0                                        | 1                                      | 0                                                      | 0                                              | 0                                      | 0                                   | 1          |
| Ferenci et al12 2015   | 0                                           | 0                                      | 2                                                      | 0                                              | 0                                      | 0                                   | 1          |
| Nishiguchi et al21 2014| 0                                        | 1                                      | 0                                                      | 1                                              | 0                                      | 0                                   | 1          |
| Izumi et al19 2014     | 0                                           | 0                                      | 0                                                      | 2                                              | 0                                      | 0                                   | 1          |
| Lawitz et al19 2014    | 0                                           | 2                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 0          |
| Muir et al20 2015      | 0                                           | 0                                      | 2                                                      | 2                                              | 0                                      | 0                                   | 1          |
| Suzuki et al46 2014    | 0                                           | 1                                      | 0                                                      | 1                                              | 0                                      | 1                                   | 0          |

0 = low risk of selection bias, 1 = moderate risk of selection bias, 2 = high risk of selection bias.

Characteristics of the included trials. We included 9 regimens according to eligible studies: SMV plus PR, BEC plus PR, TLV plus PR, FDV plus PR, DCV plus PR, LDV plus SOF, LDV plus SOF PR, LDV plus PR or PR.10–22,39–46 For the primary outcome of interest, 8 unique comparisons were available for 1611–15,18–20,22,39–45 different trials in terms of SVR24, 14 trials10–11,13,15,18–20,22,39–45 in terms of SVR24. While with respect to AEs, there were 14 trials10–11,13,15,18–20,22,39–45 providing data for fatigue and nausea, 14 trials10,13,16,18–19,21–22,39–42,44,46–47 for headache, and 10 trials10,16,21–22,39–41,42,44,46–47 for insomnia. The trials included were all 2-grouped and the mean study sample was 175.2 patients per group (minimum–maximum 4–520). Supporting Information 2 , http://links.lww.com/MD/A743 showed the results of direct comparisons, which cannot be included in the network geometry. Results of the risk of bias assessment are presented in Table 2.10–22,39–46 All studies reported low or moderate risk of bias in the domains of random sequence generation, allocation concealment, incomplete outcome data, and other bias. For the domains of blinding of participants and personnel, blinding of outcome assessment, and selective reporting, around 45% trials (10/22), 50% trials (11/22), and 4.5% trials (1/22) reported high risk of bias, respectively. In general, trials were considered to be of moderate methodological quality.

Results From Pair-Wise Comparisons

We conducted pairwise meta-analysis for the 7 different comparisons. The weighted ORs for the outcomes, SVR12, and SVR24 were calculated for each comparison. The geometric distribution of RCTs on SVR 12 weeks (Figure 2A) and SVR 24 weeks (Figure 2B) was displayed. For primary outcomes, when compared with PR, all interventions, including SMV plus PR (OR 3.55, 95% CI 2.22–5.69, P < 0.001), FDV plus PR (OR 3.61, 95% CI 1.74–7.51, P < 0.001), SOF plus PR (OR 4.41, 95% CI 1.61–12.04, P < 0.001), BEC plus PR (OR 14.64, 95% CI 10.58, 18.70, P < 0.001), DCV plus PR (OR 7.80, 95% CI 1.75–34.83, P < 0.001) and TLV plus PR (OR 3.42, 95% CI 2.03–5.75, P < 0.001), showed significant clinical efficacy for SVR12, except for LDV plus SOF plus PR, which showed a trend that it was associated with decreasing SVR12 (Table 3). Similarly, for the outcome of SVR24, therapies with BCV plus PR (OR 1.87, 95% CI 0.48–7.26), all interventions were associated with more SVR than PR in 24 weeks after the end of treatments. In the direct comparisons, combined FDV with PR (OR 2.22, 95% CI 0.99–4.96), all interventions were associated with more SVR than PR in 24 weeks after the end of treatments. In the direct comparisons, combined FDV with PR (OR 2.22, 95% CI 0.99–4.96), all interventions were associated with more SVR than PR in 24 weeks after the end of treatments. In the direct comparisons, combined FDV with PR (OR 2.22, 95% CI 0.99–4.96), all interventions were associated with more SVR than PR in 24 weeks after the end of treatments.
Overall, statistical heterogeneity was moderate (Table 2). Owing to the limited RCTs in some comparisons (LDV plus SOF plus PR vs PR, BEC plus PR vs PR, DCV plus PR vs PR, TLV plus PR vs PR), we are unable to assess statistical heterogeneity for those pair-wise comparisons. In the meta-analyses of direct comparison for SVR12, $I^2$ values $<50\%$ were recorded both in comparisons-SMV plus PR vs PR (49.8%) and SOF plus PR vs PR (37.3%), with the exception of only comparison FDV plus PR vs PR (81.8%). Whereas for the outcome of SVR24, $I^2$ values $<50\%$ were recorded in comparisons-BCV plus PR vs PR (0.0%), DCV plus PR vs PR (0.0%), and SOF plus PR vs PR (0.0%), with the exception of comparisons-SMV plus PR vs PR (75.2%) and TLV plus PR vs PR (87.6%).

### TABLE 3. Assessment of Heterogeneity and Publication Bias for Direct Comparisons and Comparison of Outcomes Between Pair-wise Meta-Analysis and Network Meta-Analysis

| Treatment Comparisons | Results of Pair-Wise Meta-Analysis | Results of Network Meta-Analysis | $I^2$ (%) | Begg Test |
|------------------------|-----------------------------------|----------------------------------|----------|-----------|
| **SVR 12 weeks**       |                                   |                                  |          |           |
| LDV plus SOF plus PR vs PR | 0.76 (0.39, 1.48) | 0.78 (0.15, 3.86) | NA | 0.317 |
| SMV plus PR vs PR     | 3.55 (2.22, 5.69) | 3.59 (1.47, 9.99) | 49.8 | 0.602 |
| FDV plus PR vs PR     | 3.61 (1.74, 7.51) | 3.72 (1.21, 10.63) | 81.8 | 0.317 |
| SOF plus PR vs PR     | 4.41 (1.61, 12.04) | 4.69 (1.20, 17.05) | 37.3 | 0.317 |
| BEC plus PR vs PR     | 14.64 (10.58, 18.70) | 13.92 (0.16, 26.15) | NA | NA |
| DCV plus PR vs PR     | 7.80 (1.75, 34.83) | 8.90 (1.06, 84.37) | NA | NA |
| TLV plus PR vs PR     | 3.42 (2.03, 5.75) | 3.49 (0.72, 18.16) | NA | NA |
| LDV plus SOF plus PR vs LDV plus SOF | 0.99 (0.37, 2.67) | 0.75 (0.12, 3.10) | NA | NA |
| **SVR 24 weeks**       |                                   |                                  |          |           |
| BCV plus PR vs PR     | 2.98 (2.38, 3.73) | 2.93 (1.12, 7.36) | 0.0 | 0.317 |
| BEC plus PR vs PR     | 1.87 (0.48, 7.26) | 1.95 (0.31, 12.80) | NA | NA |
| DCV plus PR vs PR     | 4.51 (1.58, 12.86) | 4.77 (1.30, 17.96) | 0.0 | 0.602 |
| FDV plus PR vs PR     | 1.40 (0.14, 13.57) | 1.43 (0.08, 22.74) | NA | NA |
| SMV plus PR vs PR     | 3.56 (1.40, 9.06) | 3.49 (1.35, 9.97) | 75.2 | 0.317 |
| SOF plus PR vs PR     | 4.48 (2.07, 9.68) | 4.51 (1.40, 14.76) | 0.0 | 0.317 |
| TLV plus PR vs PR     | 2.22 (0.99, 4.96) | 2.33 (0.86, 5.65) | 87.6 | 0.317 |

BCV = boceprevir, BEC = beclabuvir, DCV = daclatasvir, FDV = faldaprevir, LDV = ledipasvir, NA = not available, PR = peginterferon and ribavirin, SMV = simeprevir, SOF = sofosbuvir, SVR = sustained virological response, TLV = telaprevir.

Results From the Network Meta-analysis and Consistency of the Network

The ORs for SVR12, SVR24, and AEs (fatigue, insomnia, or headache), respectively, with 95% CIs obtained from the indirect comparisons of the included regimens are showed in Figure 3. As the network framework displayed, Following Figure 3A from left to right, compared with PR, DCV plus PR (OR 8.90, 95% CI 1.06–84.37, $P < 0.001$), FDV plus PR (OR 3.72, 95% CI 1.21–10.63, $P < 0.001$), SMV plus PR (OR 3.59, 95% CI 1.47–8.99, $P < 0.001$), SOF plus PR (OR 4.69, 95% CI 1.40–17.05, $P < 0.001$) yield a significant effect in improving SVR12. In the comparisons between active interventions, although not statistically significant, there was a trend that DCV plus PR was more efficacious than the other 8 treatments, including BEC plus PR (OR 3.90, 95% CI 0.19–74.56), LDV plus SOF (OR 16.18, 95% CI 0.86–471.86), FDV plus PR (OR 2.40, 95% CI

![FIGURE 3. Major clinical efficacy and safety of all treatments according to network meta-analysis. Treatments are reported in alphabetical order. The ORs were estimated in upper and lower triangle comparing column-defining with row-defining treatment. For clinical improvement, ORs >1 favor the column-defining treatment, whereas for adverse effects, ORs <1 favor the row-defining treatment. BCV = boceprevir, BEC = beclabuvir, DCV = daclatasvir, FDV = faldaprevir, LDV = ledipasvir, PR = peginterferon and ribavirin, SMV = simeprevir, SOF = sofosbuvir, SVR = sustained virological response, TLV = telaprevir. (A) SVR12; (B) SVR24.]
0.23–28.86), LDV plus SOF plus PR (OR 11.66, 95% CI 0.81–188.29), SMV plus PR (OR 2.47, 95% CI 0.25–27.45), SOF plus PR (OR 1.90, 95% CI 0.16–25.40), TLV plus PR (OR 5.93, 95% CI 2.54–40.64). Whereas for the outcome of SVR24, compared with PR, BCV plus PR (OR 2.93, 95% CI 1.12–7.36, \( P < 0.001 \)), SMV plus PR (OR 3.49, 95% CI 1.35–9.97, \( P < 0.001 \)), SOF plus PR (OR 4.51, 95% CI 1.40–14.76, \( P < 0.001 \)), DCV plus PR (OR 4.77, 95% CI 1.30–17.96, \( P < 0.001 \)) conferred a significant effect in improving SVR24. Statistical significance was not reached for other comparisons, FDV plus PR (OR 1.43, 95% CI 0.08–22.74), BEC plus PR (OR 1.95, 95% CI 0.31–12.60), and TLV plus PR (OR 2.33, 95% CI 0.86–5.65) also appeared to be likely to have more SVR than PR.

In the assessment of AE outcome (Supporting Information 3, http://links.lww.com/MD/A743), compared with treatment with PR, only combined therapy with LDV plus SOF and PR (OR 2.13, 95% CI 1.02–4.75, \( P < 0.001 \)) confer a significant AE in nausea, whereas in active treatment comparisons, DCV plus PR (OR 0.20, 95% CI 0.05–0.74, \( P < 0.001 \)) and SOF plus PR (OR 0.18, 95% CI 0.04–0.76, \( P < 0.001 \), respectively) provided a significant effect in reducing fatigue and nausea when compared with combined therapy with LDV plus SOF and PR. In addition, compared with FDV plus PR, DCV plus PR (OR 0.14, 95% CI 0.03–0.60, \( P < 0.001 \)) was associated with lower incidence of nausea significantly. Consistently, while for other comparisons among treatments showed no statistical significance, DCV plus PR also showed lower incidence of fatigue and nausea than other treatments. However, in terms of insomnia and headache, although not differing significantly, BEC plus PR was associated with more AEs than BCV plus PR (OR 1.98, 95% CI 0.39–13.45; OR 2.86, 95% CI 0.31–32.89, respectively), PR (OR 1.84, 95% CI 0.39–12.00; OR 3.25, 95% CI 0.45–29.68, respectively), DCV plus PR (OR 1.82, 95% CI 0.25–13.17; OR 3.38, 95% CI 0.33–45.35, respectively), FDV plus PR (OR 2.55, 95% CI 0.47–21.28; OR 3.57, 95% CI 0.32–46.42, respectively), SOF plus PR (OR 2.35, 95% CI 0.37–19.94; OR 4.02, 95% CI 0.33–47.37, respectively).

Finally, we ranked the likelihood of best treatment for each intervention at each of the 9 possible parameters (Figure 4). DCV plus PR (57%) and SOF plus PR (28%) showed the highest likelihood of improvement in SVR 12 weeks (Figure 4), suggesting DCV plus PR and SOF plus PR were more efficacious than the other remaining interventions. Similarly, DCV plus PR (34%) and SOF plus PR (28%) showed a greater probability of being the 2 most effective interventions with respect to patients’ improvement of SVR in 24 weeks, suggesting that DCV plus PR and SOF plus PR were more efficacious than the other interventions. In terms of AEs (insomnia, fatigue, headache, and nausea), DCV plus PR (81%; 70%) reduced the incidence of nausea significantly. However, BEC plus PR (76%) ranked the highest intervention with respect to insomnia and headache, and our ranking suggests that interventions with the safest effects was DCV plus PR (81%; 70%) for nausea and fatigue better than the other remaining interventions. However, BEC plus PR (76%) ranked the highest intervention with respect to insomnia and headache, and our ranking suggests that interventions with the safest effects was DCV plus PR (81%; 70%) for nausea and fatigue, FDV plus PR (40%) for insomnia, and LDV plus SOF (46%) for headache. Supporting Information (4, http://links.lww.com/MD/A743) presents a comparison-adjusted funnel plot for the interventions network, without evidence of asymmetry, which suggests the absence of small-study effects. In addition, the results of Begg test showed all \( P \) values > 0.1, suggesting no publication bias exist (Table 3).
The results of traditional pairwise and network meta-analyses are shown in Table 3. The confidence intervals from both the traditional pairwise meta-analyses and the Bayesian network meta-analyses, although the pooled estimates showed small differences, are in general consistently compatible. Hence, the results of pair-wise and network meta-analyses were consistent.

**DISCUSSION**

In the absence of head-to-head comparisons, we performed a network meta-analysis that evaluates the efficacy and safety of current combinations of DAA with PR regimes available in RCTs for treatment-naïve HCV genotype 1 patients, including SMV plus PR, BEC plus PR, TLV plus PR, FDV plus PR, DCV plus PR, LDV plus SOF, LDV plus SOF plus PR, LDV plus PR, and one monotherapy with PR. Our study found that dual DAA regime, combined therapy with DCV and PR was superior to all combinations of DAA with PR or PR for SVR12, but increased the incidence of insomnia and headache. Consistently, compared with PR, all combinations of single DAA with PR provided more clinical benefits for SVR24. Among the combinations of DAA with PR, DCV plus PR was the most effective in improving the SVR in 24 weeks. Regarding the adverse reactions, DCV plus PR was associated with least incidence of fatigue and nausea. Also, adding LDV and SOF to PR or combined therapy with SOF and LDV showed the increased fatigue or nausea than other combinations of DAA with PR. While in terms of headache and insomnia, adding FDV or LDV to PR yield the least AEs profile followed by SOF plus PR.

Our study has several strengths. The internal validity of our analysis is supported by 3 factors. First, having conducted a rigorous and extensive literature search, we are confident that all relevant RCTs have been properly identified. Second, the most induction trials included in the network are characterized by low risk of bias, assessed by Cochrane Collaboration approach and allowed a reliable synthesis of Bayesian indirect treatment effect estimates. Third, most RCTs are conceptually homogeneous in terms of study design and patient characteristics. Besides, we assessed the most comprehensive DAA regimes for treatment-naïve HCV patients, including dual or triple DAA, of which the effect was not explored by other meta-analyses. In addition, as the recent trend in HCV treatment is heading toward all-oral treatment, the effect of treatment with PR, added to the combination of DAAs, was investigated in most studies. We analyzed the most comprehensive treatments with DAAs or combination of PR by using network meta-analysis, which can combine direct and indirect evidence.

However, the strengths of this network meta-analysis should be weighed against some limitations. First, the limited number of trials and the absence of head-to-head comparisons increase the uncertainty of the findings and conclusions. Second, the indirect estimates were often very similar to those obtained in the direct comparisons because only single comparisons were available for the majority of the cases. This resulted in a less conventional geometry where our network of trials did not have any closed loops. Third, we could not assess publication bias for most comparisons. Finally, some regimes, such as DCV plus ASV plus BEC and DCV plus ASV plus BEC, were not included in the network geometry. Hence, the effects of triple DAA treatments cannot be evaluated among the other combinations of DAA and PR. However, despite of these limitations, this network meta-analysis provides the large-scale comparative information on the major clinical outcome profiles of different interventions in current use.

In the direct meta-analysis, we find that the effects of DAA plus PR, including DCV plus PR, FDV plus PR, SMV plus PR, SOF plus PR, have been demonstrated by several studies, which consistently concluded that it provided more clinical benefits significantly in terms of SVR12 or SVR24 than monotherapy with PR for patients with treatment-naïve HCV genotype 1. Two RCTs reported that dual DAAs (LDV plus SOF) with or without PR were highly effective in previously untreated patients with HCV genotype 1 infection. However, owing to the lack of clinical trials comparing PR with dual DAAs with or without PR, the effects of LDV plus SOF with or without PR still unknown when compared with PR. We are surprised to find that from the indirect evidence, PR was more efficacious than LDV plus SOF with or without PR for SVR 12 weeks. One possible explanation was that adding DAAs to PR may increase more AEs (fatigue, headache, nausea, or insomnia) so that it appeared to devalue the clinical efficacy. In the indirect meta-analyses, we showed that DCV plus PR and SOF plus PR were the 2 most effective therapies in improving SVR in 12 or 24 weeks, which are consistent with recent published systematic reviews. Two reviews demonstrated that especially SOF plus PR was recommended for the first-line drug of treatment-naïve HCV genotype 1. However, owing to lack of comprehensive analytical approach in the previous studies, comparing the efficacy of different DAA regimes need to use Bayesian analytical approach, which can be rectified in this study. Although our results did not show any significant benefit of DCV plus PR over SOF plus PR, but it had less AEs (fatigue and nausea) than SOF plus PR.

In summary, our analysis shows the superiority of using DAA regime-DCV plus PR treatment in clinical efficacy for patients with treatment-naïve HCV, but should weigh its increased AEs (headache and insomnia). The analysis also provides indirect evidence that combined therapy LDV with SOF or combination of PR was associated with higher incidence of fatigue and nausea. Direct head-to-head comparisons between dual DAAs and triple DAAs regimes should be the top priority on the research agenda, as well as large number of participants and evaluation in long-term follow-up, which is a key consideration in determining the comparative effectiveness of DAAs agents for treatment-naïve HCV genotype 1.

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