2018년 8월
박사학위 논문

C형 간염 환자에서 direct-acting antiviral(DAA) 기반 치료요법의 유효성 및 안전성 비교연구: 무작위배정 비교임상시험에 근거한 체계적 문헌고찰 및 메타분석

조 선 대 학 교 대 학 원

약 학 과

양 영 모

2018년 8월 박사학위논문

C형 간염 환자에서 direct-acting antiviral(DAA) 기반 치료요법의 유효성 및 안전성 비교연구: 무작위배정 비교임상시험에 근거한 체계적 문헌고찰 및 메타분석

양 영 모

C형 간염 환자에서 direct-acting antiviral(DAA) 기반 치료요법의 유효성 및 안전성 비교연구: 무작위배정 비교임상시험에 근거한 체계적 문헌고찰 및 메타분석

Comparative Study of Efficacy and Safety of Direct-acting Antiviral(DAA)-based Therapies in Hepatitis C Virus-infected Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials

2018년 8월 24일

조 선 대 학 교 대 학 원

약 학 과

양 영 모

C형 간염 환자에서 direct-acting antiviral(DAA) 기반 치료요법의 유효성 및 안전성 비교연구: 무작위배정 비교임상시험에 근거한 체계적 문헌고찰 및 메타분석

지도교수 최 은 주

이 논문을 약학 박사학위신청 논문으로 제출함

2018년 4월

조 선 대 학 교 대 학 원

약 학 과

양 영 모

양영모의 박사학위논문을 인준함

위원장 조선대학교 교 수 유 진 철 (인)

위 원 전남대학교 교 수 이 익 수 (인)

위 원 조선대학교 교 수 홍 준 희 (인)

위 원 조선대학교 교 수 지 준 필 (인)

위 원 조선대학교 교 수 최 은 주 (인)

2018년 6월

조 선 대 학 교 대 학 원

Table of Contents

List of Tables

List of Figures

ABSTRACT

Comparative Study of Efficacy and Safety of Direct-acting Antiviral(DAA)-based Therapies in Hepatitis C Virus-infected Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials

Young-Mo Yang
Advisor : Eun Joo Choi, Pharm.D., Ph.D.
Department of Pharmacy,
The Graduate School of Chosun University

Background: With the advent of oral direct-acting antivirals (DAAs), all oral treatments have been available for the treatment of patients with HCV infection, and it can be considered as a completely curable disease in the near future. The objectives of this systematic review and meta-analysis were to investigate the efficacy and safety of DAA-based regimens in HCV-infected patients and to provide our clinical perspectives on these regimens.

Methods: A literature search of randomized clinical trials published in PubMed and KoreaMed was performed to identify studies assessing the efficacy and safety of DAA-based regimens. A fixed-effects or random-effects meta-analysis was conducted, and heterogeneity was quantified using the I^2 statistic.

Results: A total of 31 clinical articles were examined in this study. Instead of sofosbuvir (SOF)-based regimens, various oral regimens including DAAs with different mode of actions (e.g., glecaprevir [GLE]/pibrentasvir [PIB], SOF/velpatasvir [VEL]/voxilaprevir [VOX], elbasvir [EBV]/grazoprevir [GZR], ombitasvir [OBV]/paritaprevir [PTV]/ritonavir [RTV]/dasabuvir [DSV]) are available currently. These regimens show better efficacy and safety with the high rates of sustained virologic response 12 weeks after the end of treatment (SVR12) and good tolerability. They also shorten the treatment of

duration to 8 or 12 weeks. The combinational regimen of GLE/PIB (300/120 mg) once daily for 8 or 12 weeks was highly effective for patients with HCV genotype 1-6 infection, regardless of the presence of cirrhosis. The combinational regimen of SOF/VEL/VOX (400/100/100 mg) once daily for 12 weeks showed high SVR12 rate for the treatment of patients with HCV genotype 1-6 infection who had previously received DAA-containing regimens, even including NS5A inhibitors. This SOF/VEL/VOX regimen for 8 weeks is also likely to be a good option in HCV-infected patients who have difficulty in completing a longer-duration regimen. The combinational regimen of EBV/GZR (50/100 mg) once daily for 12 weeks may be a good option for HCV genotype 1- or 4-infected patients with cirrhosis, chronic kidney disease (CKD), HIV co-infection, inherited blood disorders, and/or prior failure to peg-interferon (pegIFN)-containing therapy. In case of HCV genotype 1a-infected patients with NS5A RASs at baseline, EBV/GZR + RBV for 16 weeks can be used to achieve a high SVR12 rate. Additionally, the availability of pegIFN-free combination regimens with 2 or 3 DAAs has led to high SVR12 rates in special populations such as patients with HCV infection and CKD and those with HCV/HIV co-infection.

Conclusion: The results from this study suggest that DAA-based treatment regimens for HCV-infected patients, including those with cirrhosis, CKD, or HIV co-infection, show high efficacy and improved safety. However, it is important to closely monitor DAA-associated adverse events and drug-drug interactions that may negatively affect DAA efficacy and adherence. Currently, HCV therapies are transitioning from HCV genotype specific regimens to pan-genotypic regimens such as GLE/PIB and SOF/VEL/VOX.

Keywords: hepatitis C, direct-acting antiviral, efficacy, safety, drug-drug interaction

국문초록

C형 간염 환자에서 direct-acting antiviral(DAA) 기반 치료요법의 유효성 및 안전성 비교연구: 무작위배정 비교임상시험에 근거한 체계적 문헌고찰 및 메타분석

양 영 모

지도교수 : 최 은 주, Pharm.D., Ph.D.

조선대학교 대학원 약학과

연구배경: Direct-acting antivirals (DAAs)가 널리 상용화된 이후, C형 간염 바이러스(hepatitis C virus, HCV) 감염 환자 치료에 경구투여 약물만의 사용이 가능해졌으며, 이로 인해 가까운 미래에 HCV 감염이 완치 가능한 질병으로 여겨지고 있다. 본 연구에서는 체계적 문헌고찰과 메타분석을 통해 HCV 감염 환자에서 DAA 기반 병합요법의 유효성 및 안전성을 평가하고, 이러한 요법에 대한 임상적 견해를 기술하고자 하였다.

연구방법: DAA 기반 병합요법의 유효성 및 안전성을 평가한 무작위배정 비교임상시험을 수집하기 위해 PubMed와 KoreaMed를 활용하여 체계적 문헌고찰을 수행하였다. 고정효과 모델(fixed-effects model) 또는 변량효과 모델(random-effects model)을 활용하여 메타분석을 실시하였으며, 이질성(heterogeneity)을 정량적으로 분석하기 위해 I^2 통계량을 활용하였다.

연구결과: 본 연구에서는 총 31편의 임상논문을 평가하였다. Sofosbuvir(SOF) 기반 병합요법 대신에, 작용기전(mode of actions)이 다른 DAA 기반 병합요법(예: glecaprevir [GLE]/pibrentasvir [PIB], SOF/velpatasvir [VEL]/voxilaprevir [VOX], elbasvir [EBV]/grazoprevir [GZR], ombitasvir [OBV]/paritaprevir [PTV]/ritonavir [RTV]/dasabuvir [DSV])이 현재 사용되고 있다. 이러한 병합요법은 높은 sustained virologic response(SVR)률을 갖는 향상된 유효성과 안전성을 보여주었으며, 또한 HCV 치료기간을 8주 또는 12주로 단축하였다. 8주 또는 12주 동안 하루에 한 번씩 투여하는 GLE/PIB(300/120 mg) 병합요법은 간경변증 유무에 상관없이 HCV 유전자 1-6형에서 높은 효과를 보여주었다. 12주 동안 하루에 한 번씩 투여하는 SOF/VEL/VOX (400/100/100 mg) 병합요법은 심지어

NS5A 억제제를 포함한 DAA 기반 치료요법을 받은 경험이 있는 HCV 환자(HCV 유전자 1-6형)에서 높은 SVR률을 보여주었다. SOF/VEL/VOX 8주 병합요법은 약물순응도가 낮은 HCV 환자에서 대체요법으로 사용될 수 있을 것이다. 12주 동안 하루에 한 번씩 투여하는 EBV/GZR(50/100 mg) 병합요법은 간경변증, 만성 신장 질환, HIV 동시 감염, 유전성 혈액 질환, peg-interferon(pegIFN)을 포함한 치료요법을 받은 경험이 있는 HCV 유전자 1형 또는 4형에 감염된 환자들에서 높은 SVR률을 보여주었다. Baseline에서 NS5A resistance-associated substitution(RAS)을 갖는 HCV 1a형 감염 환자에서는 EBV/GZR + RBV 16주 병합요법이 사용될 수 있을 것이다. 또한, pegIFN을 포함하지 않고, 2-3개로 구성된 DAA 기반 병합요법은 만성 신장 질환이나 HIV 동시 감염 환자와 같은 특수한 상황에서도 높은 SVR률을 보여주었다.

결론: 본 연구의 결과는 DAA 기반 병합요법이 간경변증, 만성 신장 질환, HIV 동시 감염과 같은 특수한 상황에 있는 환자들을 포함한 HCV 감염 환자들에서 높은 치료성공률과 향상된 안전성이 있음을 보여주었다. 하지만, DAA의 유효성과 약물순응도에 부정적인 영향을 미칠지 모르는 DAA 관련 부작용과 약물상호작용을 주의 깊게 모니터링 하는 것은 중요하다. 현재, HCV 치료는 HCV 유전형에 따라 병합요법을 선택하는 형태에서 GLE/PIB나 SOF/VEL/VOX와 같은 범유전형 병합요법으로 전환되고 있다.

주제어: hepatitis C, direct-acting antiviral, efficacy, safety, drug-drug interaction

I. INTRODUCTION

A. Background and objectives

Hepatitis C is a infectious disease caused by the hepatitis C virus (HCV) which usually damages the liver.[1] HCV infection can cause acute or chronic hepatitis.[2] Acute HCV infection is generally asymptomatic and spontaneously resolved in approximately 15-45% of infected persons within 6 months without any antiviral treatments.[2] Yet, the remaining 55-85% of them may develop chronic HCV infection if appropriate treatments are not given, resulting in the progression to advanced liver damages (e.g., liver fibrosis, liver cirrhosis, liver failure and hepatocellular carcinoma [HCC]) and even death (Figure 1).[2]

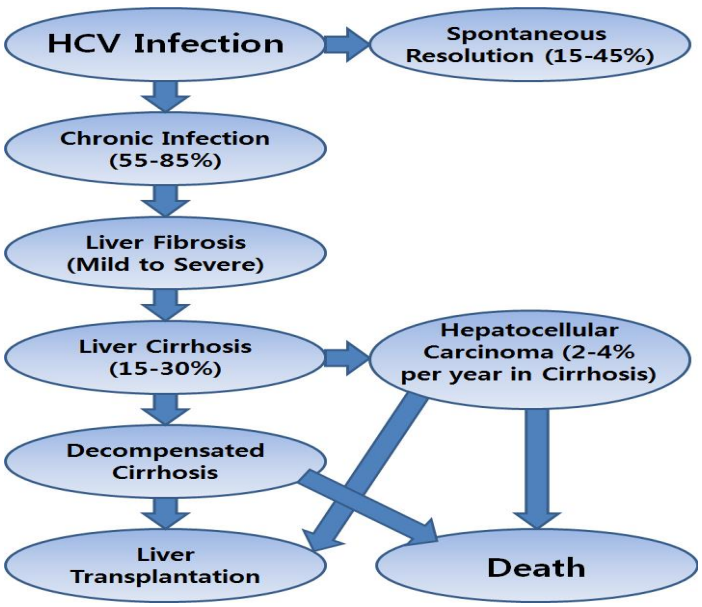


Figure 1. Natural history of HCV infection. This figure was adapted and modified from the reference 2.

According to the World Health Organization (WHO), the prevalence rate of HCV infection in 2015 was approximately 1%, which indicated that 71 million individuals had been living with HCV infection worldwide.[3] New HCV infection in 2015 occurred in 1.75 million persons globally.[3] The geographical distribution of HCV infection in the world is uneven, so the differences in its prevalence are shown across and within regions. The most prevalent areas of HCV infection include Eastern Mediterranean region (2.3%) followed by European region (1.5%) and African region (1.0%).[3] The current prevalence rate in the Korean population is between 0.6 and 0.8%.[4] Generally, HCV-infected individuals tend to live in low- and middle-income regions where initial HCV testing is not available.[2]

Until recently, pegylated interferon (pegIFN) and ribavirin (RBV) have been primarily used for HCV treatments; however, the uses of these agents are restricted due to low efficacy and frequent adverse events (AEs).[5] Consequently, the treatment for HCV infection is shifting from pegIFN-based therapy to pegIFN-free therapy including oral direct-acting antivirals (DAAs).[5,6] The pegIFN-free regimens lead to much more efficacy and better tolerability than the older regimens, thereby providing various treatment options for patients who experience therapeutic failure or are contraindicated with pegIFN and RBV.[6,7] These regimens not only shorten the duration of treatment to 12-24 weeks but also improve HCV cure rates to greater than 90%.[2,6]

The recent WHO clinical practice guideline recommends that DAA regimens for the treatment of HCV infection are used instead of regimens with pegIFN and RBV.[2] Specifically, the different combinations of sofosbuvir (SOF) and other DAAs (e.g., daclatasvir [DCV] and ledipasvir [LDV]) with or without RBV are recommended depending on cirrhosis status and HCV genotype.[2] In addition, further studies have been conducted in order to provide more improved therapeutic outcomes and shorter courses of treatment.[8-21] According to the clinical trial conducted by Zeuzem et al., the combination of glecaprevir (GLE) and pi-

brentasvir (PIB) for 8 or 12 weeks showed high rates of sustained virologic response 12 weeks after the end of treatment (SVR12), ranging from 95 to 100%, in non-cirrhotic patients with genotype 1 or 3.[8] The fixed-dose combination of DCV, asunaprevir (ASV), and beclabuvir (BCV) for 12 weeks achieved SVR12 rates greater than 95% in Japanese treatment-naive (TN) and treatment-experienced (TE) patients with genotype 1.[10] The combination of SOF, velpatasvir (VEL), and voxilaprevir (VOX) for 8 or 12 weeks also showed high rates of SVR12 ranging from 95 to 100% in TN and TE patients with genotype 1, 2, or 3.[11,12,14]

Oral pegIFN-free regimens show relatively tolerable AEs. The common AEs from these regimens include headache, fatigue, nausea, diarrhea, and insomnia, which are usually mild.[6,22-25] However, each DAA is metabolized through its own pathway, and it is likley to show different drug-drug interactions (DDIs) depending on drugs used concomitantly.[6] Therefore, it may be important to closely monitor not only AEs but also DDIs in clinical practice. Most of DDIs of DAAs are associated with drug-metabolizing enzymes, such as cytochrome P450-3A4 (CYP3A4), or hepatic/intestinal transporters, such as P-glycoprotein (P-gp).[6,26] The induction or inhibition of CYP3A4 or P-gp is likely to affect plasma concentration levels of DAAs, which may negatively contribute to the efficacy and safety of them.[6]

Various clinical trials regarding DAAs have been conducted with HCV infected patients. However, due to the lack of direct comparison outcomes in clinical trials considering various factors (e.g., HCV genotype, race, gender, cirrhosis, and prior treatment), it may be unclear to find optimal DAA regimens based on patient status. Ideally, this issue may be resolved through direct comparions of efficacy and safety of DAAs in a very large clinical trial including multiple study arms, but it is difficult to compare them in a single clinical trial.

The objectives of this systematic review and meta-analysis were to investigate the efficacy and safety of DAA-based regimens in HCV-infected patients

and to provide our clinical perspectives on these regimens.

B. HCV clinical practice guidelines

1. WHO guidelines - Updated version (April 2016)[2]

The recently published WHO guidelines for the treatment of persons with HCV infection provide recommendations for the uses of DAA combinations with or without RBV depending on HCV genotype (i.e., genotypes 1, 2, 3, 4, 5, and 6) and clinical history (i.e., non-cirrhosis and cirrhosis). These guidelines recommend that for all HCV-infected patients, DAA regimens should be used as the first-line therapy instead of regimens with pegIFN and RBV. However, there is an exception to cirrhotic patients with genotype 3 and cirrhotic and non-cirrhotic patients with genotypes 5 and 6. For these groups, SOF/pegIFN/RBV is still recommend as an alternative regimen. The regimens with boceprevir (BPV) or telaprevir (TPV) are no longer recommended for the treatment of patients with HCV infection. The recommended preferred and alternative regimens for non-cirrhotic and cirrhotic patients with HCV infection are also summarized in Tables 1-4.

Table 1. Summary of recommended preferred regimens for non-cirrhotic patients with HCV infection

Genotype	DCV/SOF	LDV/SOF	SOF/RBV
1	12 wks	12 wks*	
2			12 wks
3	12 wks		24 wks
4	12 wks	12 wks	
5		12 wks	
6		12 wks	

*Treatment may be shortened to 8 wks for non-cirrhotic, treatment-naive persons if baseline HCV RNA < 6 million (6.8 log) IU/mL, but the duration of treatment has to be reduced with caution.

Table 2. Summary of recommended preferred regimens for cirrhotic patients with HCV infection

Genotype	DCV/SOF	DCV/SOF/ RBV	LDV/SOF	LDV/SOF/ RBV	SOF/RBV
1	24 wks	12 wks	24 wks	12 wks*	
2					16 wks
3		24 wks			
4	24 wks	12 wks	24 wks	12 wks*	
5			24 wks	12 wks*	
6			24 wks	12 wks*	

*For patients with platelet count < 75 x 10^3/uL, the treatment for 24 wks with RBV should be administered.

Table 3. Summary of recommended alternative regimens for non-cirrhotic patients with HCV infection

Genotype	SMV/SOF	DCV/SOF	OBV/PTV/ RTV/DSV	OBV/PTV/ RTV/RBV	SOF/pegIFN/ RBV
1	12 wks*		12 wks#		
2		12 wks			
3					
4	12 wks			12 wks	
5					12 wks
6					12 wks

*For patients with HCV genotype 1a and positive Q80K variant, a SMV/SOF regimen is not recommended.

#For patients with HCV genotype 1a, an OBV/PTV/RTV/DSV regimen with RBV is recommended; for patients with HCV genotype 1b, an OBV/PTV/RTV/DSV regimen is recommended.

Table 4. Summary of recommended alternative regimens for cirrhotic patients with HCV infection

Genotype	DCV/SOF	SMV/ SOF	SMV/ SOF/RBV	OBV/PTV /RTV/ DSV	OBV/PTV /RTV/ RBV	SOF/ pegIFN/ RBV
1		24 wks*	12 wks*	24 wks#		
2	12 wks					
3						12 wks
4		24 wks	12 wks		24 wks	
5						12 wks
6						12 wks

*For patients with HCV genotype 1a and positive Q80K variant, a SMV/SOF regimen is not recommended.

#For patients with HCV genotype 1a, an OBV/PTV/RTV/DSV regimen with RBV for 24 wks is recommended; for patients with HCV genotype 1b, an OBV/PTV/RTV/DSV regimen with RBV for 12 wks is recommended.

2. KASL guidelines - Updated version (November 2017)[27]

The Korean Association for the Study of the Live (KASL) published new guidelines for the treatment of patients with HCV infection in November 2017. KASL guidelines include the combinations of DAAs (e.g., elbasvir [EBV]/grazoprevir [GZR], GLE/PIB, and SOF/velpatasvir [VEL]) which are not recommended by WHO guidelines published in 2016. EBV/GZR for 12 weeks is recommended for patients with HCV genotype 1a/b. However, in case of patients with HCV genotype 1a and positive non-structural protein 5A (NS5A) resistance-associated substitution (RAS), EBV/GZR/RBV for 16 weeks should be used. GLE/PIB for 8 and 12 weeks is recommended for non-cirrhotic and cirrhotic patients, respectively, regardless of HCV genotype, but GLE/PIB for 16 weeks should be administered to HCV genotype 3-infected patients with prior pegIFN/RBV treatments. SOF/VEL for 12 weeks is recommended for all HCV-infected patients except for genotype 3-infected patients with cirrhosis or previous pegIFN/RBV treatments. SOF/VEL/RBV for 12 weeks should be used for them. SOF/VEL/VOX for 8 weeks can be used as an alternative regimen for HCV genotype 3-infected patients with cirrhosis. The recommended regimens for HCV-infected patients with or without cirrhosis are summarized in Figure 2.

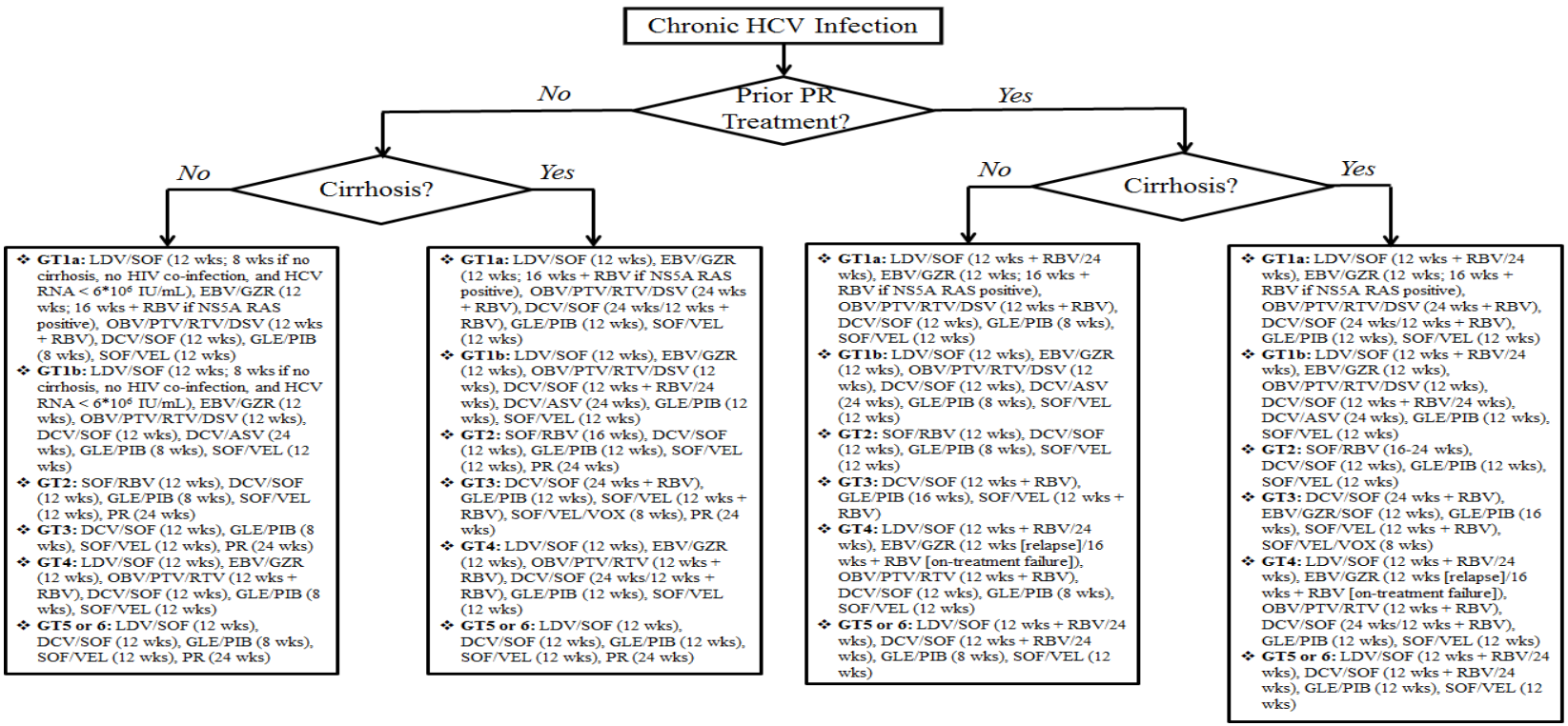


Figure 2. Flowchart of the treatment for HCV-infected patients. PR, pegIFN/RBV. This figure was adapted and modified from the reference 27.

3. Introduction of DAAs used for HCV infection

The DAA regimens lead to much more efficacy and better tolerability than the pegIFN-containing regimens, thereby providing various treatment chances for patients who experience therapeutic failure or are contraindicated with pegIFN and RBV.[6,7] DAAs target the HCV replication cycle for the inhibition of replication as depicted in Figure 3.[28]

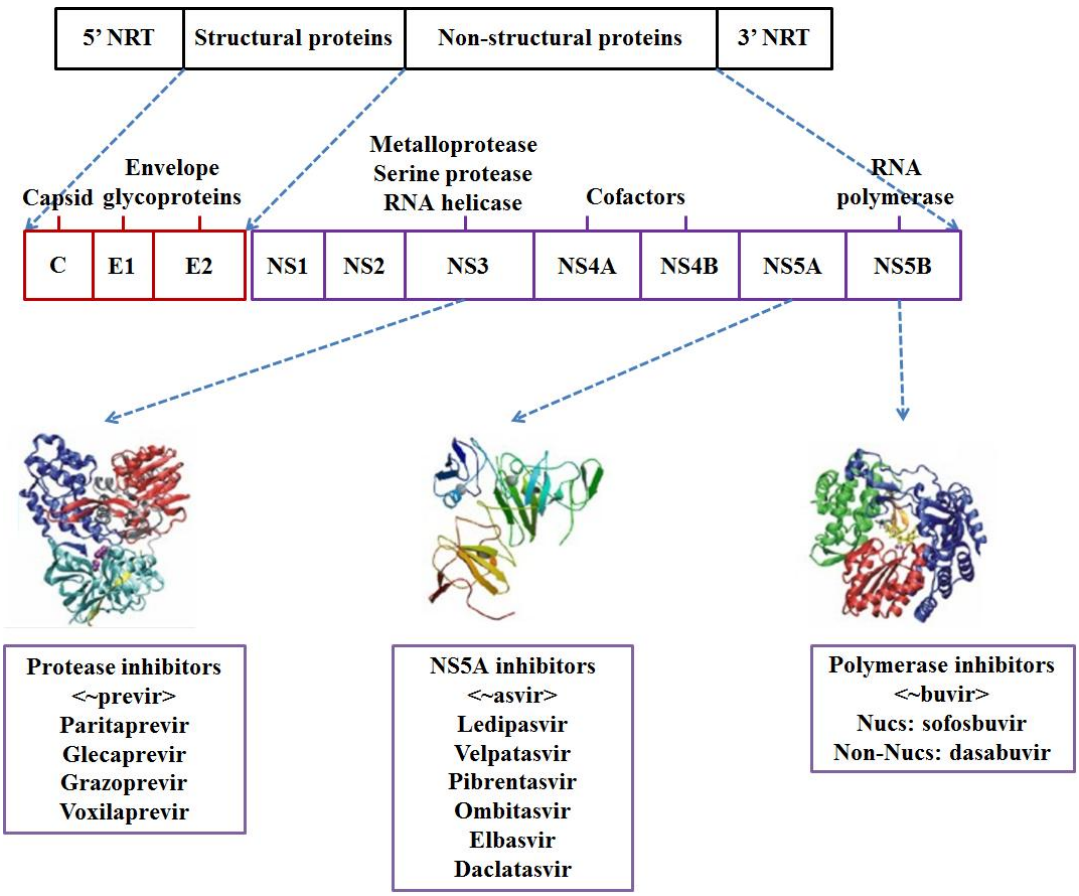


Figure 3. DAAs with different mode of actions. This figure was adapted and modified from the reference 28.

Currently, LDV/SOF, SOF, DCV, ASV, OBV/PTV/RTV, DSV, and EBV/GZR are used to treat HCV-infected patients in Korea.[27] In 2016, SOF/VEL was approved in the USA and Europe, and SOF/VEL/VOX and GLE/PIB were also approved in 2017 (Figure 4).[27,28] DAAs and RBV used for the treatment of HCV-infected patients are presented in Table 5.[27]

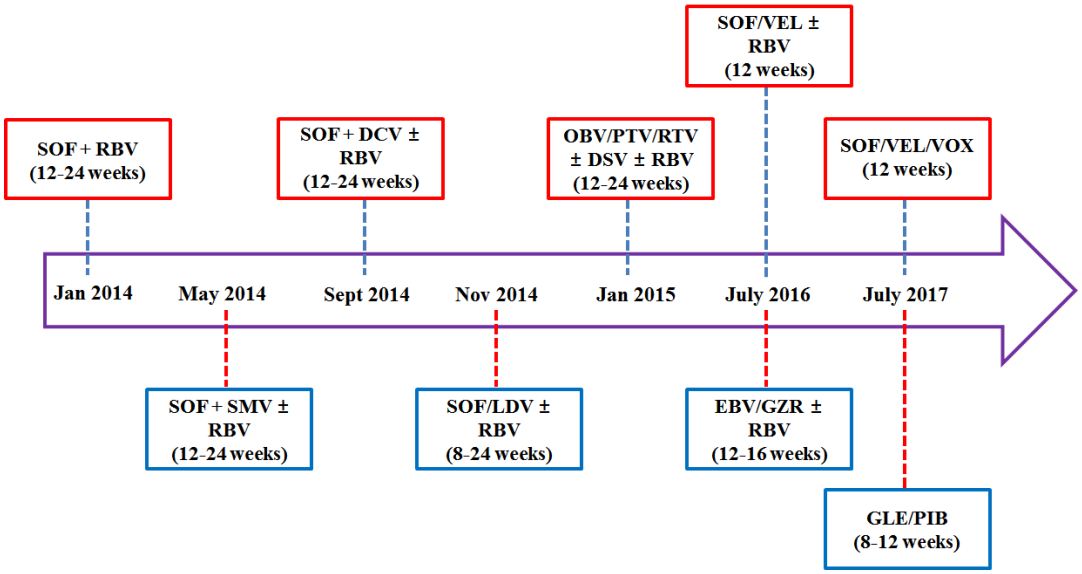


Figure 4. Development milestones of approved DAAs. SOF, sofosbuvir; LDV, ledipasvir; DCV, daclatasvir; ASV, asunaprevir; OBV, ombitasvir; PTV, paritaprevir; RTV, ritonavir; DSV, dasabuvir; EBV, elbasvir; GZR, grazoprevir; GLE, glecaprevir; PIB, pibrentasvir; VEL, velpatasvir; VOX, voxilaprevir; RBV, ribavirin. This figure was adapted and modified from the reference 28.

Table 5. DAAs and RBV used for the treatment of HCV infection

Drug	Brand name	Dosage
SOF*	Sovaldi®	SOF 400 mg (1 tablet); 1 tablet QD with or without food
LDV/SOF*	Harvoni®	LDV 90 mg/SOF 400 mg (1 tablet); 1 tablet QD with or without food
DCV*	Daklinza®	DCV 30 or 60 mg (1 tablet); 1 tablet QD with or without food
ASV*	Sunvepra®	ASV 100 mg (1 capsule); 1 capsule BID with or without food
OBV/PTV/RTV*	Viekirax®	OBV 12.5 mg/PTV 75 mg/RTV 50 mg (1 tablet); 2 tablets QD with food
DSV*	Exviera®	DSV 250 mg (1 tablet); 1 tablet BID with food
EBV/GZR*	Zepatier®	EBV 50 mg/GZR 100 mg (1 tablet); 1 tablet QD with or without food
GLE/PIB	Maviret®	GLE 100 mg/PIB 40 mg (1 tablet); 3 tablets QD with food
SOF/VEL	Epclusa®	SOF 400 mg/VEL 100 mg (1 tablet); 1 tablet QD with or without food
SOF/VEL/VOX	Vosevi®	SOF 400 mg/VEL 100 mg/VOX 100 mg (1 tablet); 1 tablet QD with food
RBV*	Viramid®	RBV 200 mg (1 capsule); 1,000 mg/day (< 75 kg) and 1,200 mg/day (≥ 75 kg)

*Approved in Korea.

SOF, sofosbuvir; LDV, ledipasvir; DCV, daclatasvir; ASV, asunaprevir; OBV, ombitasvir; PTV, paritaprevir; RTV, ritonavir; DSV, dasabuvir; EBV, elbasvir; GZR, grazoprevir; GLE, glecaprevir; PIB, pibrentasvir; VEL, velpatasvir; VOX, voxilaprevir; RBV, ribavirin

Ⅱ. METHODS

A. Literature search

This study were performed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement.[29] The systematic literature search was independently conducted by two reviewers in PubMed and KoreaMed without language restrictions. The search term "direct-acting antivirals" was used to identify clinical trials which investigated the efficacy and safety of DAAs in HCV-infected patients from inception to February 2018. The reference lists of selected articles and related reviews were also scanned to find additional clinical trials.

B. Study selection

The article titles and abstracts were independently scanned by two reviewers and identified relevant articles which may be in accordance with the following inclusion criteria: 1) only randomized controlled trials (RCTs) irrespective of blinding; 2) only patients with HCV infection; 3) DAAs must have been used for the treatment of the HCV infection; and 4) the end points had to contain the proportion of patients with SVR4, SVR12, or SVR24. Consensus was attained by discussion between two reviewers in case of any disagreement in terms of inclusion of an article for evaluation. Abstracts, conference proceedings, and unpublished articles were not considered.

C. Data extraction and quality assessment

The following data from the selected articles were independently reviewed

and extracted by two reviewers: publication year, first author, countries where the study was implemented, study design, prior treatment status, regimens, HCV genotype, IL28B genotype, cirrhosis status, number of included patients, gender, age, SVR rates, virologic failure, incidence of AEs and serious AEs (SAEs), discontinuation rate due to AEs, and death. Any discrepancy was resolved by discussion between them.

The quality assessment of each study was performed using the Cochrane Collaboration's tool to evaluate the risk of bias in RCTs.[30] Bias is assessed as reviewer's judgement (i.e., high, low, or unclear risk of bias) for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

D. Outcome measures

The primary outcome of interest was the relative efficacy of various DAA regimens in terms of SVR12 or SVR24. The secondary outcome of interest was the incidence rates of common AEs, SAEs, death, and discontinuation owing to AEs.

E. Statistical analysis

All analyses were performed with RevMan version 5.3.5 (The Cochrane Collaboration, Oxford, UK). The standardized mean difference (SMD) was calculated for continuous data, and the pooled odds ratio (OR) with 95% confidence interval (CI) was also calculated for binary data. If there was no heterogeneity in the pooled data, the fixed-effect model was used; otherwise, the random-effect model was utilized. Heterogeneity was evaluated by visually

inspecting the forest plots and measuring Chi-squared and I-squared tests. P-values less than 0.1 in the Chi-squared test were assumed to have statistically significant heterogeneity. I^2 values were calculated with the following formula: $I^2 = 100\% * (Q - df)/Q$ where Q meant Cochran's heterogeneity and df indicated degrees of freedom. Negative values of I^2 were zero, and I^2 values ranged from 0 to 100%. Zero percent of I^2 meant no heterogeneity observed, and larger values of I^2 indicated increasing heterogeneity. Specifically, I^2 values between 30 and 60% indicated moderate heterogeneity, the values between 60 and 75% were defined as considerable heterogeneity, and the values greater than 75% were considered as substantial heterogeneity. The values less than 30% were considered unimportant.[31] The analysis of a funnel plot was conducted with the Egger test to detect publication bias, and the asymmetric shape of the plot indicated possible publication bias.

F. Abbreviations used

Abbreviation	Full name
ASV	Asunaprevir
BCV	Beclabuvir
BID	Twice daily
DAN	Danoprevir
DBV	Deleobuvir
DCV	Daclatasvir
DSV	Dasabuvir
EBV	Elbasvir
FDC	Fixed-dose combination
FDV	Faldaprevir
GLE	Glecaprevir
GT	Genotype
GZR	Grazoprevir
IBLD	Inherited blood disorder
LDV	Ledipasvir
MCB	Mericitabine
N/A	Not available
OBV	Ombitasvir
pegIFN	pegylated interferon
PIB	Pibrentasvir
PTV	Paritaprevir

Abbreviation	Full name
QD	Once daily
QW	Weekly
RBV	Ribavirin
RCT	Randomized controlled trial
RTV	Ritonavir
SC	Subcutaneously
SET	Setrobuvir
SMV	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virologic response
TE	Treatment-experienced
TGV	Tegobuvir
TID	Three times a day
TN	Treatment-naive
TPV	Telaprevir
VAN	Vaniprevir
VDV	Vedroprevir
VEL	Velpatasvir
VOX	Voxilaprevir
VW	von Willebrand disorder

Ⅲ. RESULTS

A. Identification of the included studies

The study selection process for eligible studies was presented in Figure 5. A total of 3,086 articles were identified through a search of PubMed, KoreaMed, and references. During the initial screening, 11 duplicated articles and 2,879 non-clinical articles were excluded. Through a review of titles and abstracts, additional 154 non-RCT articles were excluded. The remaining 42 articles were then thoroughly reviewed for eligibility. Among these articles, 11 articles were excluded from the final analysis. The reasons for excluding them from the final review were as follows: only healthy subjects included (n = 4), DAAs not included (n = 2), and SVR4, 12, or 24 not presented (n = 5). The remaining 31 articles (36 studies) were included in qualitative synthesis, and among them, 6 articles (8 studies) were used for quantitative synthesis (meta-analysis).

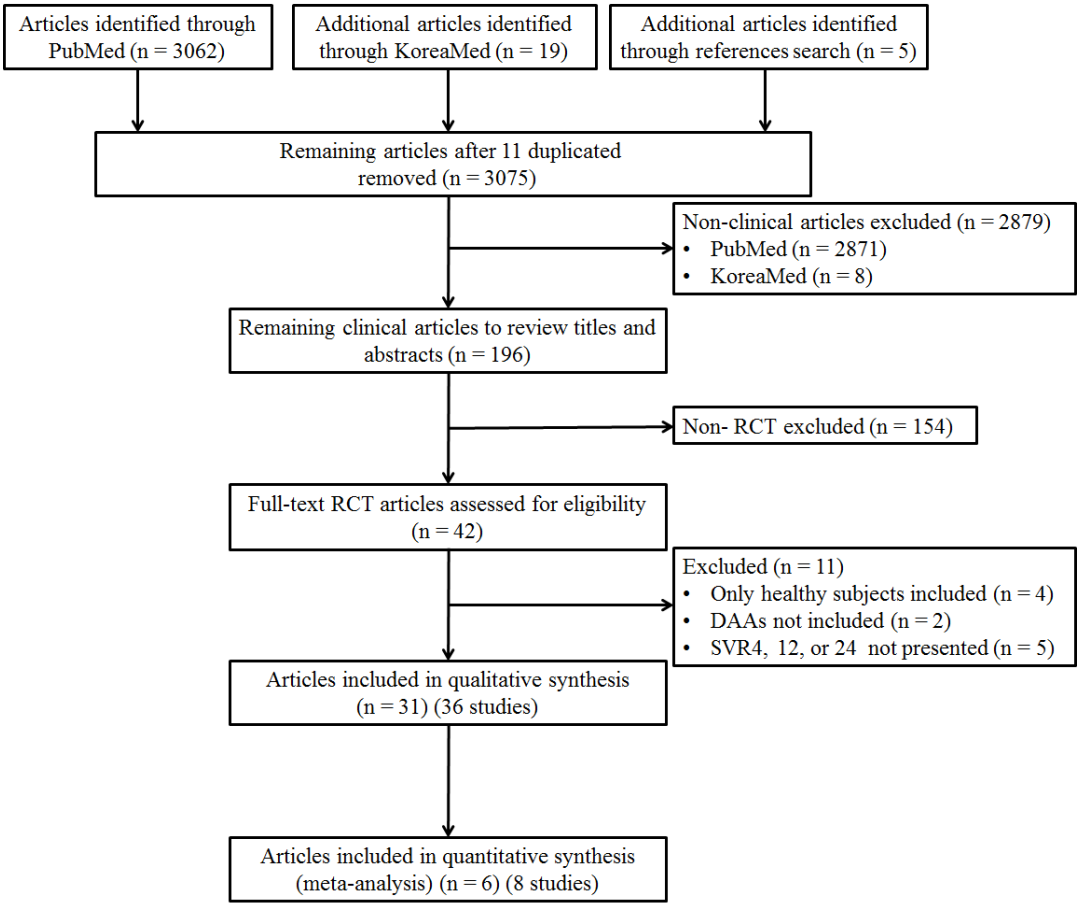


Figure 5. Flowchart of the study selection process for eligible studies in the systematic review.

B. Characteristics of the included studies

The relevant findings from 31 included articles were summarized in Tables 6 and 7.[8-25,32-44] The included articles were published between 2011[44] and 2018.[8] Most studies were conducted in North and South Americas, Australia, New Zealand, and Europe, and only 3 studies were carried out in Japan[10,13] and Thailand.[16] Only 1 study was phase I[40], 20 were phase II[9,12,15,18,19,21,22,24,25,32-37,39,41-43], and 14 were phase III.[8,10,11,13,14,16,17,20,23,38,44] Overall, 9,202 patients from the 36 studies were included in qualitative synthesis. Among them, 1,911 patients from the 8 studies were included for quantitative synthesis.[12,14,17,18,24,33] Various DAA regimens with or without addition of pegIFN and/or RBV were administered, and the duration of treatment varied between 8 and 48 weeks. The ages of all patients ranged from 18 to 85 years old. The majority of patients included in the studies were infected by HCV genotype 1. Most SVR12 rates ranged from 80 to 100% depending on the DAA regimens used.

Table 6. Summary of selected randomized controlled trials of different drug combination regimens for the treatemnt of patients with HCV infection

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Zeuzem et al. (2018)[8] (ENDURANCE -1/3)	Multi-regions	RCT (3)	TN & TE	GLE 300 mg QD + PIB 120 mg QD (8 wks)	GT	GT1	167/184	53.0 (19-84)	-	348/351 (99.15)	-	1/351 (0.28)	0/351 (0.00)
						GT3	92/65	47.0 (20-76)	-	149/157 (94.90)	-	1/157 (0.64)	5/157 (3.18)
				GLE 300 mg QD + PIB 120 mg QD (12 wks)	GT	GT1	176/176	52.0 (21-77)	-	351/352 (99.72)	-	0/352 (0.00)	0/352 (0.00)
						GT3	121/112	48.0 (22-71)	-	222/233 (95.28)	-	1/233 (0.43)	3/233 (1.29)
				SOF 400 mg QD + DCV 60 mg QD (12 wks)	GT	GT3	52/63	49.0 (20-70)	-	111/115 (96.52)	-	0/115 (0.00)	1/115 (0.87)
Bourgeois et al. (2017)[9]	Belgium, Germany	RCT (2a)	TN & TE	SMV 75 mg QD + TMC647055/ RTV 450/30 mg QD + JNJ-56914845 30 mg QD (12 wks)	GT	GT1a	16/6	50.5 (24-70)	-	10/14 (71.43)	-	0/14 (0.00)	4/14 (28.57)
						GT1b			-	8/8 (100.00)	-	0/8 (0.00)	0/8 (0.00)
				SMV 75 mg QD + TMC647055/ RTV 450/30 mg QD + JNJ-56914845 60 mg QD (12 wks)	GT	GT1a	17/5	48.0 (27-58)	-	14/15 (93.33)	-	1/15 (6.67)	0/15 (0.00)
						GT1b			-	7/7 (100.00)	-	0/7 (0.00)	0/7 (0.00)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Toyota et al. (2017)[10]	Japan	RCT (3)	TN & TE	DCV 30 mg + ASV 200 mg + BCV 75 mg (FDC, BID 12 wks)	Previous treatment	TN GT1b	44/105	64.0 (27-80)	-	143/149 (95.97)	-	0/149 (0.00)	1/149 (0.67)
						TE GT1b	23/41	64.0 (36-79)	-	62/64 (96.88)	-	0/64 (0.00)	1/64 (1.56)
				DCV 60 mg QD + ASV 100 mg BID (24 wks)	Previous treatment	TN GT1b	29/46	61.0 (26-81)	-	65/75 (86.67)	-	3/75 (4.00)	7/75 (9.33)
				DCV 30 mg + ASV 200 mg + BCV 75 mg (FDC, BID 12 wks)	IL28B GT	CC	-	-	-	123/129 (95.35)	-	-	-
						Non-CC	-	-	-	84/86 (97.67)	-	-	-
				DCV 60 mg QD + ASV 100 mg BID (24 wks)	IL28B GT	CC	-	-	-	44/51 (86.27)	-	-	-
						Non-CC	-	-	-	21/24 (87.50)	-	-	-
				DCV 30 mg + ASV 200 mg + BCV 75 mg (FDC, BID 12 wks)	Cirrhosis	Cirrhotic	-	-	-	44/46 (95.65)	-	-	-
						Non-cirrhotic	-	-	-	164/171 (95.91)	-	-	-
				DCV 60 mg QD + ASV 100 mg BID (24 wks)	Cirrhosis	Cirrhotic	-	-	-	13/14 (92.86)	-	-	-
						Non-cirrhotic	-	-	-	52/61 (85.25)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Bourliere et al. (2017)[11] (POLARIS-1)	USA, Canada, New Zealand, Australia, France, Germany, United Kingdom	RCT (3)	TE	SOF 400 mg QD + VEL 100 mg QD + VOX 100 mg QD (12 wks)	-	-	200/63	58.0 (27-84)	257/263 (97.72)	253/263 (96.20)	-	1/263 (0.38)	6/261 (2.30)
					GT	GT1a	-	-	-	97/101 (96.04)	-	-	-
						GT1b	-	-	-	45/45 (100.00)	-	-	-
						GT2	-	-	-	5/5 (100.00)	-	-	-
						GT3	-	-	-	74/78 (94.87)	-	-	-
						GT4	-	-	-	20/22 (90.91)	-	-	-
						GT5	-	-	-	1/1 (100.00)	-	-	-
						GT6	-	-	-	6/6 (100.00)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Bourliere et al. (2017)[11] (POLARIS-4)	USA, Canada, New Zealand, Australia, France, Germany, United Kingdom	RCT (3)	TE	SOF 400 mg QD + VEL 100 mg QD + VOX 100 mg QD (12 wks)	-	-	143/39	57.0 (24-85)	179/182 (98.35)	178/182 (97.80)	-	0/182 (0.00)	1/182 (0.55)
					GT	GT1a	-	-	-	53/54 (98.15)	-	-	-
						GT1b	-	-	-	23/24 (95.83)	-	-	-
						GT2	-	-	-	31/31 (100.00)	-	-	-
						GT3	-	-	-	52/54 (96.30)	-	-	-
						GT4	-	-	-	19/19 (100.00)	-	-	-
				SOF 400 mg QD + VEL 100 mg QD (12 wks)	-	-	114/37	57.0 (24-80)	138/151 (91.39)	136/151 (90.07)	-	1/151 (0.66)	14/150 (9.33)
					GT	GT1a	-	-	-	39/44 (88.64)	-	-	-
						GT1b	-	-	-	21/22 (95.45)	-	-	-
						GT2	-	-	-	32/33 (96.97)	-	-	-
						GT3	-	-	-	44/52 (84.62)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Lawitz et al. (2017)[12]	USA	RCT (2)	TE	SOF 400 mg QD + VEL 100 mg QD + VOX 100 mg QD (12 wks)	GT	GT1	16/8	54.0 (18-71)	-	24/24 (100.00)	-	0/24 (0.00)	0/24 (0.00)
				SOF 400 mg QD + VEL 100 mg QD + VOX 100 mg QD + RBV 1,000 or 1,200 mg/day (12 wks)			16/9	54.0 (22-75)	-	24/25 (96.00)	-	0/25 (0.00)	1/25 (4.17)
Sato et al. (2017)[13] (GIFT-II)	Japan	RCT (3)	TN & TE	OBV 25 mg QD + PTV 150 mg QD + RTV 100 mg QD + RBV 600, 800, or 1,000 mg/day (12 wks)	Previous treatment, Cirrhosis, GT	Non-cirrhotic, TN, GT2	45/40	-	-	36/48 (75.00)	-	-	5/41 (12.20)
						Non-cirrhotic, TE, GT2			-	22/32 (68.75)	-	-	2/24 (8.33)
						Cirrhotic, GT2			-	4/5 (80.00)	-	-	0/4 (0.00)
				OBV 25 mg QD + PTV 150 mg QD + RTV 100 mg QD + RBV 600, 800, or 1,000 mg/day (16 wks)		Non-cirrhotic, TN, GT2	38/48	-	-	43/47 (91.49)	-	-	0/43 (0.00)
						Non-cirrhotic, TE, GT2			-	25/33 (75.76)	-	-	0/25 (0.00)
						Cirrhotic, GT2			-	2/6 (33.33)	-	-	0/2 (0.00)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Jacobson et al. (2017)[14] (POLARIS-2)	USA, Canada, New Zealand, Australia, France, Germany, United Kingdom	RCT (3)	TN & TE	SOF 400 mg QD + VEL 100 mg QD + VOX 100 mg QD (8 wks)	-	-	255/246	53.0 (18-78)	483/501 (96.41)	477/501 (95.21)	-	0/501 (0.00)	21/501 (4.19)
					GT	GT1a	-	-	-	155/169 (91.72)	-	-	-
						GT1b	-	-	-	61/63 (96.83)	-	-	-
						GT2	-	-	-	61/63 (96.83)	-	-	-
						GT3	-	-	-	91/92 (98.91)	-	-	-
						GT4	-	-	-	59/63 (93.65)	-	-	-
						GT5	-	-	-	17/18 (94.44)	-	-	-
						GT6	-	-	-	30/30 (100.00)	-	-	-
				SOF 400 mg QD + VEL 100 mg QD (12 wks)	-	-	237/203	55.0 (19-82)	435/440 (98.86)	432/440 (98.18)	-	0/440 (0.00)	3/440 (0.68)
					GT	GT1a	-	-	-	170/172 (98.84)	-	-	-
						GT1b	-	-	-	57/59 (96.61)	-	-	-
						GT2	-	-	-	53/53 (100.00)	-	-	-
						GT3	-	-	-	86/89 (96.63)	-	-	-
						GT4	-	-	-	56/57 (98.25)	-	-	-
						GT6	-	-	-	9/9 (100.00)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Jacobson et al. (2017)[14] (POLARIS-3)	USA, Canada, New Zealand, Australia, France, Germany, United Kingdom	RCT (3)	TN & TE	SOF 400 mg QD + VEL 100 mg QD + VOX 100 mg QD (8 wks)	Cirrhosis & GT	Cirrhotic, GT3	74/36	54.0 (25-75)	107/110 (97.27)	106/110 (96.36)	-	0/110 (0.00)	2/110 (1.82)
				SOF 400 mg QD + VEL 100 mg QD (12 wks)			100/9	55.0 (31-69)	106/109 (97.25)	105/109 (96.33)	-	0/109 (0.00)	1/109 (0.92)
Poordad et al. (2017)[15] (MAGELLAN-1)	USA	RCT (2)	TE	GLE 200 mg QD + PIB 80 mg QD (12 wks)	Cirrhosis & GT	Non-cirrhotic, GT1	3/3	59.0 (39-61)	-	6/6 (100.00)	-	0/6 (0.00)	0/6 (0.00)
				GLE 300 mg QD + PIB 120 mg QD + RBV 800 mg QD (12 wks)			20/2	56.0 (39-64)	-	21/22 (95.45)	-	0/22 (0.00)	1/22 (4.55)
				GLE 300 mg QD + PIB 120 mg QD (12 wks)			18/4	59.0 (46-70)	-	19/22 (86.36)	-	1/22 (4.55)	0/22 (0.00)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Hezode et al. (2017)[16]	USA, Europe, Australia, Canada, Israel, Thailand	RCT (3)	TN & TE	EBV 50 mg QD + GZR 100 mg QD (12 wks)	–	–	80/27	44.2 (11.2)	–	100/107 (93.46)	–	–	6/107 (5.61)
					Previous treatment	TN	–	–	–	46/53 (86.79)	–	–	–
						TE	–	–	–	54/54 (100.00)	–	–	–
					Race	White	–	–	–	77/81 (95.06)	–	–	–
						Black	–	–	–	17/19 (89.47)	–	–	–
						Asian	–	–	–	5/6 (83.33)	–	–	–
					GT	GT1a	–	–	–	43/47 (91.49)	–	–	–
						GT1b	–	–	–	44/46 (95.65)	–	–	–
						GT4	–	–	–	11/12 (91.67)	–	–	–
					IL28B	CC	–	–	–	24/27 (88.89)	–	–	–
						Non-CC	–	–	–	74/78 (94.87)	–	–	–
					Cirrhosis	Cirrhotic	–	–	–	26/26 (100.00)	–	–	–
						Non-cirrhotic	–	–	–	74/81 (91.36)	–	–	–
					IBLD	Sickle cell anemia	–	–	–	18/19 (94.74)	–	–	–
						β-thalassemia	–	–	–	40/41 (97.56)	–	–	–
						Hemophilia A/B or VW	–	–	–	42/47 (89.36)	–	–	–

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Dore et al. (2016)[17] (MALACHITE-I)	Australia, Canada, Europe, South America	RCT (3b)	TN	OBV 25 mg QD + PTV 150 mg QD + RTV 100 mg QD + DSV 250 mg BID + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (12 wks)	GT	GT1a	48/21	46.1 (12.3)	-	67/69 (97.10)	-	-	0/69 (0.00)
				TPV 750 mg TID + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (12 wks)			17/17	44.5 (14.1)	-	28/34 (82.35)	-	-	0/34 (0.00)
				OBV 25 mg QD + PTV 150 mg QD + RTV 100 mg QD + DSV 250 mg BID + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (12 wks)		GT1b	38/46	46.2 (11.3)	-	83/84 (98.81)	-	-	1/84 (1.19)
				OBV 25 mg QD + PTV 150 mg QD + RTV 100 mg QD + DSV 250 mg BID (12 wks)			40/43	47.1 (11.3)	-	81/83 (97.59)	-	-	0/83 (0.00)
				TPV 750 mg TID + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (12 wks)			17/24	45.9 (10.8)	-	32/41 (78.05)	-	-	2/32 (6.25)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Dore et al. (2016)[17] (MALACHITE-II)	Australia, Europe, South America	RCT (3b)	TE	OBV 25 mg QD + PTV 150 mg QD + RTV 100 mg QD + DSV 250 mg BID + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (12 wks)	GT	GT1	55/46	46.9 (12.2)	-	100/101 (99.01)	-	-	0/101 (0.00)
				TPV 750 mg TID + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (12 wks)			28/19	45.0 (10.4)	-	31/47 (65.96)	-	-	2/32 (6.25)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Everson et al. (2016)[18]	USA	RCT (2b)	TN	DCV 30 mg BID + ASV 200 mg BID + BCV 75 mg BID (12 wks)	-	-	55/25	54.0 (23-68)	73/80 (91.25)	71/80 (88.75)	-	2/80 (2.50)	4/80 (5.00)
					Cirrhosis	Cirrhotic	-	-	-	8/8 (100.00)	-	-	-
						Non-cirrhotic	-	-	-	63/72 (87.50)	-	-	-
					GT	GT1a	-	-	-	59/67 (88.06)	-	-	-
						GT1b	-	-	-	12/13 (92.31)	-	-	-
					IL28B	CC	-	-	-	23/25 (92.00)	-	-	-
						Non-CC	-	-	-	48/55 (87.27)	-	-	-
				DCV 30 mg BID + ASV 200 mg BID + BCV 150 mg BID (12 wks)	-	-	57/29	54.0 (23-69)	77/86 (89.53)	77/86 (89.53)	-	3/86 (3.49)	2/86 (2.33)
					Cirrhosis	Cirrhotic	-	-	-	5/7 (71.43)	-	-	-
						Non-cirrhotic	-	-	-	72/79 (91.14)	-	-	-
					GT	GT1a	-	-	-	62/69 (89.86)	-	-	-
						GT1b	-	-	-	15/17 (88.24)	-	-	-
					IL28B	CC	-	-	-	27/29 (93.10)	-	-	-
						Non-CC	-	-	-	50/56 (89.29)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Everson et al. (2016)[18]	USA	RCT (2b)	TN	DCV 30 mg BID + ASV 200 mg BID + BCV 75 mg BID + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (12 wks)	-	-	9/12	50.0 (23-64)	18/21 (85.71)	18/21 (85.71)	-	1/21 (4.76)	0/21 (0.00)
					Cirrhosis	Cirrhotic	-	-	-	1/1 (100.00)	-	-	-
						Non-cirrhotic	-	-	-	17/20 (85.00)	-	-	-
					GT	GT1a	-	-	-	16/19 (84.21)	-	-	-
						GT1b	-	-	-	2/2 (100.00)	-	-	-
					IL28B	CC	-	-	-	1/2 (50.00)	-	-	-
						Non-CC	-	-	-	17/19 (89.47)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Zeuzem et al. (2016)[19]	USA, Argentina, France, Germany, Hungary, Spain	RCT (2)	TN & TE	DCV 30 mg QD + SMV 150 mg QD (12 wks or 24 wks)	Previous treatment	TN GT1b	22/31	54.0 (21-83)	-	45/53 (84.91)	-	4/53 (7.55)	2/45 (4.44)
						TE GT1b	12/11	56.0 (27-75)	-	16/23 (69.57)	-	4/23 (17.39)	1/16 (6.25)
					Previous treatment, Cirrhosis	TN, Cirrhotic, GT1b	-	-	-	5/6 (83.33)	-	-	-
						TN, Non-cirrhotic, GT1b	-	-	-	40/47 (85.11)	-	-	-
						TE, Cirrhotic, GT1b	-	-	-	5/9 (55.56)	-	-	-
						TE, Non-cirrhotic, GT1b	-	-	-	11/14 (78.57)	-	-	-
				DCV 30 mg QD + SMV 150 mg QD RBV 1,000 or 1,200 mg/day based on weight (12 wks or 24 wks)	Previous treatment	TN GT1b	25/26	53.0 (28-81)		38/51 (74.51)		6/51 (11.76)	2/38 (5.26)
						TE GT1b	9/11	59.0 (20-78)		19/20 (95.00)		1/20 (5.00)	0/20 (0.00)
					Previous treatment, Cirrhosis	TN, Cirrhotic, GT1b	-	-	-	4/7 (57.14)	-	-	-
						TN, Non-cirrhotic, GT1b	-	-	-	34/44 (77.27)	-	-	-
						TE, Cirrhotic, GT1b	-	-	-	4/4 (100.00)	-	-	-
						TE, Non-cirrhotic, GT1b	-	-	-	15/16 (93.75)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Jacobson et al. (2016)[20]	USA, Argentina, Australia, Austria, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Poland, Russia, Spain, Switzerland, United Kingdom	RCT (3)	TN	DCV 60 mg QD + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (24 wks)	GT	GT1b	159/109	46.0 (18-71)	-	228/268 (85.07)	226/268 (84.33)	11/268 (4.10)	12/244 (4.92)
					Race	White	-	-	-	208/243 (85.60)	-	-	-
						Black	-	-	-	11/16 (68.75)	-	-	-
						Asian	-	-	-	6/6 (100.00)	-	-	-
					Cirrhosis	Cirrhotic	-	-	-	20/26 (76.92)	-	-	-
						Non-cirrhotic	-	-	-	208/242 (85.95)	-	-	-
					IL28B	CC	-	-	-	51/53 (96.23)	-	-	-
						CT	-	-	-	132/161 (81.99)	-	-	-
						TT	-	-	-	44/53 (83.02)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Jacobson et al. (2016)[20]	USA, Argentina, Australia, Austria, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Poland, Russia, Spain, Switzerland, United Kingdom	RCT (3)	TN	TPV 750 mg TID + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 mg/day (< 75 kg) or 1,200 (≥ 75 kg) mg/day (12 wks)	GT	GT1b	72/62	48.0 (19-69)	-	109/134 (81.34)	108/134 (80.60)	-	20/131 (15.27)
					Race	White	-	-	-	105/129 (81.40)	-	-	-
						Black	-	-	-	2/3 (66.67)	-	-	-
						Asian	-	-	-	2/2 (100.00)	-	-	-
					Cirrhosis	Cirrhotic	-	-	-	10/15 (66.67)	-	-	-
						Non-cirrhotic	-	-	-	99/119 (83.19)	-	-	-
					IL28B	CC	-	-	-	23/27 (85.19)	-	-	-
						CT	-	-	-	69/86 (80.23)	-	-	-
						TT	-	-	-	17/21 (80.95)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Jensen et al. (2016)[21]	Australia, Germany, New Zealand, Poland, USA	RCT (2b)	TN	Lead-in MCB 1,000 mg BID + RBV 1,000 mg (< 75 kg) or 1,200 mg (≥ 75 kg) divided BID (2 wks) followed by (SET 800 mg BID on 1st day → 400 mg BID) + DAN 100 mg BID + RTV 100 mg BID + RBV (12 wks)	Cirrhosis, GT	Non-cirrhotic, GT1a	21/6	47.3 (8.3)	-	3/7 (42.86)	-	-	4/7 (57.14)
						Non-cirrhotic, GT1b	11/12	48.6 (13.5)	-	22/23 (95.65)	-	-	1/23 (4.35)
				Lead-in MCB 1,000 mg BID + RBV 1,000 mg (< 75 kg) or 1,200 mg (≥ 75 kg) divided BID (2 wks) followed by (SET 800 mg BID on 1st day → 400 mg BID) + DAN 100 mg BID + RTV 100 mg BID + RBV (24 wks)	Cirrhosis, GT	Non-cirrhotic, GT1a	15/12	47.2 (12.8)	-	20/27 (74.07) 33/47 (70.21)*	-	-	3/23 (13.04) 9/42 (21.43)*

*This included 20 patients whose treatment regimen was extended due to low SVR12 rates.

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Ruane et al. (2015)[22]	USA	RCT (2)	TN & TE	SOF 400 mg QD + RBV 1,000 mg/day (< 75 kg) or 1,200 mg/day (≥ 75 kg) (12 wks)	GT	GT4	22/9	53.0 (26-72)	-	21/31 (67.74)	-	-	-
					Sex	Male	-	-	-	13/22 (59.09)	-	-	-
						Female	-	-	-	8/9 (88.89)	-	-	-
					Age	< 65 years	-	-	-	19/27 (70.37)	-	-	-
						≥ 65 years	-	-	-	2/4 (50.00)	-	-	-
					Cirrhosis	Cirrhotic	-	-	-	3/7 (42.86)	-	-	-
						Non-cirrhotic	-	-	-	18/24 (75.00)	-	-	-
					IL28B	CC	-	-	-	4/4 (100.00)	-	-	-
						Non-CC	-	-	-	17/27 (62.96)	-	-	-
					Previous treatment	TN	-	-	-	11/14 (78.57)	-	-	-
						TE	-	-	-	10/17 (58.82)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Ruane et al. (2015)[22]	USA	RCT (2)	TN & TE	SOF 400 mg QD + RBV 1,000 mg/day (< 75 kg) or 1,200 mg/day (≥ 75 kg) (24 wks)	GT	GT4	19/10	55.0 (27-75)	-	27/29 (93.10)	-	-	-
					Sex	Male	-	-	-	17/19 (89.47)	-	-	-
						Female	-	-	-	10/10 (100.00)	-	-	-
					Age	< 65 years	-	-	-	20/20 (100.00)	-	-	-
						≥ 65 years	-	-	-	7/9 (77.78)	-	-	-
					Cirrhosis	Cirrhotic	-	-	-	7/7 (100.00)	-	-	-
						Non-cirrhotic	-	-	-	20/22 (90.91)	-	-	-
					IL28B	CC	-	-	-	6/6 (100.00)	-	-	-
						Non-CC	-	-	-	21/23 (91.30)	-	-	-
					Previous treatment	TN	-	-	-	14/14 (100.00)	-	-	-
						TE	-	-	-	13/15 (86.67)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Forns et al. (2015)[23] (TURQUOISE-II)	Multi-regions	RCT (3)	TN & TE	OBV 25 mg QD + PTV 150 mg QD + RTV 100 mg QD + DSV 250 mg BID + RBV 1,000 mg/day (< 75 kg) or 1,200 mg/day (≥ 75 kg) (12 wks)	Cirrhotic, GT1, Platelet count, Previous treatment	GT1a, Platelet count < $100*10^9$/L	36/9	55.4 (7.4)	-	27/31 (87.10)	-	-	-
						GT1b, Platelet count < $100*10^9$/L			-	13/14 (92.86)	-	-	-
						TN, Platelet count < $100*10^9$/L			-	15/17 (88.24)	-	-	-
						TE, Platelet count < $100*10^9$/L			-	25/28 (89.29)	-	-	-
					Cirrhotic, GT1, Albumin level, Previous treatment	GT1a, Albumin < 3.5 g/dL	22/3	55.9 (6.2)	-	12/16 (75.00)	-	-	-
						GT1b, Albumin < 3.5 g/dL			-	9/9 (100.00)	-	-	-
						TN, Albumin < 3.5 g/dL			-	10/11 (90.91)	-	-	-
						TE, Albumin < 3.5 g/dL			-	11/14 (78.57)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Forns et al. (2015)[23] (TURQUOISE-II)	Multi-regions	RCT (3)	TN & TE	OBV 25 mg QD + PTV 150 mg QD + RTV 100 mg QD + DSV 250 mg BID + RBV 1,000 mg/day (< 75 kg) or 1,200 mg/day (≥ 75 kg) (24 wks)	Cirrhotic, GT1, Platelet count, Previous treatment	GT1a, Platelet count < $100*10^9$/L	25/8	55.9 (7.6)	-	22/23 (95.65)	-	-	-
						GT1b, Platelet count < $100*10^9$/L			-	10/10 (100.00)	-	-	-
						TN, Platelet count < $100*10^9$/L			-	11/12 (91.67)	-	-	-
						TE, Platelet count < $100*10^9$/L			-	21/21 (100.00)	-	-	-
					Cirrhotic, GT1, Albumin level, Previous treatment	GT1a, Albumin < 3.5 g/dL	11/7	56.1 (10.3)	-	14/16 (87.50)	-	-	-
						GT1b, Albumin < 3.5 g/dL			-	2/2 (100.00)	-	-	-
						TN, Albumin < 3.5 g/dL			-	8/10 (80.00)	-	-	-
						TE, Albumin < 3.5 g/dL			-	8/8 (100.00)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Gane et al. (2015)[24]	New Zealand	RCT (2)	TN & TE	SOF 400 mg QD + LDV 90 mg QD (12 wks)	GT, Previous treatment	GT3, TN	13/12	43.0 (10.2)	17/25 (68.00)	16/25 (64.00)	-	-	8/25 (32.00)
						GT6, TN or TE	16/9	51.0 (13.9)	24/25 (96.00)	24/25 (96.00)	-	-	1/25 (4.00)
				SOF 400 mg QD + LDV 90 mg QD + RBV 1,000 or 1,200 mg/day divided BID (12 wks)		GT3, TN	11/15	48.0 (9.2)	26/26 (100.00)	26/26 (100.00)	-	-	0/25* (0.00)
						GT3, TE	39/11	52.0 (8.2)	42/50 (84.00)	41/50 (82.00)	-	-	8/50 (16.00)
Foster et al. (2015)[25] (ASTRAL-2)	USA	RCT (3)	TN & TE	SOF 400 mg QD + VEL 100 mg QD (12 wks)	GT	GT2	86/48	57.0 (26-81)	133/134 (99.25)	133/134 (99.25)	-	-	0/134 (0.00)
				SOF 400 mg QD + RBV 1,000 mg/day (< 75 kg) or 1,200 mg/day (≥ 75 kg) (12 wks)			72/60	57.0 (23-76)	127/132 (96.21)	124/132 (93.94)	-	-	6/132 (4.55)

*This included patients who had previous treatment and HCV genotype 6 infection.

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Foster et al. (2015)[25] (ASTRAL-3)	USA, Canada, France, Germany, Italy, United Kingdom, Australia, New Zealand	RCT (3)	TN & TE	SOF 400 mg QD + VEL 100 mg QD (12 wks)	GT	GT3	170/107	49.0 (21-76)	268/277 (96.75)	264/277 (96.75)	-	-	11/276 (3.99)
					GT3, Previous treatment, Cirrhosis	TN, Cirrhotic	-	-	-	40/43 (93.02)	-	-	-
						TN, Non-cirrhotic	-	-	-	160/163 (98.16)	-	-	-
						TE, Cirrhotic	-	-	-	33/37 (89.19)	-	-	-
						TE, Non-cirrhotic	-	-	-	31/34 (91.18)	-	-	-
				SOF 400 mg QD + RBV 1,000 mg/day (< 75 kg) or 1,200 mg/day (≥ 75 kg) (24 wks)	GT	GT3	174/101	50.0 (19-74)	225/275 (81.82)	221/275 (80.36)	-	-	38/272 (13.97)
					GT3, Previous treatment, Cirrhosis	TN, Cirrhotic	-	-	-	33/45 (73.33)	-	-	-
						TN, Non-cirrhotic	-	-	-	141/156 (90.38)	-	-	-
						TE, Cirrhotic	-	-	-	22/38 (57.89)	-	-	-
						TE, Non-cirrhotic	-	-	-	22/31 (70.97)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Kowdley et al. (2014)[32]	USA, Australia, Canada, France, Germany, New Zealand, United Kingdom, Puerto Rico, Spain	RCT (2b)	TN & TE	A	GT, Cirrhosis, Previous treatment	GT1, Non-cirrhotic, TN	46/34	50.1 (9.99)	-	-	70/80 (87.50)	-	-
				B			18/23	50.8 (9.84)	-	-	34/41 (82.93)	-	-
				C			25/14	51.1 (8.07)	-	-	33/39 (84.62)	-	-
				D			20/20	49.0 (10.59)	-	-	37/40 (92.50)	-	-
				E			45/34	48.3 (10.53)	-	-	70/79 (88.61)	-	-
				F			20/19	49.4 (9.72)	-	-	38/39 (97.44)	-	-
				G			24/16	51.0 (11.08)	-	-	38/40 (95.00)	-	-
				H			18/22	51.5 (11.95)	-	-	37/40 (92.50)	-	-
				I			16/24	51.5 (9.78)	-	-	36/40 (90.00)	-	-

❖ A: PTV 150 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (8 wks)

❖ B: PTV 150 mg QD + RTV 100 mg QD + DSV 400 mg BID + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (12 wks)

❖ C: PTV 100 mg QD + RTV 100 mg QD + OBV 25 mg QD + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (12 wks)

❖ D: PTV 200 mg QD + RTV 100 mg QD + OBV 25 mg QD+ RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (12 wks)

❖ E: PTV 150 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID (12 wks)

❖ F: PTV 100 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (12 wks)

❖ G: PTV 150 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (12 wks)

❖ H: PTV 100 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID+ RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (24 wks)

❖ I: PTV 150 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (24 wks)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Kowdley et al. (2014)[32]	USA, Australia, Canada, France, Germany, New Zealand, United Kingdom, Puerto Rico, Spain	RCT (2b)	TN & TE	J	GT, Cirrhosis, Previous treatment	GT1, Non-cirrhotic, TE	27/18	50.6 (11.19)	-	-	40/45 (88.89)	-	-
				K			16/7	48.5 (12.91)	-	-	21/23 (91.30)	-	-
				L			12/10	51.2 (12.07)	-	-	21/22 (95.45)	-	-
				M			15/8	51.5 (9.06)	-	-	21/23 (91.30)	-	-
				N			12/8	54.6 (11.78)	-	-	20/20 (100.00)	-	-

❖ J: PTV 200 mg QD + RTV 100 mg QD + OBV 25 mg QD + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (12 wks)

❖ K: PTV 100 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID+ RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (12 wks)

❖ L: PTV 150 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (12 wks)

❖ M: PTV 100 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (24 wks)

❖ N: PTV 150 mg QD + RTV 100 mg QD + OBV 25 mg QD + DSV 400 mg BID + RBV 1,000 (< 75 kg) or 1,200 mg/day (≥ 75 kg) divided BID (24 wks)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Everson et al. (2014)[33]	USA, France	RCT (2a)	TN	DCV 60 mg QD + ASV 200 mg BID + BCV 75 mg BID (24 wks)	GT, Cirrhosis	GT1, Non-cirrhotic	10/6	49.0 (44-61)	15/16 (93.75)	15/16 (93.75)	14/16 (87.50)	0/16 (0.00)	0/16 (0.00)
				DCV 60 mg QD + ASV 200 mg BID + BCV 75 mg BID (12 wks)			7/9	47.0 (24-67)	15/16 (93.75)	15/16 (93.75)	15/16 (93.75)	0/16 (0.00)	0/16 (0.00)
				DCV 60 mg QD + ASV 200 mg BID + BCV 150 mg BID (24 wks)			9/7	55.0 (25-67)	15/16 (93.75)	15/16 (93.75)	-	1/16 (6.25)	0/16 (0.00)
				DCV 60 mg QD + ASV 200 mg BID + BCV 150 mg BID (12 wks)			13/5	49.0 (29-68)	16/18 (88.89)	16/18 (88.89)	-	1/18 (5.56)	1/18 (5.56)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Zeuzem et al. (2014)[34] (ASPIRE)	USA, Australia, Austria, Belgium, Canada, France, Germany, Israel, New Zealand, Norway, Poland, Portugal, Russia, United Kingdom	RCT (2b)	TE	SMV 100 mg QD (12 wks) followed by pegIFN + RBV (36 wks)	GT	GT1	44/22	51.5 (20-68)	-	-	46/66 (69.70)	7/66 (10.61)	5/54 (9.26)
				SMV 100 mg QD (24 wks) followed by pegIFN + RBV (24 wks)			44/21	50.0 (20-68)	-	-	43/65 (66.15)	9/65 (13.85)	7/51 (13.73)
				SMV 100 mg QD + pegIFN + RBV (48 wks)			45/21	50.0 (22-69)	-	-	40/66 (60.61)	9/66 (13.64)	9/50 (18.00)
				SMV 150 mg QD (12 wks) followed by pegIFN + RBV (36 wks)			45/21	48.0 (20-63)	-	-	44/66 (66.67)	6/66 (9.09)	6/51 (11.76)
				SMV 150 mg QD (24 wks) followed by pegIFN + RBV (24 wks)			43/25	51.5 (25-68)	-	-	49/68 (72.06)	7/68 (10.29)	8/57 (14.04)
				SMV 150 mg QD + pegIFN + RBV (48 wks)			48/17	50.0 (21-69)	-	-	52/65 (80.00)	5/65 (7.69)	3/55 (5.45)

❖ pegIFN 180 μg SC QW + RBV 1,000 or 1,200 mg/d based on weight

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Lok et al. (2014)[35]	USA, Puerto Rico, France	RCT (2a)	TE	DCV 60 mg QD + ASV 200 mg BID (24 wks)	GT, Cirrhosis	GT1b, Non-cirrhotic	11/7	57.0	16/18 (88.89)	14/18 (77.78)	15/18 (83.33)	2/18 (11.11)	0/18 (0.00)
				DCV 60 mg QD + ASV 200 mg QD (24 wks)			13/7	54.0	13/20 (65.00)	13/20 (65.00)	12/20 (60.00)	6/20 (30.00)	1/20 (5.00)
				DCV 60 mg QD + ASV 200 mg BID + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (24 wks)		GT1a/1b, Non-cirrhotic	10/10	54.0	18/20 (90.00)	19/20 (95.00)	18/20 (90.00) GT1a: 15/17 (88.24) GT1b: 3/3 (100.00)	0/20 (0.00)	1/20 (5.00)
				DCV 60 mg QD + ASV 200 mg QD + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (24 wks)			12/9	50.0	20/21 (95.24)	20/21 (95.24)	20/21 (95.24) GT1a: 18/19 (94.74) GT1b: 2/2 (100.00)	0/21 (0.00)	1/21 (4.76)
				DCV 60 mg QD + ASV 200 mg BID + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (24 wks)			13/9	55.0	5/22 (22.73) GT1a: 1/18 (5.56) GT1b: 4/4 (100.00)	-	-	10/22 (45.45)	0/22 (0.00)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Rodriguez-Torres et al. (2014)[36]	N/A	RCT (2b)	TE	VAN 600 mg BID + pegIFN + RBV (24 wks)	GT, Cirrhosis	GT1, Cirrhotic	11/5	55.5 (48-62)	-	-	9/15 (60.00)	1/15 (6.67)	4/15 (26.67)
						GT1, Cirrhotic & Non-cirrhotic	-	-	-	-	36/53 (67.92)	-	-
				VAN 600 mg BID + pegIFN + RBV (24 wks) followed by Placebo + pegIFN + RBV (24 wks)		GT1, Cirrhotic	7/7	55.5 (42-65)	-	-	9/13 (69.23)	3/13 (23.08)	-
						GT1, Cirrhotic & Non-cirrhotic	-	-	-	-	41/51 (80.39)	-	-
				VAN 300 mg BID + pegIFN + RBV (48 wks)		GT1, Cirrhotic	11/4	54.0 (38-62)	-	-	8/15 (53.33)	1/15 (6.67)	4/15 (26.67)
						GT1, Cirrhotic & Non-cirrhotic	-	-	-	-	34/54 (62.96)	-	-
				VAN 600 mg BID + pegIFN + RBV (48 wks)		GT1, Cirrhotic	11/4	58.0 (45-63)	-	-	10/13 (76.92)	1/13 (7.69)	-
						GT1, Cirrhotic & Non-cirrhotic	-	-	-	-	42/54 (77.78)	-	-
				Placebo + pegIFN + RBV (48 wks)		GT1, Cirrhotic	9/5	52.0 (45-63)	-	-	2/14 (14.29)	-	-
						GT1, Cirrhotic & Non-cirrhotic	-	-	-	-	10/56 (17.86)	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Wyles et al. (2014)[37]	N/A	RCT (2)	TN	LDV 30 mg QD + VDV 200 mg QD + TGV 30 mg BID + RBV 1,000 (< 75 kg) 1,200 (≥ 75 kg) mg/day (24 wks)	GT, Cirrhosis	GT1, Non-cirrhotic	25/21	47.0 (21-67)	24/46 (52.17)	22/46 (47.83)	–	–	2/23* (8.70)
					GT, Cirrhosis	GT1a, Non-cirrhotic	–	–	–	15/35 (42.86)	–	–	–
						GT1b, Non-cirrhotic	–	–	–	7/11 (63.64)	–	–	–
					GT, Cirrhosis, IL28B	GT1, Non-cirrhotic, CC	–	–	–	11/16 (68.75)	–	–	–
						GT1, Non-cirrhotic, Non-CC	–	–	–	11/30 (36.67)	–	–	–
				LDV 90 mg QD + VDV 200 mg QD + TGV 30 mg BID + RBV 1,000 (< 75 kg) 1,200 (≥ 75 kg) mg/day (12 or 24 wks based on response at wk 2)	GT, Cirrhosis	GT1, Non-cirrhotic	55/39	49.0 (18-66)	62/94 (65.96)	55/94 (58.51)	–	–	7/64* (10.94)
					GT, Cirrhosis	GT1a, Non-cirrhotic	–	–	–	39/68 (57.35)	–	–	–
						GT1b, Non-cirrhotic	–	–	–	17/26 (65.38)	–	–	–
					GT, Cirrhosis, IL28B	GT1, Non-cirrhotic, CC	–	–	–	23/37 (62.16)	–	–	–
						GT1, Non-cirrhotic, Non-CC	–	–	–	33/57 (57.89)	–	–	–

*Among patients who completed treatment

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Forns et al. (2014)[38]	USA, Australia, Austria, Belgium, Canada, France, Germany, New Zealand, Poland, Puerto Rico, Russia, Spain, United Kingdom	RCT (3)	TE	SMV 150 mg QD + pegIFN alpha-2a 180 μg QW + RBV 1,000-1,200 mg/day (12 wks) followed by pegIFN + RBV (12 or 36 wks by response-guided treatment)	GT	GT1	179/81	52.0 (20-70)	-	206/260 (79.23)	-	-	46/249 (18.47)
					GT	GT1a	-	-	-	76/109 (69.72)	-	-	-
						GT1b	-	-	-	128/149 (85.91)	-	-	-
					IL28B	CC	-	-	-	55/62 (88.71)	-	-	-
						CT	-	-	-	131/167 (78.44)	-	-	-
						TT	-	-	-	20/31 (64.52)	-	-	-
					METAVIR fibrosis score	F0-F2	-	-	-	137/167 (82.04)	-	-	-
						F3-F4	-	-	-	61/83 (73.49)	-	-	-
						F3	-	-	-	32/44 (72.73)	-	-	-
						F4	-	-	-	29/39 (74.36)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Forns et al. (2014)[38]	USA, Australia, Austria, Belgium, Canada, France, Germany, New Zealand, Poland, Puerto Rico, Russia, Spain, United Kingdom	RCT (3)	TE	Placebo QD + pegIFN alpha-2a 180 μg QW + RBV 1,000-1,200 mg/day (12 wks) followed by pegIFN + RBV (36 wks)	GT	GT1	79/54	52.0 (21-71)	-	48/133 (36.09)	-	-	45/93 (48.39)
					GT	GT1a	-	-	-	15/54 (27.78)	-	-	-
						GT1b	-	-	-	34/79 (43.04)	-	-	-
					IL28B	CC	-	-	-	18/34 (52.94)	-	-	-
						CT	-	-	-	28/83 (33.73)	-	-	-
						TT	-	-	-	3/16 (18.75)	-	-	-
					METAVIR fibrosis score	F0-F2	-	-	-	40/98 (40.82)	-	-	-
						F3-F4	-	-	-	8/34 (23.53)	-	-	-
						F3	-	-	-	3/15 (20.00)	-	-	-
						F4	-	-	-	5/19 (26.32)	-	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Manns et al. (2014)[39]	USA, Argentina, Canada, France, Germany, Israel, Italy, Puerto Rico	RCT (2)	TN	GZR **100 mg** QD + pegIFN alpha-2b 1.5 μg/kg/wk SC + RBV 300-700 mg BID (12 wks) followed by pegIFN alpha-2b + RBV (12 or 36 wks by response-guided therapy	GT, Cirrhosis	GT1, Non-cirrhotic	41/25	49.0 (18-65)	-	59/66 (89.39)	59/66 (89.39)	-	-
					GT, Cirrhosis	GT1a, Non-cirrhotic	-	-	-	-	36/43 (83.72)	-	-
						GT1b, Non-cirrhotic	-	-	-	-	23/23 (100.00)	-	-
					GT, Cirrhosis, IL28B	GT1, Non-cirrhotic, CC	-	-	-	-	17/17 (100.00)	-	-
						GT1, Non-cirrhotic, Non-CC	-	-	-	-	42/49 (85.71)	-	-
				GZR **200 mg** QD + pegIFN alpha-2b 1.5 μg/kg/wk SC + RBV 300-700 mg BID (12 wks) followed by pegIFN alpha-2b + RBV (12 or 36 wks by response-guided therapy	GT, Cirrhosis	GT1, Non-cirrhotic	36/32	50.0 (18-71)	-	62/68 (91.18)	63/68 (92.65)	-	-
					GT, Cirrhosis	GT1a, Non-cirrhotic	-	-	-	-	37/41 (90.24)	-	-
						GT1b, Non-cirrhotic	-	-	-	-	26/27 (96.30)	-	-
					GT, Cirrhosis, IL28B	GT1, Non-cirrhotic, CC	-	-	-	-	18/19 (94.74)	-	-
						GT1, Non-cirrhotic, Non-CC	-	-	-	-	44/49 (89.80)	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Manns et al. (2014)[39]	USA, Argentina, Canada, France, Germany, Israel, Italy, Puerto Rico	RCT (2)	TN	GZR **400 mg** QD + pegIFN alpha-2b 1.5 μg/kg/wk SC + RBV 300-700 mg BID (12 wks) followed by pegIFN alpha-2b + RBV (12 or 36 wks by response-guided therapy	GT, Cirrhosis	GT1, Non-cirrhotic	40/27	49.0 (20-68)	-	61/67 (91.04)	61/67 (91.04)	-	-
					GT, Cirrhosis	GT1a, Non-cirrhotic	-	-	-	-	31/37 (83.78)	-	-
						GT1b, Non-cirrhotic	-	-	-	-	28/28 (100.00)	-	-
					GT, Cirrhosis, IL28B	GT1, Non-cirrhotic, CC	-	-	-	-	16/17 (94.12)	-	-
						GT1, Non-cirrhotic, Non-CC	-	-	-	-	45/50 (90.00)	-	-
				GZR **800 mg** QD + pegIFN alpha-2b 1.5 μg/kg/wk SC + RBV 300-700 mg BID (12 wks) followed by pegIFN alpha-2b + RBV (12 or 36 wks by response-guided therapy	GT, Cirrhosis	GT1, Non-cirrhotic	37/28	54.0 (21-72)	-	56/65 (86.15)	56/65 (86.15)	-	-
					GT, Cirrhosis	GT1a, Non-cirrhotic	-	-	-	-	30/37 (81.08)	-	-
						GT1b, Non-cirrhotic	-	-	-	-	26/28 (92.86)	-	-
					GT, Cirrhosis, IL28B	GT1, Non-cirrhotic, CC	-	-	-	-	14/18 (77.78)	-	-
						GT1, Non-cirrhotic, Non-CC	-	-	-	-	42/47 (89.36)	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Zeuzem et al. (2013)[40] (SOUND-C1)	Australia, Austria, France, Germany, New Zealand, Portugal, Romania, Spain, Switzerland, USA	RCT (1b)	TN	DBV **400 mg** TID + FDV 120 mg QD + weight-based RBV (4 wks) followed by response-guided FDV 120 mg QD + pegIFN alpha-2a + RBV to wk 24 or 48	GT	GT1	8/7	50.8 (10.0)	-	-	11/15 (73.33)	-	-
				DBV **600 mg** TID + FDV 120 mg QD + weight-based RBV (4 wks) followed by response-guided FDV 120 mg QD + pegIFN alpha-2a + RBV to wk 24 or 48			10/7	50.8 (11.5)	-	-	16/17 (94.12)	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Zeuzem et al. (2013)[41] (SOUND-C2)	Australia, Austria, France, Germany, New Zealand, Portugal, Romania, Spain, Switzerland, USA	RCT (2b)	TN	FDV 120 mg QD + DBV 600 mg TID + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (**16 wks**)	GT	GT1a	45/36	48.6 (11.33)	–	13/34 (38.24)	–	8/34 (23.53)	9/22 (40.91)
						GT1b			–	35/47 (74.47)	–	1/47 (2.13)	2/37 (5.41)
					GT, IL28B	GT1, CC	–	–	–	14/21 (66.67)	–	–	–
						GT1, Non-CC	–	–	–	34/60 (56.67)	–	–	–
				FDV 120 mg QD + DBV 600 mg TID + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (**28 wks**)	GT	GT1a	41/39	47.3 (11.21)	–	14/32 (43.75)	–	11/32 (34.38)	0/15 (0.00)
						GT1b			–	33/48 (68.75)	–	3/48 (6.25)	1/35 (2.86)
					GT, IL28B	GT1, CC	–	–	–	14/21 (66.67)	–	–	–
						GT1, Non-CC	–	–	–	32/58 (55.17)	–	–	–
				FDV 120 mg QD + DBV 600 mg TID + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (**40 wks**)	GT	GT1a	36/41	48.9 (10.68)	–	16/34 (47.06)	–	7/34 (20.59)	1/17 (5.88)
						GT1b			–	24/43 (55.81)	–	8/43 (18.60)	0/25 (0.00)
					GT, IL28B	GT1, CC	–	–	–	12/19 (63.16)	–	–	–
						GT1, Non-CC	–	–	–	28/58 (42.28)	–	–	–

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Zeuzem et al. (2013)[41] (SOUND-C2)	Australia, Austria, France, Germany, New Zealand, Portugal, Romania, Spain, Switzerland, USA	RCT (2b)	TN	FDV 120 mg QD + DBV 600 mg **BID** + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (**28 wks**)	GT	GT1a	41/37	47.9 (11.14)	-	13/30 (43.33)	-	14/30 (46.67)	0/13 (0.00)
						GT1b			-	41/48 (85.42)	-	4/48 (8.33)	0/41 (0.00)
					GT, IL28B	GT1, CC	-	-	-	16/19 (84.21)	-	-	-
						GT1, Non-CC	-	-	-	38/59 (64.41)	-	-	-
				FDV 120 mg QD + DBV 600 mg TID (**28 wks**)	GT	GT1a	24/22	45.3 (12.96)	-	2/18 (11.11)	-	10/18 (55.56)	1/4 (25.00)
						GT1b			-	16/28 (57.14)	-	9/28 (32.14)	1/17 (5.88)
					GT, IL28B	GT1, CC	-	-	-	7/12 (58.33)	-	-	-
						GT1, Non-CC	-	-	-	11/33 (33.33)	-	-	-
Lok et al. (2012)[42]	USA	RCT (2a)	TE	DCV 60 mg QD + ASV 600 mg BID (24 wks)	GT, Cirrhosis	GT1, Non-cirrhotic	9/2	54.0 (36-61)	4/11 (36.36)	4/11 (36.36)	4/11 (36.36)	6/11 (54.55)	1/11 (9.09)
				DCV 60 mg QD + ASV 600 mg BID + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (24 wks)			4/6	56.5 (38-63)	10/10 (100.00)	10/10 (100.00)	9/10 (90.00)	-	-

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Pol et al. (2012)[43]	USA, France	RCT (2a)	TN	DCV **3 mg** QD + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (48 wks)	GT, Cirrhosis	GT1, Non-cirrhotic	9/3	52.0 (38-66)	-	5/12 (41.67)	5/12 (41.67)	2/12 (16.67)	2/12 (16.67)
				DCV **10 mg** QD + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (48 wks)			8/4	50.5 (37-68)	-	11/12 (91.67)	10/12 (83.33)	0/12 (0.00)	1/12 (8.33)
				DCV **60 mg** QD + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (48 wks)			7/5	51.0 (43-67)	-	10/12 (83.33)	10/12 (83.33)	1/12 (8.33)	1/12 (8.33)
				Placebo QD + pegIFN alpha-2a 180 μg SC QW + RBV 1,000 (< 75 kg) or 1,200 (≥ 75 kg) mg/day (48 wks)			8/4	49.5 (28-67)	-	3/12 (25.00)	3/12 (25.00)	0/12 (0.00)	5/12 (41.67)

Table 6. (*continued*)

Study (Year)	Region	Study design (Phase)	Previous treatment status	Regimen	Category of subgroups	Subgroups	Gender (male/female)	Median or mean age (range or SD), years	SVR, n/N (%)			Virologic failure, n/N (%)	
									SVR4	SVR12	SVR24	Breakthrough	Relapse
Zeuzem et al. (2011)[44]	Australia, Israel, Europe, North American, South America	RCT (3)	TE	A	GT, Previous treatment	GT1, Previous relapse	183/83	51.0 (23-69)	-	-	121/145 (83.45)	-	-
						GT1, Previous partial response			-	-	29/49 (59.18)	-	-
						GT1, No previous response			-	-	21/72 (29.17)	-	-
				B		GT1, Previous relapse	189/75	51.0 (24-70)	-	-	124/141 (87.94)	-	-
						GT1, Previous partial response			-	-	26/48 (54.17)	-	-
						GT1, No previous response			-	-	25/75 (33.33)	-	-
				C		GT1, Previous relapse	88/44	50.0 (21-69)	-	-	16/68 (23.53)	-	-
						GT1, Previous partial response			-	-	4/27 (14.81)	-	-
						GT1, No previous response			-	-	2/37 (5.41)	-	-

❖ A: TPV 750 mg TID + pegIFN alpha-2a 180 μg SC QW + RBV 1,000-1,200 mg/day (12 wks) followed by placebo + pegIFN + RBV (4 wks) then pegIFN + RBV (32 wks)

❖ B: Placebo + pegIFN alpha-2a 180 μg SC QW + RBV 1,000-1,200 mg/day (4 wks) followed by TPV 750 mg TID + pegIFN + RBV (12 wks) then pegIFN + RBV (32 wks)

❖ C: Placebo + pegIFN alpha-2a 180 μg SC QW + RBV 1,000-1,200 mg/day (16 wks) followed by pegIFN + RBV (32 wks)

Table 7. Safety of different drug combination regimens for the treatment of patients with HCV infection

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Zeuzem et al. (2018)[8] (ENDURANCE-1/3)	GLE + PIB (8 wks)	GT	GT1	216/351 (61.54)	68/351 (19.37)	31/351 (8.83)	19/351 (5.41)	–	–	–	5/351 (1.42)	0/351 (0.00)	0/351 (0.00)
			GT3	98/157 (62.42)	31/157 (19.75)	20/157 (12.74)	19/157 (12.10)	–	–	–	3/157 (1.91)	0/157 (0.00)	1/157 (0.64)
	GLE + PIB (12 wks)		GT1	234/352 (66.48)	62/352 (17.61)	43/352 (12.22)	29/352 (8.24)	–	–	–	4/352 (1.14)	1/352 (0.28)	1/352 (0.28)
			GT3	177/233 (75.97)	60/233 (25.75)	44/233 (18.88)	32/233 (13.73)	–	–	–	5/233 (2.15)	3/233 (1.29)	0/233 (0.00)
	SOF + DCV (12 wks)		GT3	80/115 (69.57)	23/115 (20.00)	16/115 (13.91)	15/115 (13.04)	–	–	–	2/115 (1.74)	1/115 (0.87)	1/115 (0.87)
Bourgeois et al. (2017)[9]	SMV + TMC647055/RTV + JNJ-56914845 30 mg (12 wks)	GT	GT1a/b/other	20/22 (90.91)	–	–	–	–	–	–	0/22 (0.00)	0/22 (0.00)	0/22 (0.00)
	SMV + TMC647055/RTV + JNJ-56914845 60 mg (12 wks)		GT1a/b/other	22/22 (100.00)	–	–	–	–	–	–	0/22 (0.00)	0/22 (0.00)	0/22 (0.00)
Toyota et al. (2017)[10]	DCV + ASV + BCV (12 wks)	Previous treatment	TN GT1b	–	13/149 (8.72)	–	–	12/149 (8.05)	–	–	10/149 (6.71) 6/149* (4.03)	17/149 (11.41)	0/149 (0.00)
			TE GT1b	–	10/64 (15.63)	–	–	7/64 (10.94)	–	–	2/64 (3.13) 1/64* (1.56)	4/64 (6.25)	0/64 (0.00)
	DCV + ASV (24 wks)		TN GT1b	–	7/75 (9.33)	–	–	10/75 (13.33)	–	–	8/75 (10.67) 2/75* (2.67)	7/75 (9.33)	0/75 (0.00)

*Treatment-related serious AEs

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Bourliere et al. (2017)[11] (POLARIS-1/4)	SOF + VEL + VOX (12 wks)	GT	GT1a/b, GT2, GT3, GT4, GT5, GT6	206/263 (78.33)	66/263 (25.10)	56/263 (21.29)	37/263 (14.07)	47/263 (17.87)	19/263 (7.22)	-	5/263 (1.90)	1/263 (0.38)	0/263 (0.00)
	SOF + VEL + VOX (12 wks)	GT	GT1a/b, GT2, GT3, GT4	140/182 (76.92)	50/182 (27.47)	43/182 (23.62)	22/182 (12.09)	36/182 (19.78)	12/182 (6.59)	-	4/182 (2.20)	0/182 (0.00)	1/182 (0.55)
	SOF + VEL (12 wks)	GT	GT1a/b, GT2, GT3	111/151 (73.51)	43/151 (28.48)	43/151 (28.48)	12/151 (7.95)	7/151 (4.64)	3/151 (1.99)	-	4/151 (2.65)	1/151 (0.66)	0/151 (0.00)
Lawitz et al. (2017)[12]	SOF + VEL + VOX (12 wks)	GT	GT1	11/24 (45.83)	-	0/24 (0.00)	0/24 (0.00)	3/24 (12.50)	-	0/24 (0.00)	1/24 (4.17)	0/24 (0.00)	0/24 (0.00)
	SOF + VEL + VOX + RBV (12 wks)	GT	GT1	15/25 (60.00)	-	9/25 (36.00)	2/25 (8.00)	0/25 (0.00)	-	4/25 (16.00)	0/25 (0.00)	0/25 (0.00)	0/25 (0.00)
Sato et al. (2017)[13] (GIFT-II)	OBV + PTV + RTV + RBV (12 wks)	Cirrhosis	Cirrhotic	3/5 (60.00)	-	-	-	-	-	-	0/5 (0.00)	0/5 (0.00)	0/5 (0.00)
		Cirrhosis	Non-cirrhotic	66/80 (82.50)	-	-	-	-	-	-	0/80 (0.00)	0/80 (0.00)	0/80 (0.00)
	OBV + PTV + RTV + RBV (16 wks)	Cirrhosis	Cirrhotic	4/6 (66.67)	-	-	-	-	-	-	0/6 (0.00)	0/6 (0.00)	0/6 (0.00)
		Cirrhosis	Non-cirrhotic	70/80 (87.50)	-	-	-	-	-	-	3/80 (3.75)	0/80 (0.00)	0/80 (0.00)

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Jacobson et al. (2017)[14] (POLARIS-2/3)	SOF + VEL + VOX (8 wks)	GT	GT1a/b, GT2, GT3, GT4, GT5 GT6	361/501 (72.06)	134/501 (26.75)	106/501 (21.16)	80/501 (15.97)	88/501 (17.56)	25/501 (4.99)	_	15/501 (2.99)	0/501 (0.00)	0/501 (0.00)
	SOF + VEL (12 wks)		GT1a/b, GT2, GT3, GT4, GT6	303/440 (68.86)	99/440 (22.50)	90/440 (20.45)	40/440 (9.09)	32/440 (7.27)	21/440 (0.48)	_	7/440 (1.59)	2/440 (0.05)	0/440 (0.00)
	SOF + VEL + VOX (8 wks)	Cirrhosis, GT	Cirrhotic, GT3	83/110 (75.45)	27/110 (24.55)	28/110 (25.45)	23/110 (20.91)	17/110 (15.45)	6/110 (5.45)	_	2/110 (1.82)	0/110 (0.00)	1/110 (0.91)
	SOF + VEL (12 wks)			81/109 (74.31)	32/109 (29.36)	31/109 (28.44)	10/109 (9.17)	5/109 (4.59)	5/109 (4.59)	_	3/109 (2.75)	1/109 (0.92)	0/109 (0.00)
Poordad et al. (2017)[15] (MAGELLAN-1)	GLE 200 mg + PIB 80 mg (12 wks)	Cirrhosis, GT	Non-cirrhotic, GT1	5/6 (83.33)	1/5 (20.00)	1/5 (20.00)	1/5 (20.00)	_	0/5 (0.00)	_	_	0/5 (0.00)	_
	GLE 300 mg +PIB 80 mg + RBV (12 wks)			19/22 (86.36)	5/22 (22.73)	8/22 (36.36)	6/22 (27.27)	_	6/22 (27.27)	_	_	0/22 (0.00)	_
	GLE 300 mg + PIB 120 mg (12 wks)			18/22 (81.82)	8/22 (36.36)	4/22 (18.18)	3/22 (1.36)	_	0/22 (0.00)	_	_	0/22 (0.00)	_
Hezode et al. (2017)[16]	EBV + GZR (12 wks)	GT	GT1a/b, GT4	77/107 (71.96)	23/107 (21.50)	18/107 (16.82)	9/107 (8.41)	_	_	_	3/107 (2.80)	0/107 (0.00)	0/107 (0.00)

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Dore et al. (2016)[17] (MALACHITE-I/II)	OBV + PTV + RTV + DSV + RBV (12 wks)	Previous treatment, GT	TN, GT1a/b	115/153 (75.16)	41/153 (26.80)	21/153 (13.73)	32/153 (20.92)	-	14/153 (9.15)	10/153 (18.87)	1/153 (0.65)	1/153 (0.65)	-
	OBV + PTV + RTV + DSV (12 wks)			41/83 (49.40)	16/83 (19.28)	4/83 (4.82)	7/83 (8.43)	-	0/83 (0.00)	1/83 (1.20)	0/83 (0.00)	0/83 (0.00)	-
	TPV + pegIFN + RBV (12 wks)			74/75 (98.67)	23/75 (30.67)	23/75 (30.67)	30/75 (40.00)	-	7/75 (9.33)	34/75 (45.33)	9/75 (12.00)	6/75 (8.00)	-
	OBV + PTV + RTV + DSV + RBV (12 wks)	Previous treatment, GT	TE, GT1	63/101 (62.38)	29/101 (28.71)	12/101 (11.88)	10/101 (9.90)	-	6/101 (5.94)	3/101 (2.97)	1/101 (0.99)	0/101 (0.00)	-
	TPV + pegIFN + RBV (12 wks)			43/47 (91.49)	21/47 (44.68)	12/47 (25.53)	20/47 (42.55)	-	10/47 (2.13)	16/47 (34.04)	5/47 (10.64)	5/47 (10.64)	-
Everson et al. (2016)[18]	DCV + ASV + BCV 75 mg (12 wks)	Previous treatment, Cirrhosis, GT	TN, Cirrhotic/ Non-cirrhotic, GT1a/b	-	17/80 (21.25)	12/80 (15.00)	10/80 (12.50)	12/80 (15.00)	-	-	-	1/80 (1.25)	-
	DCV + ASV + BCV 150 mg (12 wks)			-	24/86 (27.91)	7/86 (8.14)	7/86 (8.14)	13/86 (15.12)	-	-	-	1/86 (1.16)	-
	DCV + ASV + BCV 75 mg + RBV (12 wks)			-	3/21 (14.29)	4/21 (19.05)	2/21 (9.52)	3/21 (14.29)	-	-	-	0/21 (0.00)	-

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Zeuzem et al. (2016)[19]	DCV + SMV (12 wks or 24 wks)	Previous treatment, Cirrhosis, GT	TN, TE, Cirrhotic/ Non-cirrhotic, GT1b	57/76 (75.00)	16/76 (21.05)	6/76 (7.89)	14/76 (18.42)	-	-	11/76 (14.47)	7/76 (9.21)	2/76 (2.63)	1/76 (1.32)
	DCV + SMV + RBV (12 wks or 24 wks)		TN, TE, Cirrhotic/ Non-cirrhotic, GT1a/b	88/92 (95.65)	16/92 (17.39)	18/92 (19.57)	15/92 (16.30)	-	-	1/92 (1.09)	4/92 (4.35)	2/92 (2.17)	0/92 (0.00)
Jacobson et al. (2016)[20]	DCV + pegIFN +RBV (24 wks)	Previous treatment, Cirrhosis, GT	TN, Cirrhotic/ Non-cirrhotic, GT1	-	137/402 (34.08)	140/402 (34.83)	88/402 (21.89)	-	-	96/402 (23.88)	26/402 (6.47)	28/402 (6.97)	1/402 (0.25)
	DCV + pegIFN +RBV (12 wks)			-	57/200 (28.50)	81/200 (40.50)	74/200 (37.00)	-	-	99/200 (49.50)	20/200 (10.00)	37/200 (18.50)	1/200 (0.50)
Jensen et al. (2016)[21]	Lead-in MCB + RBV (2 wks) followed by SET + DAN + RTV + RBV (12 wks)	Previous treatment, Cirrhosis, GT	TN, Non-cirrhotic, GT1a/b	49/50 (98.00)	17/50 (34.00)	19/50 (38.00)	8/50 (16.00)	8/50 (16.00)	8/50 (16.00)	-	0/50 (0.00)	1/50 (2.00)	0/50 (0.00)
	Lead-in MCB + RBV (2 wks) followed by SET + DAN + RTV + RBV (24 wks)		TN, Non-cirrhotic, GT1a	25/27 (92.59)	10/27 (37.04)	9/27 (33.33)	10/27 (37.04)	5/27 (18.52)	3/27 (11.11)	-	0/27 (0.00)	0/27 (0.00)	0/27 (0.00)

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Ruane et al. (2015)[22]	SOF + RBV (12 wks)	Previous treatment, Cirrhosis, GT	TN, TE, Cirrhotic/ Non-cirrhotic, GT4	28/31 (90.32)	18/31 (58.06)	14/31 (45.16)	2/31 (6.45)	1/31 (3.23)	16/31 (51.61)	_	0/31 (0.00)	0/31 (0.00)	_
	SOF + RBV (24 wks)			29/29 (100.00)	19/29 (65.52)	15/29 (51.72)	6/29 (20.69)	6/29 (20.69)	14/29 (48.28)	_	3/29 (10.34)	0/29 (0.00)	_
Forns et al. (2015)[23] (TURQUOISE -II)	OBV + PTV + RTV + DSV + RBV (12 wks or 24 wks	Previous treatment, Cirrhosis, GT, Platelet	TN, TE, Cirrhotic, GT1, Platelet < 100*10^9/L	73/78 (93.59)	23/78 (29.49)	30/78 (38.46)	16/78 (20.51)	14/78 (17.95)	14/78 (17.95)	10/78 (12.82)	5/78 (6.41)	2/78 (2.56)	_
		Previous treatment, Cirrhosis, GT, Albumin	TN, TE, Cirrhotic, GT1, Albumin < 3.5 g/dL	38/43 (88.37)	12/43 (27.91)	17/43 (39.53)	6/43 (13.95)	10/43 (23.26)	8/43 (18.60)	4/43 (9.30)	6/43 (13.95)	2/43 (4.65)	_
Gane et al. (2015)[24]	SOF + LDV (12 wks)	Previous treatment, GT	TN, GT3	25/25 (100.00)	10/25 (40.00)	5/25 (20.00)	9/25 (36.00)	2/25 (8.00)	3/25 (12.00)	0/25 (0.00)	4/25 (16.00)	1/25 (4.00)	0/25 (0.00)
			TN, TE, GT6	21/25 (84.00)	2/25 (8.00)	6/25 (24.00)	0/25 (0.00)	4/25 (16.00)	0/25 (0.00)	0/25 (0.00)	1/25 (4.00)	0/25 (0.00)	0/25 (0.00)
	SOF + LDV + RBV (12 wks)		TN, GT3	23/26 (88.46)	8/26 (30.77)	2/26 (7.69)	4/26 (15.38)	0/26 (0.00)	3/26 (11.54)	4/26 (15.38)	0/26 (0.00)	0/26 (0.00)	0/26 (0.00)
			TE, GT3	45/50 (90.00)	13/50 (26.00)	13/50 (26.00)	5/50 (10.00)	4/50 (8.00)	10/50 (20.00)	1/50 (2.00)	1/50 (2.00)	0/50 (0.00)	0/50 (0.00)
Foster et al. (2015)[25] (ASTRAL-2/3)	SOF + VEL (12 wks)	Previous treatment, GT	TN, TE, GT2	92/134 (68.66)	24/134 (17.91)	20/134 (14.93)	14/134 (10.45)	_	6/134 (4.48)	_	2/134 (1.49)	1/134 (0.75)	2/134 (1.49)
	SOF + RBV (12 wks)			101/132 (76.52)	29/132 (21.97)	47/132 (35.61)	19/132 (14.39)	_	18/132 (13.64)	_	2/132 (1.52)	0/132 (0.00)	0/132 (0.00)
	SOF + VEL (12 wks)	Previous treatment, Cirrhosis, GT	TN, TE, Cirrhotic/ Non-cirrhotic, GT3	245/277 (88.45)	90/277 (32.49)	71/277 (25.63)	46/277 (16.61)	_	31/277 (11.19)	_	6/277 (2.17)	0/277 (0.00)	0/277 (0.00)
	SOF + RBV (24 kws)			260/275 (94.55)	89/275 (32.36)	105/275 (38.18)	58/275 (21.09)	_	74/275 (26.91)	_	15/275 (5.45)	9/275 (3.27)	3/275 (1.09)

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Kowdley et al. (2014)[32]	Group 1	Previous treatment, Cirrhosis, GT	TN, Non-cirrhotic, GT1	-	28/80 (35.00)	29/80 (36.25)	12/80 (15.00)	8/80 (10.00)	10/80 (12.50)	5/80 (6.25)	0/80 (0.00)	1/80 (1.25)	-
	Group 2			-	13/41 (31.71)	13/41 (31.71)	7/41 (17.07)	10/41 (24.39)	8/41 (19.51)	1/41 (2.44)	0/41 (0.00)	0/41 (0.00)	-
	Group 3			-	23/79 (29.11)	22/79 (27.85)	16/79 (20.25)	8/79 (10.13)	9/79 (11.39)	3/79 (3.80)	2/79 (2.53)	0/79 (0.00)	-
	Group 4			-	15/79 (18.99)	16/79 (20.25)	11/79 (13.92)	13/79 (16.46)	6/79 (7.59)	1/79 (1.27)	2/79 (2.53)	0/79 (0.00)	-
	Group 5			-	21/79 (26.58)	22/79 (27.85)	19/79 (24.05)	10/79 (12.66)	16/79 (20.25)	7/79 (8.86)	1/79 (1.27)	2/79 (2.53)	-
	Group 6			-	29/80 (36.25)	30/80 (37.50)	20/80 (25.00)	11/80 (13.75)	20/80 (25.00)	6/80 (7.50)	1/80 (1.25)	3/80 (3.75)	-
	Group 7		TE, Non-cirrhotic, GT1	-	15/45 (33.33)	12/45 (26.67)	6/45 (13.33)	7/45 (15.56)	8/45 (17.78)	3/45 (6.67)	0/45 (0.00)	1/45 (2.22)	-
	Group 8			-	13/45 (28.89)	12/45 (26.67)	9/45 (20.00)	8/45 (17.78)	6/45 (13.33)	3/45 (6.67)	0/45 (0.00)	0/45 (0.00)	-
	Group 9			-	14/43 (32.56)	9/43 (20.93)	8/43 (18.60)	8/43 (18.60)	7/43 (16.28)	2/43 (4.65)	2/43 (4.65)	1/43 (2.33)	-

❖ Group 1: PTV + RTV + OBV + DSV + RBV (8 wks)
❖ Group 2: PTV + RTV + DSV + RBV (12 wks)
❖ Group 3: PTV + RTV + OBV + RBV (12 wks)
❖ Group 4: PTV + RTV + OBV + DSV (12 wks)
❖ Group 5: PTV + RTV + OBV + DSV + RBV (12 wks)
❖ Group 6: PTV + RTV + OBV + DSV + RBV (24 wks)
❖ Group 7: PTV + RTV + OBV + RBV (12 wks)
❖ Group 8: PTV + RTV + OBV + DSV + RBV (12 wks)
❖ Group 9: PTV + RTV + OBV + DSV + RBV (24 wks)

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Everson et al. (2014)[33]	DCV + ASV + BCV 75 mg (24 wks)	Previous treatment, Cirrhosis, GT	TN, Non-cirrhotic, GT1	-	4/16 (25.00)	-	1/16 (6.25)	2/16 (12.50)	-	-	0/16 (0.00)	0/16 (0.00)	-
	DCV + ASV + BCV 75 mg (12 wks)			-	6/16 (37.50)	-	2/16 (12.50)	6/16 (37.50)	-	-	1/16 (6.25)	0/16 (0.00)	-
	DCV + ASV + BCV 150 mg (24 wks)			-	4/16 (25.00)	-	2/16 (12.50)	2/16 (12.50)	-	-	0/16 (0.00)	0/16 (0.00)	-
	DCV + ASV + BCV 150 mg (12 wks)			-	4/18 (22.22)	-	4/18 (22.22)	1/18 (5.56)	-	-	0/18 (0.00)	0/18 (0.00)	-
Zeuzem et al. (2014)[34] (ASPIRE)	SMV 100 mg (12 wks) followed by pegIFN + RBV (36 wks)	Previous treatment, GT	TE, GT1	-	18/66 (27.27)	30/66 (45.45)	-	-	-	15/66 (22.73)	3/66 (4.55)	7/66 (10.6)	-
	SMV 100 mg (24 wks) followed by pegIFN + RBV (24 wks)			-	19/65 (29.23)	28/65 (43.08)	-	-	-	11/65 (16.92)	5/65 (7.69)	4/65 (6.15)	-
	SMV 100 mg + pegIFN + RBV (48 wks)			-	23/66 (34.85)	34/66 (51.52)	-	-	-	12/66 (18.18)	3/66 (4.55)	5/66 (7.58)	-
	SMV 150 mg (12 wks) followed by pegIFN + RBV (36 wks)			-	29/66 (43.94)	26/66 (39.39)	-	-	-	10/66 (15.15)	7/66 (10.61)	5/66 (7.58)	-
	SMV 150 mg (24 wks) followed by pegIFN + RBV (24 wks)			-	26/68 (38.24)	28/68 (41.18)	-	-	-	16/68 (23.53)	5/68 (7.35)	7/68 (10.29)	-
	SMV 150 mg + pegIFN + RBV (48 wks)			-	24/65 (36.92)	28/65 (43.08)	-	-	-	13/65 (20.00)	8/65 (12.31)	7/65 (10.77)	-

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Lok et al. (2014)[35]	DCV + ASV BID (24 wks)	Previous treatment, Cirrhosis, GT	TE, Non-cirrhotic, GT1b	17/18 (94.44)	8/18 (44.44)	5/18 (27.78)	3/18 (16.67)	5/18 (27.78)	3/18 (16.67)	0/18 (0.00)	1/18 (5.56)	0/18 (0.00)	0/18 (0.00)
	DCV + ASV QD (24 wks)			20/20 (100.00)	8/20 (40.00)	2/20 (10.00)	3/20 (15.00)	6/20 (30.00)	3/20 (15.00)	0/20 (0.00)	2/20 (10.00)	0/20 (0.00)	0/20 (0.00)
	DCV + ASV BID + pegIFN + RBV (24 wks)		TE, Non-cirrhotic, GT1a/b	20/20 (100.00)	12/20 (60.00)	8/20 (40.00)	7/20 (35.00)	9/20 (45.00)	9/20 (45.00)	0/20 (0.00)	3/20 (15.00)	0/20 (0.00)	0/20 (0.00)
	DCV + ASV QD + pegIFN + RBV (24 wks)			21/21 (100.00)	10/21 (47.62)	5/21 (23.81)	3/21 (14.29)	7/21 (33.33)	3/21 (14.29)	1/21 (4.76)	0/21 (0.00)	0/21 (0.00)	0/21 (0.00)
	DCV + ASV BID + RBV (24 wks)			22/22 (100.00)	10/22 (45.45)	7/22 (31.82)	4/22 (18.18)	5/22 (22.73)	9/22 (40.91)	1/22 (4.55)	0/22 (0.00)	1/22 (4.55)	0/22 (0.00)
Rodriguez-Torres et al. (2014)[36]	VAN + pegIFN + RBV	Previous treatment, Cirrhosis, GT	TE, Cirrhotic, GT1	60/60 (100.00)	–	–	–	–	–	–	3/60 (5.00)	2/60 (3.33)	0/60 (0.00)
			TE, Non-cirrhotic, GT1	166/169 (98.22)	–	–	–	–	–	–	15/169 (8.88)	11/169 (6.51)	0/169 (0.00)
	Placebo + pegIFN + RBV		TE, Cirrhotic/ Non-cirrhotic, GT1	55/56 (98.21)	–	–	–	–	–	–	0/56 (0.00)	1/56 (1.79)	0/56 (0.00)
Wyles et al. (2014)[37]	LDV 30 mg + VDV + TGV + RBV	Previous treatment, Cirrhosis, GT	TN, Non-cirrhotic, GT1	–	9/46 (19.57)	16/46 (34.78)	8/46 (17.39)	5/46 (10.87)	–	6/46 (13.04)	1/46 (2.17)	1/46 (2.17)	–
	LDV 90 mg + VDV + TGV + RBV			–	20/94 (21.28)	17/94 (18.09)	13/94 (13.83)	14/94 (14.89)	–	6/94 (6.38)	0/94 (0.00)	2/94 (2.13)	–

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Forns et al. (2014)[38]	SMV + pegIFN + RBV (12 wks) followed by pegIFN + RBV (12 wks or 36 wks)	Previous treatment, Cirrhosis, GT	TE, Cirrhotic/ Non-cirrhotic, GT1	253/260 (97.31)	86/260 (33.08)	84/260 (32.31)	-	-	-	44/260 (16.92)	14/260 (5.38)	6/260 (2.31)	-
	Placebo + pegIFN + RBV (12 wks) followed by pegIFN + RBV (36 wks)			125/133 (93.98)	48/133 (36.09)	58/133 (43.61)	-	-	-	27/133 (20.30)	10/133 (7.52)	7/133 (5.26)	-
Manns et al. (2014)[39]	GZR **100 mg** + pegIFN + RBV (12 wks) followed by pegIFN + RBV (12 wks or 36 wks)	Previous treatment, Cirrhosis, GT	TN, Non-cirrhotic, GT1	65/66 (98.48)	28/66 (42.42)	27/66 (40.91)	25/66 (37.88)	11/66 (16.67)	-	11/66 (16.67)	6/66 (9.09)	3/66 (4.55)	0/66 (0.00)
	GZR **200 mg** + pegIFN + RBV (12 wks) followed by pegIFN + RBV (12 wks or 36 wks)			66/68 (97.06)	31/68 (45.59)	31/68 (45.59)	25/68 (36.76)	11/68 (16.18)	-	18/68 (26.47)	9/68 (13.24)	4/68 (5.88)	0/68 (0.00)
	GZR **400 mg** + pegIFN + RBV (12 wks) followed by pegIFN + RBV (12 wks or 36 wks)			65/67 (97.01)	20/67 (29.85)	28/67 (41.79)	21/67 (31.34)	10/67 (14.93)	-	7/67 (10.45)	7/67 (10.45)	6/67 (8.96)	0/67 (0.00)
	GZR **800 mg** + pegIFN + RBV (12 wks) followed by pegIFN + RBV (12 wks or 36 wks)			64/65 (98.46)	29/65 (44.62)	31/65 (47.69)	35/65 (53.85)	23/65 (35.38)	-	13/65 (20.00)	6/65 (9.23)	5/65 (7.69)	0/65 (0.00)

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Zeuzem et al. (2013)[41] (SOUND-C2)	FDV + DBV TID + RBV (16 wks)	Previous treatment, Cirrhosis, GT	TN, Cirrhotic/ Non-cirrhotic, GT1	78/81 (96.30)	-	18/81 (22.22)	41/81 (50.52)	33/81 (40.74)	-	0/81 (0.00)	3/81 (3.70)	4/81 (4.94)	-
	FDV + DBV TID + RBV (28 wks)			71/80 (88.75)	-	14/80 (17.50)	42/80 (52.50)	29/80 (36.25)	-	1/80 (1.25)	8/80 (10.00)	10/80 (12.50)	-
	FDV + DBV TID + RBV (40 wks)			74/77 (96.10)	-	21/77 (27.27)	41/77 (53.25)	33/77 (42.86)	-	0/77 (0.00)	5/77 (6.49)	19/77 (24.68)	-
	FDV + DBV BID + RBV (28 wks)			73/78 (93.59)	-	21/78 (26.92)	39/78 (50.00)	25/78 (32.05)	-	1/78 (1.28)	8/78 (10.26)	6/78 (7.69)	-
	FDV + DBV TID (28 wks)			44/46 (95.65)	-	7/46 (15.22)	26/46 (56.52)	10/46 (21.74)	-	0/46 (0.00)	3/46 (6.52)	5/46 (10.87)	-
Lok et al. (2012)[42]	DCV + ASV (24 wks)	Previous treatment, Cirrhosis, GT	TE, Non-cirrhotic, GT1	-	5/11 (45.45)	6/11 (54.55)	2/11 (18.18)	8/11 (72.73)	3/11 (27.27)	0/11 (0.00)	0/11 (0.00)	0/11 (0.00)	0/11 (0.00)
	DCV + ASV + pegIFN + RBV (24 wks)			-	5/10 (50.00)	7/10 (70.00)	5/10 (50.00)	7/10 (70.00)	3/10 (30.00)	2/10 (20.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)
Pol et al. (2012)[43]	DCV 3 mg + pegIFN + RBV (48 wks)	Previous treatment, Cirrhosis, GT	TN, Non-cirrhotic, GT1	-	7/12 (58.33)	7/12 (58.33)	5/12 (41.67)	-	4/12 (33.33)	3/12 (25.00)	1/12 (8.33)	1/12 (8.33)	-
	DCV 10 mg + pegIFN + RBV (48 wks)			-	9/12 (75.00)	6/12 (50.00)	4/12 (33.33)	-	4/12 (33.33)	5/12 (41.67)	1/12 (8.33)	1/12 (8.33)	-
	DCV 60 mg + pegIFN + RBV (48 wks)			-	3/12 (25.00)	6/12 (50.00)	4/12 (33.33)	-	5/12 (41.67)	6/12 (50.00)	1/12 (8.33)	4/12 (33.33)	-
	Placebo + pegIFN + RBV (48 wks)			-	3/12 (25.00)	9/12 (75.00)	6/12 (50.00)	-	6/12 (50.00)	5/12 (41.67)	0/12 (0.00)	2/12 (16.67)	-

Table 7. (*continued*)

Study (Year)	Regimen	Category of Subgroups	Subgroup	Any AEs, n/N (%)	Common AEs, n/N (%)						Serious AEs, n/N (%)	Discontinuation due to AEs, n/N (%)	Death, n/N (%)
					Headache	Fatigue	Nausea	Diarrhea	Insomnia	Anemia			
Zeuzem et al. (2011)[44]	A	Previous treatment, Cirrhosis, GT	TE, Cirrhotic/ Non-cirrhotic, GT1	260/266 (97.74)	112/266 (42.11)	145/266 (54.51)	94/266 (35.34)	66/266 (24.81)	68/266 (25.56)	79/266 (29.70)	33/266 (12.41)	39/266 (14.66)	-
	B			260/264 (98.48)	109/264 (41.29)	131/264 (49.62)	87/264 (32.95)	69/264 (26.14)	84/264 (31.82)	94/264 (35.61)	32/264 (12.12)	29/264 (10.98)	-
	C			126/132 (95.45)	49/132 (37.12)	53/132 (40.15)	31/132 (23.48)	18/132 (13.64)	34/132 (25.76)	20/132 (15.15)	7/132 (5.30)	4/132 (3.03)	-

❖ A: TPV + pegIFN + RBV (12 wks) followed by placebo + pegIFN + RBV (4 wks) then pegIFN + RBV (32 wks)

❖ B: Placebo + pegIFN + RBV (4 wks) followed by TPV + pegIFN + RBV (12 wks) then pegIFN + RBV (32 wks)

❖ C: Placebo + pegIFN + RBV (16 wks) followed by pegIFN + RBV (32 wks)

C. Results from qualitative synthesis

1. GLE/PIB ± RBV regimens

GLE plus PIB with and without RBV was used in 3 RCTs.[8,15] In 2 phase III, open-label, multi-center trials conducted by Zeuzem et al[8], 1,208 patients without cirrhosis who had HCV genotype 1 or 3 infection were enrolled. In the ENDURANCE-1 study, 351 and 352 patients with HCV genotype 1 infection received GLE (300 mg QD) and PIB (120 mg QD) for 8 and 12 weeks, respectively. The rates of SVR12 (HCV RNA < 15 IU/mL) were 99.15% and 99.72% in the 8-week and 12-week groups, respectively. In the ENDURANCE-3 study conducted with HCV genotype 3-infected patients, 157 and 233 received GLE/PIB for 8 and 12 weeks, respectively, and 115 received SOF (400 mg QD) and DCV (60 mg QD) for 12 weeks. The 8-week and 12-week groups of GLE/PIB yielded 94.90% and 95.28% of SVR12, respectively, and the SOF/DCV group yielded 96.52% of SVR12. The incidence rates of any AEs were approximately 62-76% in any treatment groups, and that of AEs which led to discontinuation of treatment were no more than 1% of patients in any treatment groups.

In another phase II, open-label study (MAGELLAN-1) conducted by Poordad et al[15], 50 non-cirrhotic patients with HCV genotype 1 infection and previous DAA treatment were enrolled and randomly assigned to one of the following groups: 6 patients with GLE (200 mg QD) and PIB (80 mg QD) for 12 weeks (group A); 22 with GLE (300 mg QD), PIB (120 mg QD), and RBV (800 mg QD) for 12 weeks (group B); and 22 with GLE (300 mg QD) and PIB (120 mg QD) for 12 weeks (group C). The rates of SVR12 (HCV RNA < 15 IU/mL) were achieved in 100.00%, 95.45%, and 86.36% of patients in groups A, B, and C, respectively. Virologic failure took place in 1 patient each in group B and C.

The incidence rates of any AEs were about 81-86% in any treatment groups, and discontinuation due to AEs did not occurred in any groups.

2. SOF/VEL ± VOX regimens

SOF plus VEL with or without VOX was used in 7 RCTs.[11,12,14,25] In 2 phase III trials (POLARIS-1 and POLARIS-4)[11], 596 patients who had previously experienced DAA-containing regimens were enrolled. The patients were randomly assigned to one of the following groups: SOF (400 mg QD), VEL (100 mg QD), and VOX (100 mg QD) for 12 weeks or SOF and VEL for 12 weeks. In the POLARIS-1, the rate of SVR12 (HCV RNA < 15 IU/mL) was 96.20% with SOF/VEL/VOX compared to 0% with placebo. In the POLARIS-4, the rates of SVR12 were achieved in 97.80% and 90.07% of patients receiving SOF/VEL/VOX and SOF/VEL, respectively. The percentages of patients who had any AEs and discontinued treatment owing to AEs were 78.33% and 0.38%, respectively, in the SOF/VEL/VOX group of the POLARIS-1. The incidence rates of any AEs were 76.92% and 73.51% in the SOF/VEL/VOX and SOF/VEL groups of the POLARIS-4, respectively. The percentage of patients who discontinued treatment due to AEs was no more than 1% in any treatment groups.

In a phase II, open-label study conducted in a single center of the United States[12], 49 HCV genotype 1-infected patients who had previously experienced DAA-containing regimens were enrolled and randomly assigned to receive either SOF (400 mg QD), VEL (100 mg QD), and VOX (100 mg QD) with or without weight-based RBV (1,000 or 1,200 mg/day) for 12 weeks. The proportions of patients with SVR12 (HCV RNA < 15 IU/mL) were 100.00% receiving SOF/VEL/VOX alone and 96.00% receiving SOF/VEL/VOX/RBV. The percentage of patients with any AEs was higher in the SOF/VEL/VOX/RBV group (60.00%) than in the SOF/VEL/VOX group (45.83%). Fatigue and anemia oc-

curred most commonly in the SOF/VEL/VOX/RBV group.

In 2 phase III, open-label trials (POLARIS-2 and POLARIS-3) conducted in the USA, Canada, New Zealand, Australia, and Europe[14], 1,160 HCV-infected patients who had not experienced previous DAA treatments received either SOF (400 mg QD), VEL (100 mg QD), and VOX (100 mg QD) for 8 weeks or SOF and VEL for 12 weeks. In the POLARIS-2 which enrolled non-cirrhotic or cirrhotic patients with HCV infection, except for HCV genotype 3-infected patients with cirrhosis, the percentages of SVR12 (HCV RNA < 15 IU/mL) were achieved in 95.21% and 98.18% of patients receiving SOF/VEL/VOX and SOF/VEL, respectively. This result was likely to be due to the lower rate of SVR12 in HCV genotype 1a-infected patients (91.72%) of the SOF/VEL/VOX group. In the POLARIS-3 which enrolled cirrhotic patients with HCV genotype 3 infection, the SOF/VEL/VOX and SOF/VEL groups yielded 96.36% and 96.33% of SVR12, respectively. Overall, the incidence rates of any AEs were similar in both groups of POLARIS-2 and POLARIS-3. However, nausea and diarrhea occurred more frequently in patients receiving VOX. The percentage of patients who discontinued treatment due to AEs ranged from 0 to 1%.

In 2 phase III, open-label trials (ASTRAL-2 and ASTRAL-3) conducted in the USA[25], non-cirrhotic or cirrhotic patients with or without previous HCV treatment were enrolled and randomly assigned to receive either SOF (400 mg QD) and VEL (100 mg QD) for 12 weeks or SOF and weight-adjusted RBV (1,000 or 1,200 mg/day) for 12 weeks. In the ASTRAL-2 involving patients with HCV genotype 2 infection, the rates of SVR12 (HCV RNA < 15 IU/mL) were 99.25% in the SOF/VEL group and 93.94% in the SOF/RBV group. In the ASTRAL-3 which enrolled HCV genotype 3-infected patients, the SOF/VEL and SOF/RBV groups yielded 96.75% and 80.36% of SVR12, respectively. The incidence rates of any AEs were higher in the SOF/RBV group than in the SOF/VEL group. Fatigue and insomnia occurred more frequently in patients with RBV. Discontinuation owing to AEs also occurred more frequently in pa-

tients receiving RBV.

3. DCV/ASV ± BCV regimens

DCV plus ASV with or without BCV were administered to HCV patients in 3 RCTs.[10,18,33] In a phase III, mixed open-label and double-blind trial conducted in Japan[10], 288 HCV genotype 1b-infected patients were enrolled. Treatment-naive patients were randomly assigned to receive either fixed-dose combination (FDC) of DCV (30 mg), ASV (200 mg), and BCV (75 mg) BID for 12 weeks or DCV (60 mg QD) and ASV (100 mg BID) for 24 weeks. Previous pegIFN-experienced patients received FDC of DCV/ASV/BCV BID for 12 weeks. The rates of SVR12 (HCV RNA < 25 IU/mL) were achieved in 95.97% and 96.88% of TN and TE patients receiving FDC of DCV/ASV/BCV, respectively, and TN patients receiving DCV/ASV yielded 86.67% of SVR12. Both DCV/ASV/BCV and DCV/ASV regimens exhibited comparable safety profiles.

In a phase II, open-label study conducted in the USA[18], 187 TN patients with HCV genotype 1 infection were enrolled and randomly assigned to receive one of the following treatment regimens: DCV (30 mg BID), ASV (200 mg BID), and BCV (75 mg BID) for 12 weeks (group A); DCV, ASV, and BCV (150 mg BID) for 12 weeks (group B); and DCV, ASV, BCV (75 mg BID), and weigh-based RBV (1,000 or 1,200 mg/day) for 12 weeks (group C). The rates of SVR12 (HCV RNA < 25 IU/mL) were achieved in 88.75%, 89.53%, and 85.71% of patients in groups A, B, and C, respectively. More frequent hemoglobin reductions from baseline occurred in group C than in groups A and C.

In a phase II, open-label trial conduced in the USA and France[33], 66 TN and non-cirrhotic patients with HCV genotype 1 infection were enrolled and randomly assigned to receive one of the following treatment regimens: DCV (60 mg QD), ASV (200 mg BID), and BCV (75 or 150 mg BID) for 12 or 24 week. The rates of SVR12 (HCV RNA < 25 IU/mL) were achieved in 93.75% of pa-

tients who received 75 mg BCV for 12 and 24 weeks and 150 mg BCV for 24 weeks. Patients receiving 150 mg BCV for 12 weeks yielded 88.89% of SVR12. The most common AEs were headache and gastrointestinal symptoms such as nausea and diarrhea. No death and discontinuation due to AEs occurred in any treatment groups.

4. DCV/ASV ± pegIFN ± RBV regimens

DCV plus ASV with or without pegIFN or RBV were used in 2 RCTs.[35,42] In a phase II, open-label study conducted in the USA, Puerto Rico, and France[35], 101 TE patients with HCV genotype 1 infection were enrolled and randomly assigned to one of the following treatment regimens for 24 weeks: DCV (60 mg QD) and ASV (200 mg) twice daily (group A) or once daily (group B) for HCV genotype 1b-infected patients; DCV, ASV twice daily (group C) or once daily (group D), pegIFN (180 μg SC QW), and weight-adjusted RBV (1,000 or 1,200 mg/day) for HCV genotype 1a/b-infected patients; and DCV, ASV twice daily, and weight-based RBV for HCV genotype 1a/b-infected patients (group E). The rates of SVR12 (HCV RNA < 25 IU/mL) were 77.78%, 65.00%, 95.00%, and 95.24% in groups A, B, C, and D, respectively. Most patients with HCV genotype 1a infection in group E experienced virologic breakthrough. In addition, most patients in any treatment groups experienced at least 1 AE during the treatment period, and only 1 patients in group E discontinued treatment due to AEs. No death occurred in any treatment groups.

In another phase II, open-label study conducted in the USA[42], 21 non-cirrhotic and TE patients with HCV genotype 1 infection were enrolled and randomly assigned to receive either DCV (60 mg QD) and ASV (600 mg BID) for 24 weeks (group A) or DCV, ASV, pegIFN (180 μg SC QW), and weight-adjusted RBV (1,000 or 1,200 mg/day) for 24 weeks (group B). SVR12 rates (HCV RNA < 25 IU/mL) of groups A and B were achieved in 36.36% and 100.00%,

respectively. Viral breakthrough occurred in 6 HCV genotype 1a-infected patients of group A who had resistance mutations to both DCV and ASV, and relapse were shown in 1 patient of group A. The most common AE was diarrhea in both groups, and compared with group A, anemia occurred more frequently in group B receiving pegIFN/RBV. No serious AEs, discontinuation due to AEs, and death occurred in both groups.

5. OBV/PTV/RTV ± DSV ± RBV regimens

OBV/PTV/RTV with or without DSV or RBV were administered to HCV patients in 5 RCTs.[13,17,23,32] In a phase III, open-label study (GIFT-II) conducted in Japan[13], 171 TN or TE patients with HCV genotype 2 infection were enrolled and randomly assigned to receive OBV/PTV/RTV (25/150/100 mg QD) plus weight-based RBV (600, 800, or 1,000 mg/day) for 12 (group A) or 16 weeks (group B). Overall, SVR12 rates (HCV RNA < 25 IU/mL) were achieved in 72.94% and 81.40% of patients in groups A and B, respectively. Among TN and non-cirrhotic patients, SVR12 rates were 75.00% and 91.49% in groups A and B, respectively, and 5 patients in group A had relapse whereas no patients in group B experienced relapse. The most common AEs were anemia, increase in blood bilirubin, and nasopharyngitis. No discontinuation due to AEs and death occurred.

In 2 phase III, open-label trials (MALACHITE-I/II) conducted in Australia, Canada, Europe, and South America[17], 459 non-cirrhotic patients with HCV genotype 1 infection were enrolled. In the MALACHITE-I, TN and genotype 1a-infected patients received either OBV (25 mg QD), PTV (150 mg QD), RTV (100 mg QD), DSV (250 mg BID), and weight-adjusted RBV (1,000 or 1,200 mg/day) for 12 weeks (group A) or TPV (750 mg TID), pegIFN (180 μg SC QW), and weigh-adjusted RBV for 12 weeks (group B), and TN and genotype 1b-infected patients also received OBV/PTV/RTV/DSV/RBV (group C),

OBV/PTV/RTV/DSV (group D), or TPV/pegIFN/RBV (group E) for 12 weeks. The rates of SVR12 (HCV RNA < 25 IU/mL) were achieved in 97.10%, 98.81%, and 97.59% of patients in groups A, C, and D, respectively; however, those of SVR12 in groups B and E were relatively lower (82.35% and 78.05%, respectively) compared with other groups. Any AEs occurred much more frequently in patients receiving OBV/PTV/RTV/DSV/RBV or TPV/pegIFN/RBV compared with those who received OBV/PTV/RTV/DSV. Discontinuation due to AEs also occurred in 1 and 6 patients receiving OBV/PTV/RTV/DSV/RBV and TPV/pegIFN/RBV, respectively. In the MALACHITE-II, TE patients with HCV genotype 1 infection received either OBV/PTV/RTV/DSV/RBV (group F) or TPV/pegIFN/RBV (group G) for 12 weeks. Patients in groups F and G yielded 99.01% and 65.96% of SVR12 rates, and 2 patients in group G experienced relapse. Patients in group G experienced more any AEs compared with those in group F, and 5 pateints in group G discontinued treatment owing to AEs.

In a phase III trial in conducted in multi-regions[23], 121 cirrhotic patients with HCV genotype 1 infection were randomly assigned to either OBV (25 mg QD), PTV (150 mg QD), RTV (100 mg QD), DSV (250 mg BID), and weight-adjusted RBV (1,000 or 1,200 mg/day) for 12 or 24 weeks. Overall, SVR12 rates (HCV RNA < 25 IU/mL) of patients who had platelet count < $100*10^9$/L in the 12-week and 24-week groups were 88.89% (40/45) and 96.97% (32/33), respectively, and patients who had albumin < 3.5 g/dL yielded in the 12-week and 24-week groups yielded 84.00% (21/25) and 88.89% (16/18) of SVR12, respectively.

In a phase II, open-label study with 14 treatment subgroups conducted in the USA, Canada, Australia, New Zealand, Puerto Rico, and Europe[32], 571 non-cirrhotic patients with or without previous treatment were enrolled and randomly assigned to OBV/PTV/RTV ± DSV ± weight-based RBV for 8, 12, or 24 weeks. Overall, SVR24 rates (HCV RNA < 25 IU/mL) ranged from 83 to 100%. Fatigue, headache, nausea, and insomnia occurred most frequently, and 8 pa-

tients discontinued due to AEs.

6. Other DAA regimens

In a phase II, open-label trial by Ruane et al. in the USA[22], 60 TN or TE patients of Egyptian ancestry with HCV genotype 4 infection were enrolled and randomly assigned to receive either SOF (400 mg QD) and weight-adjusted RBV (1,000 or 1,200 mg/day) for 12 or 24 weeks. With patients in the 12-week and 24 week groups, 67.74% and 93.10%, respectively, reached SVR12 (HCV RNA < 25 IU/mL). Among TN patients in the 12-week and 24-week groups, 78.57% and 100.00%, respectively, reached SVR12. The rates of SVR12 among TE patients in the 12-week and 24-week groups were 58.82% and 86.67%, respectively. The rates of SVR12 were achieved in 42.86% and 100.00% of cirrhotic patients in the 12-week and 24-week groups, respectively. Non-cirrhotic patients in the 12-week and 24-week groups yielded 75.00% and 90.91% of SVR12, respectively. More than 90% of patients in both groups had at least 1 AE, and 3 patients in the 24-week group experienced serious AEs. The most common AEs were headache, fatigue, and insomnia, and no discontinuation owing to AEs occurred in both groups.

In a phase II, open-label trial was conducted by Gane et al. in New Zealand[24], 126 TN or TE patients with HCV genotype 3 or 6 were enrolled and randomly assigned to receive one of the following regimens: 12 weeks of treatment with SOF (400 mg QD) and LDV (90 mg QD) for TN and HCV genotype 3-infected patients (group A), 12 weeks of treatment with SOF/LDV for TN or TE patients with HCV genotype 6 infection (group B), and 12 weeks of treatment with SOF/LDV with weight-based RBV (1,000 or 1,200 mg/day) for TN (group C) or TE (group D) patients with HCV genotype 3 infection. The percentages of patients with SVR12 (HCV RNA < 15 IU/mL) were 64.00%, 96.00%, 100.00%, and 82.00% in groups A, B, C, and D, respectively. The incidence rate

of relapse was higher in group A (32.00%) compared with those in other groups (4.00% in group B; 0.00% in group C; and 16.00% in group D). The majority of patients in all groups experienced at least 1 AE, and the most common AEs included headache, fatigue, and upper respiratory infection. Anemia occurred in groups C and D receiving RBV. One patient in group A discontinued treatment owing to an AE (diverticular perforation) which was not associated with treatment drugs. No death occurred in any treatment groups.

In a phase III trial by Hezode et al. in the USA, Australia, Canada, Israel, and Thailand1[16], 107 patients with HCV infection and inherited bleeding disorders (i.e., sickle cell anemia, thalassemia, or hemophilia A/B or von Willebrand disease) received an oral, once-daily, fixed-dose combination of EBV (50 mg) and GZR (100 mg) for 12 weeks. Overall, the rate of SVR12 (HCV RNA < 15 IU/mL) was achieved in 93.46% of patients. Patients with sickle cell anemia, thalassemia, and hemophilia A/B or von Willebrand disease yielded 94.74%, 97.56%, and 89.36% of SVR12, respectively. Patients with HCV genotype 1a, 1b, and 4 yielded 91.49%, 95.65%, and 91.67% of SVR12, respectively. Non-cirrhotic and cirrhotic patients yielded 91.36% and 100.00% of SVR12, respectively. Relapse occurred in 6 patients, but no breakthrough took place. Any AEs occurred in 71.96% of patients, and serious AEs occurred in 2.80% of patients. There were no death and discontinuation owing to AEs.

D. Results from quantitative synthesis (meta-analysis)

1. Risk of bias

The results from the risk of bias assessment by the Cochrane Risk of Bias tool were presented in Table 8. Overall, the assessed risk of bias in most of studies ranged from moderate to low in the domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Five studies did not report allocation concealment[12,14,18,33], and 2 studies showed high risk of bias for the domain of allocation concealment.[17] Two studies showed high risk of bias for the domain of blinding of participants and personnel.[18,33] In addition, all studies reported pre-defined inclusion and exclusion criteria and clearly described the clinical outcomes of interest.

Table 8. The risk of bias assessment for the studies included in the meta-analysis

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 sources of bias
Jacobson (POLARIS-2) 2017[14]	Low	Unclear	Low	Low	Low	Low	Low
Jacobson (POLARIS-3) 2017[14]	Low	Unclear	Low	Low	Low	Low	Low
Lawitz 2017[12]	Low	Unclear	Low	Low	Low	Low	Low
Everson 2016[18]	Low	Unclear	High	Low	Low	Low	Low
Dore (MALACHITE-I) 2016[17]	Low	High	Low	Low	Low	Low	Low
Dore (MALACHITE-II) 2016[17]	Low	High	Low	Low	Low	Low	Low
Gane 2015[24]	Low	Low	Low	Low	Low	Low	Low
Everson 2014[33]	Low	Unclear	High	Low	Low	Low	Low

2. Virologic response outcomes

a. SOF/VEL/VOX vs. SOF/VEL

The results from 2 studies[14] comparing the efficacy of SOF/VEL/VOX vs. SOF/VEL were quantitatively synthesized. In the POLARIS-2 study, TN or TE patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection were randomly assigned to either SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks. In the POLARIS-3 study, TN or TE patients with HCV genotype 3 infection and cirrhosis received one of the two treatment regimens. The overall effect showed significant difference in terms of SVR12 rate (OR = 0.46, 95% CI [0.23, 0.92], p = 0.03) without significant heterogeneity observed (Chi-square = 1.48 [p = 0.22], I-square = 32%) between two treatment groups (Figure 6A). However, when the patients were sub-grouped by HCV genotype 3, the overall effect for SVR12 rate showed no significant difference (OR = 1.44, 95% CI [0.45, 4.61], p = 0.54) without significant heterogeneity detected (Chi-square = 0.70 [p = 0.40], I-square = 0%) (Figure 6B). The overall effect showed significant difference with regard to relapse rate (OR = 5.31, 95% CI [1.82, 15.47], p = 0.002), and no significant heterogeneity was observed between both treatment groups (Chi-square = 0.71 [p = 0.40], I-square = 0%) (Figure 6C).

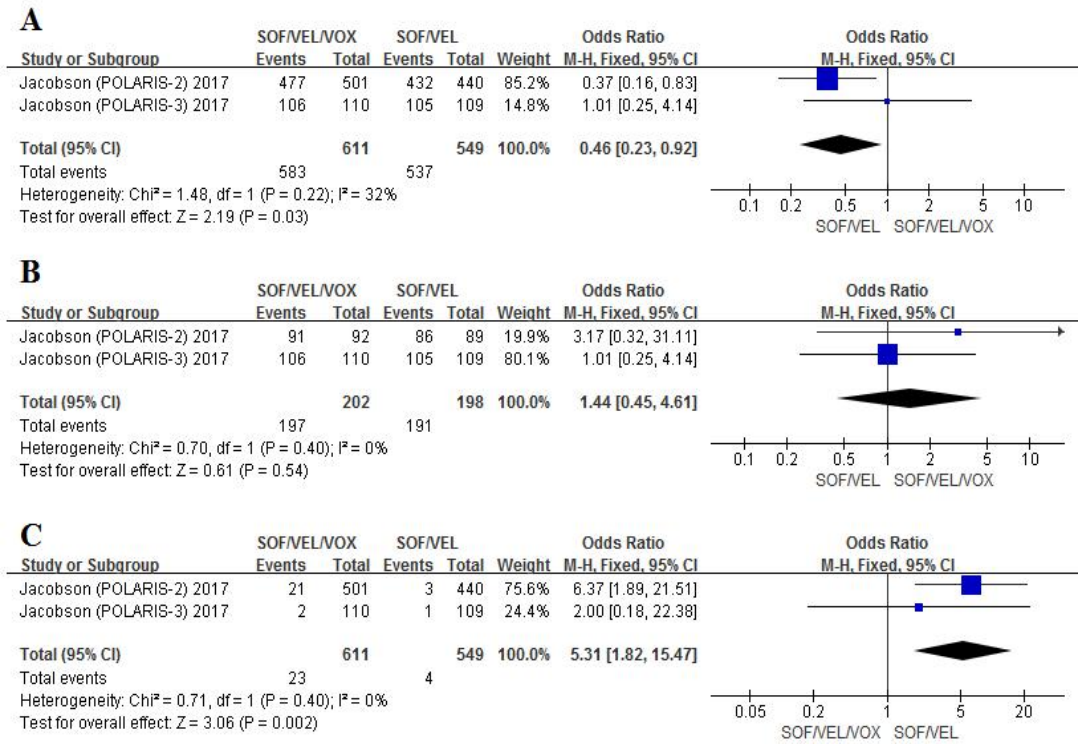


Figure 6. Meta-analysis forest plots of virologic response outcomes (SOF/VEL/VOX for 8 weeks vs. SOF/VEL for 12 weeks). (A) SVR12 rate in patients with HCV infection, (B) SVR12 rate in patients with HCV genotype 3 infection, (C) Relapse rate in patients with HCV infection.

b. SOF-based regimens with vs. without RBV

The results from 2 studies[12,24] comparing the efficacy of SOF-based regimens with or without RBV were quantitatively synthesized. In the study by Lawitz et al.[12], TE patients with HCV genotype 1 infection were randomly assigned to either SOF/VEL/VOX/RBV or SOF/VEL/VOX for 12 weeks. In the study by Gane et al.[24], TN or TE patients with HCV genotype 3 or 6 received SOF/LDV for 12 weeks, and those who received SOF/LDV/RBV for 12 weeks were infected by HCV genotype 3. Although no significant heterogeneity was detected (Chi-square = 0.99 [p = 0.32], I-square = 0%), the overall effect for SVR12 rate showed no significant difference (OR = 1.55, 95% CI [0.62, 3.90], p = 0.35) (Figure 7A). In addition, there was no significant difference in the overall effect in terms of relapse rate (OR = 0.66, 95% CI [0.25, 1.72], p = 0.40) without significant heterogeneity observed (Chi-square = 0.97 [p = 0.32], I-square = 0%) (Figure 7B).

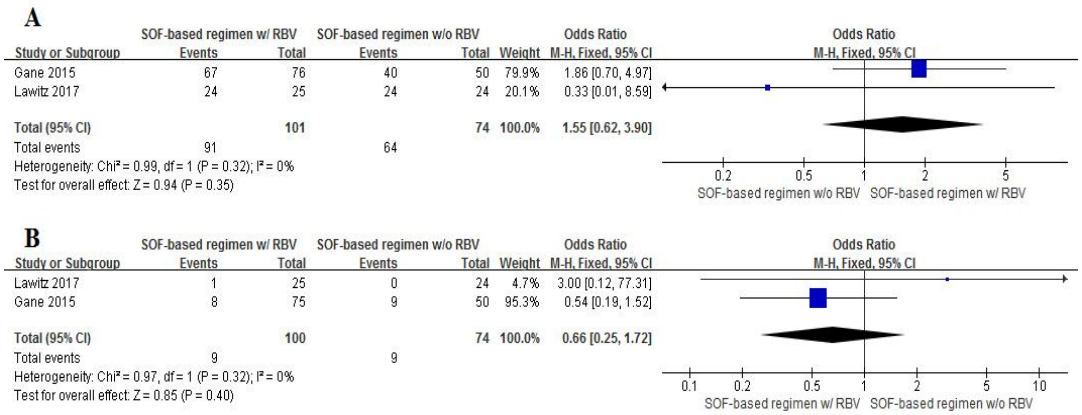


Figure 7. Meta-analysis forest plots of virologic response outcomes (SOF/VEL/VOX/RBV vs. SOF/VEL/VOX for 12 weeks; SOF/LDV/RBV vs. SOF/LDV for 12 weeks). (A) SVR12 rate in patients with HCV infection, (B) Relapse rate in patients with HCV infection.

c. DCV/ASV/BCV (75 mg vs. 150 mg)

The results from 2 studies[18,33] which compared the efficacy between DCV/ASV/BCV-75 mg and DCV/ASV/BCV-150 mg were quantitatively synthesized. In the study conducted by Everson et al. in 2016[18], TN patients with HCV genotype 1 infection were randomly assigned to either DCV/ASV/BCV-75 mg or DCV/ASV/BCV-150 mg for 12 weeks. In the study conducted by Everson et al. in 2014[33], TN and non-cirrhotic patients with HCV genotype 1 infection received one of the two treatment regimens. The overall effect for SVR12 rate showed no significant difference (OR = 1.02, 95% CI [0.41, 2.52], p = 0.97) with no significant heterogeneity detected (Chi-square = 0.27 [p = 0.60], I-square = 0%) (Figure 8A). When the patients were sub-grouped by non-cirrhosis status, the overall effect for SVR12 rate also showed no significant difference (OR = 0.80, 95% CI [0.31, 2.06], p = 0.64) with no significant heterogeneity observed (Chi-square = 0.54 [p = 0.46], I-square = 0%) (Figure 8B). There was no significant difference in the overall effect for relapse rate (OR = 1.41, 95% CI [0.34, 5.88], p = 0.63) with no significant heterogeneity detected (Chi-square = 0.95 [p = 0.33], I-square = 0%) (Figure 8C). In addition, there was no significant difference in the overall effect for breakthrough rate (OR = 0.59, 95% CI [0.12, 2.86], p = 0.51) with no significant heterogeneity observed (Chi-square = 0.13 [p = 0.71], I-square = 0%) (Figure 8D).

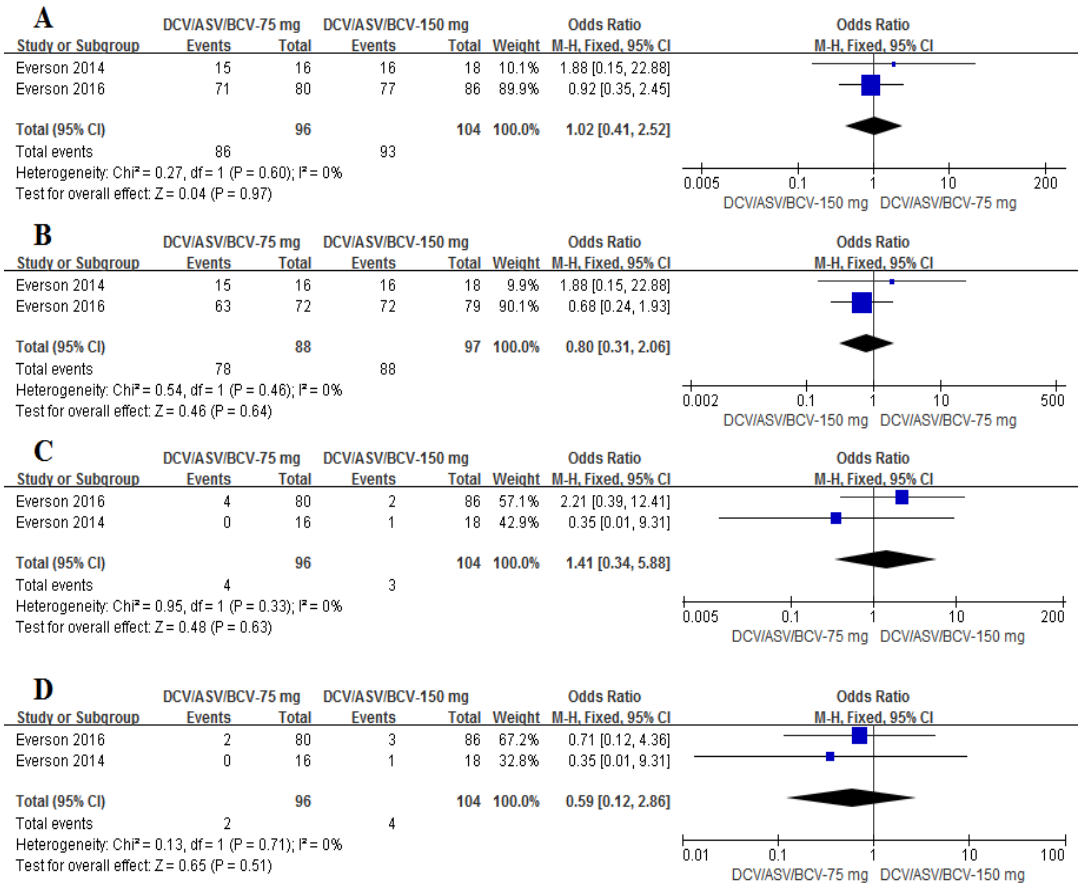


Figure 8. Meta-analysis forest plots of virologic response outcomes (DCV/ASV/BCV-75 mg vs. DCV/ASV/BCV-150 mg for 12 weeks). (A) SVR12 rate in TN patients with HCV genotype 1 infection, (B) SVR12 rate in TN and non-cirrhotic patients with HCV genotype 1 infection, (C) Relapse rate in TN patients with HCV genotype 1 infection, (D) Breakthrough rate in TN patients with HCV genotype 1 infection.

d. OBV/PTV/RTV/DSV/RBV vs. TPV/pegIFN/RBV

The results from two studies[17] comparing the efficacy of OBV/PTV/RTV/DSV/RBV vs. TPV/pegIFN/RBV for 12 weeks were quantitatively synthesized. The MALACHITE-I study included TN patients with HCV genotype 1 infection, and the MALACHITE-II study included TE patients with HCV genotype 1 infection. The overall effect for SVR12 rate showed significant difference (OR = 20.70, 95% CI [7.20, 59.55], p < 0.00001) with no significant heterogeneity observed (Chi-square = 1.36 [p = 0.24], I-square = 26%) between two treatment groups (Figure 9A). The overall effect for relapse rate also showed significant difference (OR = 0.12, 95% CI [0.02, 0.78], p = 0.03) with no significant heterogeneity detected (Chi-square = 0.40 [p = 0.53], I-square = 0%) between two treatment groups (Figure 9B).

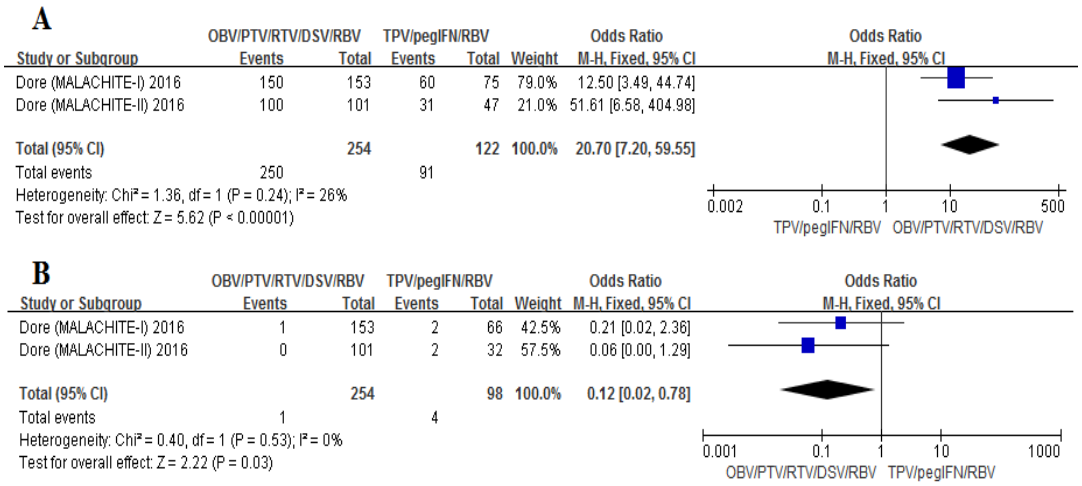
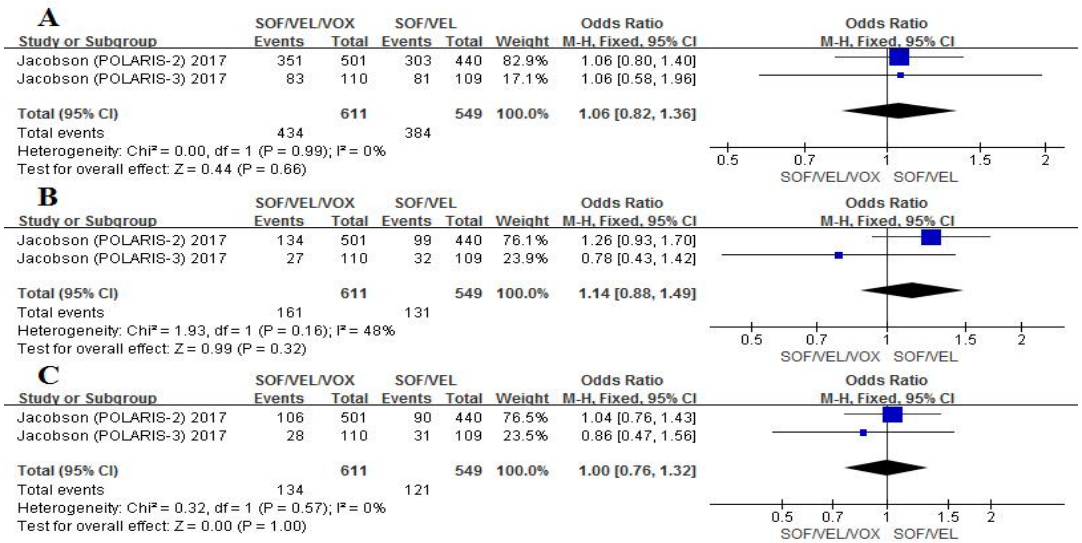


Figure 9. Meta-analysis forest plots of virologic response outcomes (OBV/PTV/RTV/DSV/RBV vs. TPV/pegIFN/RBV for 12 weeks). (A) SVR12 rate in TN or TE patients with HCV genotype 1 infection, (B) Relapse rate in TN or TE patients with HCV genotype 1 infection.

3. Adverse events

a. SOF/VEL/VOX vs. SOF/VEL

The results of AEs from two studies[14] which compared the safety of SOF/VEL/VOX vs. SOF/VEL were quantitatively synthesized. The overall effects showed no significant differences in terms of any AEs (Figure 10A), headache (Figure 10B), fatigue (Figure 10C), insomnia (Figure 10F), serious AEs (Figure 10G), and discontinuation due to AEs (Figure 10H) with no significant heterogeneity detected between two treatment groups. However, with no significant heterogeneity observed (Chi-square = 0.49 [p = 0.48], I-square = 0%), the incidence rate of nausea was significantly higher in the SOF/VEL/VOX group than in the SOF/VEL group (OR = 2.03, 95% CI [1.42, 2.91], p = 0.0001) (Figure 10D). Similarly, with no significant heterogeneity detected (Chi-square = 0.35 [p = 0.56], I-square = 0%), the incidence rate of diarrhea was also significantly higher in the SOF/VEL/VOX group than in the SOF/VEL group (OR = 2.86, 95% CI [1.93, 4.24], p < 0.00001) (Figure 10E).



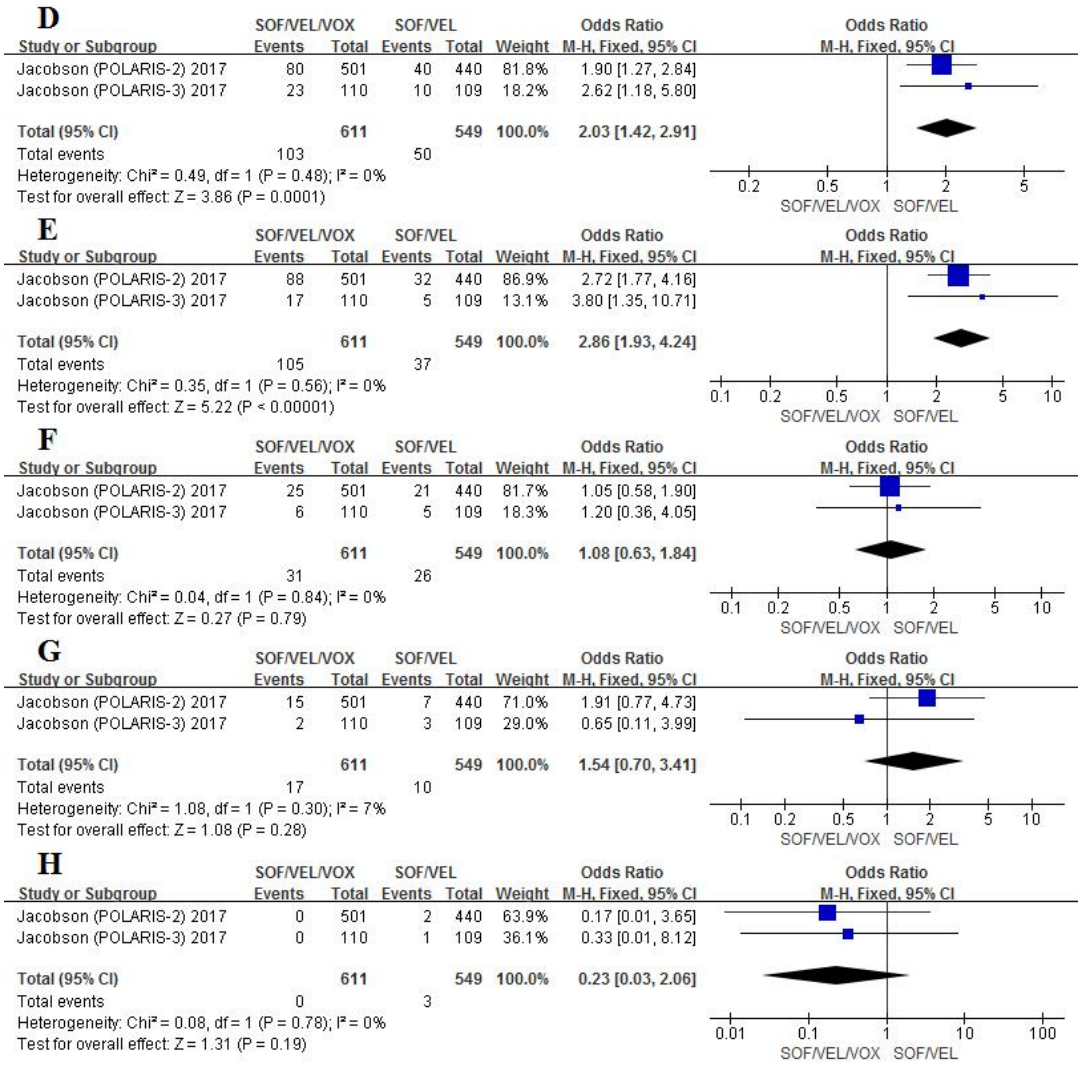
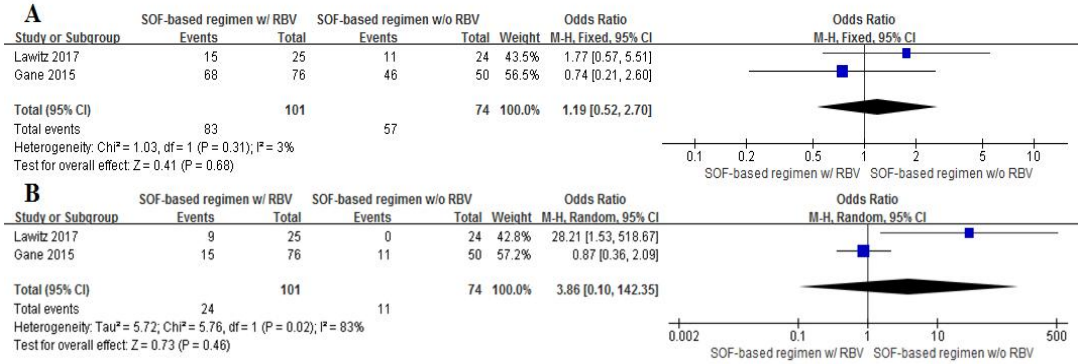


Figure 10. Meta-analysis forest plots of AEs (SOF/VEL/VOX for 8 weeks vs. SOF/VEL for 12 weeks). (A) Any AEs, (B) Headache, (C) Fatigue, (D) Nausea, (E) Diarrhea, (F) Insomnia, (G) Serious AEs, (H) Discontinuation due to AEs.

b. SOF-based regimens with vs. without RBV

The results of AEs from two studies[12,24] comparing the safety of SOF-based regimens with RBV vs. without RBV were quantitatively synthesized. The overall effects showed no significant differences in terms of any AEs (Figure 11A), nausea (Figure 11C), and diarrhea (Figure 11D) with no significant heterogeneity observed between two treatment groups. Based on the Chi-square and I-square analyses, significant heterogeneity in terms of fatigue was detected between two treatment groups (Tau-square = 5.72, Chi-square = 5.76 [p = 0.02], I-square = 83%), so a random-effects model was used to synthesize the results. The overall effect for fatigue showed no significant difference between two treatment groups (OR = 3.86, 95% CI [0.10, 142.35], p = 0.46) (Figure 11B). However, with no significant heterogeneity detected (Chi-square = 0.02 [p = 0.90], I-square = 0%), the incidence rate of anemia was significantly higher in the treatment groups with RBV than without RBV (OR = 8.84, 95% CI [1.09, 71.55], p = 0.04) (Figure 11E). In addition, with no significant heterogeneity observed (Chi-square = 0.22 [p = 0.64], I-square = 0%), the incidence rate of serious AEs was significantly higher in the treatment groups without RBV than with RBV (OR = 0.16, 95% CI [0.03, 0.95], p = 0.04) (Figure 11F).



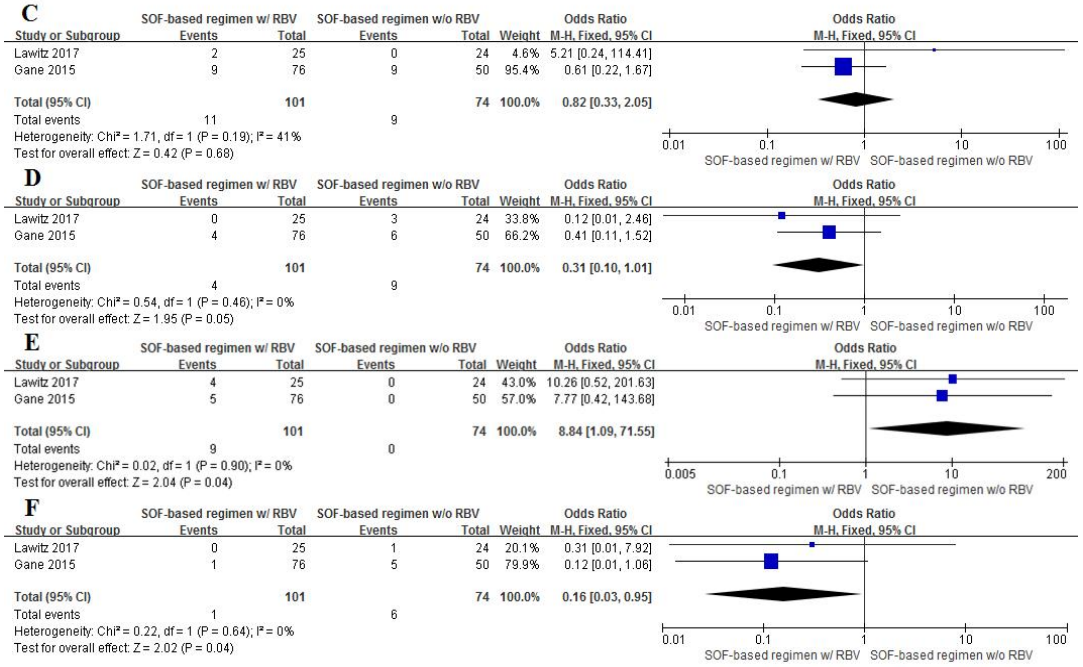


Figure 11. Meta-analysis forest plots of AEs (SOF/VEL/VOX/RBV vs. SOF/VEL/VOX for 12 weeks; SOF/LDV/RBV vs. SOF/LDV for 12 weeks). (A) Any AEs, (B) Fatigue, (C) Nausea, (D) Diarrhea, (E) Anemia, (F) Serious AEs.

c. DCV/ASV/BCV (75 mg vs. 150 mg)

The results of AEs from two studies[18,33] comparing the safety of DCV/ASV/BCV-75 mg vs. DCV/ASV/BCV-150 mg were quantitatively synthesized. The overall effect for headache showed no significant difference (OR = 0.86, 95% CI [0.45, 1.62], p = 0.64) with no significant heterogeneity detected (Chi-square = 1.69 [p = 0.19], I-square = 41%) between two treatment groups (Figure 12A). The overall effect for nausea also showed no significant difference (OR = 1.21, 95% CI [0.51, 2.90], p = 0.66) with no significant heterogeneity detected (Chi-square = 1.18 [p = 0.28], I-square = 15%) between two treatment groups (Figure 12B). Based on the Chi-square and I-square analyses, significant heterogeneity in terms of diarrhea was detected between treatment groups (Tau-square = 2.01, Chi-square = 3.66 [p = 0.06], I-square = 73%), so a random-effects model was used to synthesize the results. The overall effect for diarrhea showed no significant difference between two treatment groups (OR = 2.50, 95% CI [0.26, 23.92], p = 0.43) (Figure 12C).

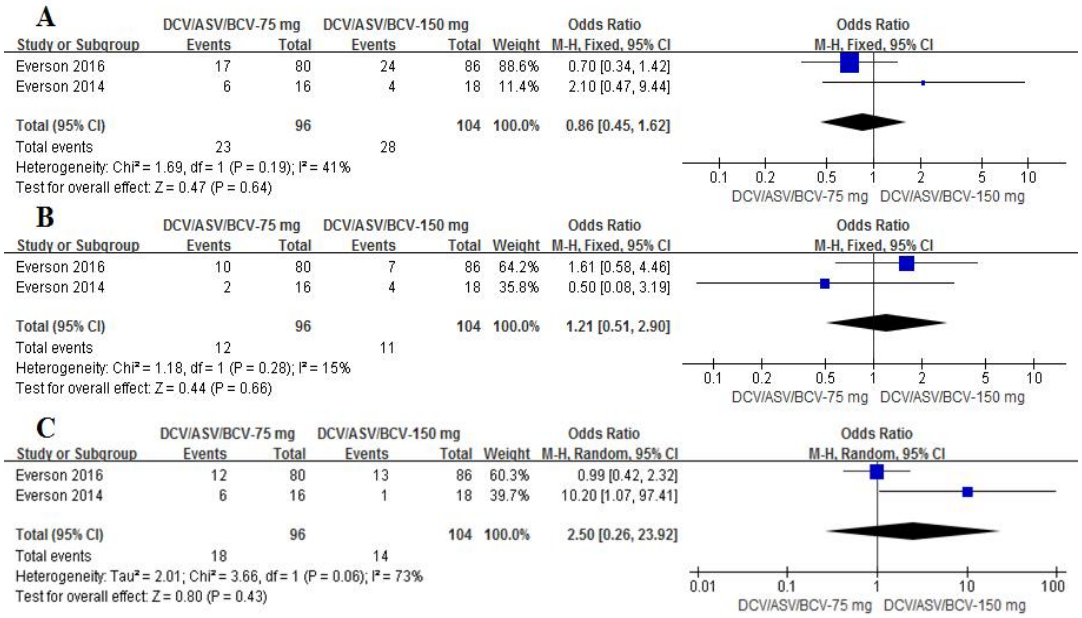
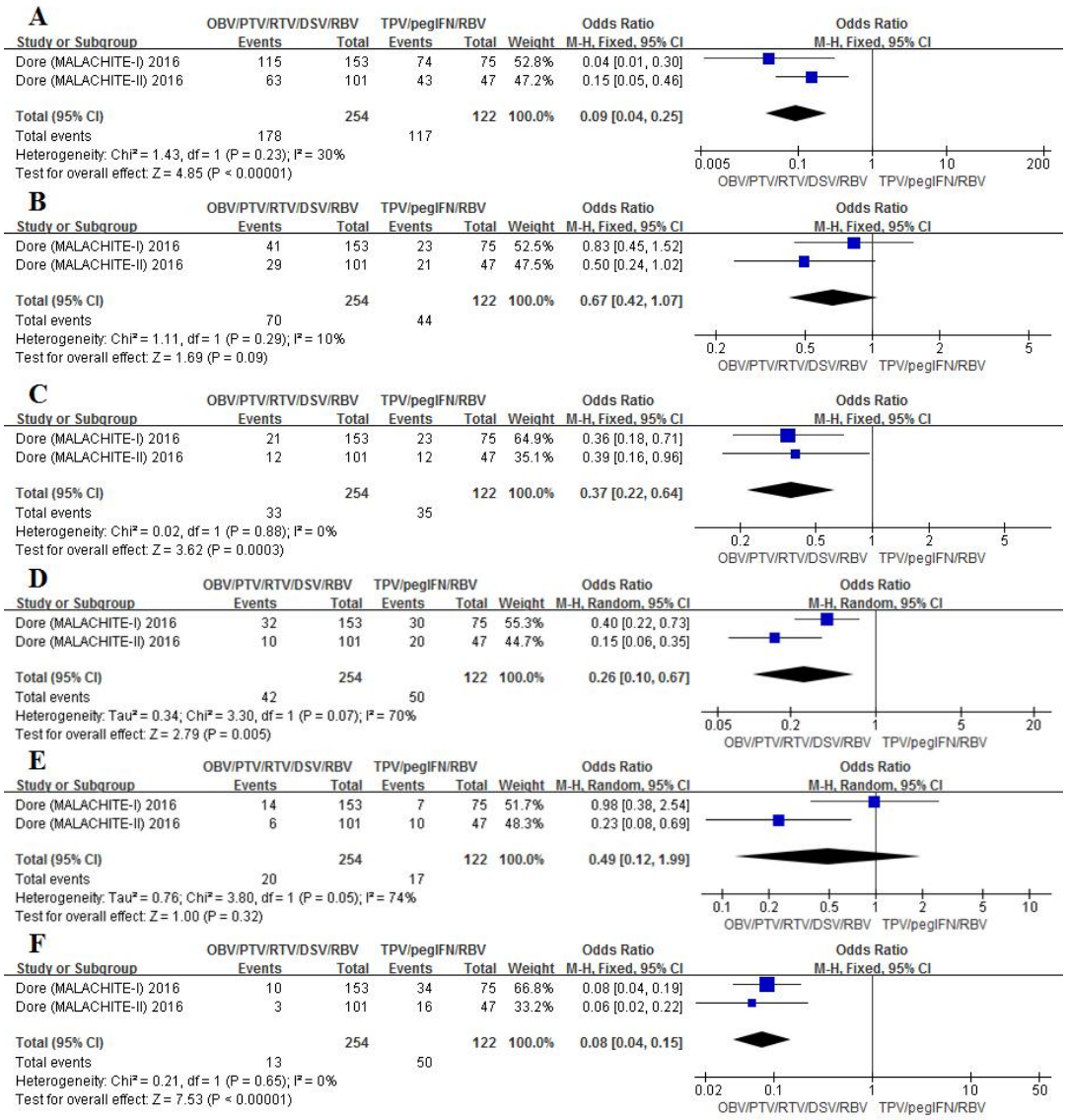


Figure 12. Meta-analysis forest plots of AEs (DCV/ASV/BCV-75 mg vs. DCV/ASV/BCV-150 mg for 12 weeks). (A) Headache, (B) Nausea, (C) Diarrhea.

d. OBV/PTV/RTV/DSV/RBV vs. TPV/pegIFN/RBV

The results of AEs from two studies[17] which compared the safety of OBV/PTV/RTV/DSV/RBV vs. TPV/pegIFN/RBV were quantitatively synthesized. The overall effects showed no significant differences in terms of headache (Figure 13B) and insomnia (Figure 13E) with no significant heterogeneity observed between two treatment groups. However, with no significant heterogeneity detected (Chi-square = 1.43 [p = 0.23], I-square = 30%), the incidence rate of any AEs was significantly higher in the TPV/pegIFN/RBV group than in the OBV/PTV/RTV/DSV/RBV group (OR = 0.09, 95% CI [0.04, 0.25], p < 0.00001) (Figure 13A). With no significant heterogeneity observed (Chi-square = 0.02 [p = 0.88], I-square = 0%), the incidence rate of fatigue was significantly higher in the TPV/pegIFN/RBV group than in the OBV/PTV/RTV/DSV/RBV group (OR = 0.37, 95% CI [0.22, 0.64], p = 0.0003) (Figure 13C). Using a random-effects model due to the detection of significant heterogeneity (Tau-square = 0.34, Chi-square = 3.30 [p = 0.07], I-square = 70%), the incidence rate of nausea was significantly higher in the TPV/pegIFN/RBV group than in the OBV/PTV/RTV/DSV/RBV group (OR = 0.26, 95% CI [0.10, 0.67], p = 0.005) (Figure 13D). With no significant heterogeneity observed (Chi-square = 0.21 [p = 0.65], I-square = 0%), the incidence rate of anemia was significantly higher in the TPV/pegIFN/RBV group than in the OBV/PTV/RTV/DSV/RBV group (OR = 0.08, 95% CI [0.04, 0.15], p < 0.00001) (Figure 13F). With no significant heterogeneity observed (Chi-square = 0.13 [p = 0.72], I-square = 0%), the incidence rate of serious AEs was significantly higher in the TPV/pegIFN/RBV group than in the OBV/PTV/RTV/DSV/RBV group (OR = 0.06, 95% CI [0.01, 0.27], p = 0.0003) (Figure 13G). With no significant heterogeneity observed (Chi-square = 0.14 [p = 0.71], I-square = 0%), the incidence rate of discontinuation due to AEs was significantly higher in the TPV/pegIFN/RBV group than in the

OBV/PTV/RTV/DSV/RBV group (OR = 0.06, 95% CI [0.01, 0.32], p = 0.001) (Figure 13H).



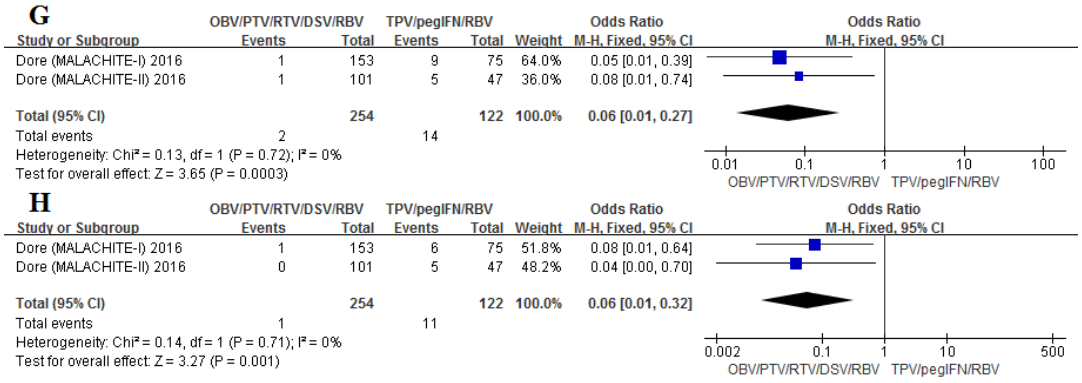


Figure 13. Meta-analysis forest plots of AEs (OBV/PTV/RTV/DSV/RBV vs. TPV/pegIFN/RBV for 12 weeks). (A) Any AEs, (B) Headache, (C) Fatigue, (D) Nausea, (E) Insomnia, (F) Anemia, (G) Serious AEs, (H) Discontinuation due to AEs.

Ⅳ. DISCUSSION

The results from this systematic review and meta-analysis suggest that the DAA-based therapies for HCV-infected patients show better efficacy and safety with high treatment-response rates and good tolerability compared with previous pegIFN/RBV-based therapies. Specifically, through the use of DAAs in HCV-infected patients, an SVR was achieved to almost 100%, and the treatment duration was reduced. The incidence rate of anemia which commonly occurred in HCV-infected patients with RBV was reduced in those who received DAA-based regimens.

SOF-based regimens (e.g., SOF/DCV ± RBV, SOF/LDV ± RBV, SOF/SMV, SOF/VEL ± RBV, and SOF/RBV ± pegIFN) have been usually used to treat HCV infection in the earlier era of DAAs, and these regimens are at least effective and safe for HCV-infected patients with or without cirrhosis.[6] However, various oral regimens (e.g., GLE/PIB, SOF/VEL/VOX, DCV/ASV/BCV, and EBV/GZR) including DAAs with different mode of actions are currently available as demonstrated in this study. These regimens shorten the treatment of duration to 8 or 12 weeks, and they have a favorable safety profile and a good tolerability.

GLE/PIB is the most recently approved DAA-based regimen in the USA for the treatment of HCV infection.[27] GLE and PIB are an NS3/4A inhibitor and an NS5A inhibitor, and the FDC regimen of both agents shows a highly potent antiviral activity in HCV-infected patients regardless of HCV genotypes.[28] In the ENDURANCE-1 study where HCV genotype 1-infected patients without cirrhosis received GLE/PIB (300/120 mg) QD for 8 and 12 weeks, the SVR12 rates were achieved in more than 99% of patients in both groups.[8] In the ENDURANCE-3 study conducted with non-cirrhotic and HCV genotype 3-infected patients, the 8-week and 12-week groups of GLE/PIB yielded 94.90% and 95.28% of SVR12, respectively, compared with 96.52% of SVR12 in patients

receiving SOF/DCV (400/60 mg) QD for 12 weeks.[8] In the integrated analysis of the results from the 8-week and 12-week GLE/PIB (300/120 mg QD) regimens for the treatment of 2,041 non-cirrhotic patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection, SVR12 was achieved in 97.72% and 98.51% of patients in the 8-week and 12-week groups, respectively.[45] The difference in the rates was not statistically significant ($p = 0.2$). In the MAGELLAN-2 study, non-cirrhotic patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection and liver ($n = 80$) or kidney ($n = 20$) transplant with $\geq$ 3 months post-transplant received GLE/PIB (300/120 mg) QD for 12 weeks.[46] The overall SVR12 was obtained in 98.00% of the patients. In the EXPEDITION-2 study, GLE/PIB (300/120 mg) QD for 8 and 12 weeks in non-cirrhotic and cirrhotic patients with HCV/HIV-1 co-infection, respectively, achieved the overall SVR12 in 98.04% of the patients.[47] GLE/PIB was well-tolerated, and most AEs from GLE/PIB were mild.[8,45-47] Comprehensively, once-daily GLE/PIB (300/120 mg) for 8 or 12 weeks is likely to be highly effective for non-cirrhotic or cirrhotic patients with HCV genotype 1-6 infection. Additionally, this GLE/PIB regimen may be a good option for the treatment of HCV infection in patients with liver or kidney transplant and in those with HCV/HIV-1 co-infection.

In 2017, the FDC of SOF/VEL/VOX (400/100/100 mg) was approved in the USA and Europe for the treatment of TN or TE patients with HCV genotype 1-6 infection.[48,49] In the POLARIS-1 and POLARIS-4 studies[11], the FDC of SOF/VEL/VOX for 12 weeks showed high SVR12 rate for the treatment of patients with HCV genotype 1, 2, 3, 4, 5, or 6 who had previously received DAA-containing regimens, even including NS5A inhibitors. In particular, although a number of patients with RASs at baseline were enrolled in both studies, the presence of such RASs did not affect the rates of SVR12 in patients with SOF/VEL/VOX for 12 weeks.[11] This regimen is likely to be a good option for patients who have previously received an HCV NS5A inhibitor-containing regimen because viral genome substitutions conferring

resistance to NS5A inhibitors seem to be maintained after an unsuccessful outcome and negatively affect the rates of SVR12 in most subsequent DAA-based treatments.[11,50]

In the POLARIS-2 and POLARIS-3 studies[14], it was not determined that SOF/VEL/VOX for 8 weeks was non-inferior to SOF/VEL for 12 weeks for the treatment of non-cirrhotic or cirrhotic patients with HCV infection who had not previously received DAA-based treatments, which may result from the lower rate of SVR12 in HCV genotype 1a-infected patients, compared with the other patients, receiving SOF/VEL/VOX for 8 weeks. However, both regimens showed similar efficacy in TN patients with cirrhosis and HCV genotype 3 infection.[14] This can be supported in part by the results of meta-analyses in this study. When the results from both studies were quantitatively synthesized, the overall effect for SVR12 rate showed significant difference between two treatment regimens in favor of SOF/VEL for 12 weeks. However, when the patients were sub-grouped by HCV genotype 3 infection, the overall effect for SVR12 was not significantly different between both regimens. Additionally, the overall effect for relapse rate was significantly different between both regimens due to the higher rate of relapse among HCV genotype 1a-infected patients who received SOF/VEL/VOX for 8 weeks.[14] Both SOF/VEL/VOX and SOF/VEL regimens showed comparable safety profiles, but nausea and diarrhea were significantly higher in patients receiving SOF/VEL/VOX for 8 weeks than in those receiving SOF/VEL for 12 weeks. Comprehensively, SOF/VEL/VOX for 8 weeks is likely to be a possible new option for TN patients with HCV infection who have difficulty in completing a longer-duration regimen.

A high rate of SVR12 was obtained in patients with HCV genotype 1 infection who received the FDC therapy with DCV/ASV/BCV (30/200/75 mg) BID for 12 weeks. The SVR12 rate of this FDC was ≥ 90% in both HCV genotype 1a and 1b. In the study by Toyota et al[10], SVR12 was achieved in 95.97% and 96.88% of TN and TE Japanese patients with HCV genotype 1b

infection who received DCV/ASV/BCV for 12 weeks, respectively. These results are comparable to SVR12 rates reported in previous studies conducted in the USA, Canada, France, and Australia. In the study by Poordad et al[51], non-cirrhotic patients with HCV genotype 1 infection received the FDC therapy with DCV/ASV/BCV for 12 weeks, and SVR12 was observed in 91.99% and 89.32% of TN and TE patients. SVR12 rates were lower in patients with HCV genotype 1a infection than in those with HCV genotype 1b (Total, 88.82% vs. 98.20%; TN, 89.96% vs. 97.59%; TE, 85.33% vs. 100.00%). In the study by Muir et al[52], patients with HCV genotype 1 infection and cirrhosis were treated with the FDC therapy of DCV/ASV/BCV with or without RBV for 12 weeks. SVR12 rates were lower in TN and TE patients receiving the FDC alone than in those receiving the FDC with RBV (TN, 92.98% vs. 98.18%; TE, 86.67% vs. 93.33%). Interestingly, this tendency was mostly observed among patients with HCV genotype 1a infection (TN, 90.00% vs. 97.44%; TE, 85.71% vs. 91.43%). In addition, according to the meta-analyses in this study, there were no significant differences in SVR12, relapse, and breakthrough rates between DCV/ASV/BCV-75 mg and DCV/ASV/BCV-150 mg among TN patients with HCV genotype 1 infection, and both regimens showed comparable safety profiles. Comprehensivley, the FDC of DCV/ASV/BCV BID for 12 weeks is likely to be a good option for the treatment of TN or TE patients with or without cirrhosis who have HCV genotype 1 infection. Although the contribution of RBV to SVR12 remains unclear, the addition of RBV to the FDC of DCV/ASV/BCV may be considered to treat patients with HCV genotype 1a infection.

The combination of OBV/PTV/RTV/DSV with or without RBV is approved for the treatment of HCV genotype 1-infected patients.[53,54] Two tablets of OBV/PTV/RTV (12.5/75/50 mg per tablet) should be taken QD with food, and one tablet of DSV (250 mg) should be administered BID with food in combination with OBV/PTV/RTV.[27,55] Weight-based RBV (1,000 mg/day if < 75

kg or 1,200 mg/day if ≥ 75 kg) should be added to this combinational regimen when HCV genotype 1a-infected patients are treated.[27] According to previous studies[17,55-58], the regimen of OBV/PTV/RTV/DSV with or without RBV showed high SVR12 rates in HCV genotype 1-infected patients with or without cirrhosis. In the MALACHITE-I/II studies[17], SVR12 was achieved in ≥ 97% of TN and TE patients with HCV genotype 1 infection who received OBV/PTV/RTV/DSV ± RBV for 12 weeks. In the retrospective study by Preda et al[55], SVR12 was achieved in 96.57% of Romanian patients with HCV genotype 1b infection and cirrhosis who received OBV/PTV/RTV/DSV ± RBV for 12 weeks; however, a relapse rate was very low (0.48%). In the TURQUOISE-IV study[56], 36 Russian and Belarusian patients received OBV/PTV/RTV/DSV ± RBV for 12 weeks, and all patients achieved SVR12. In the retrospective study by Liu et al[57], 103 HCV genotype 1b-infected patients in Taiwan received OBV/PTV/RTV/DSV ± RBV for 12 weeks, and 98.06% achieved SVR12. Baseline characteristics (e.g., sex, age, body mass index, previous treatment experience, RBV use, viral load at baseline and week 2, renal function, and hepatic fibrosis stage) are unlikely to affect SVR12 in HCV genotype 1b-infected patients receiving OBV/PTV/RTV/DSV ± RBV for 12 weeks.[56,57] In the AMBER study[58], 209 patients with HCV genotype 1 (n = 200) or 4 (n = 9) infection received OBV/PTV/RTV ± DSV ± RBV for 12 or 24 weeks, and 99.04% achieved SVR12, ranging from 96.4% to 100.0% depending on subgroups. In the prospective study conducted in Australia, England, and New Zealand[59], 30 HCV genotype 1-infected patients with duration of infection < 12 months, including those with HIV co-infection (n = 23), received OBV/PTV/RTV/DSV with or without RBV for 8 weeks, and SVR12 was observed in 96.67% and 100.00% of total patients and those with HIV co-infection, respectively. No relapse or reinfection occurred. Based on the results of the retrospective study in Czech Republic[60], OBV/PTV/RTV/DSV with or without for 12 weeks was highly effective for the treatment of HCV

genotype 1-infected patients with severe renal impairment. As shown in the meta-analyses, OBV/PTV/RTV/DSV ± RBV was also highly effective compared with the regimen including pegIFN/RBV. In addtion, OBV/PTV/RTV/DSV ± RBV showed good safety profiles[17,55-58]; however, serious AEs mostly occurred in patients with cirrhosis.[55,57,58] Consequently, OBV/PTV/RTV/DSV ± RBV for 12 weeks is likelty to be the first-line option for the treatment of patients infected with HCV genotype 1, particularly genotype 1b, but cirrhotic patients with this regimen should be closely monitored so as to timely detect and manage possibly life-threatening decompensation of cirrhosis. This regimen may be shortened to 8 weeks for the treatment of recent HCV genotype 1-infected patients likely to have poor adherence.

The combination of EBV/GZR (50/100 mg) with or without RBV is approved for the treatment of HCV genotype 1 and 4 infection.[27,61] This combination regimen showed high efficacy in several clinical trials where it was administered for 12 weeks to HCV-infected patients with cirrhosis, chronic kidney disease (CKD), HIV co-infection, or inherited blood disorders and who previously failed pegIFN-containing therapy.[16,61-70] In the study by George et al[61], SVR12 was achieved in 92.80% (232/250) of TN patients with HCV genotype 1, 4, or 6 infection from Asia-Pacific countries and Russia who received EBV/GZR once daily for 12 weeks. Specifically, SVR12 was observed in 88.46% (23/26), 98.93% (185/187), 100% (2/2), and 62.86% (22/35) of the patients with HCV genotype 1a, 1b, 4, and 6 infection, respectively. The lower rates of SVR12 in the patients with HCV genotype 1a and 6 infection are likely to be associated with NS5A RASs at baseline. For instance, SVR12 was achieved in 66.67% (4/6) of the patients with HCV genotype 1a infection and baseline NS5A RASs compared with 97.44% (38/39) of those with HCV genotype 1b infection and baseline NS5A RASs. The 16-week regimen of EBV/GZR + RBV can be beneficial for the HCV genotype 1a-infected patients with baseline NS5A RASs.[27,61] Additionally, in the study by Hezode et al[16],

HCV-infected pateints with inherited bleeding disorders received EBV/GZR once daily for 12 weeks, and SVR12 was achieved in 91.49% (43/47), 95.65% (44/46), 91.67% (11/12) of the patients with HCV genotype 1a, 1b, and 4 infection, respectively. Compared with placebo, the 12-week regimen of EBV/GZR generally showed comparable safety profiles with similar frequencies of AEs and SAEs.[16,61,64,65] Comprehensively, the combinational regimen of EBV/GZR (50/100 mg) once daily for 12 weeks may be a good option for the treatment of HCV genotype 1- or 4-infected patients who have cirrhosis, CKD, HIV co-infection, inherited blood disorders, and/or prior failure to pegIFN-containing therapy. In case of HCV genotype 1a-infected patients with NS5A RASs at baseline, EBV/GZR + RBV for 16 weeks can be used to achieve a high SVR12 rate. However, if these patients have hemoglobinopathy, other DAA-containing therapies (e.g., GLE/PIB for 8 or 12 weeks depending on cirrhosis status) may be considered in order to prevent hemolytic anemia resulting from the use of RBV.

Additionally, the availability of pegIFN-free combination regimens consisting of 2 or 3 DAAs has changed the landscape of therapy for special populations such as patients with HCV infection and CKD and those with HCV/HIV co-infection. HCV infection is associated with a higher risk of renal impairment, and conversely, renal impairment, especially stage 4 or 5 CKD, leads to an increase in HCV infection.[71] That is why more effective DAA-based regimens are necessary for this patient population. In the EXPEDITION-4 study[72], 104 TN and TE patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection and stage 4 or 5 CKD, including hemodialysis patients (81.73%) and cirrhotic patients (19.23%) received GLE/PIB (300/120 mg) QD for 12 weeks, and SVR12 was observed in 98.08% of the patients. No virologic failure occurred during the treatment, and no virologic relapse occurred after the end of treatment. This regimen also showed a satisfactory safety profile. In the C-SURFER study[65], 122 TN and TE patients with HCV genotype 1 infection and stage 4 or 5 CKD,

including hemodialysis patients (75.41%) and cirrhotic patients (5.74%), received EBV/GZR (50/100 mg) QD for 12 weeks. SVR12 was achieved in 99.14% (115/116), and one relapse occurred 12 weeks after the end of treatment. This regimen had a low rate of AEs. The combination of GLE/PIB for 12 weeks seems to be the first-line option for patients with any HCV genotype infection and CKD, but the combination of EBV/GZR for 12 weeks can be used as an alternative therapy for HCV genotype 1-infected patients with CKD.

HCV infection can increase a risk of hepatic fibrosis, hepatic decompensation, renal insufficiency, and even death in HIV-infected patients[71]; thus, it is necessary not only to suppress HIV viral loads and eradicate HCV in patients with HCV/HIV co-infection. In the EXPEDITION-2 study[47], the combination regimen of GLE/PIB (300/120 mg) was administered once daily to 153 TN and TE patients with HCV genotype 1-6/HIV co-infection for 8 week (non-cirrhotic patients) and 12 weeks (16 cirrhotic patients). SVR12 was observed in 98.04% (150/153) of the patients. No virologic failure occurred in non-cirrhotic patients, but one cirrhotic patients with HCV genotype 3 infection had on-treatment virologic failure. Most AEs were mild in severity. The ASTRAL-5 study included 106 TN and TE patients with HCV genotype 1-6/HIV co-infection, including cirrhotic patients (17.92%), who received SOF/VEL (400/100 mg) once daily for 12 weeks.[73] SVR12 was observed in 95.28% (101/106) of the patients. Specifically, SVR12 was achieved in 95.45% (63/66), 91.67% (11/12), 100.00% (11/11), 91.67% (11/12), and 100.00% (5/5) of patients with HCV genotype 1a, 1b, 2, 3, and 4 infections, respectively. HCV treatment history and cirrhosis status were less likely to affect SVR12. Two patients experienced post-treatment HCV relapse. Two discontinued treatment owing to AEs, and 2 experienced serious AEs. These results suggest that both therapeutic options may be highly effective for patients with HCV/HIV co-infection. Although the current evidence on the efficacy and safety of SOF/VEL/VOX in patients with HCV/HIV co-infection are not available, this regimen may have similar efficacy

and safety profiles to those of SOF/VEL based on the previous studies.[11,14]

Now that the efficacy and safety of various DAA-based regimens in HCV-infected patients have been proved through several clinical trials and they have been approved in the USA and Europe, HCV infection can be considered as a completely curable disease in the near future. However, it is important to recognize and manage potential DDIs before they occur in order to reduce possible adverse drug reactions (ADRs) and increase drug adherence. Most potential DDIs from DAA-based regimens are closely associated with drug-metabolizing enzymes, such as CYP3A4, P-gp, organic anion-transporting polypeptides (e.g., OATP1B1 and OATP1B3), and breast cancer resistance protein (BCRP).[6,26,74] Concomitant administration of DAAs with the inducers or inhibitors of these metabolic pathways may affect plasma concentration levels of DAAs, thereby negatively contributing to their efficacy and safety.[6,74] Based on data identified in Micromedex® Solutions, a drug information database, the examples of DDIs between DAAs and other concomitant drugs are summarized in Table 9. As presented in the table, DDIs are likely to occur in patients who receive DAA-based regimens. Medications which are strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, St John's wort) may decrease plasma concentrations of DAAs. For example, rifampin is contraindicated when used with most DAAs because of the risk for loss of DAA efficacy. The risk for serious bradycardia may increase when DAAs are co-administered with amiodarone. Specifically, the co-administration of SOF-containing regimens with amiodarone is highly likely to induce serious bradycardia; therefore, this co-administration should be avoided. If amiodarone is required in patients receiving SOF-based regimens, their cardiac symptoms should be closely monitored.

In patients with HCV/HIV co-infection, DDIs between DAAs and antiretroviral agents may occur. Efavirenz which is a known CYP3A4 inducer is contraindicated when used with OBV/PTV/RTV due to increased efavirenz and

RTV exposure, elevated liver enzymes, and increased QT prolongation. The co-administration of efavirenz with EBV/GZR, GLE/PIB, and SOF/VEL/VOX may decrease DAA plasma concentrations, which leads to the risk for loss of DAA efficacy. However, the use of protease inhibitors (e.g., atazanavir, lopinavir) with EBV/GZR, GLE/PIB, and SOF/VEL/VOX may increase DAA plasma concentrations and lead to increased incidence of DAA-associated AEs. In addition, because of a potential increase in tenofovir disoproxil fumarate (TDF)-associated toxicities such as impaired renal function and reduced bone mineral density, TDF should be used with caution in patients receiving LDV/SOF or SOF/VEL/VOX.[74] In the study by Poizot-Martin et al[75], the contraindications and potential DDIs between DAAs and antiretroviral agents were analyzed with 1,161 HIV/HCV co-infected patients. SMV (78.8%) was most contraindicated with antiretroviral agents, followed by OBV/PTV/RTV (with or without DSV) (34.4%). The low rates of contraindications were expected between antiretroviral agents and respectively SOF (0.2%), LDV/SOF (0.2%), and DCV (0.0%). The potential DDIs were expected between antiretroviral agents and respectively LDV/SOF (67.6%), OBV/PTV/RTV (with or without DSV) (52.2%), DCV (49.4%), SMV (0.0%), and SOF (0.0%).[75] Comprehensively, OBV/PTV/RTV with or without DSV should be avoided in HIV/HCV coinfected patients. Concerning antiretroviral agents, DCV/SOF is the most favorable regimen for this patient group because the low rate of contraindications was expected with antiretroviral agents as demonstrated in the previous study.[76]

Elderly patients with HCV infection may be more frequently exposed to DAA-associated DDIs compared with their counterparts because of the increased use of co-medications to treat chronic diseases. Vermehren and colleagues reported that HCV-infected patients who aged ≥ 65 years received significantly more co-medications than those who aged < 65 years (79% vs. 51%; $p < 0.0001$).[77] Especially, HCV-infected and cirrhotic patients who aged ≥

65 years tended to receive the highest number of co-medications per patient. In addition, using the hep-druginteractions database, the proportion of predicted DDIs between DAAs and co-medications was significantly higher in elderly patients with HCV infection than that of their counterparts (54% vs. 28%; $p < 0.0001$).[77]

The DDIs between DAAs and concomitant drugs can cause very serious harm or potentially death in patients with HCV infection; therefore, it is critical to identify and manage potential DDIs before initiating DAA-based therapies in order to optimize the efficacy of them and minimize the frequency of AEs due to the DDIs. Pharmacists may be well-suited to this role because they understand the pharmacokinetics and pharmacodynamics profiles of the drugs associated with interactions. In the retrospective study by Langness et al[78], pharmacists through the review of baseline medication list identified the DDIs between DAAs and respectively proton pump inhibitor (PPI)/H_2-receptor antagonist (H_2RA) agents (117/664; 17.6%), antacids (72/664; 10.8%), analgesics (67/664; 10.1%), and hypertensive agents (53/664; 8.0%). The pharmacists took the following steps for the management of these DDIs: discontinuation of the medications associated with interactions (28.9%), frequent monitoring for toxicities (24.1%), separation of medication or administration (18.2%), and dose reduction (11.1%).[78] In another retrospective study by Ottman et al[79], clinical pharmacists identified 554 DDIs in a total of 300 patients with HCV infection. The most common DDIs were associated with acid suppression agents (20%), and the most commonly recommended intervention was patient monitoring, followed by dose adjustment of the medications associated with interactions (30%). The pharmacists made a total of 227 actionable recommendations, and 84.1% of them were accepted.[79]

Table 9. Examples of DDIs between DAAs and other concomitant drugs

Drug	Interaction drug	Severity[a]	Quality of evidence[b]	Summary
SOF	Rifampin	Contraindicated	Excellent	Reduced SOF exposure
	Amiodarone	Major	Excellent	Increased risk of serious bradycardia
	Warfarin	Major	Fair	Fluctuations in INR
	Rifapentine	Major	Fair	Reduced SOF exposure
	P-gp inducers (e.g., phenytoin, carbamazepine, fosphenytoin, St. John′s wort, Tipranavir)	Major	Fair	Decreased SOF exposure
LDV/SOF	Rifampin	Contraindicated	Excellent	Reduced SOF exposure
	Amiodarone	Major	Excellent	Increased risk of serious bradycardia
	SMV	Major	Excellent	Increased LDV and SMV exposure
	Warfarin	Major	Fair	Fluctuations in INR
	H_2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine)	Major	Fair	Decreased LDV exposure and loss of efficacy
	Anticonvulsants (e.g., phenytoin, phenobarbital, oxcarbazepine, fosphenytoin)	Major	Fair	Decreased LDV exposure and loss of efficacy
	Digoxin	Major	Fair	Increased digoxin exposure
	Proton pump inhibitors (e.g., omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole)	Major	Fair	Decreased LDV exposure and loss of efficacy
	Rifabutin, rifapentine	Major	Fair	Decreased LDV exposure and loss of efficacy
	Amiodarone	Major	Fair	Serious symptomatic bradycardia
	P-gp inducers	Major	Fair	Decreased LDV exposure and loss of efficacy
	Antacids	Major	Fair	Decreased LDV exposure and loss of efficacy
	Tenofovir disoproxil fumarate	Major	Fair	Increased tenofovir concentrations

Table. 9 (*continued*)

Drug	Interaction drug	Severity[a]	Quality of evidence[b]	Summary
DCV	Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, St. John's wort)	Contraindicated	Fair	Reduced DCV exposure
	Digoxin	Major	Good	Increased digoxin concentration
	Warfarin	Major	Fair	Fluctuations in INR
	Conivaptan	Major	Fair	Increased DCV exposure
	Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, ritonavir, grapefruit juice)	Major	Fair	Increased DCV exposure
	Amiodarone	Major	Fair	Increased risk of bradycardia
	Cobicistat	Major	Fair	Increased DCV exposure
	Etravirine	Major	Fair	Decreased DCV exposure
OBV/ PTV/ RTV	Ethinyl estradiol	Contraindicated	Excellent	Elevation of ALT
	Sildenafil	Contraindicated	Excellent	Increased risk of sildenafil AEs (e.g., hypotension, syncope, visual changes, priapism)
	Colchicine	Contraindicated	Excellent	Increased colchicine exposure and increased risk of colchicine toxicity
	Efavirenz	Contraindicated	Excellent	Increased efavirenz and RTV exposure; elevated liver enzymes; increased QT prolongation
	Amiodarone	Contraindicated	Good	Increased risk of amiodarone toxicity (e.g., hypotension, bradycardia, sinus arrest)
	Rifampin	Contraindicated	Good or Fair	Decreased RTV or OBV exposure
	Triazolam	Contraindicated	Good	Increased risk of extreme sedation and respiratory depression
	Simvastatin	Contraindicated	Good	Increased risk of myopathy or rhabdomyolysis
	Lovastatin	Contraindicated	Fair	Increased risk of myopathy or rhabdomyolysis
	Strong CYP3A inducers	Contraindicated	Fair	Decreased PTV exposure

Table. 9 (*continued*)

Drug	Interaction drug	Severity[a]	Quality of evidence[b]	Summary
DSV	Anticancer agents (e.g., mitotane, enzalutamide)	Contraindicated	Fair	Decreased DSV exposure
	Anticonvulsants (e.g., phenytoin, carbamazepine, phenobarbital, fosphenytoin)	Contraindicated	Fair	Decreased DSV exposure
	Gemfibrozil	Contraindicated	Fair	Increased DSV exposure
	St. John's wort	Contraindicated	Fair	Decreased DSV exposure
	Nevirapine, etravirine	Contraindicated	Fair	Decreased DSV exposure
	Efavirenz	Contraindicated	Fair	Liver enzyme elevation
	Ethinyl estradiol	Contraindicated	Fair	Increased risk of ALT elevation
	Rifampin	Contraindicated	Fair	Decreased DSV exposure
	Metformin	Major	Fair	Increased risk of lactic acidosis
	Darunavir	Major	Fair	Decreased darunavir trough concentrations
	Warfarin	Major	Fair	Fluctuations in INR
	CYP2C8 inhibitors and BCRP substrates (e.g., lapatinib, pixantrone)	Major	Fair	Increased DSV and BCRP substrate plasma concentrations
	Dolutegravir	Major	Fair	Increased DSV and dolutegravir concentrations
	CYP2C8 inhibitors (e.g., montelukast, atazanavir)	Major	Fair	Increased DSV concentration
	Rosuvastatin	Major	Fair	Increased rosuvastatin exposure
	Alprazolam	Major	Fair	Increased alprazolam exposure
	Furosemide	Major	Fair	Increased furosemide exposure
	Amiodarone	Major	Fair	Increased DSV and amiodarone concentrations
	Rilpivirine	Major	Fair	Increased rilpivirine exposure
	Pravastatin	Major	Fair	Increased DSV and pravastatin exposure
	Omeprazole	Major	Fair	Increased DSV exposure and decreased omeprazole exposure

Table. 9 (*continued*)

Drug	Interaction drug	Severity[a]	Quality of evidence[b]	Summary
EBV/GZR	Efavirenz	Contraindicated	Fair	Reduced EBV or GZR exposure and loss of EBV or GZR efficacy
	Protease inhibitors (e.g., saquinavir, lopinavir, tipranavir, atazanavir)	Contraindicated	Fair	Increased GZR exposure and increased risk of ALT elevations
	RTV	Contraindicated	Fair	Increased risk of ALT elevation
	Strong CYP3A inducers	Contraindicated	Fair	Reduced EBV or GZR exposure and loss of EBV or GZR efficacy
	OATP1B1/3 inhibitors (e.g., cyclosporine)	Contraindicated	Fair	Increased GZR exposure and increased risk of ALT elevations
	Rifampin	Contraindicated	Fair	Increased or decreased GZR levels
	Tacrolimus	Major	Excellent	Increased tacrolimus exposure
	Rosuvastatin	Major	Excellent	Increased rosuvastatin exposure
	Atorvastatin	Major	Excellent	Increased atorvastatin exposure
	Warfarin	Major	Fair	Fluctuations in INR
	Etravirine	Major	Fair	Reduced EBV or GZR exposure and loss of EBV or GZR efficacy
	Statins (e.g., lovastatin, simvastatin, fluvastatin)	Moderate	Fair	Increased statin concentrations

Table. 9 (*continued*)

Drug	Interaction drug	Severity[a]	Quality of evidence[b]	Summary
GLE/PIB	Rifampin	Contraindicated	Excellent	Reduced GLE or PIB exposure and reduced GLE or PIB efficacy
	Atazanavir	Contraindicated	Excellent	Increased GLE or PIB exposure
	RTV	Major	Excellent	Increased GLE or PIB exposure
	Lopinavir	Major	Excellent	Increased GLE or PIB exposure
	Darunavir	Major	Excellent	Increased GLE or PIB exposure
	Statins (e.g., simvastatin, lovastatin, atorvastatin)	Major	Excellent	Increased statin concentrations and increased risk of myopathy
	Carbamazepine	Major	Excellent	Reduced GLE or PIB exposure and reduced GLE or PIB efficacy
	Cyclosporine	Major	Excellent	Increased GLE or PIB exposure
	Efavirenz	Major	Fair	Reduced GLE or PIB exposure and reduced GLE or PIB efficacy
	Ethinyl estradiol	Major	Fair	Increased risk of ALT elevations
	St. John's wort	Major	Fair	Reduced GLE or PIB exposure and reduced GLE or PIB efficacy
	Digoxin	Moderate	Excellent	Increased digoxin plasma levels
	Statins (e.g., rosuvastatin, pravastatin)	Moderate	Excellent	Increased statin concentrations and increased risk of myopathy
	Statins (e.g., fluvastatin, pitavastatin)	Moderate	Fair	Increased statin concentrations and increased risk of myopathy

Table. 9 (*continued*)

Drug	Interaction drug	Severity[a]	Quality of evidence[b]	Summary
SOF/VEL ± VOX	Rifampin	Contraindicated	Excellent	Reduced SOF, VEL, or VOX exposure
	Amiodarone	Major	Excellent	Increased risk of serious bradycardia
	Atazanavir	Major	Excellent	Increased VOX exposure
	Cyclosporine	Major	Excellent	Increased VOX exposure
	Warfarin	Major	Fair	Fluctuations in INR
	Rifapentine	Major	Fair	Reduced VEL or VOX exposure
	Strong or moderate CYP3A4 inducers (e.g., nafcillin, primidone, phenobarbital, dexamethasone, prednisone)	Major	Fair	Reduced VEL or VOX exposure
	Strong or moderate dual inducers of CYP2B6 and CYP3A4 (e.g., primidone, phenobarbital, nevirapine, efavirenz)	Major	Fair	Reduced VEL exposure
	Rifapentine	Major	Fair	Reduced SOF exposure
	Strong or moderate dual inducers of CYP3A4 and P-gp (e.g., phenytoin, fosphenytoin, St. John's wort)	Major	Fair	Reduced VEL or VOX exposure
	BCRP substrates (e.g., topotecan, rosuvastatin)	Major	Fair	Increased concentrations of BCRP substrates
	Carbamazepine	Major	Fair	Reduced VEL exposure
	Tipranavir	Major	Fair	Reduced VEL or VOX exposure
	P-gp inducers (e.g., phenytoin, carbamazepine, fosphenytoin, St. John's wort, tipranavir)	Major	Fair	Reduced SOF exposure

Table. 9 (*continued*)

Drug	Interaction drug	Severity[a]	Quality of evidence[b]	Summary
	Lopinavir	Major	Fair	Increased VOX exposure
	Proton pump inhibitors (e.g., omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole)	Major	Fair	Decreased VEL exposure
	Pravastatin	Moderate	Excellent	Increased pravastatin exposure
	Digoxin	Moderate	Good	Increased digoxin levels
SOF/VEL ± VOX	Antacids (e.g., calcium carbonate, magnesium carbonate, sodium bicarbonate, aluminum bicarbonate)	Moderate	Fair	Decreased VEL exposure
	Statins (e.g., lovastatin, simvastatin, fluvastatin, atorvastatin)	Moderate	Fair	Increased statin exposure
	H_2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine)	Moderate	Fair	Reduced VEL exposure
	Pitavastatin	Moderate	Fair	Increased pitavastatin concentrations

[a]*Contraindicated* - the drugs are contraindicated for concurrent use; *Major* - the interaction may be life-threatening and/or need medical intervention to minimize or prevent serious adverse effects; *Moderate* - the interaction may exacerbate the patient's condition and/or need an alternative therapy; *Minor* - the interaction may cause an increase in the frequency or severity of side effects but would not need a major alternative therapy; *Unknown* - unknown.

[b]*Excellent* - the existence of the interaction have clearly been established through controlled studies; *Good* - the existence of the interaction is strongly suggested through documentation, but well-controlled studies are rare; *Fair* - available documentation is poor, but pharmacologic concerns lead clinicians to suspect the existence of the interaction or documentation regarding pharmacologically similar drug is good; *Unknown* - unknown.

This study had some limitations which must be addressed. Although there were other databases available, only two electronic databases (i.e., PubMed and KoreaMed) were utilized to identify relevant clinical trials. This limitation could have restricted our chances to find additional valuable and relevant clinical trials. Almost all of the selected clinical trials reported that DAA-based combination therapies for HCV-infected patients were effective and safe, but the results were usually obtained from clinical trials conducted with Western populations. Only 3 studies were carried out in Japan and Thailand. Additionally, to determine a difference in the efficacy and safety of DAAs according to race, the subgroup analyses were conducted in some clinical trials; however, the relatively small number of Asians was included in them. These may lead to inconclusive results concerning DAA-based combination therapies in Asian populations. There may be also a gender difference in the efficacy and safety of DAAs, but most of the selected clinical trials did not specifically report this difference. Therefore, this point should be addressed in the future study. Real-life studies, such as retrospective or case-control studies, should have been included in this study. Most clinical trials included in this study mentioned that AEs were mild, and almost all of significant AEs were not associated with study drugs. However, severe AEs including DDIs or drug-disease interactions which were not reported in clinical trials may occur in real-life settings, which may compromise the rates of SVR12 in the real world. This could have limited our abilities to identify additional studies and lead to more conclusive results regarding DAA-based combination treatments. In order to complement this limitation, the DDIs between DAAs and other drugs which can be co-administered in real-life setting were presented with the use of drug information database in Table 9. The number of clinical studies included in the meta-analysis was small because the designs of the final selected clinical studies through the systematic review of the literature were various.

V. CONCLUSION

The results from this systematic review and meta-analysis suggest that DAA-based treatment regimens for HCV-infected patients show better efficacy and safety with high SVR12 rates and good tolerability. In the earlier era of DAAs, SOF-based regimens have been usually used for the treatment of HCV infection. However, various oral regimens including DAAs with different mode of actions are currently available. These regimens reduce the treatment of duration to 8 or 12 weeks, and they have improved safety profiles. They also show improved efficacy and safety profiles in HCV-infected patients with cirrhosis, CKD, or HIV co-infection. The DDIs between DAAs and concomitant drugs can cause very serious harm or potentially death in patients with HCV infection. Therefore, it is critical to identify and manage potential DDIs before initiating DAA-based therapies in order to optimize the efficacy of them and minimize the frequency of AEs due to the DDIs.

Ⅵ. REFERENCES

1. WHO. Hepatitis C. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/ (accessed on March 27, 2018).
2. Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection - Updated version, April 2016. Available at: http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/ (accessed on March 27, 2018).
3. Global hepatitis report, 2017. Available at: http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/ (accessed on March 27, 2018).
4. Jeong SH, Jang ES, Choi HY, et al. Current status of hepatitis C virus infection and countermeasures in South Korea. Epidemiol Health. 2017;39:e2017017.
5. Ahmad T, Yin P, Saffitz J, et al. Cardiac dysfunction associated with a nucleotide polymerase inhibitor for treatment of hepatitis C. *Hepatology.* 2015;62(2):409-416.
6. Yang YM, Choi EJ. Efficacy and safety outcomes of sofosbuvir-based treatment regimens for hepatitis C virus-infected patients with or without cirrhosis from phase III clinical trials. Ther Clin Risk Manag. 2017;13:477-497.
7. Ahmed AM, Doheim MF, Mattar OM, et al. Beclabuvir in combination with asunaprevir and daclatasvir for hepatitis C virus genotype 1 infection: A systematic review and meta-analysis. J Med Virol. 2017;1-12.
8. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-Pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med. 2018;378:354-369.
9. Bourgeois S, Vlierberghe HV, Moreno C, et al. Efficacy, safety and pharmacokinetic of simeprevir and TMC647055/ritonavir with or without ribavirin and JNJ-56914845 in HCV genotype 1 infection. BMC Gastroenterol.

2017;17(1):26.

10. Toyota J, Karino Y, Suzuki F, et al. Daclatasvir/asunaprevir/beclabuvir fixed-dose combination in Japanese patients with HCV genotype 1 infection. J Gastroenterol. 2017;52:385-395.
11. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV Infection. N Engl J Med. 2017;376(22):2134-2146.
12. Lawitz E, Poordad F, Wells J, et al. Sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin in direct-acting antiviral-experienced patients with genotype 1 hepatitis C virus. Hepatology. 2017;65(6):1803-1809.
13. Sato K, Chayama K, Alves K, et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir and ribavirin for hepatitis C virus genotype 2-infected Japanese patients. Adv Ther. 2017;34:1449-1465.
14. Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV Infection: 2 phase 3 randomized trials. Gastroenterology. 2017;153(1):113-122.
15. Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. Hepatology. 2017;66:389-397.
16. Hezode C, Colombo M, Bourliere M, et al. Elbasvir/grazoprevir for patients with hepatitis C virus infection and inherited blood disorders: a phase III study. Hepatology. 2017;66:736-745.
17. Dore GJ, Conway B, Luo Y, et al. Efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir compared to IFN-containing regimens in genotype 1 HCV patients: The MALACHITE-I/II trials. J Hepatol. 2016;64(1):19-28.
18. Everson GT, Sims KD, Thuluvath PJ, et al. Daclatasvir + asunaprevir + beclabuvir ± ribavirin for chronic HCV genotype 1-infected treatment-naive patients. Liver Int. 2016;36(2):189-97.

19. Zeuzem S, Hézode C, Bronowicki JP, et al. Daclatasvir plus simeprevir with or without ribavirin for the treatment of chronic hepatitis C virus genotype 1 infection. J Hepatol. 2016;64(2):292-300.
20. Jacobson I, Zeuzem S, Flisiak R, et al. Daclatasvir vs telaprevir plus peginterferon alfa/ribavirin for hepatitis C virus genotype 1. World J Gastroenterol. 2016;22(12):3418-3431.
21. Jensen DM, Brunda M, Elston R, et al. Interferon-free regimens containing setrobuvir for patients with genotype 1 chronic hepatitis C: a randomized, multicenter study. Liver Int. 2016;36:505-514.
22. Ruane PJ, Ain D, Stryker R, et al. Sofosbuvir plus ribavirin for the treatment of chronic genotype 4 hepatitis C virus infection in patients of Egyptian ancestry. J Hepatol. 2015;62:1040-1046.
23. Forns X, Poordad F, Pedrosa M, et al. Ombitasvir/paritaprevir/r, dasabuvir and ribavirin for cirrhotic HCV patients with thrombocytopaenia and hypoalbuminaemia. Liver Int. 2015;35:2358-2362.
24. Gane EJ, Hyland RH, An D, et al. Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin, for 12 Weeks in Patients With HCV Genotype 3 or 6 Infection. Gastroenterology. 2015;149:1454-1461.
25. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. 2015;373:2608-2617.
26. Talavera Pons S, Boyer A, Lamblin G. Managing drug-drug interactions with new direct-acting antiviral agents in chronic hepatitis C. Br J Clin Pharmacol. 2016. doi: 10.1111/bcp.13095. [Epub ahead of print].
27. The Korean Association for the Study of the Liver. Guidelines for the treatment of persons with chronic hepatitis C infection - Updated version, November 2017. Available at: http://www.kasl.org/bbs/index.html?code=guide&category=&gubun=&idx=&page=1&number=3359&mode=view&order=&sort=&keyfield=&key= (accessed on April 2, 2018).

28. Asselah T, Marcellin P, Schinazi RF. Treatment of hepatitis C virus infection with direct-acting antiviral agents: 100% cure? Liver Int. 2018;38(Suppl. 1):7-13.
29. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6:1000100.
30. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ. 2011;343:d5928.
31. Lee MD. On the complexity of additive clustering models. J Mathematical Psychol. 2001;45:131-148.
32. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med. 2014;370(3):222-232.
33. Everson GT, Sims KD, Rodriguez-Torres M, et al. Efficacy of an interferon- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naive patients with HCV genotype 1 infection. Gastroenterology. 2014;146(2):420-429.
34. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014;146(2):430-441.
35. Lok AS, Gardiner DF, Hézode C, et al. Randomized trial of daclatasvir and asunaprevir with or without PegIFN/RBV for hepatitis C virus genotype 1 null responders. J Hepatol. 2014;60(3):490-499.
36. Rodriguez-Torres M, Stoehr A, Gane EJ, et al. Combination of vaniprevir with peginterferon and ribavirin significantly increases the rate of SVR in treatment-experienced patients with chronic HCV genotype 1 infection and cirrhosis. Clin Gastroenterol Hepatol. 2014;12(6):1029-1037.
37. Wyles DL, Rodriguez-Torres M, Lawitz E, et al. All-oral combination of ledipasvir, vedroprevir, tegobuvir, and ribavirin in treatment-naïve patients

with genotype 1 HCV infection. 2014;60(1):56-64.

38. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. Gastroenterology. 2014;146(7):1669-1679.
39. Manns MP, Vierling JM, Bacon BR, et al. The combination of MK-5172, peginterferon, and ribavirin is effective in treatment-naive patients with hepatitis C virus genotype 1 infection without cirrhosis. Gastroenterology. 2014;147(2):366-376.
40. Zeuzem S, Asselah T, Angus P, et al. Faldaprevir (BI 201335), deleobuvir (BI 207127) and ribavirin oral therapy for treatment-naive HCV genotype 1: SOUND-C1 final results. Antivir Ther. 2013;18(8):1015-1019.
41. Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med. 2013;369(7):630-639.
42. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012;366(3):216-224.
43. 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(9):671-677.
44. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364(25):2417-2428.
45. Puoti M, Foster GR, Wang S, et al. High SVR12 with 8-week and 12-week Glecaprevir/Pibrentasvir: Integrated Analysis of HCV Genotype 1-6 Patients Without Cirrhosis. J Hepatol. 2018; pii: S0168-8278(18)30165-X. doi: 10.1016/j.jhep.2018.03.007. [Epub ahead of print].
46. Reau N, Kwo PY, Rhee S, et al. Glecaprevir/Pibrentasvir Treatment in Liver or Kidney Transplant Patients With Hepatitis C Virus Infection. Hepatology. 2018; doi: 10.1002/hep.30046. [Epub ahead of print].

47. Rockstroh JK, Lacombe K, Viani RM, et al. Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients Co-infected with Hepatitis C Virus and Human Immunodeficiency Virus-1: the EXPEDITION-2 Study. Clin Infect Dis. 2018; doi: 10.1093/cid/ciy220. [Epub ahead of print].
48. Gilead Sciences Inc. US prescribing information: Vosevi® (sofosbuvir, velpatasvir, voxilaprevir) tablets. Available at: http://www.gilead.com/ (accessed on May 19, 2018).
49. European Medicines Agency. Vosevi 400 mg/100 mg/100 mg film-coated tablets: summary of product characteristics Available at: http://www.ema.europa.eu./ema/ (accessed on May 19, 2018).
50. Heo YA, Deeks ED. Sofosbuvir/velpatasvir/voxilaprevir: a review in chronic hepatitis C. Drugs. 2018;78(5):577-587.
51. Poordad F, Sievert W, Mollison L, et al. Fixed-dose combination therpay with daclatasvir, asunaprevir, and beclabuvir for noncirrhotic patients with HCV genotype 1 infection. JAMA. 2015;313(17):1728-1735.
52. Muir AJ, Poordad F, Lalezari J, et al. Daclatasvir in combination with asunaprevir and beclabuvir for hepatitis C vrius genotype 1 infection with compensated cirrhosis. JAMA. 2015;313(17):1736-1744.
53. Deeks ED. Ombitasvir/paritabrevir/ritonavir plus dasabuvir: a review in chronic HCV genotype 1 infection. Drugs. 2015;75(9):1027-1038.
54. Klibanov OM, Gale SE, Santevecchi B. Ombitasvir/paritaprevir/ritonavir and dasabuvir tablets for hepatitis C virus genotype 1 infection. Ann Pharmacother. 2015;49(5):566-581.
55. Preda CM, Popescu CP, Baicus C, et al. Real-world efficacy and safety of ombitasvir, paritaprevir/r+dasabuvir+ribavirin in genotype 1b patients with hepatitis C virus cirrhosis. Liver Int. 2018;38(4):602-610.
56. Isakov V, Paduta D, Viani RM, et al. Ombitasvir/paritaprevir/ritonavir+dasabuvir+ribavirin for chronic hepatitis C virus genotype 1b-infected cirrhotics (TURQUOISE-IV). Eur J Gastroenterol

Hepatol. 2018. doi: 10.1097/MEG.0000000000001166. [Epub ahead of print].

57. Liu CH, Liu CJ, Su TH, et al. Real-world effectiveness and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir with or without ribavirin for patients with chronic hepatitis C virus genotype 1b infection in Taiwan. J Gastroenterol Hepatol. 2018;33(3):710-717.
58. Flisiak R, Janczewska E, Wawrzynowicz-Syczewska M, et al. Real-world effectiveness and safety of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in hepatitis C: AMBER study. Aliment Pharmacol Ther. 2016;44(9):946-956.
59. Martinello M, Bhagani S, Gane E, et al. Shortened therapy of eight weeks with paritaprevir/ritonavir/ombitasvir and dasabuvir is highly effective in people with recent HCV genotype 1 infection. J Viral Hepat. 2018. doi: 10.1111/jvh.12917. [Epub ahead of print].
60. Sperl J, Kreidlova M, Merta D, et al. Paritaprevir/ritonavir/ombitasvir plus dasabuvir regimen in the treatment of genotype 1 chronic hepatitis C infection in patients with severe renal impairment and end-stage renal disease: a real-life cohort. Kidney Blood Press Res. 2018;43:594-605.
61. George J, Burnevich E, Sheen IS, et al. Elbasvir/grazoprevir in Asia-Pacific/Russian participants with chronic hepatitis C virus genotype 1, 4, or 6 infection. Hepatol Commun. 2018;2(5):595-606.
62. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1075-1086.
63. Sulkowski M, Hezode C, Gerstoft J, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus

genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1087-1097.

64. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med. 2015;163(1):1-13.
65. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386(10003):1537-1545.
66. Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV. 2015;2(8):e319-327.
67. Kwo P, Gane E, Peng C-Y, et al. Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection. Gastroenterology. 2017;152(1):164-175.
68. Sperl J, Horvath G, Halota W, et al. Efficacy and safety of elbasvir/grazoprevir and sofosbuvir/pegylated interferon/ribavirin: a phase III randomized controlled trial. J Hepatol. 2016;65(6):1112-1119.
69. Forns X, Gordon SC, Zuckerman E, et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. J Hepatol. 2015;63(3):564-572.
70. Dore GJ, Altice F, Litwin AH, et al. Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med. 2016;165(9):625-634.
71. Pol S, Parlati L. Treatment of hepatitis C: the use of the new pangenotypic

direct-acting antivirals in "special populations". Liver Int. 2018;38(Suppl 1);28-33.

72. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med. 2017;377(15):1448-1455.
73. Wyles D, Brau N, Kottilil S, et al. Sofosbuvir and velpatasvir for the treatment of hepatitis C virus in patients coinfected with human immunodeficiency virus type 1: an open-label, phase 3 study. Clin Infect Dis. 2017;65(1):6-12.
74. Chahine EB, Kelley D, Childs-Kean LM. Sofosbuvir/velpatasvir/voxilaprevir: a pan-genotypic direct-acting antiviral combination for hepatitis C. Ann Pharmacother. 2018;52(4):352-363.
75. Poizot-Martin I, Naqvi A, Obry-Roquet V, et al. Potential for drug-drug interactions between antiretrovirals and HCV direct acting antivirals in a large cohort of HIV/HCV coinfected patients. PLoS One. 2015;10(10):e0141164.
76. Smolders EJ, Smit C, T M M de Kanter C, et al. Brief report: high need to switch cART or comedication with the initiation of DAAs in elderly HIV/HCV-coinfected patients. J Acquir Immune Defic Syndr. 2017;76(2):193-199.
77. Vermehren J, Peiffer KH, Welsch C, et al. The efficacy and safety of direct acting antiviral treatment and clinical significance of drug-drug interactions in elderly patients with chronic hepatitis C virus infection. Aliment Pharmacol Ther. 2016;44(8):856-865.
78. Langness JA, Nguyen M, Wieland A, Everson GT, Kiser JJ. Optimizing hepatitis C virus treatment through pharmacist interventions: identification and management of drug-drug interactions. World J Gastroenterol. 2017;23(9):1618-1626.
79. Ottman AA, Townsend ML, Hashem MG, DiMondi VP, Britt RB. Incidence

of drug interactions identified by clinical pharmacists in veterans initiating treatment for chronic hepatitis C infection. Ann Pharmacother. 2018;1060028018766507. doi: 10.1177/1060028018766507. [Epub ahead of print].