Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

# 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*

*Gui-Qi Zhu, MD, Zhuo-Lin Zou, MD, Ji-Na Zheng, MD, Da-Zhi Chen, MD, Tian-Tian Zou, MD, Ke-Qing Shi, MD, PhD, and Ming-Hua Zheng, MD, PhD*

**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, $P < 0.001$), faldaprevir plus PR (OR 3.72, $P < 0.001$), simeprevir plus PR (OR 3.59, $P < 0.001$), sofosbuvir plus PR (OR 4.69, $P < 0.001$) yield a significant effect in improving SVR12. Consistently, simeprevir plus PR (OR 3.49, $P < 0.001$), sofosbuvir plus PR (OR 4.51, $P < 0.001$), daclatasvir plus PR (OR 4.77, $P < 0.001$) 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, $P < 0.001$) confer a significant AE in nausea, whereas daclatasvir plus PR (OR 0.20, $P < 0.001$ and OR 0.18, $P < 0.001$, 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.

(*Medicine* 95(9):e3004)

**Abbreviations**: ASV = asunaprevir, BCV = boceprevir, BEC = beclabuvir, CI = confidence interval, DCV = daclatasvir, FDV = faldaprevir, LDV = ledipasvir, OR = odds ratio, PR = peginterferon-ribavirin, RCT = randomized controlled trials, SMV = simeprevir, SOF = sofosbuvir, SVR = sustained virological response, TLV = telaprevir.

## 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.[8–9] 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 simeprevir (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.

Editor: Ahmed El Shamy.
Received: December 12, 2015; revised: January 22, 2016; accepted: February 11, 2016.
From the Department of Infection and Liver Diseases, Liver Research Center, the First Affiliated Hospital of Wenzhou Medical University (G-QZ, J-NZ, D-ZC, T-TZ, K-QS, M-HZ), School of the First Clinical Medical Sciences, Wenzhou Medical University, Wenzhou (G-QZ, J-NZ, T-TZ), Department of Infection Diseases, the First Hospital of Jiaxing, Jiaxing (Z-LZ), Queen Mary Hospital, University of Hong Kong, Hong Kong (D-ZC), and Institute of Hepatology (K-QS, M-HZ), Wenzhou Medical University, Wenzhou, China.
Correspondence: Ming-Hua Zheng, MD, PhD, Department of Infection and Liver Diseases, Liver Research Center, the First Affiliated Hospital of Wenzhou Medical University; Institute of Hepatology, Wenzhou Medical University. No. 2 Fuxue Lane, Wenzhou 325000, China (e-mail: zhengmh@wmu.edu.cn).
G-QZ and Z-LZ are the co-first authors.
Authors' contributions: G-QZ, K-QS, Z-LZ, and M-HZ designed the study. G-QZ and Z-LZ screened studies and extracted data. J-NZ, D-ZC, and T-TZ did the statistical analyses. K-QS and T-TZ prepared figures. G-QZ, Z-LZ, K-QS, and M-HZ reviewed the results, interpreted data, and wrote the manuscript. All authors saw and approved the final version of the paper.
This work was supported with grants from the National Natural Science Foundation of China (81500665), Health Bureau of Zhejiang Province (2010KYB070), Research Foundation of Education Bureau of Zhejiang Province (Y201009942), and Project of New Centur9 551 Talent Nurturing in Wenzhou.
The authors have no conflicts of interest to disclose.
Supplemental Digital Content is available for this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003004

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.[23–25] In doing so, we aimed to summarize a much broader evidence base and to compare such main clinical outcomes or safety profile with 9 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).[26] We identified RCTs (RCTs) published up to July 31, 2015, comparing different strategies for treatment-naïve hepatitis C 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-naïve 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 a electronic standardized form, by 2 authors independently: study characteristics—first author, time

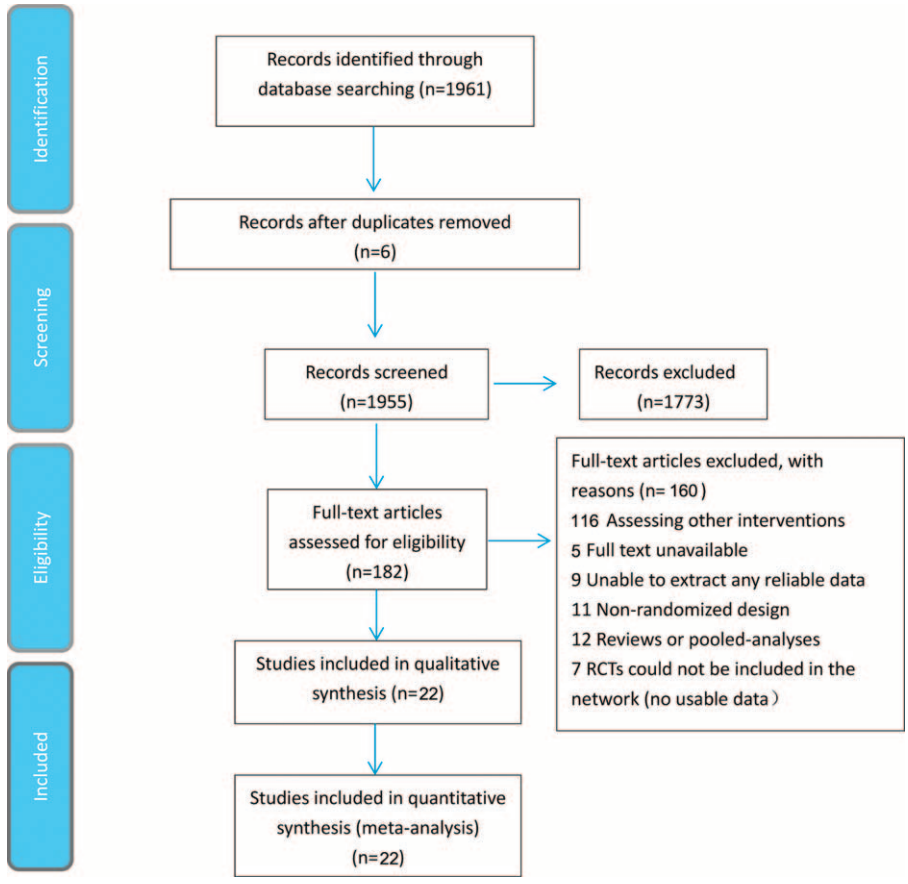


**FIGURE 1.** Literature search and selection.

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.[27] 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.[28]

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,[29] which accounts for multiple comparisons within a trial when there are more than two treatment groups.[30–31] Detail information of Bayesian methods can be seen in our previous published network meta-analyses.[32–38] The pooled ORs from the network meta-analysis were compared with corresponding ORs from pair-wise 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

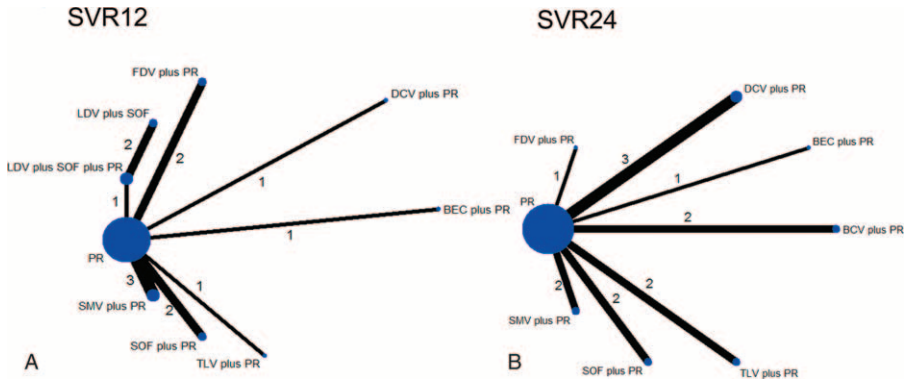


**FIGURE 2.** Evidence network of eligible comparisons for network meta-analysis. The numbers along the link lines indicate the number of trials or pairs of trial arms. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible controlled trials. The width of the lines represents the cumulative number of trials for each comparison and the size of every node is proportional to the number of enrolled participants (sample size). Different nodes referred to different interventions accordingly. 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.

**TABLE 1.** Characteristics of Included Studies

| Author (Year) | Region | Mean Age (Range) | Body Mass Index (Range) | Treatments | Treatment Duration | | Study Size | SVR12 | SVR24 | Adverse Events | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Treatment | Control | | Treatment/ Control | Treatment/ Control | Insomnia Treatment/ Control | Headache Treatment/ Control | Nausea Treatment/ Control | Fatigue Treatment/ Control |
| Afdhal et al[11] (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 al[13] (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 al[14] (2014) | Japan | 55.5 (23–69) | 22.16 (16.9–33.2) | 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 al[15] (2009) | France, Germany, the United Kingdom, and Austria | 45 (18–65) | 23.75 (17–41) | TLV plus PR02 vs PR | 12 wk/12–24 wk | 48 wk | 323 | 72/43 | 55/46 | NR/NR | NR/NR | 42/40 | 29/37 |
| Jacobson et al[17] (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 | NR/NR | 28/31 | 57/57 |
| Kowdley et al[18] (2014) | United States | 52.3 (20–75) | 28 (18–56) | LDV plus SOF plus PR vs PR | 8 wk | 8–12 wk | 647 | 93/95 | NR/NR | NR/NR | 25/15 | 18/9 | 35/22 |
| Kwo et al[47] (2010) | USA, Canada, and Europe | 47.3 (18–60) | NR | BCV plus PR vs PR | 24–48 wk/28–48 wk | 48 wk | 520 | NR/NR | 63/38 | NR/NR | 46/43 | 45/43 | 62/55 |
| Lawitz et al[39] (2013) | USA | 49.6 (18–70) | 27.1 (NR) | SOF plus PR vs PR | 12 wk/24–48 wk | 24–48 wk | 121 | 91/58 | 87/58 | 35/38 | 37/58 | 38/35 | 67/54 |
| Manns et al[40] (2014) | Europe, North America, and South America | 46.3 (18–73) | 26 (18.1–53.5) | SMV plus PR vs PR | 12 wk/24–48 wk | 24–48 wk | 391 | 81/50 | NR/NR | 24/31 | 39/37 | NR/NR | 37/42 |
| Pol et al[41] (2012) | USA and France | 51 (28–68) | NR | DCV plus PR vs PR | 48 wk | 48 wk | 48 | 72/25 | 69/25 | NR/NR | 53/25 | 36/50 | 53/75 |
| Poordad et al[10] (2011) | N | 49.3 (NR) | NR | BCV plus PR vs PR | 24–44 wk | 48 wk | 1097 | NR/NR | 65/38 | 36/50 | 46/42 | 46/42 | 55/60 |
| Rodriguez-Torres et al[22] (2013) | United States (and Puerto Rico) | 45 (18–65) | 28.2 (19.3–35.6) | SOF plus PR vs PR | 28 days/48 wk | 48 wk | 63 | 71/50 | 73/43 | 33/33 | 31/14 | 35/36 | 45/43 |
| Sulkowski et al[43] (2014) | United States | 54.9 (18–70) | NR | DCV plus SOF plus PR vs DCV plus SOF | 12–24 wk | 12–24 wk | 126 | 96/100 | 95/96 | 14/14 | NR/NR | NR/NR | NR/NR |
| Tatum et al[44] (2015) | N | 48 (22–63) | 28 (21–35) | BEC plus PR vs PR | 48 wk | 48 wk | 39 | 58/38 | 54/NR | NR/NR | 46/23 | 35/15 | 46/38 |
| Zeuzem et al[45] (2013) | Europe, Australia, and New Zealand. | 47.8 (18–75) | 25.2 (20–30) | FDV plus DLV plus PR vs DCV plus DLV | 16–40 wk | 28 wk | 362 | 60/39 | NR/NR | 35/23 | NR/NR | NR/NR | 23/26 |
| Sulkowski et al[42] (2013) | Argentina, Australia, Austria, Canada, Czech Republic, and United States | 46 (18–65) | 26 (22–32) | FDV plus PR vs PR | 24 wk/48 wk | 48 wk | 429 | 76/56 | NR/NR | NR/NR | 35/38 | 42/20 | 25/34 |
| Ferenci et al[12] (2015) | European countries and Japan | 47.8 (18–70) | 25 (NR) | FDV plus PR vs PR | 12–24 wk | 24 wk | 781 | 60/23 | NR/NR | 18/24 | NR/NR | NR/NR | NR/NR |
| Nishiguchi et al[21] (2014) | N | 52.3 (NR) | 23 (NR) | FDV plus PR vs PR | 4 wk/48 wk | 48 wk | 16 | NR/NR | 58/50 | NR/NR | 25/25 | 25/25 | NR/NR |
| Izumi et al[16] (2014) | Antivir Ther | 55.7 (28–67) | NR | DCV plus PR vs PR | 24–48 wk | 48 wk | 25 | NR/NR | 94/75 | 17/25 | 18/50 | NR/NR | 35/50 |
| Lawitz et al[19] (2014) | USA | 48.1 (NR) | 28.9 (NR) | LDV plus SOF plus PR vs LDV plus SOF | 8 wk | 8–12 wk | 60 | 100/95 | NR/NR | 41/25 | 14/5 | 10/8 | NR/NR |
| Muir et al[20] (2015) | United States, Canada, France, and Australia. | 58.5 (19–76) | NR | DCV plus ASV plus BEC plus PR vs DCV plus ASV plus BEC | 12 wk | 12 wk | 112 | 98/93 | NR/NR | NR/NR | NR/NR | NR/NR | NR/NR |
| Suzuki et al[46] (2014) | Japan | 52.2 (21–66) | NR | DCV plus PR vs PR | 24–48 wk | 48 wk | 27 | NR/NR | 79/63 | 26/13 | 53/63 | 11/38 | 16/38 |

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

| | 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 |
|---|---|---|---|---|---|---|---|
| Afdhal et al[11] 2014 | 0 | 0 | 2 | 2 | 0 | 0 | 0 |
| Fried et al[13] (2013) | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| Hayashi et al[14] (2014) | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Hézode et al[15] (2009) | 0 | 1 | 2 | 2 | 0 | 0 | 0 |
| Jacobson et al[17] (2011) | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Kowdley et al[18] (2014) | 0 | 0 | 2 | 2 | 0 | 0 | 1 |
| Kwo et al[47] (2010) | 0 | 0 | 2 | 2 | 0 | 0 | 0 |
| Lawitz et al[39] (2013) | 0 | 0 | 2 | 2 | 0 | 0 | 0 |
| Manns et al[40] (2014) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pol (2012) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Poordad et al[10] (2011) | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Rodriguez-Torres (2013) | 0 | 1 | 0 | 0 | 0 | 2 | 1 |
| Sulkowski et al[43] (2014) | 0 | 1 | 2 | 2 | 0 | 0 | 1 |
| Tatum et al[44] (2015) | 0 | 1 | 0 | 2 | 0 | 0 | 1 |
| Zeuzem et al[45] (2013) | 0 | 1 | 2 | 2 | 0 | 0 | 0 |
| Sulkowski et al[42] (2013) | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Ferenci et al[12] (2015) | 0 | 0 | 0 | 2 | 0 | 0 | 1 |
| Nishiguchi et al[21] (2014) | 0 | 1 | 0 | 1 | 0 | 0 | 1 |
| Izumi et al[16] (2014) | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Lawitz et al[19] (2014) | 0 | 0 | 2 | 2 | 0 | 0 | 0 |
| Muir et al[20] (2015) | 0 | 0 | 2 | 2 | 0 | 0 | 1 |
| Suzuki et al[46] (2014) | 0 | 1 | 0 | 1 | 0 | 0 | 1 |

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 plus PR, LDV plus PR or PR.[10–22,39–46] For the primary outcome of interest, 8 unique comparisons were available for 16[11–15,18–20,22,39–45] different trials in terms of SVR12, 14 trials[10–11,13–18,21–22,39,41,43,46] in terms of SVR24. While with respect to AEs, there were 14 trials [10–11,13,15,17–19,21–22,39,41–42,44,46–47] providing data for fatigue and nausea, 14 trials [10,13,16,18–19,21–22,39–42,44,46–47] for headache, and 10 trials [10,16,21–22,39,41–42,44,46–47] 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 2.98, 95% CI 2.38–3.73, $P < 0.001$), DCV plus PR (OR 4.51, 95% CI 1.58–12.86, $P < 0.001$), SMV plus PR (OR 3.56, 95% CI 1.40–9.06, $P < 0.001$) and SOF plus PR (OR 4.48, 95% CI 2.07–9.68, $P < 0.001$) all provided significant benefits in improving SVR24 when compared with PR (Table 2), whereas for BEC plus PR (OR 1.87, 95% CI 0.48–7.26), FDV plus PR OR 1.40, 95% CI 0.14–13.57), and TLV plus 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 DLV and PR (OR 0.43, 95% CI 0.23–0.81, $P < 0.001$) provided significant benefits in improving SVR in 12 weeks compared with DCV plus DLV. Whereas for other comparisons, DCV plus ASV plus BEC (OR 0.25, 95% CI 0.03–2.27) plus PR was more efficacious than DCV plus ASV plus BEC for SVR12. Consistently, DCV plus SOF plus PR (OR 1.26, 95% CI 0.25–6.52) was also more efficacious than DCV plus

**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, 8.99) | 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, 12.60) | 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.

SOF for SVR24 (Supporting Information 2, http://links.lww.com/MD/A743).

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%).

## 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 1.20–17.05, $P < 0.001$) 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

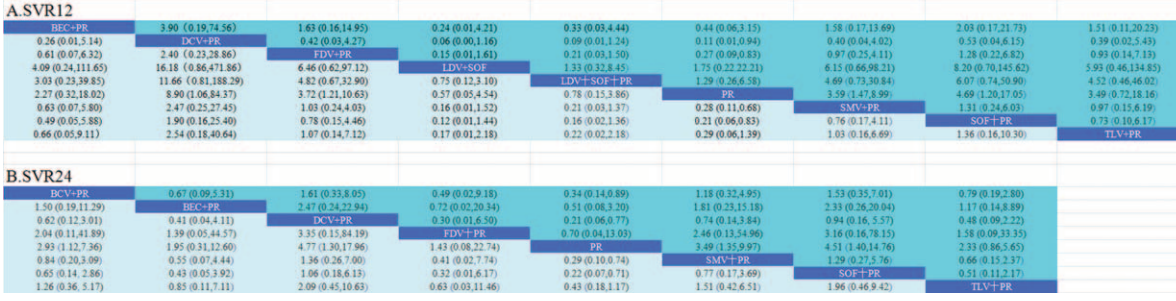


**FIGURE 3.** Major clinical efficacy and safety of all treatments according to network meta-analysis. Treatments are reported in alphabetical order. The ORs were estimated in upper and lower triangle comparing column-defining with row-defining treatment. For clinical improvement, ORs >1 favor the column-defining 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.

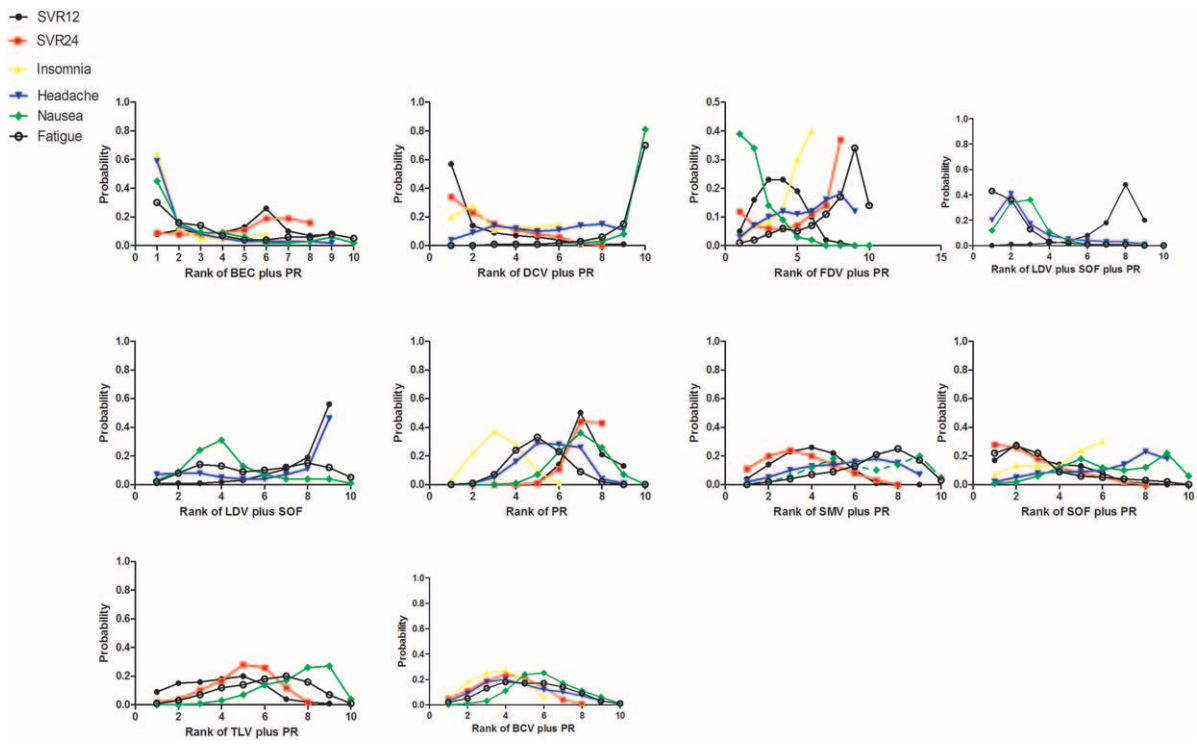


**FIGURE 4.** Rankograms showing probability of each strategy having each specific rank (1–4) for SVR12 or SVR 24. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on. Rank 1 is best and rank N is worst. BCV = boceprevir, BEC = beclabuvir, DCV = daclatasvir, FDV = faldaprevir, LDV = ledipasvir, PR = peginterferon and ribavirin, SMV = simeprevir, SOF = sofosbuvir, SVR = sustained virological response, TLV = telaprevir.

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 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 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 regimens 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,[48–54] 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.[11,19] 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.[55–56] 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 regimens 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.

## REFERENCES


1. Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol.* 2006;45:529–538.
2. Deuffic-Burban S, Poynard T, Sulkowski MS, et al. Estimating the future health burden of chronic hepatitis C and human immunodeficiency virus infections in the United States. *J Viral Hepatitis.* 2007;14:107–115.
3. Kanwal F, Hoang T, Kramer JR, et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. *Gastroenterology.* 2011;140:1182–1188e1181.
4. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology (Baltimore, Md ).* 2009;49:1335–1374.
5. Negro F, Alberti A. The global health burden of hepatitis C virus infection. *Liver Int.* 2011;31(Suppl 2:):1–3.
6. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology (Baltimore, Md ).* 2007;45:579–587.

7. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med.* 2007;147:677–684.
8. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med.* 2002;347:975–982.
9. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med.* 2004;140:346–355.
10. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med.* 2011;364: 1195–1206.
11. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl j Med.* 2014;370: 1889–1898.
12. Ferenci P, Asselah T, Foster GR, et al. STARTVerso1: A randomized trial of faldaprevir plus pegylated interferon/ribavirin for chronic HCV genotype-1 infection. *J Hepatol.* 2015;62:1246–1255.
13. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology (Baltimore, Md).* 2013;58:1918–1929.
14. Hayashi N, Izumi N, Kumada H, et al. Simeprevir with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1 patients in Japan: CONCERTO-1, a phase III trial. *J Hepatol.* 2014;61:219–227.
15. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med.* 2009;360:1839–1850.
16. Izumi N, Yokosuka O, Kawada N, et al. Daclatasvir combined with peginterferon alfa-2a and ribavirin in Japanese patients infected with hepatitis C genotype 1. *Antivir Ther.* 2014;19:501–510.
17. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med.* 2011;364:2405–2416.
18. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014;370:1879–1888.
19. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet.* 2014;383:515–523.
20. Muir AJ, Poordad F, Lalezari J, et al. Daclatasvir in combination with asunaprevir and beclabuvir for hepatitis C virus genotype 1 infection with compensated cirrhosis. *JAMA.* 2015;313:1736–1744.
21. Nishiguchi S, Sakai Y, Kuboki M, et al. Safety and efficacy of faldaprevir with pegylated interferon alfa-2a and ribavirin in Japanese patients with chronic genotype-1 hepatitis C infection. *Liver Int.* 2014;34:78–88.
22. Rodriguez-Torres M, Lawitz E, Kowdley KV, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naive patients with HCV genotype 1: a randomized 28-day, dose-ranging trial. *J Hepatol.* 2013;58:663–668.
23. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ.* 2003;326:472.
24. Ades AE, Sculpher M, Sutton A, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. *Pharmacoeconomics.* 2006;24:1–19.
25. Sutton A, Ades AE, Cooper N, et al. Use of indirect and mixed treatment comparisons for technology assessment. *Pharmacoeconomics.* 2008;26:753–767.
26. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8:336–341.
27. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343:d5928.
28. Lee MD. On the complexity of additive clustering models. *J Mathematical Psychol.* 2001;45:131–148.
29. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 1: introduction. *Med Decis Making.* 2013;33:597–606.
30. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making.* 2013;33:607–617.
31. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. *BMC Med Res Methodol.* 2010;10:54.
32. Zhu GQ, Huang S, Huang GQ, et al. Optimal drug regimens for primary biliary cirrhosis: a systematic review and network meta-analysis. *Oncotarget.* 2015;6:24533–24549.
33. Zhu GQ, Shi KQ, Huang GQ, et al. A network meta-analysis of the efficacy and side effects of udca-based therapies for primary sclerosing cholangitis. *Oncotarget.* 2015;6:26757–26769.
34. Zhu GQ, Shi KQ, Huang S, et al. Network meta-analysis of randomized controlled trials: efficacy and safety of UDCA-based therapies in primary biliary cirrhosis. *Medicine.* 2015;94:e609.
35. Zhu GQ, Shi KQ, Huang S, et al. Systematic review with network meta-analysis: the comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. *Aliment Pharmacol Ther.* 2015;41:624–635.
36. Zhu GQ, Shi KQ, You J, et al. Systematic review with network meta-analysis: adjuvant therapy for resected biliary tract cancer. *Aliment Pharmacol Ther.* 2014;40:759–770.
37. Zhu GQ, Shi KQ, Yu HJ, et al. Optimal adjuvant therapy for resected hepatocellular carcinoma: a systematic review with network meta-analysis. *Oncotarget.* 2015;6:18151–18161.
38. Zhu GQ, You J, Shi KQ, et al. Systematic review with network meta-analysis: adjuvant chemotherapy for resected colorectal liver metastases. *Medicine.* 2015;94:e379.
39. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis.* 2013;13:401–408.
40. Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2014;384:414–426.
41. Pol S, Ghalib RH, Rustgi VK, et al. Daclatasvir for previously untreated chronic hepatitis C genotype-1 infection: a randomised, parallel-group, double-blind, placebo-controlled, dose-finding, phase 2a trial. *Lancet Infect Dis.* 2012;12:671–677.
42. Sulkowski MS, Asselah T, Lalezari J, et al. Faldaprevir combined with pegylated interferon alfa-2a and ribavirin in treatment-naive patients with chronic genotype 1 HCV: SILEN-C1 trial. *Hepatology (Baltimore, Md ).* 2013;57:2143–2154.
43. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med.* 2014;370:211–221.

44. Tatum H, Thuluvath PJ, Lawitz E, et al. A randomized, placebo-controlled study of the NS5B inhibitor beclabuvir with peginterferon/ribavirin for HCV genotype 1. *J Viral Hepatitis.* 2015;22: 658–664.

45. Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. *N Engl J Med.* 2013;369:630–639.

46. Suzuki F, Toyota J, Ikeda K, et al. A randomized trial of daclatasvir with peginterferon alfa-2b and ribavirin for HCV genotype 1 infection. *Antivir Ther.* 2014;19:491–499.

47. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet.* 2010;376:705–716.

48. Beuers U, Spengler U, Kruis W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. *Hepatology (Baltimore, Md ).* 1992;16:707–714.

49. De Maria N, Colantoni A, Rosenbloom E, et al. Ursodeoxycholic acid does not improve the clinical course of primary sclerosing cholangitis over a 2-year period. *Hepato-gastroenterology.* 1996;43:1472–1479.

50. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med.* 1997;336:691–695.

51. Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology (Baltimore, Md).* 2009;50:808–814.

52. Mitchell SA, Bansi DS, Hunt N, et al. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology.* 2001;121:900–907.

53. Olsson R, Boberg KM, de Muckadell OS, et al. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology.* 2005;129:1464–1472.

54. Sinakos E, Marschall HU, Kowdley KV, et al. Bile acid changes after high-dose ursodeoxycholic acid treatment in primary sclerosing cholangitis: Relation to disease progression. *Hepatology (Baltimore, Md).* 2010;52:197–203.

55. Feeney ER, Chung RT. Antiviral treatment of hepatitis C. *BMJ (Clinical research ed ).* 2014;348:g3308.

56. Kohli A, Shaffer A, Sherman A, et al. Treatment of hepatitis C: a systematic review. *Jama.* 2014;312:631–640.