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Efficacy and safety of glecaprevir/pibrentasvir for chronic hepatitis C virus genotypes 1–6 infection: A systematic review and meta-analysis

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ABSTRACT

This systematic review and meta-analysis investigated the efficacy and safety of glecaprevir and pibrentasvir (G/P) for chronic hepatitis C virus (HCV) infection. Pubmed, Embase, Cochrane Library and Scopus were searched to identify relevant studies through August 2018. Data from eligible studies were pooled and sustained virological response rates at 12 weeks' post-treatment (SVR12) were calculated. Thirteen studies with 3082 patients were included and the overall SVR12 rate was 97.8%. The SVR12 rates of subgroups were: G/P 300 mg/120 mg and 200 mg/120 mg: 97.9% and 98.3%; HCV genotype (GT)1, GT2, GT3 and GT4-6: 99.8%, 99.2%, 96.1% and 100%; G/P and G/P plus ribavirin (RBV): 97.9% and 98.2%; G/P (300 mg/120 mg) for 8 weeks, 12 weeks and 16 weeks: 98.8%, 98.5% and 95.6%; treatment-naïve and treatment-experienced patients: 96.7% and 98.3%; patients without and with compensated cirrhosis: 99.4% and 98.8%; patients without and with human immunodeficiency virus (HIV) co-infection: 97.8% and 99.4%; and patients without and with severe renal impairment (SRI): 97.8% and 99.4%. Virological failure and relapse and serious drug-related adverse events were rare. These results indicate that 8- or 12-week G/P treatment achieved high SVR12 rates in HCV GTs 1-6 patients without or with compensated cirrhosis, with good safety profiles, irrespective of dose, RBV use, treatment-experience, HIV co-infection and renal impairment. Due to the limited number of evaluated patients with GT3 infection, further studies are needed to define optimal treatment duration for GT3 cirrhosis patients and patients with prior treatment experience of direct-acting antivirals.

1. Introduction

Chronic hepatitis C virus (HCV) infection is a main cause of chronic liver disease, affecting approximately 185 million people worldwide [1]. Around 55-85% of the population infected with HCV will develop chronic infection, which is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). Approximately 700 000 people die each year due to HCV-related liver complications [2,3]. Six major HCV genotypes (GTs) and more than 100 subtypes have so far been documented [4,5], and these may contribute to the variable responses to different treatment regimens. HCV infection remains a serious public health issue worldwide.

Interferon (IFN)-based regimens have been widely used for the treatment of HCV infection, but these regimens are associated with severe adverse events (AEs) and frequent discontinuation of treatment [6,7]. Complex drug administration and dosage reduces patient adherence to these regimens. The development of new direct-acting antivirals (DAAs) has dramatically revolutionized the treatment of HCV infection [8]. DAAs have different mechanisms of action and provide much more efficacious and well-tolerated therapeutic strategies compared with IFN-based regimens [9]. DAAs were initially used in combination with IFNs to treat HCV infection to reduce the dose of IFNs and thereby reduce the associated AEs. Subsequently, DAAs with different mechanisms of action were used in combination in IFN-free regimens to overcome the disadvantages of IFNs [10,11]. The World Health Organization (WHO) recommended several IFN-free regimens, such as the combination of daclatasvir and sofosbuvir, ledipasvir and sofosbuvir, or simeprevir and sofosbuvir [12].

The development of new generation DAAs and studies of novel combinations of DAAs provided more therapeutic options with

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better treatment outcomes irrespective of GT or underlying cirrhosis [13]. Several clinical trials have investigated an all-oral, two-drug combination of glecaprevir (formerly ABT-493), an NS3/4A protease inhibitor, and pibrentasvir (formerly ABT-530), an NS5A inhibitor. This glecaprevir/pibrentasvir (G/P) combination exhibited potent antiviral activity across all major HCV GTs [14]. The G/P regimen is currently being evaluated as a pan-genotypic regimen for HCV patients, including "difficult-to-treat" subgroups, such as patients with compensated cirrhosis or chronic renal failure, and those who failed to respond to previous DAA-based therapy [15].

Factors such as HCV GT; treatment regimen, including addition of ribavirin (RBV); treatment duration; patient characteristics, e.g., treatment experience, disease severity and comorbidities; and sample size can differ between studies. These factors may compromise the generalizability of individual studies. Therefore, this systematic review and meta-analysis was conducted to investigate the efficacy and safety of the G/P regimen in the treatment of chronic HCV infection.

2. Methods

2.1. Search strategy

A complete systematic and comprehensive literature search was performed on multiple databases including Embase, PubMed, Scopus, and Cochrane databases up to August 2018. The following MESH search terms were used: "Glecaprevir", "ABT-493", "Pibrentasvir", "ABT-530", "Hepatitis C", "Hepatitis C, Chronic", "HCV", and "CHC". A manual search was also conducted by reviewing the citations within the included publications and reviewing the related references presented in PubMed. There were no language restrictions.

2.2. Selection criteria

The following criteria were used to include studies in the analysis: studies reporting the efficacy and safety of the combination of G/P for the treatment of HCV infection.

The following criteria were used to exclude studies from the analysis: (a) Studies that did not report on the SVR12 of G/P for HCV infection or the SVR12 cannot be calculated; (b) Except for HIV co-infection, studies that were performed in patients who had hepatitis B co-infection or had any cause of liver disease other than chronic HCV infection; (c) Studies that investigated the pharmacokinetics of glecaprevir and/or pibrentasvir in healthy volunteers; (d) Studies comprising post-transplanted patients; (f) Book chapters, abstract-only articles, conference papers, reviews, theses, posters, editorials, and letters.

2.3. Outcome measures

The primary outcome was virological response, which was defined as HCV RNA concentration with a lower limit of quantitation of 15 or 25 IU/mL according to the difference of HCV GT and/or research institute. The assessed outcome was the sustained virological response at 12 weeks' post-treatment (SVR12). Additional secondary outcomes were the rate of on-treatment virological failure and post-treatment relapse. Any patient who met one of the following criteria was considered to have had on-treatment virological failure: an increase in the HCV RNA level of at least 100 IU/mL after a measurement showing an HCV RNA level of less than 15 IU/mL during treatment; a confirmed increase in the HCV RNA level of more than 1 log10 IU/mL from the nadir during the treatment period, or an HCV RNA level of at least 15 IU/mL after 6 weeks of treatment [26,29,30]. Patients who completed treatment and had an HCV RNA level of less than 15 IU/mL at the end of treatment were considered to have had a virological relapse if they had a confirmed HCV RNA level of at least 15 IU/mL between the end of treatment and 12 weeks after the last dose of the trial drug [26,29,30].

The safety of the G/P regimen for HCV-infected patients was evaluated by the rate of drug-related AEs and laboratory abnormalities.

2.4. Literature screening

Search results from the four aforementioned search databases were imported into Endnote X7 software for format unification and deletion of duplicates. Literature screening was conducted independently by two researchers (XW and XF) using the predetermined selection criteria. The first selection was made by reading the titles and abstracts of the studies after removing duplication. The full texts of the selected studies were filtered to determine which studies were to be included in the final analysis. Any conflict in the screening process was discussed by the two reviewers to reach a consensus. If consensus was not reached, a third researcher (ZL) was consulted as necessary.

2.5. Data extraction

Two researchers (XW and XF) independently extracted the data from the included studies. The extracted data included: first author, year of publication, designation and characteristics of clinical trial, demographic data (country, race, age, sex, body mass index [BMI]), period of study, HCV RNA level, regimen, treatment duration, total number of patients, subgroup number of patients, the number of patients who achieved SVR12 and the SVR12 rate in each subgroup, the number of patients who did not receive SVR12 (including on-treatment virological failure, post-treatment relapse, discontinued treatment, and lost to follow-up), the number of patients with AEs, including any AEs, drug-related AEs, serious AEs (SAEs), drug-related SAEs, and AEs leading to discontinuation, and the number of laboratory abnormalities, including alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin and hemoglobin. The resolution of any discrepancy was the same as for the literature screening.

2.6. Assessment of quality

Eight of the included studies were non-randomized, four were randomized, and one study had three clinical trials (one trial was randomized and two were non-randomized trials). The quality of each included study was independently assessed by two reviewers. The quality of non-randomized studies was assessed using methodological index for non-randomized studies (MINORS) [16,17], and the quality of randomized studies was assessed using the Cochrane Collaboration's tool [18]. The study that included one randomized and two non-randomized trials was assessed using MINORS and the Cochrane Collaboration's tool simultaneously.

There are 12 evaluation indicators in MINORS, each of which is divided into 0-2 points: 0 points for non-reporting, 1 point for reporting but insufficient information, and 2 points for reporting and providing sufficient information. The first 8 items are applied to assess studies with no control group, and the highest score is 16 points. Together with the first 8 items, the last 4 items are used to assess studies with a control group, and the highest score is 24 points. Low quality is 0-8 or 0-12 points, moderate quality is 9-12 or 13-18 points and high quality is 13-16 or 19-24 points.

The Cochrane Collaboration's tool is a two-part tool, addressing seven specific domains including: randomization, allocation concealment, blinding of subjects, blinding of outcome assessors, reporting of incomplete outcome data, selective outcome reporting,

and other potential sources of bias. In each domain, each study took one of three categories; 'low risk,' 'high risk,' or 'unclear risk' of bias.

2.7. Statistical analysis

A meta-analysis of the data from 13 eligible studies was performed using STATA 13.0 and RevMan 5.3 software. As the primary endpoint rates of the included studies were all over 80%, the double arcsine method was adopted to calculate event rate and the corresponding standard error [19]. To facilitate the interpretation of data, the event rates calculated by the double arcsine method were converted into proportions with 95% confidence intervals (CI). The data were pooled using a random-effects or fixed-effects model depending on the heterogeneity of the included studies. Heterogeneity among studies was tested with the Cochrane Q test and I^2 statistic [20]. Significant heterogeneity was considered when I^2 value >50% or the *P*-value of Cochrane Q test <0.1. When significant heterogeneity existed in the included studies, the random-effect model was adopted, otherwise a fixed-effect model was employed. A meta-regression was used to investigate the sources of heterogeneity. The covariates in regression analyses included sample size, race, sex, mean age, mean BMI, and mean HCV RNA load. The *P*-value <0.10 was considered significant in meta-regression analyses. The pooled rates of on-treatment virological failure, virological relapse, discontinued treatment, and lost to follow-up were performed.

In the efficacy analyses, subgroup meta-analysis was performed for SVR12 (according to the drug doses, HCV GTs, treatment regimens, treatment durations, treatment history, presence or absence of cirrhosis, HIV co-infection, and comorbidity of severe renal impairment [SRI]). SRI was defined as a glomerular filtration rate (GFR) of less than 30 mL/1.75m^2/min. In the safety analyses, subgroup analysis was conducted from several aspects, including any AEs, drug-related AEs, SAEs, drug-related SAEs, AEs leading to discontinuation and laboratory abnormalities, including grade 3 abnormalities of hemoglobin (<8 g/L), ALT (>5 upper limit of normal [ULN]), AST (>5 ULN), and total bilirubin (>3 ULN).

3. Results

3.1. Literature selection and basic information

The initial literature search identified a total of 334 articles; 136 duplicate articles were removed by EndNote software to give 198 articles. Of these 198 studies, 179 studies were excluded by the title and abstract screening, and 6 studies were excluded by full-text screening based on predetermined inclusion and exclusion criteria. Overall, 13 studies were included in our study [21–33]. The flow chart of the literature screening is summarized in Fig. 1.

The 13 studies included in the meta-analysis had a total of 3082 patients. All subjects were HCV chronically infected patients with GT1-6, with or without compensated cirrhosis, HIV co-infection, SRI, and treatment experience. The treatment regimens used in the eligible studies were fixed-dose combinations of glecaprevir (300 mg) and pibrentasvir (120 mg) with or without RBV and combinations of glecaprevir (200 mg) and pibrentasvir (120 mg). The course of treatment included 8 weeks, 12 weeks, and 16 weeks. Of the 13 eligible studies, the patients from 10 studies [24–33] were mostly white (more than 55%), and the patients from 3 studies were Japanese [21–23]. The data for the study period were not retrievable in two included studies [25,27]. The details of the 13 included studies are summarized in Tables 1 and 2.

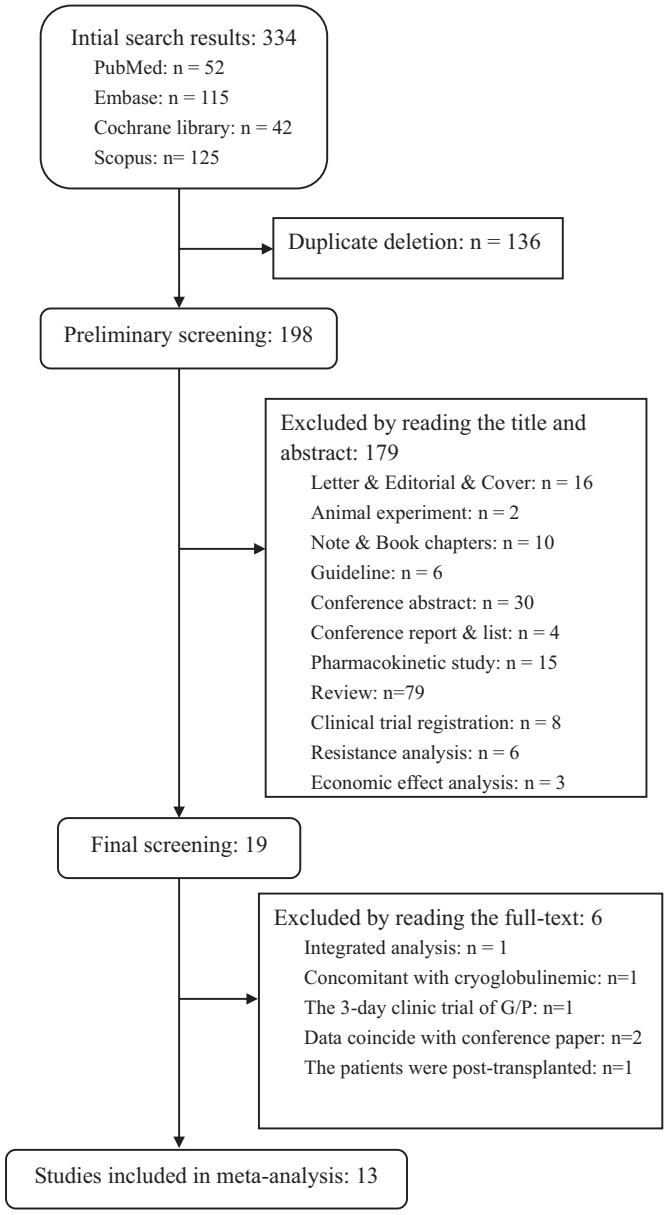

Fig. 1. Flowchart of the literature selection process.

3.2. Quality assessment

Eight non-randomized studies [21–23,26,27,29,32,33] and one study [24] that included two non-randomized trials were assessed by MINORS. All these studies were of moderate quality. The results of MINORS are exhibited in Table 1.

Four randomized studies [25,28,30,31] and one study [24] that included a randomized trial were assessed using the Cochrane Collaboration's tool. Among the assessed items, allocation concealment was reported in one study [30], and others were not reported. Furthermore, the participants were blinded in only one study [24]. The results are represented in Fig. S1.

3.3. Efficacy of glecaprevir and pibrentasvir

3.3.1. SVR12 rate

Thirteen eligible studies [20–33] involving 3082 patients investigated SVR12 of the combination of G/P treatment for HCV infection. Significant heterogeneity was found among these studies

Table 1
Characteristics and quality of the studies included in this comprehensive analysis.

Author	Year	Clinical trial	Characteristic of clinical trial	Period	Country	Race	HCV genotype	Regimen	Duration (Weeks)	Total number	MINORS
Kumada	2018	CERTAIN-I	Phase III, multicenter trial	Feb.-Jun.2016	Japan	Japanese	GT-1/2,3	G/P 300/120 mg	8, 12	57	9
Chayama	2018	CERTAIN-II	Phase III, multicenter trial	Feb.-Jun. 2016	Japan	Japanese	GT-1	G/P 300/120 mg	8, 12	167	9
Toyoda	2018	CERTAIN-II	Phase III, multicenter trial	Feb.-July.2016	Japan	Japanese	GT-2	G/P300/120 mg	8, 12	108	9
Asselah	2018	ENDURANCE-II, ENDURANCE-IV, SURVEYOR-II	One RCT; two Phase III, multicenter trial	Oct.2014-Oct.2016	13 countries	White >60%	GT-2,4-6	G/P300/120 mg	8, 12	526	12*
Poordad	2017	MAGELLAN-I	Phase II, randomized, multicenter trial	NA	US	Black<50%	GT-1	G/P300/120mg ±800mg RBV	12	44	-
Gane	2017	EXPEDITION-IV	Phase III, single-arm, multicenter trial	Dec.2015-Mar.2016	9 countries: UK, US, Australia, Italy, Belgium, Canada, France, Greece, New Zealand	White 62%, Black 24%	GT 1-6	G/P 300/120 mg	12	104	12
Kwo	2017	SURVEYOR-ISURVEYOR-II	Phase II, multicenter trials	NA	US, Australia, Canada, Europe, New Zealand, Puerto Rico	White 87%	GT 1-6	G/P 200/120 mg G/P 300/120 mg	8, 12	380	9
Poordad	2018	MAGELLAN-1	Phase III, randomized, multicenter trial	Jan.2016-Mar.2016	Australia, France, Spain, UK, and US (including Puerto Rico)	White>75%	GT 1, 4	G/P 300/120 mg	12, 16	91	-
Forns	2017	EXPEDITION-I	Phase III, single-arm, multicenter trial	Dec.2015-May 2016	Belgium, US, Canada, Germany, South Africa, Spain	White 82%,	GT 1, 2, 4, 5, 6	G/P 300/120 mg	12	146	12
Zeuzem	2018	ENDURANCE-1ENDURANCE-3	Phase III, randomized, multicenter trials	Oct.2015-May.2016	Germany, Canada, Australia, New Zealand, US, UK, France, South Korea	White>80%	GT 1,3	G/P 200/120 mg G/P 300/120 mg	8, 12	1093	-
Wyles	2018	SURVEYOR-II, Part 3	Phase III, randomized, multicenter trial.	Jan.2016-Apr.2016	US, Australia, Canada, France, New Zealand, UK.	White> 7%	GT 3	G/P300/120 mg	12, 16	131	-
Gane	2016	SURVEYOR-I SURVEYOR-II	Phase II	Aug.2014-Jul.2015	US, Canada, UK, New Zealand, Australia, Puerto Rico	White>89%	GT 1,3	G/P300/120 mg ± 800 mg RBV	12, 16	82	10
Rockstroh	2018	EXPEDITION-2	Phase III, multicenter trial	May 2016-Sep.2016	Australia, Belarus, France, Poland, Germany, Russia, Puerto Rico, UK, US	White>77%	GT 1–6	G/P 300/120 mg	8, 12	153	12

HCV: hepatitis C virus, MINORS: methodological index for non-randomized studies, GT: genotype, G/P: Glecaprevir/pibrentasvir, NA: not available, US: United States, UK: United Kingdom.
* The score was made by MINORS depending on the two non-randomized trials of the study.

Table 2
Treatment and patient characteristics of the studies included in this comprehensive analysis.

Author	Year	Main groups	Duration (weeks)	Number	Sex (male %)	Age (y)	Mean BMI (kg/m^2)	HCV RNA (log10 IU/mL)
Kumada	2018	GT 1/2 with DAA-failures	12	33	39	67 (53 - 80)	24.0 ± 3.5	6.0 ± 0.5
		GT 1/2 with SRI	12	12	50	69 (54 - 78)	22.2 ± 3.6	5.8 ± 1.2
		GT3	12	12	50	57 (23 - 70)	23.5 ± 3.9	6.2 ± 0.7
Chayama	2018	GT1 without cirrhosis	8	129	36	64 (21 - 86)	24 ± 4	6.1 ± 0.8
		GT1 with cirrhosis	12	38	45	73(48 - 85)	24 ± 5	6.0 ± 0.8
Toyoda	2018	GT2 without cirrhosis	8	90	47	57 (26-83)	22.9 ± 3.3	6.0 ± 0.8
		GT2 with cirrhosis	12	18	39	70 (49-85)	22.2 ± 3.5	5.3 ± 1.0
Asselah	2018	GT2 without cirrhosis	12	202	49	57 ± 12.8	25.8 ± 4.7	6.25 (2.5 - 7.3)
		GT 4-6 without cirrhosis	12	121	64	53 ± 11.0	25.7 ± 4.8	6.3 (3.6 - 7.3)
		GT2 without cirrhosis	8	145	42	54 ± 11.8	28.5 ± 6.9	6.67(0.75 - 7.62)
		GT 4-6 without cirrhosis	8	58	64	48 ± 13.8	25.9 ± 5.0	5.45(4.3 - 7.5)
Poordad	2017	G/P 300/120 mg+ 800 mg RBV	12	22	91	56 (39-64)	28 (22-34)	6.7 (5.0-7.3)
		G/P 300/120 mg	12	22	82	59 (46-70)	28 (19-37)	6.6 (5.5-7.2)
Gane	2017	GT 1-6 with SRI	12	104	76	57 (28 - 83)	26 (18 - 45)	5.9 (3.4 - 7.5)
Kwo	2017	GT 1 with 12W	12	40	52	52.5 ± 10.3	28.0 ± 4.7	6.7 ± 0.6
		GT 1 with 8W	8	34	56	53.5 ± 10.3	27.3 ± 5.0	6.3 ± 1.1
		GT2 with 12W	12	74	64	53.6 ± 11.8	26.9 ± 4.5	6.8 ± 0.7
		GT2 with 8W	8	54	61	55.3 ± 9.7	26.9 ± 4.9	6.6 ± 0.8
		GT3 with 12W	12	115	58	49.3 ± 11.2	26.9 ± 4.3	6.5 ± 0.8
		GT3 with 8W	8	29	52	47.2 ± 11.9	25.6 ± 3.8	6.3 ± 0.7
		GT4,5,6 with 12W	12	34	47	55 ± 10.8	27.6 ± 4.3	6.3 ± 0.7
Poordad	2018	GT 1, 4with 12W	12	44	70	57 (22-67)	28 (21 -41)	6.1 (4.7-7.2)
		GT 1, 4 with 16W	16	47	70	56 (36-70)	29 (20-52)	6.3 (4.7-7.1)
Forns	2017	GT 1, 2, 4, 5, 6 with compensated cirrhosis	12	146	62	60 (26 - 88)	29.2 ± 5.8	6.1 ± 0.7/ (3.1 - 7.4)
Zeuzem	2018	GT 1 with 8W	8	351	48	53 (19 - 84)	25 (18 - 41)	6.1 (1.2 - 7.6)
		GT 1with 12W	12	352	50	52 (21 - 77)	25 (18 - 54)	6.1 (3.3 - 7.4)
		GT 3 with 8W	8	157	59	47 (20 - 76)	26 (18 - 44)	6.1 (1.2 - 7.6)
		GT 3 with 12W	12	233	52	48 (22 - 71)	25 (17 - 49)	6.1 (3.5 - 7.5)
Wyles	2018	GT 3 TE without cirrhosis	12	22	64	56 (35 - 68)	26 (19 - 42)	6.6 (5.1 - 7.5)
		GT 3 TE without cirrhosis	16	22	64	59 (29 - 66)	28 (22 - 48)	6.1 (4.7 - 7.3)
		GT 3 TN with cirrhosis	12	40	60	56 (36 - 70)	29 (21 - 51)	6.2 (4.2 - 7.1)
		GT 3 TE with cirrhosis	16	47	77	59 (47 - 70)	27 (21 - 42)	6.5 (4.6 - 7.2)
Gane	2016	GT 1 G/P 200/120 mg	12	27	74	58.9 ± 5.5	27.7 ± 4.0	6.6 ± 0.4
		GT 3 G/P 300/120 mg	12+16	28	54	55.2 ± 6.8	27.8 ± 5.2	6.4 ± 0.5
		GT 3 G/P 300/120 mg+ 800 mg RBV with cirrhosis	16	27	67	55.7 ± 7.6	27.0 ± 3.8	6.2 ± 0.7
Rockstroh	2018	GT 1–6 without cirrhosis	8	137	82	45 (23 - 74)	25.0 (18.1 - 40.6)	6.2 (4.0 - 7.4)
		GT 1–6 with cirrhosis	12	16	94	50 (35 - 62)	27.6 (21.6 - 38.2)	6.1 (4.4 - 7.0)

BMI: body mass index, HCV: hepatitis C virus, DAA: direct-acting antivirals. GT: genotype, SRI: severe renal impairment, RBV: ribavirin, TN: treatment-naive, TE: treatment-experienced, G/P: glecaprevir/pibrentasvir.

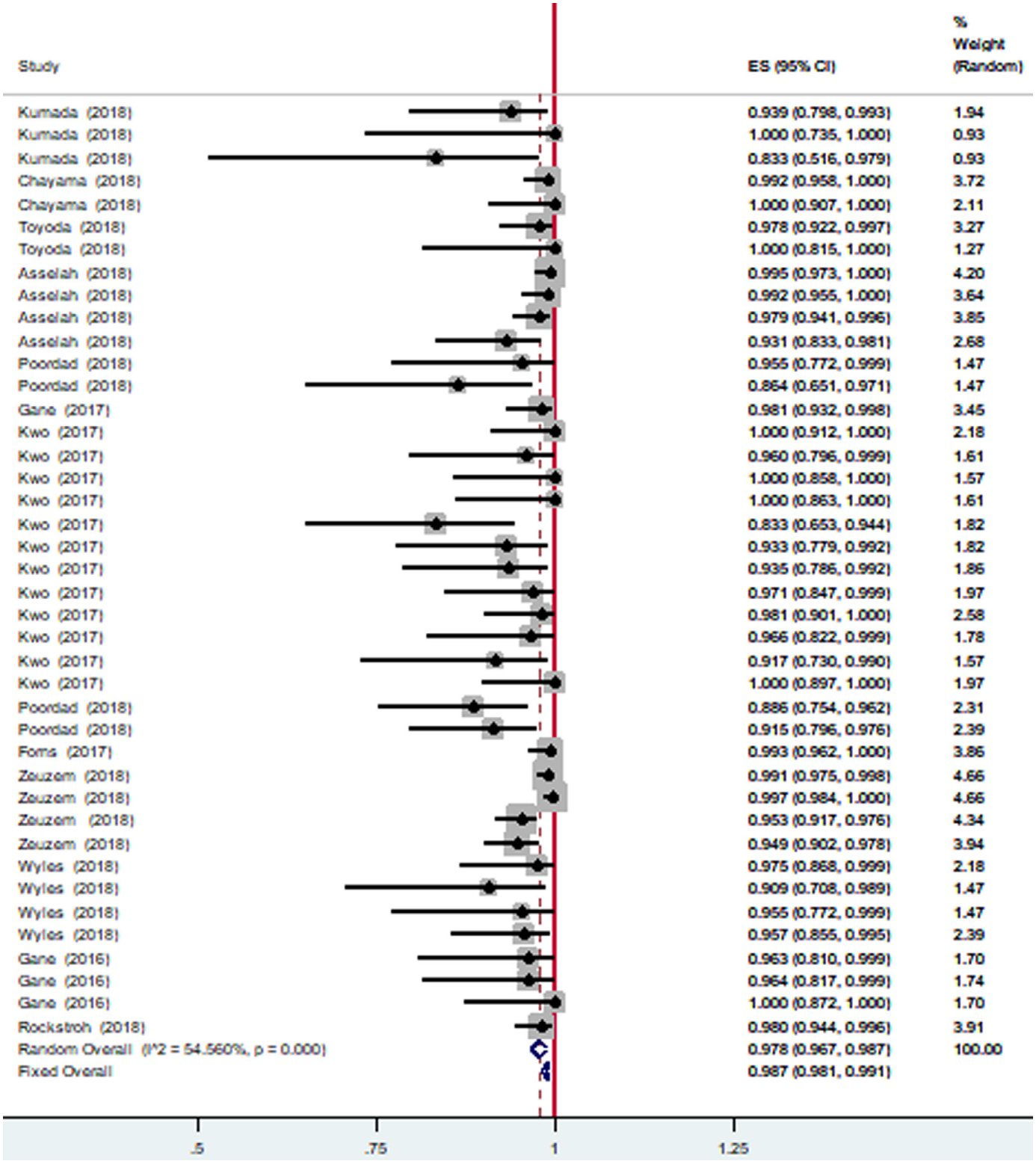

Fig. 2. Meta-analysis forest plots of sustained virological response 12 weeks' post-treatment (SVR12) rates of glecaprevir/pibrentasvir for chronic HCV infection.

(I^2=54.56%, P<0.001). A meta-regression was performed to explore potential sources of heterogeneity: no sources of heterogeneity were found (Table S1). A random-effect model was adopted and the total SVR12 rate of G/P with or without RBV in HCV patients including GT1-6 was 97.8% (95%CI, 96.7-98.7%, Fig. 2).

Among the included studies, only 14 of the 3082 HCV patients treated with G/P had a virological failure during treatment, and the pooled rate was 0.00% (95%CI, 0.00-0.0025%, Fig. S2). Twenty-nine of the 3082 patients had a virological relapse within 12 weeks after the end of treatment, and the pooled rate was 0.02% (95%CI, 0.00-0.19%, Fig. S3). Thirteen of the 3082 patients discontinued treatment and the pooled rate was 0.00% (95%CI, 0.00-0.06%, Fig. S4). Twenty of the 3082 patients were lost to follow-up and the pooled rate was 0.01% (95%CI, 0.00-0.17%, Fig. S5). In the study by Zeuzem

Table 3
Subgroup analysis of SVR12 of G/P for chronic HCV infection.

Response	HCV GT 1-6				
	Study number	Total, N	n	Rate (%)	95%CI
G/P dose					
G/P 300/120 mg	13	2905	2832	97.9	96.7-98.8%
G/P 200/120 mg	2	177	172	98.3	95.2-99.9%
HCV genotype					
GT 1	5	1035	1024	99.8	99.1-100%
GT 2	4	568	560	99.2	98.1-99.9%
GT 3	5	671	638	96.1%	94.2-97.8%
GT 4-6	3	238	233	100	99.3-100%
GT 1,2,4,5,6	9	1977	1942	98.5	97.3-99.5%
Regimens					
G/P	13	2977	2902	97.9	96.8-98.8%
G/P + RBV	3	105	102	98.2	93.9-100%
Treatment duration					
8 weeks	7	1192	1167	98.8	97.9-99.5%
12 weeks	13	1591	1551	98.5	96.6-99.7%
16 weeks	3	98	91	95.6	89.3-99.6%
Treatment history					
TN patients	4	528	506	96.7	94.7-98.3%
TE patients	7	574	554	98.3	94.8-100%
DAA-experienced patients	4	152	142	96.1	91.2-99.4%
DAA-naïve patients	4	632	624	99.7	98.8-100%
Presence or absence of cirrhosis					
Non-cirrhosis	8	1202	1174	99.4	98.6-99.9%
Cirrhosis	8	1463	1433	98.8	97.1-99.9%
HIV co-infection					
Non-HIV	12	2719	2649	97.8	96.6-98.8%
HCV/HIV	2	186	183	99.4	97.1-100%
Comorbidity of SRI					
Non-SRI	13	2893	2820	97.8	96.6-98.8%
SRI	2	116	114	99.4	96.0-100%

CI: confidence interval; DAA: direct-acting antivirals; G/P: glecaprevir/pibrentasvir; HCV: hepatitis C virus; RBV: ribavirin; GT: genotype; TN: treatment-naïve; TE: treatment-experienced; HIV: human immunodeficiency virus; SRI: severe renal impairment.

et al [30], one patient withdrew treatment, one patient was non-adherent, and three patients died of heroin overdose in combination with acute ethanol and methadone toxicity. In the study by Gane et al [26], one patient died due to cerebral hemorrhage.

3.3.2. SVR12 rate by subgroup analysis

G/P dose. The majority of HCV-infected patients were treated with G/P 300 mg/120 mg [21–33] and the pooled SVR12 was 97.9% (95%CI, 96.7–98.8%). A total of 177 patients from 2 studies received G/P 200 mg/120 mg therapy [27,32] and the pooled SVR12 was 98.3% (95% CI, 95.2-99.9%, Table 3).

HCV genotype. A total of 393 patients (13.5%) with G/P (300 mg/120 mg) treatment could not be analyzed according to GTs. Among the patients treated with G/P (300 mg/120 mg) who had HCV GT available for analysis, 1035 were GT1 [22,25,27,29,30], 568 were GT2 [22,24,27,29], 671 were GT3 [21,27,31,32], 238 were GT4-6 [24,27,29], and 1977 were GT1,2,4,5,6 [21–25,27–30]. The pooled SVR12 rates in GT1, GT2, GT3, GT4-6, and GT1,2,4,5,6 were 99.8% (95%CI, 99.1-100%), 99.2% (95%CI, 98.1-99.9%), 96.1% (95%CI, 94.2-97.8%), 100% (95%CI, 99.3-100%), and 98.5% (95%CI, 97.3-99.5%), respectively (Table 3).

G/P with or without ribavirin. The SVR12 rate of 2977 patients treated with G/P without RBV was 97.9% (95%CI, 96.8-98.8%). One hundred and five patients from 3 studies [25,27,31] received G/P + RBV regimen and the pooled SVR12 was 98.2% (95%CI, 93.9-100%, Table 3). Further analysis showed that patients treated with G/P 300 mg/120 mg without RBV had a pooled SVR12 of 97.8% (95% CI, 96.6-98.8%) and those who received G/P 300 mg/120 mg + RBV (n=49 from 2 studies [25,31]) had an SVR12 rate of 98.8% (95%CI, 92.5-100%). Patients treated with G/P 200 mg/120 mg without RBV (n=121 from 2 studies [27,31]) had a pooled SVR12 of 98.6% (95% CI, 94.9-100%) and those who received G/P 200 mg/120 mg + RBV (n=56 from 2 single-arm trials [27]) had an SVR12 of 97.5% (95%CI, 90.9-100%).

Table 4
Rate of AEs and SAEs of G/P for patients with HCV genotypes 1-6 infection.

	Total, N	n	Rate (%)	95%CI
Any AEs	3082	2057	68.20	65.21-71.12%
Drug-related AEs	3082	80	1.33	0.13-3.30%
SAEs	3082	88	2.15	1.08-3.46%
Drug-related SAEs	3082	0	0	-
AE leading to discontinuation	3082	18	0	0.00-0.10%

AE: adverse event; CI: confidence interval; G/P: glecaprevir/pibrentasvir; SAE: serious adverse event.

Duration of treatment. A total of 1192 patients from 7 studies received G/P (300 mg/120 mg) for 8 weeks [21–24,27,30,33], and the pooled SVR12 was 98.8% (95%CI, 97.9-99.5%). Among the eligible studies, 1591 patients from 13 studies [21–33] were treated for 12 weeks and the SVR12 was 98.5% (95%CI, 96.6-99.7%), and 98 patients from 2 studies [28,31] received G/P for 16 weeks and the pooled SVR12 was 95.6% (95%CI, 89.3-99.6%, Table 3).

Treatment history. There were 528 treatment-naïve patients from 4 studies [27,30–32] and 574 treatment-experienced patients from 7 studies [21,25,27,28,30–32]. The SVR12 rates in treatment-naïve and treatment-experienced patients were 96.7% (95%CI, 94.7-98.3%) and 98.3% (95%CI, 94.8-100%), respectively (Table 4). One hundred and fifty-two patients in the treatment-experienced group had previously received DAAs [21,25,28,31] and the SVR12 was

96.1% (95%CI, 91.2-99.4%). DAA-naïve patients from 4 studies (n=632) [21–24] had an SVR12 of 99.7% (95%CI, 98.8-100%).

Presence or absence of cirrhosis. There were 1463 patients with cirrhosis from 8 studies [21,23,29–33] and 1202 patients without cirrhosis from 5 studies [21–25,27,31,33]. SVR12 was achieved in 99.4% (95% CI, 98.6-99.9%) and 98.8% (95% CI, 97.7-99.9%) of the patients without and with compensated cirrhosis, respectively (Table 3).

HIV co-infection. Among the included studies, 2719 patients from 12 studies [21–32] did not have HIV infection, and the SVR12 was 97.8% (95%CI, 96.6-98.8%, Table 3). Among 186 patients who were co-infected with HIV from 2 studies [30,33], SVR12 was achieved in 99.4% (95%CI, 97.1-100%).

Comorbidity of SRI. The SVR12 rate in 2893 patients without SRI from 13 studies [21–33] was 97.8% (95%CI, 96.6-98.8%). A total of 116 patients with SRI from 2 studies [21,26] achieved a high SVR12 rate (99.4%, 95%CI, 96-100%, Table 3).

3.4. Safety

3.4.1. Adverse events

Throughout the included studies, the number of any AEs, drug-related AEs, and SAEs were 2057, 80 and 88, respectively, and the rates of any AEs, drug-related AEs, and SAEs were 68.2% (95%CI, 65.2-71.1%, Fig. S6), 1.3% (95%CI, 0.1-3.3%, Fig. S7), and 2.1% (95%CI, 1.1- 3.5%, Fig. S8), respectively (Table 4). No drug-related SAEs were observed. Eighteen patients discontinued treatment because of AEs (Fig. S9).

3.4.2. Laboratory abnormalities

Grade 3 treatment-related laboratory abnormalities were observed in only 22 patients. The most-frequent laboratory abnormalities were grade 3 elevation of ALT (4/3082), AST (2/3082) and total bilirubin (11/3082) and reduction of hemoglobin (6/3082). One patient with reduced hemoglobin was reported and this was due to RBV.

4. Discussion

Over the last few years, important advancements have been made in the treatment of HCV infection with DAAs, which directly inhibit multiple steps of the HCV replication cycle. The new generation of DAAs, including glecaprevir and pibrentasvir, has proven to be effective for HCV infection, including GTs1-6. This systematic review and meta-analysis of phase II and III clinical trials support the high treatment-response rate of 8 or 12 weeks with the G/P combination for HCV GTs 1-6 in both naïve and treatment-experienced patients, regardless of patient sex, HCV RNA load or other demographic factors. The addition of RBV to the G/P regimen did not improve the efficacy. In addition, underlying cirrhosis did not compromise the treatment response rate. Virological failure on treatment and virological relapse within 12 weeks after treatment discontinuation were minimal with G/P treatment.

The overall SVR12 rate for the G/P combination was 97.8% in HCV patients, and the SVR12 rate was ≥98.5% in GT 1, 2, 4-6 HCV patients. The SVR12 rate of G/P was 96.1% in GT3 HCV, which explains the advantage of these drugs in all HCV GTs.

Patients with GT3 infection yielded lower SVR12 rates compared with other GTs. HCV GT3 accounts for about 50 million HCV-infected individuals worldwide [34], and GT3 patients with cirrhosis were a historically difficult-to-treat population in the DAA era. In previous studies, the SVR12 rates of sofosbuvir-containing regimens were less than 95%, particularly in patients with cirrhosis [35–37]. However, the SVR12 of G/P was higher in HCV patients with and without cirrhosis in the present analysis. The G/P treatment for GT3 patients with cirrhosis from 3 studies [30–32] achieved an SVR12 of 98.0%. These data indicate that cirrhosis did not compromise the response rate of treatment in GT3 infection. The SVR12 of GT3 HCV patients was 95.6% (n=186), 96.4% (n=412), and 97.9% (n=51) for 8-week [27,30], 12-week [21,27,30–32], and 16-week [31,32] G/P treatment regimens, respectively. The extended treatments for patients with GT3 appear to improve the virological response rate. However, both cirrhosis and non-cirrhosis patients were included in the 12-week treatment subgroup. The subgroup was further divided into cirrhosis [27,30] and non-cirrhosis [31,32] groups and the SVR12 was 97.8% (n=125) and 95.5% (n=287), respectively. There was no difference between 8 and 12 weeks' treatment in GT3 HCV patients without cirrhosis (n=473), and there was no obvious difference in SVR12 between 12 and 16 weeks' treatment in GT3 HCV-associated cirrhosis (n=176). The subgroup of GT3 HCV patients with cirrhosis who received 16 weeks of treatment was only very small (n=51) [32]; therefore, further studies are needed to define the optimal treatment duration for patients with GT3 cirrhosis.

The addition of RBV did not increase the response rate of G/P in HCV in our subgroup analysis. However, only two studies reported the findings of the regimen G/P with RBV. One study included GT1 HCV patients and showed that the addition of RBV did not increase the SVR12 [25]. The other study included a small sample of GT3 HCV patients and reported an improved virological response of G/P with the addition of RBV [32]. Similarly, a meta-analysis investigating the efficacy of sofosbuvir plus velpatasvir showed that the addition of RBV significantly increased SVR12 in GT3 but not in GT1 patients [38]. Two other meta-analyses of DAAs for HCV GT1 showed that adding RBV neither improved the virological response [39,40] nor decreased the virological breakthrough [40]. Based on these data and the results of the present meta-analyses, RBV may be excluded from most of the DAA combination regimens without influencing the SVR12 rate for GT1, other than the regimen sofosbuvir plus velpatasvir for GT3. The regimen of G/P plus RBV for GT3, however, requires further study.

Interestingly, six single-arm trials from 2 studies [27,32] reported the efficacy of a low-dose G/P (200 mg/120 mg) regimen for HCV patients without cirrhosis and the SVR12 was 98.3%. There were no significant differences between G/P 200 mg/120 mg and G/P 300 mg/120 mg when administered for 12 weeks (98.3% vs. 98.5%).

In terms of treatment duration, no significant difference was noted between patients with GTs 1-6 treated for 8 weeks or 12 weeks. All the patients in the 12-week treatment subgroup were without cirrhosis. Therefore, 8-week G/P treatment may be recommended for HCV patients without cirrhosis. Only three studies with 98 patients reported 16-week G/P treatment. Two of these studies reported a total of 51 GT3 HCV patients with cirrhosis, and all the patients had a treatment history, including interferon and RBV or DAAs. Patients who had treatment experience and were treated for 16 weeks had about 7.6% (51/671) overlap with patients with GT3 +/- cirrhosis. Unexpectedly, patients with compensated cirrhosis treated for 16 weeks showed a lower SVR12 rate compared with 12 weeks of treatment (95.6% vs. 98.5%). However, all patients in the 16-week treatment subgroup were cirrhotic, the majority of patients in this subgroup had previously received DAA, and the subgroup included only GTs 1, 3 and 4, with the GT3 patients accounting for 52.04% (51/98). Further subgroup analysis showed that DAA-experience decreased the SVR12 rate of G/P compared with the DAA-naïve group (96.1% vs. 99.7%). Therefore, DAA-experience and the potential differences in characteristics, such as presence of cirrhosis and HCV GT3, in patients recruited in the 16-week and 12-week treatments might explain this phenomenon.

According to the efficacy analysis, 12-week G/P treatment appears to be efficacious for DAA-naïve HCV patients with compensated cirrhosis. However, the efficacy of different G/P treatment durations in cirrhosis patients with prior DAA experience and certain HCV GTs, such as GT3, requires further study.

G/P treatment for HCV/HIV co-infected patients was highly efficacious in this study. Up to 7 million patients are estimated to be infected with both HIV and HCV worldwide [41]. Although numerous new DAAs have been developed, treatment of HCV in HCV/HIV co-infected patients remains complicated, with challenges including drug-drug interactions between HIV drugs and HCV protease inhibitors, high rates of AEs, high pill burden and long treatment duration [42]. Meta-analysis evaluating sofosbuvir-based treatment in HCV/HIV co-infected patients showed an SVR12 of 94.0% [43]. The G/P regimen achieved a higher SVR12 of 99.4%. Notably, HCV/HIV co-infected patients achieved a higher SVR12 rate compared with patients with HCV without HIV infection (99.4% vs. 97.8%). There was no significant difference in the outcomes of G/P treatment for patients with and without HIV infection. There is currently no explanation for this phenomenon; however, the differences in the characteristics of patients recruited in the co-infected group and the HCV only group may be important. The data in this study indicate that the G/P regimen in HIV co-infected patients may achieve an SVR12 as high as that in HIV non-infected patients.

The G/P regimen is a current recommended therapy for patients with estimated glomerular filtration rate (eGFR) <30 mL min/1.73 m^2 [44]. One study showed that treatment with grazoprevir and elbasvir cured 94% of patients with stage 4-5 chronic kidney disease (CKD) who had GT1 or GT4 HCV infection [45]. The combination regimen of paritaprevir, ombitasvir, and dasabuvir was very effective in patients with advanced CKD or on dialysis, but the sample size of the study was small [46,47]. The SVR12 of G/P for HCV patients with SRI was 99.4%. Therefore, the G/P regimen is a good choice for HCV patients with SRI.

G/P therapy was well tolerated in the current study. The pooled rate of drug-related AEs was 1.3%, and no drug-related SAEs were observed. Furthermore, the number of treatment-related laboratory abnormalities was minimal. The most frequent laboratory abnormalities were alterations of ALT, AST, total bilirubin and hemoglobin, but these were in only a small number of patients.

The presented comprehensive analysis has several strengths. First, this is the first study to systematically explore the efficacy and safety of G/P for HCV infections including GT1-6. Second, this analysis provided the pooled rates of SVR12, AEs, SAEs and laboratory abnormalities in various subgroups. Third, subgroup analyses were performed based on various factors that may affect the patient response rate to G/P, and further explored the response of patients with different situations to G/P regimen. These findings might help clinicians select the best regimens for patients with HCV GT1-6 infection in various disease conditions and with comorbidities. These findings might also provide references for future studies, such as defining optimal treatment regimen and duration for patients with HCV GT3 infection and cirrhosis.

Compared with the pooled analysis of FDA reviews [48,49], the results obtained from this analysis confirmed that G/P 8-week or 12-week treatments may achieve high SVR12 rates for HCV GTs 1-6; patients with GT3 infection yielded a lower SVR12 rate compared with other GTs; extended treatment duration for GT3 patients may improve the SVR12 rate, and G/P therapy was well tolerated. Furthermore, the analysis results provide information about G/P treatment, e.g., the addition of RBV to G/P did not improve SVR12 rate and the G/P regimen was highly efficacious for both HCV/HIV co-infected patients and HCV patients with SRI.

This study also has some limitations. First, most of the studies included in the analysis were non-controlled trials. The single-arm trials limited the ability to derive definitive conclusions regarding the safety and efficacy of this regimen. Second, the numbers of patients in certain studies were relatively small. The conclusions based on small size studies could lead to heterogeneity and thus affect the estimates, although no heterogeneity sources were found in both the single logistic regression model and the multiple logistic regression analysis. Third, the majority of included studies were performed in white patients (over 55%), and only 3 studies were carried out in Japanese patients. Fourth, considering the variance of studies and the 95% CIs of the pooled weighted proportions, we failed to make a comparative analysis. Therefore, large-scale, well-designed, randomized controlled trials with detailed patient information are needed to assess the combination of G/P therapy.

5. Conclusions

This comprehensive analysis shows that the G/P regimen was highly efficacious in patients with HCV GTs 1-6 infection, including treatment-experienced and compensated cirrhotic patients. Adding RBV to a G/P regimen did not improve SVR12 rates. For patients without cirrhosis, 8 weeks of treatment may be recommended, whereas for DAA-naïve, compensated cirrhosis patients, 12 weeks of treatment may be recommended. In addition, the G/P regimen was a good choice for both HCV/HIV co-infected patients and HCV patients with SRI.

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Declarations

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Authors' contributions

X.W, X.F, Y.L and Z.L developed the protocol, conducted the literature search, assessed the methodological quality, performed data extraction, and conducted the statistical analysis. X.W and Z.L wrote the manuscript; X.W, H.D, and K.Z assessed methodological quality; X.Z, N.L, Y.L and Q.H reviewed the analysis, protocol and the manuscript. All the authors approved the final version of the manuscript.

Supplementary materials

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