Review Article

Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients with Chronic HCV Infection

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Abstract

Hepatitis C virus (HCV) infection is a major cause of end-stage liver disease, including decompensated cirrhosis and hepatocellular carcinoma. Over 95% of patients with HCV infection have achieved sustained virologic response at 12 weeks under the treatment of several pan-genotypic regimens approved for patients with HCV infection. The glecaprevir/pibrentasvir (G/P) regimen has some features that distinguish it from others and is the only 8-week regimen approved for treatment-naive patients and patients experienced in regimens containing (peg)interferon, ribavirin, and/or sofosbuvir, without an HCV NS3/4A protease inhibitor or NS5A inhibitor (except those with genotype 3). This review aims to summarize the efficacy and safety of G/P in HCV-infected patients from clinic trials and real-world studies, including those who have historically been considered difficult to cure.

Citation of this article: Liu X, Hu P. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic HCV infection. J Clin Transl Hepatol 2021;9(1):125–132. doi: 10.14218/JCTH.2020.00078.

Introduction

Hepatitis C virus (HCV) infection threatens the health of people around the world. According to the World Health Organization, about 71 million people worldwide suffer from chronic HCV infection, and in 2016 approximately 399,000 patients died from end-stage HCV infection, mainly from cirrhosis and hepatocellular carcinoma.[1] Direct-acting antiviral agent (DAA)-induced sustained virologic response (SVR) has been associated with a reduction in the risk of cirrhosis, hepatocellular carcinoma, and mortality.[2,3]

All of the three pan-genotypic antiviral regimens [sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, glecaprevir/pibrentasvir (G/P)] approved for the treatment of patients with chronic HCV infection in recent years have high efficacy, and more than 95% of patients administered them have achieved SVR at 12-week post-treatment (SVR12).[3–7]

However, the fixed-dose combination of Glecaprevir (300 mg) and pibrentasvir (120 mg), an all-oral, once-daily, ribavirin-free pan-genotypic regimen approved in 2017, has certain characteristics that distinguish it from other pan-genotypic antiviral regimens, including shorter duration of therapy for most patients; it has been approved for use in patients with end-stage renal disease and adolescent patients aged 12–17 years.[8]

Both glecaprevir and pibrentasvir have potent anti-HCV activity across genotypes 1 through 6 *in vitro*, which harbor a high genetic barrier to resistance.[8] The former is a second-generation NS3/4A protease inhibitor (PI), essential for the cleavage of the HCV unprocessed polyprotein and viral replication; the latter is a second-generation NS5A inhibitor, critical for viral RNA replication and virion assembly.[9]

Glecaprevir and pibrentasvir are mainly excreted through the biliary-fecal route, with only a minor fraction (less than 1%) excreted in urine; renal impairment and hemodialysis appeared to have no significant influence on glecaprevir or pibrentasvir exposures.[8,10] Compared with patients with normal renal function, HCV-infected patients with end-stage renal disease, including dialysis, were observed to have an 86% increase in glecaprevir and a 54% increase in area under the curve for pibrentasvir.[8] In chronic HCV-infected patients with compensated cirrhosis, exposure to glecaprevir was 160% higher and pibrentasvir exposures showed little difference in outcome compared to patients without cirrhosis.[10] Meanwhile, there was no statistically significant difference in the exposure rates of gelcaprevir and pibrentasvir between Japanese or Han Chinese and Whites.[11] But, we should note that patients with decompensated cirrhosis are not recommended for treatment with a PI-containing regimen (*e.g.*, glecaprevir, grazoprevir, and voxilaprevir).

Most patients with chronic HCV infection are at risk of drug-drug interactions (DDIs) with co-medication.[12] Both glecaprevir and pibrentasvir are substrates and inhibitors of P-glycoprotein and breast cancer resistance protein. Moreover, glecaprevir is a substrate and inhibitor for organic anion transporting polypeptide (OATP) 1B1 and OATP1B3. Pibrentasvir is an inhibitor of OATP1B1/3. Therefore, coadministration of G/P with drugs that inhibit hepatic P-glycoprotein, breast cancer resistance protein, or OATP1B1/3 may increase the plasma concentrations of glecaprevir and/or pibrentasvir.[8] As per the drug label, G/P is contraindicated in combination with atazanavir or rifampin.[8]

The main purpose of this review is to comprehensively evaluate the efficacy and safety of G/P in patients with HCV infection, including those in the so-called "special population" that have historically been considered difficult to treat.

Keywords: Hepatitis C; Mavyret; Glecaprevir; Pibrentasvir; Treatment outcome.
Abbreviations: AE, adverse event; ARA, acid-reducing agent; CKD, chronic kidney disease; DAA, direct-acting antiviral agent; DDI, drug-drug interaction; G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; ITT, intention to treat; OATP, organic anion transporting polypeptide; OST, opioid substitution therapy; PI, protease inhibitor; PPI, proton pump inhibitor; PRS, prior treatment experience with regimens containing (peg)interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor; SVR, sustained virologic response; SVR12, SVR at 12-week post-treatment.
Received: 18 August 2020; Revised: 3 December 2020; Accepted: 22 December 2020
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Efficacy

The clinic trails and real-world studies that have evaluated the efficacy of G/P against HCV are summarized in Tables 1 and 2,[13–47] respectively.

Treatment-naïve or patients experienced in regimens containing (peg)interferon, ribavirin, and/or sofosbuvir, without an HCV NS3/4A PI or NS5A inhibitor, without cirrhosis

In a pooled analysis of nine clinical trials, treatment-naïve or patients experienced in regimens containing (peg)interferon, ribavirin, and/or sofosbuvir, without an HCV NS3/4A PI or NS5A inhibitor (PRS) with HCV genotypes 1-6 infections but without cirrhosis achieved an overall SVR12 rate of 98% (943/965) in the intention-to-treat (ITT) population when treated for 8 weeks, which showed no significant difference from patients treated with 12 weeks (1,060/1,076, 99%).[48] But, all 478 patients infected with genotype 3 were treatment-naïve in that study. CRETIN-1 and CRETAIN-2 were not included in the pooled analysis described previously, and the authors also demonstrated that G/P treatment for 8 weeks was highly effective in patients with HCV genotypes 1-2 infections without cirrhosis, of which 99.2% (128/129) and 98% (88/90) patients achieved SVR12, respectively.[13,14] The ENDURANCE-5,6 trial, an open-label, multicenter, phase 3b trial, demonstrated that 98.6% (74/75) of non-cirrhotic patients infected with HCV genotype 5 or 6 treated with G/P for 8 weeks achieved SVR12.[15]

Data from a combined analysis of 18 real-world studies showed that the SVR rate for treatment-naïve patients without cirrhosis who received G/P treatment for 8 weeks was 98.2% (*n*=697) in the ITT population and 99.3% (*n*=3,657) in the modified ITT population.[49] For patients with treatment experience, the SVR rate was 90.7% (49/54), among which 4 patients were lost to follow-up.[16]

Treatment-naïve or PRS-experienced patients with compensated cirrhosis

The efficacy of 8-week G/P reported in the EXPEDITION-8 clinical trial is comparable to the 12-week regimen for treatment-naïve patients with genotypes 1-6 infections and compensated cirrhosis.[17] The SVR rate was 97.7% (335/343) in the ITT population and 99.7% (334/335) in the per protocol population after treatment with G/P once daily for 8 weeks.[17] After 12 weeks of treatment with G/P, the SVR12 rates of HCV genotype 3- and non-genotype 3-infected compensated cirrhosis patients without treatment experience were 97.1% (67/69)[50] and 100% (110/110),[18] respectively.

For PRS-experienced patients with compensated cirrhosis and non-genotype 3 infection, the EXPEDITION-1 trial reported that 97.2% (35/36) of patients treated for 12 weeks achieved SVR12, with one genotype 1a-infected patient relapsing at post-treatment week 8.[18] The CRETAIN-1, subgroup 2 trial evaluated the efficacy of a 12-week course of G/P in 38 genotype 1-infected patients with compensated cirrhosis. All of the 38 patients (100%) achieved SVR12, of which 12 were interferon-experienced.[13]

Data from real-world studies showed that the SVR12 rate for patients with compensated cirrhosis who received G/P treatment was 97.8% (*n*=676) in the ITT population and 98.2% (N=822) in the modified ITT population.[49] For treatment-naive patients with compensated cirrhosis treated for 12 weeks, the SVR12 rate was 99.0% (*n*=362).[49] To our knowledge, currently there is no real-world data to evaluate the efficacy of G/P treatment for 8 weeks in treatment-naïve patients with compensated cirrhosis.

"Special population"

Patients with HCV genotype 3 infection

Patients with HCV genotype 3 infection are among the most difficult to treat in the DAA-era. According to the studies described above, treatment-naïve and genotype 3-infected patients treated with G/P for 8 weeks had high SVR12 rate, regardless of cirrhosis, but the efficacy in PRS-experienced patients is still uncertain.

In the SURVEYOR-II trial, parts 1 and 2, the efficacy of G/P for 12 weeks was studied in PR-experienced patients with genotype 3 infection and without cirrhosis. In total, 91.7% (22/24) achieved SVR12, with 1 patient having a breakthrough at treatment week 6 and 1 other relapsing at post-treatment week 8.[19] The SURVEYOR-II trial, part 3, a partially-randomized, open-label, phase 3 study, assessed the efficacy of G/P in patients with genotype 3 infection with prior treatment experience, and found that 91% (20/22) and 96% (21/22) of PRS-experienced patients without cirrhosis achieved SVR12 for 12 weeks and 16 weeks, respectively. Among the 47 treatment-experienced patients with compensated cirrhosis, SVR12 were achieved by 96% (45/47) of patients treated with G/P for 16 weeks.[20] An integrated cirrhosis of five phase 2 or 3 trials that evaluated G/P in patients with chronic HCV genotype 3 infection also demonstrated G/P was efficacious for those patients, regardless of cirrhosis or prior treatment experience.[50]

Data from real-world studies also demonstrated that over 95% of HCV genotype 3-infected patients treated with the G/P regimen achieved SVR.[21,49] But, we should point out that almost all of the above-mentioned research studies were conducted in areas where subtype 3a is dominant, and subtype 3b accounts for less than 1% of all genotype 3 cases. Therefore, more attention should be paid to the efficacy of G/P in HCV subtype 3b-infected patients. Nozaki *et al*.[22] recently reported that only 33.3% (2/6) of patients with HCV subtype 3b infection achieved SVR12. Another study conducted by Tamori *et al*.[23] found that only 50% (2/4) of patients with HCV genotype 3b infection achieved SVR12. Moreover, one out of three patients with genotype 3a/b experienced virologic failure in the study of Toyoda *et al*.[24]

Patients with severe renal impairment

The investigators of the EXPEDITION-4 study examined the efficacy of G/P administered for 12 weeks in adults with chronic HCV genotypes 1-6 infections and stage 4 or 5 chronic kidney disease (CKD).[25] Of the 104 patients enrolled, 44 (42%) had prior treatment experience for HCV, but treatment-experienced patients who had genotype 3 infection were excluded and 20 (19%) had compensated cirrhosis at baseline. Up to 98% (102/104) of the patients achieved SVR12, with no patients experiencing virologic failure.[25] In the phase 3 EXPEDITION-5 trial, the rate of SVR was 97% (98/101) in the ITT population and 100% (98/98) in the modified ITT population after treatment with G/P. Of the 101 enrolled adults with CKD stages 3b, 4 or 5, 84 patients without cirrhosis were assigned to receive G/P for 8 weeks and 4 PRS-experienced patients with genotype 3 infection were assigned to 16 weeks of treatment; all others were in the 12-week treatment group.[26] Real-world studies also demonstrated G/P was highly effective for patients with CKD stages 4-5 (including patients undergoing hemodialy-

Table 1. Efficacy of G/P in clinical trials

Study	HCV genotype	Population	Number	Duration	SVR12, *n*/total (%)[a]
EXPEDITION-1[18]	1, 2, 4, 5, 6	TN with CC PRS-exp with CC	110 36	12 w	110/110 (100) 35/36 (97.2)
EXPEDITION-2[29]	1–6	TN or PRS-exp[b], HIV coinfection, ±CC	153	8/12 w	150/153 (98.0)
EXPEDITION-4[25]	1–6	TN or PRS-exp, ±CC, CKD stages 4-5	104	12 w	102/104(98.1)
EXPEDITION-5[26]	1–6	TN or PRS-exp, ±CC, CKD stages 3b, 4, 5	101	8/12/16 w	98/101 (97.0)
EXPEDITION-8[17]	1–6	TN with CC	343	8 w	335/343 (97.7)
Fontana[41]	1–6	TN with NC	230	12 w	222/230 (96.5)
ENDURANCE-5, 6[15]	5,6	TN or PRS-exp, NC CC	84	 8 w 12 w	82/84 (97.6) 74/75 (98.7) 8/9 (88.9)
ENDURANCE-1[39]	1	TN or PRS-exp, NC	703	8 w 12 w	348/351 (99.1) 351/352 (99.7)
ENDURANCE-2[38]	2	TN or PRS-exp, NC	202	12 w	201/202 (99.5)
ENDURANCE-3[39]	3	TN with NC	390	8 w 12 w	149/157 (94.9) 222/233 (95.3)
ENDURANCE-4[38]	4–6	TN or PRS-exp, NC	121	12 w	120/121 (99.2)
SURVEYOR-I, II, part 1, 2[19]	1–6	TN or PRS-exp, NC	230	8 w 12 w[e]	114/117 (97.4) 108/113 (95.6)
SURVEYOR-II, part 3[20]	3	TN or PRS-exp, ±CC	131	12 w 16 w	59/62 (95.2) 66/69 (95.7)
SURVEYOR-II, part 4[38]	2,4–6	TN or PRS-exp, NC	203	8 w	196/203 (96.6)
CERTAIN-1, substudy 1, 2[13]	1	TN or PRS-exp, without CC with CC	167	 8 w 12 w	166/167 (99.4) 128/129 (99.2) 38/38 (100)
CERTAIN-2[14]	2	TN or PRS-exp, NC	90	8 w	88/90 (97.8)
MAGELLAN-1, part 1	1	TE with NS3/4A and/or NS5A inhibitor, NC	22	12w	19/22 (86.4)
MAGELLAN-1, part 2[32]	1,4[c]	TE with NS3/4A and/or NS5A inhibitor, ±CC	91	12 w 16 w	39/44 (88.6) 43/47 (91.5)
MAGELLAN-2[30]	1–6	TN or PRS-exp, NC, with liver or kidney transplant	100	12 w	98/100 (98.0)
Lok *et al*.[42]	1	TE with sofosbuvir plus an NS5A inhibitor, ±CC	177	12 w[d] 16 w	88/99 (88.9) 74/78 (94.9)
DORA part 1[34]	1–4	TN or PRS-exp, ±CC, adolescent	47	8/16 w	47/47 (100)

[a]SVR12 rates in the ITT population.

[b]Patients with treatment experience and genotype 3 infection were excluded.

[c]In MAGELLAN-1 part 2, only four patients had the genotype 4 infection.

[d]Patients with CC received G/P+ribavirin for 12 weeks.

[e]Genotype 3-infected patients with TN received G/P for 8 weeks, with PR-exp for 12 weeks.

Abbreviations: ±CC, with or without compensated cirrhosis; HIV, human immunodeficiency virus; NC, non-cirrhotic; PRS-exp, prior treatment experience with regimens containing (peg)interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor; TE, treatment-experienced; TN, treatment-naïve; w, week.

Table 2. Efficacy of G/P in real-world studies

Study	Country/ region	HCV genotype	Number	Population	Duration	SVR, *n*/total (%)
D'Ambrosio *et al*.[35]	Italy	1–4	723	TN or PR-exp, ±CC	8/12/16 w	680/723 (94.1)
Atsukawa *et al*.[27]	Japan	1–3	141	With CKD stages 4-5	8 w 12 w	90/91 (98.9) 50/50 (100)
Hsu *et al*.[36]	Taiwan	1–3, 6	110	With hepatic fibrosis F3-4	8 w 12/16 w	45/45 (100) 65/65 (100)
Ikeda *et al*.[37]	Japan	1, 2[a]	571	DAA-naïve, NC	8 w	530/571 (92.8)
Osawa *et al*.[40]	Japan	1–3	30	DAA-exp, ±CC	12 w	28/30 (93.3)
Persico *et al*.[43]	Italy	1–4	1,177	TN (85%), genotype 3 (10%), CC (9%)	8/12/16 w (1,061/109/6)	1,163/1,177 (98.8)
Tamori *et al*.[23]	Japan	1–4	423	NC, DAA-naïve CC/DAA-exp/genotype 3 or 4	8 w 12 w	220/246 (89.4) 164/177 (92.7)[d]
Toyoda *et al*.[24]	Japan	1–3[a]	509	DAA-exp/CC/genotype 3	12 w	504/509 (99.0)
Ueda *et al*.[31]	Japan	1, 2	25	With liver transplant	8/12 w	24/25 (96.0)
Liu *et al*.[28]	Taiwan	1, 2, 3, 6	108	With CKD stage 4 or 5	8/12 w	107/108 (99.1)
Nozaki *et al*.[22]	Japan	1–3[a]	1,439	TN or TE, NC or CC	8/12 w	1,397/1,439(97.1)
Liu *et al*.[44]	Taiwan	1–3, 6	658	TN or TE, ±CC	8/12/16 w	646/658 (98.2)
Soria *et al*.[21]	Italy	3	152	TN or TE, ±CC	8/12/16 w	147/152 (96.7)
Berg *et al*. (DHC-R)[16]	German	1–6	552[b]	TN or TE, ±CC	8/12/16 w	534/552 (96.7)
Sugiura *et al*.[45]	Japan	1–3	182	TN or TE, ±CC	8/12/16 w	178/182 (97.8)
Uemura *et al*.[33]	Japan	1–3	42	DAA-exp, ±CC	12 w	39/42 (92.9)[c]
Kusakabe *et al*.[46]	Japan	2	28	PRS-exp	12 w	28/28 (100)
Sezak *et al*.[47]	Japan	1–3[a]	271	TN or PR-exp DAA-exp	8/12 w 12 w	180/183 (98.4) 85/88 (96.6)

[a]Patients with baseline P32del were excluded.

[b]Patients with on-label treatment.

[c]Three patients with genotype 1b HCV with NS5A P32del experienced virologic failure.

[d]The SVR rate of genotype 3 patients is 4/7 (57), and there are 2 genotype 3b patients among patients who do not reach SVR12.

Abbreviations: ±CC, with or without compensated cirrhosis; NC: non-cirrhotic; PRS-exp, prior treatment experience with regimens containing (peg)interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor; TE, treatment-experienced; TN, treatment-naïve.

sis), and more than 98% of patients achieved SVR.[22,27,28,51]

Patients with human immunodeficiency virus-1/HCV coinfection

EXPEDITION-2 was a phase 3, multicenter study to evaluate the efficacy of G/P in 156 human immunodeficiency virus/HCV-coinfected adults with compensated liver diseases.[29] All patients with genotype 3 infection were treatment-naïve for HCV. Patients were either antiretroviral therapy-naïve or on a qualifying antiretroviral therapy regimen for at least 8 weeks. The antiretroviral therapy drugs used by more than 20 patients included tenofovir disoproxil fumarate, abacavir, emtricitabine, lamivudine, raltegravir, dolutegravir, and rilpivirine. As high as 99.3% (136/137) of the patients without cirrhosis treated for 8 weeks achieved SVR12, and 87.6% (14/16) of the patients with compensated cirrhosis treated for 12 weeks achieved SVR12. No one experienced virologic failure, except one HCV treatment-naïve patient with genotype 3 infection and compensated cirrhosis.[29]

Patients with liver or kidney transplantation

MAGELLAN-2, a phase 3, open-label trial, evaluated the efficacy of G/P for 12 weeks in patients who had chronic HCV genotypes1-6 infections and had received a liver (n=80) or kidney (n=20) transplant at least 3 months prior.[30] Patients with cirrhosis were excluded and all genotype 3-infected patients were treatment-naïve. Overall, SVR was achieved in 98% (98/100) of the patients, with one genotype 3a-infected patient who had received a liver transplant experiencing virologic relapse.[30] Ueda *et al*.[31] reported that 96% (24/25) of patients with recurrent HCV infection after liver transplantation treated with 8 or 12 weeks of G/P achieved SVR12, including patients with severe renal impairment, liver cirrhosis, prior DAA experience, or jaundice after liver transplantation. But, no virologic failure occurred.

Patients with psychiatric disorders

An integrated analysis of 10 phase 2 and phase 3 clinical trials assessed the efficacy of G/P for 8, 12 or 16 weeks in chronic HCV genotypes 1-6-infected patients with psychiatric disorders.[52] The overall patients' treatment adherence was very high (>95%), regardless of whether there was a psychiatric disorder. Of the 2,522 patients receiving G/P, 97.3% (768/789) of those with a psychiatric disorder achieved SVR12 compared to 97.5% (1,689/1,733) of those without a psychiatric disorder. Among all patients receiving a neuropsychiatric co-medication with potential DDIs with G/P, the SVR rate was still high, including quetiapine (100%, 47/47), oxycodone (93.8%, 76/81) and hydrocodone (97.4%, 75/77).[52] Meanwhile, patients with psychiatric disorder had overall high SVR rate (98.9%) in the modified ITT population in real-word studies.[49]

Patients with NS3/4 PI and/or NS5A inhibitor treatment experience

In part 1 of the MAGELLAN-1 trail, 22 genotype 1-infected non-cirrhotic patients with past failure to NS3/4 PI and/or NS5A inhibitor were treated with G/P for 12 weeks.[53] SVR was achieved by 86% (19/22) in the ITT population and 95% (19/20) in the modified ITT population. Virologic failure occurred in one patient with past treatment experience with both NS3/4A PI and NS5A inhibitor.[53] MAGELLAN-1, part 2, a randomized, open-label, multicenter phase 3 study, enrolled 91 HCV genotypes 1 or 4-infected patients with compensated liver disease (with or without cirrhosis) who had past treatment experience with NS3/4A PI and/or NS5A inhibitor.[32] Patients enrolled were randomized to receive 12 or 16 weeks of G/P. Patients with NS3/4A PI experience alone (NS5A inhibitor-naïve) had 100% SVR12, regardless of treatment duration. Patients with NS5A inhibitor experience alone (NS3/4A PI-naïve) had 88% (14/16) and 94% (17/18) SVR rate among those treated with G/P for 12 weeks and 16 weeks, respectively. Patients with both NS3/4A PI and NS5A inhibitor experience had 79% (11/14) and 81% (13/16) SVR rate among those treated for 12 weeks and 16 weeks, respectively. All (4/4) patients with genotype 4 infection achieved SVR12 and 10.3% (9/87) of patients with chronic HCV genotype 1 infection experienced virologic failure. In CRETAIN-1 and -2 trials, The SVR rate in the HCV subtype1b-infected patients with PI and NS5A inhibitor experience was 93.3% (28/30). Virologic failure occurred in two patients with NS5A P32del.[54]

Research conducted by Uemura *et al*.,[33] in which 34 of 42 patients had both NS3 and NS5A inhibitors treatment experience, reported that the SVR12 rate of chronic hepatitis c patients with prior DAA treatment experience treated with G/P for 12 weeks was 92.9% (39/42). All genotype 1b-infected patients carrying the NS5A P32del (3/35) experienced virologic failure.[33]

Adolescent patients aged 12–17

The DORA part 1, nonrandomized, open-label, multicenter clinical trial assessed the efficacy of G/P in adolescent patients with chronic HCV genotypes 1-4 infections.[34] Of the 47 enrolled patients, 36 patients were HCV treatment-naïve and the others were interferon-based regimen-experienced. Except for three patients with HCV genotype 3 infections and treatment experience, who received G/P for 16 weeks, all patients received 8 weeks of therapy. The SVR12 rate of overall patients was 100% (47/47).[34]

Patients who used drugs recently or were receiving opioid substitution therapy

Among 15.6 million patients who inject drugs, an estimated 52.3% are HCV-antibody positive.[55] A pooled analysis of clinic trials revealed that SVR12 was achieved by 92.9% (91/98), 97.0% (592/610), and 99.5% (1,106/1,111) of recent, former, and non-drug users, respectively. But, the overall rates of virologic failure were ≤1.5%, regardless of drug use status.[56] An integrated analysis of eight clinical trials compared the efficacy of G/P in HCV-infected patients receiving opioid substitution therapy (OST) and those not receiving OST. SVR rates were 96.2% (151/157) and 97.9% (2,055/2,099) in the OST and non-OST patients, respectively.[57] Methadone was the most commonly prescribed OST (76%).[57] An integrated analysis of 18 real-word studies demonstrated that 98.9% of chronic HCV patients using OST achieved SVR12 in the modified ITT analysis.[49]

Patients with concurrent use of acid-reducing agents

Proton pump inhibitors (PPIs) were among the most frequently used co-medication in patients treated for chronic HCV infection.[12] An integrated analysis of nine phase 2 and phase 3 clinic trails showed that in patients treated with G/P, SVR rates were 97.0% (389/401) and 97.5% (1,918/1,968)

for patients using concomitant acid-reducing agents (ARAs) and those not concurrently using ARAs, respectively.[58] SVR was achieved in 96.3% (105/109) of patients taking a high-dose PPI and 97.4% (150/154) taking a low-dose PPI. The overall virologic failure rate in patients taking an ARA was less than 1% (4/401) compared with 1.5% (29/1,968) in patients not taking any ARAs.[58] The SVR rate of patients with chronic HCV infection receiving PPI was 97.9% (n=180) in real-world studies.[49]

Tolerability and safety

HCV N3/4A PIs have been shown to have concentration-dependent hepatotoxicity and are contraindicated in patients with decompensated cirrhosis. Therefore, patients with factors known to affect the exposure to glecaprevir need to be carried out, including those on patients with renal impairment, DDIs, advanced age, female sex, and cirrhosis status.[59]

A pooled analysis of nine clinical trials evaluated the tolerability and safety of G/P in chronic HCV-infected patients and studied by subgroup.[60] In general, the prevalence of adverse events (AEs) were 68% (1,603/2,369), and the most commonly reported AEs with an incidence rate exceeding 5% included headache, fatigue, nausea, and pruritus.[60] Serious AEs occurred in 73 (3%) patients but only one (<1%) was reported as DAA-related. Although 55% (11/20) of patients with compensated cirrhosis and CKD stages 4 or 5 developed serious AEs, none were reported as G/P-related.[60] No matter whether concurrent with end-stage renal disease or not, DAA-related serious AEs and AEs leading to G/P discontinuation were rare (<1%).[60] Hepatic decompensation and death occurred in 1 and 7 patients, respectively, but none were considered related to G/P. Patients with laboratory abnormalities grade ≥3 were rare among both patients with compensated cirrhosis and without cirrhosis.[60] Alanine aminotransferase elevations greater than 5 times the upper limit of normal occurred in two (<0.1%) patients without cirrhosis, and elevations of total bilirubin at least 3-times the upper limit of normal occurred in nine (0.4%) patients, including three (0.1%) with cirrhosis and six (0.3%) without cirrhosis. Overall, this combined analysis demonstrated that the recommended dose of G/P for patients with compensated liver disease and/or with any degree of renal impairment is safe and well-tolerated. The fixed-dose of G/P was also demonstrated safe and tolerable in patients with psychiatric disorders,[52] those with recent drug use,[56] those receiving OST therapy[57] or acid-reducing agents,[58] and patients aged 65 years or older[61] by data from clinical trials and additional subgroup analysis. The safety profile of G/P in adolescents was consistent with that in adults, as demonstrated in the DORA part 1 trial published recently.[34]

Data from real-world studies have demonstrated that the safety is similar among clinic trials.[16,27,35–37,59] The prevalence rate of patients with AEs was 17.7% (1,271/7,199), and the most commonly reported AEs were the same as in the clinical trials. Only 1% (55/5,522) of patients reported serious AEs, and 0.6% (33/5,595) of patients discontinued study treatment because of AEs. Only 4 of 2,333 (0.2%) patients experienced hepatic decompensation events.[49]

Although patients with G/P had a high prevalence of AEs, ENDURANCE-2 reported that the frequency and severity of AEs and laboratory abnormalities in the HCV genotype 2-infected patients treated with G/P were similar to those treated with placebo.[38]

Conclusions

Although the data from clinical trials and real-world studies described above demonstrated that G/P could help a vast majority of chronic hepatitis c patients to safely eliminate HCV, even in patients who are not fully adherent to G/P regimen,[62] there are still some problems that deserve attention.

Several studies have demonstrated that the A30K substitution significantly decreases the SVR12 rate in genotype 3 patients treated with the G/P regimen.[39,63] Patients with subtype 3b naturally possess A30K, and over 95% of patients with subtype 3b harbor the paired A30K+L31M substitutions,[64,65] which showed a >20-fold increase in 50% effect concentration for pibrentasvir.[64] Research conducted by Nozaki *et al*.[22] and Tamori *et al*.[23] showed SVR rates were 33.3% (2/6) and 50% (2/4), respectively. Therefore, the efficacy of G/P in patients with subtype 3b is worthy of attention, especially in Asia, where the prevalence of subtype 3b is much higher than that in other continents.[66,67] Nevertheless, most clinical studies have been conducted in Europe and North America, where the proportion of subtype 3b is less than 1% for genotype 3.[67] Evaluation of the efficacy of G/P in patients with HCV subtype 3b infection is still lacking and needs further study.

All patients with NS5A-P32del have experienced virologic failure after receiving G/P treatment, according to the limited data.[23,33,40,54] P32del confers an >1,000-fold change resistance to pibrentasvir and >10,000-fold change resistance to velpatasvir in the HCV genotype 1b Con replicon[54] appearing in 5% to 10% of genotype 1b patients who experienced virologic failure with daclatasvir-containing therapies and sofosbuvir/ledipasvir treatment, but which has not been found among treatment-naïve patients.[68,69] Therefore, patients with prior NS5A inhibitor treatment experience, especially those with genotype 1b infection, should pay attention to P32del and switch to other treatment options when P32del occurs.

Currently, although G/P has been approved for children aged 12 years and older or weighing at least 45 kg without dose changing, the efficacy and safety of G/P for adolescents with genotypes 5 and 6 infections or previous sofosbuvir experience were inferred from adult data and have not been directly evaluated.[34] More evidence from clinical trials and real-world studies is needed to prove effectiveness and safety in adolescents.

In conclusion, G/P is highly efficacious and well-tolerated in chronic HCV-infected patients with compensated liver disease, including patients with compensated cirrhosis, HCV/human immunodeficiency virus coinfection, end-stage renal disease, liver or kidney transplants, recent drug use or in adolescents, according to data from clinic trails and real-world studies. In the DAA era, the characteristics of HCV patients have changed greatly, including for treatment-experienced patients and patients with cirrhosis that has decreased over time.[70,71] The fixed-dose G/P regimen for 8-week duration has been approved for treatment-naïve HCV-infected patients with compensated liver disease (with or without cirrhosis) by the European Commission[72] and the USA Food and Drug Administration,[8] which means a shorter duration of therapy can benefit the vast majority of chronic hepatitis c patients. However, patients with HCV subtype 3b infection or NS5A-P32del need special attention.

Funding

This work was supported in part by the Kuanren Talents Program of the Second Affiliated Hospital of Chongqing Medical University.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Wrote the manuscript (XL), critically revised the manuscript and provided study supervision (PH).

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