High efficacy of Glecaprevir/Pibrentasvir for HCV-Infected individuals with active drug use

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Lay Summary/Key Points:

- Active drug use is independently associated with lower SVR rates to G/P.
- Voluntary dropout in patients with active drug users is up to 4-fold higher compared to those with past drug use and up to 11-fold compared to those who never used drugs.
- G/P could be particularly beneficial in this scenario but specific strategies designed to increase the retention in care of active drug users are needed.

Ethical aspects: Both the study design and development complied with the Helsinki declaration and was approved by the local Ethics Committee of the Hospital Universitario Virgen de Valme (Seville). All patients gave their written informed consent to participate in the study.

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Abstract

Objectives: Real world data on glecaprevir/pibrentasvir (G/P) among active drug users are scarce. We evaluated the sustained virological response (SVR) rates of G/P among individuals with and without active drug use in routine clinical practice.

Methods: Two ongoing prospective multicenter cohorts of individuals starting G/P were analyzed. Overall SVR intention-to-treat (ITT), discontinuations due to adverse effects and dropouts were evaluated. Results in patients with active, past and without active drug use were compared.

Results: Overall, 644 individuals started G/P and have reached the date of SVR evaluation. Of them, 613 (95.2%) individuals achieved SVR. There were two (0.3%) relapses, one (0.2%) discontinuation due to side effects and 35 (5.4%) dropouts. SVR rates for patients with active drug use, past drug use and those who never used drugs were 85.4%(n/N=70/82), 96.1%(n/N=320/333) and 97.4%(n/N=223/229) respectively ($p<0.001$). After adjustment by sex, age, HCV genotype and opioid agonist therapy, active drug use was the only factor independently associated with SVR (ITT) [adjusted OR (95%confidence interval): 0.29(0.09-0.99),p=0.048].

Conclusions: Active drug use was independently associated with lower SVR rates to G/P, mainly due to voluntary dropout. G/P could be particularly beneficial in this scenario but specific strategies designed to increase the retention in care are needed.

Keywords: Glecaprevir/pibrentasvir; HCV therapy; Drug use; Opiate Agonist Therapy; PWID.

INTRODUCTION

Elimination of viral hepatitis was adopted by The World Health Assembly as a public health objective by 2030.[1] This ambitious target needs sufficient coverage for a number of core interventions in order to be reached.[2] HCV treatment and cure was one of those interventions. HCV infection has become a curable disease in nearly all patients thanks to highly effective and safe direct-acting antiviral (DAA) combinations. However, drug users, currently or previously, have far higher prevalence of hepatitis C virus (HCV) infection than the general population.[3, 4] Unfortunately, uptake of treatment is still low among drug users[5] and even today, some clinicians are hesitant to prescribe DAAs to people who inject drugs (PWID) due to concerns over poor adherence, reduced tolerability, and the risk of HCV reinfection.[6]

Lower sustained viral response (SVR) rates in drug users with DAA may be found in clinical practice compared to clinical trials, mainly due to a greater likelihood of losses to follow-up and lower adherence. We found that HCV-infected PWID with active drug use had the lowest SVR rate to DAA combinations in clinical practice.[7] Higher rates of discontinuations due to adverse events and, especially, of losses to follow-up were the main factors responsible for those lower SVR rates. SVR rates among PWID and patients who never used drugs were similar when active drug use was accounted for.[7] These results were obtained before Glecaprevir/Pibrentasvir (G/P) was widely available.

G/P has demonstrated high efficacy and tolerability in a variety of settings.[8-12] In the setting of drug use, G/P is supported by a meta-analysis from patients with HCV genotypes 1-6 who were treated with G/P for 8, 12, or 16 weeks in eight Phase 2 and 3 trials showing that G/P is highly efficacious and well tolerated in HCV-infected patients receiving opioid agonist therapy (OAT) .[13] Sustained viral response (SVR) was high and no HCV reinfections occurred through post-treatment week 12. However, real world data on G/P in the setting of drug use are still scarce. Furthermore, post-hoc analyses of data from clinical trials showed that virologic failure was not associated with G/P treatment interruption, which may be related to its high drug forgiveness.[14] It is not known whether the efficacy of G/P in the setting of clinical trials may be replicated among active drug users in clinical practice.

For these reasons, our aim was to compare the rates of SVR to G/P among HCV-Infected individuals with ongoing drug use, previous drug use and those who never injected drugs in daily practice.

METHOD

Patients and study design

The HEPAVIR-DAA cohort (NCT02057003), which includes HIV/HCV-coinfected patients, and the GEHEP-MONO cohort (NCT02333292), which recruits HCV monoinfected individuals, are ongoing prospective multicenter cohorts of patients receiving DAA combinations prescribed in clinical practice, outside clinical trials. Patients included in these cohorts with chronic HCV infection who started G/P and achieved the SVR evaluation date were included in the present analysis. Patients taking at least one dose of the combination were eligible. Cirrhosis was diagnosed with a liver biopsy showing fibrosis stage 4, or with liver stiffness ≥12.5 kPa, or with a previous hepatic decompensation.

Medications and follow-up

G/P was used as prescription medication to treat HCV infection in routine clinical practice in the cohorts. The standard duration of the combination G/P was 8 weeks for treatment-naïve patients without cirrhosis.[15] Since 2019, treatment-naïve patients with compensated cirrhosis could be treated for 8 weeks. The achievement of plasma HCV RNA below the limit of detection 12 weeks after the end of therapy with G/P was defined as SVR. The efficacy of therapy was assessed by the SVR rate. Discontinuations due to adverse effects, dropouts and

virological failures (breakthrough or relapse) were analyzed in patients according to drug use.

Active drug use was defined as ongoing drug use 12 months before starting G/P. Past drug use was defined as use of drugs more than 12 months before starting G/P. Drug use was self-reported and assessed by physician-driven interview during clinical visits. All individuals with current or past injecting drug use were considered as PWID. Individuals using cannabis alone were not classified as active drug users. In Spain, OAT is managed by drug addiction facilities. Data on OAT use among patients included in the cohorts were prospectively recorded.

Statistical analyses

The rates of SVR were estimated by an intention-to-treat analysis (ITT), considering all missing data at the date of SVR assessment as failures. Discontinuations due to adverse effects, virological failure and dropouts were also evaluated. In addition, a per-protocol (PP) approach was used to calculate the SVR rates excluding patients discontinuing therapy because of non-treatment- related reasons.

Continuous variables were expressed as median (Q1-Q3) and categorical variables as number (%). The chi-square test was used to compare proportions among treatment groups. The Mann Whitney U or the Kruskal-Wallis tests were applied for comparisons of continuous variables among groups. A multivariate

logistic regression was carried out to identify factors independently associated with SVR. Variables associated with SVR with a univariate p-value ≤0.1, age categorized by the median and gender were entered into the model. Data were analyzed using IBM SPSS 28.0 version (IBM Corporation, Somers, NY, USA) and STATA 16.0 (StataCorp LP, College Station, TX, USA).

Ethical aspects

Both the study design and development complied with the Helsinki declaration and was approved by the local Ethics Committee of the Hospital Universitario Virgen de Valme (Seville). All patients gave their written informed consent to participate in the study.

Results

Baseline characteristics of the patients

Overall, 5585 patients included in the cohorts started interferon-free DAA combinations since November 2017. Seven hundred and two patients started G/P. Of them, 644 (91.7%) have reached the date of SVR evaluation (figure 1). Out of them, 229 (35.6%) had never used drugs, 333 (51.7%) had used drugs more than 12 months before the start of treatment and 82 (12.7%) were active drug users. The characteristics of the patients at the date of starting G/P are summarized in table 1. Fifty-three (8.2%) individuals had cirrhosis at baseline. There were significant differences among patients according to drug use in factors such as the frequency of male sex, age, HIV infection, PWID, OAT, HCV genotype, 8 week treatment duration, and liver stiffness (table 1).

Global response to treatment

Global response to G/P was 95.2% [95% confidence interval (95%CI): 94%–97%, n/N=613/644] in the ITT analysis (figure 2). No individuals showed virological breakthrough before the end of treatment. One cirrhotic patient with Child-Pugh score B7 developed hepatic encephalopathy and G/P was discontinued. In the PP analysis, SVR was 99.5% (95% CI: 99%–100%, n/N=600/603).

SVR response according to active drug use

Virological and non-virological outcomes by study group are summarized in table 2. SVR was 97.4% (95% CI: 95%–99%, n/N = 223/229) among patients who never used drugs, 96.1% (95% (CI: 94%–98%, n/N = 320/333) among patients with past drug use and 85.4% (95% CI: 78%–93%, n/N = 70/82) among patients with active drug use. There were significant differences among groups in virological and non-virological outcomes only in voluntary discontinuation of treatment (table 2). In the PP analysis, SVR was 99.1% (95% CI: 98%–100%, n/N = 220/229) among patients who never used drugs, 99.7% (95% CI: 90%–100%, n/N = 314/333) among patients with past drug use and 100% (66/66) among patients with active drug use (p=0.513).

SVR response according to HCV genotype

SVR (ITT) rates by genotype were 95.2% (n/N=217/228) for genotype 1a, 99.2% (n/N=129/130) for genotype 1b, 100% (n/N=16/16) for genotype 1 other subtypes, 100% (n/N=16/16) for genotype 2, 91.6% (n/N=109/119) for genotype 3, and 93.6% (n/N=102/109) for genotype 4 (p=0.055). One (0.4%) patient with genotype 1a and one (0.8%) with genotype 3 relapsed.

Factors associated with response to treatment

In the univariate analysis, HCV genotype 3 and drug use were associated with lower rates of SVR (table 3). After multivariate analysis adjusted by sex, age, OAT and HCV genotype 3, active drug use was the only variable independently associated with SVR (table 3).

DISCUSSION

In this study, we found that the overall SVR rates achieved with G/P were high in real-world conditions of use. Active drug use is independently associated with lower SVR rates, mainly due to voluntary dropout. Notwithstanding, a high percentage of active drug users achieve SVR. Hence, active drug users should receive treatment along with specific strategies designed to increase their retention in care and adherence.

SVR rates with G/P for active drug users were higher than those recently reported for other DAAs in our cohorts.[7] This may be related to G/P drug forgiveness, high antiviral potency and short treatment duration. In this study performed on individuals managed in routine clinical practice, lower SVR rates were not independently associated to PWID or OAT, although both factors have been associated with lower SVR rates.[16] In this regard, our results on the influence of OAT are in agreement with a recent meta-analysis.[17] Moreover, an integrated analysis of eight clinical trials evaluating the efficacy of G/P reported similar SVR rates for PWID receiving OAT and not receiving OAT.[18] In our study, active drug users did not show a higher likelihood of virologic failure. Lower SVR rates among individuals with active drug use were related to voluntary discontinuation of treatment and losses to follow-up. Hence, treatment with G/P for active drug users needs to be complemented with some sort of strategy to ensure adherence. Several potential interventions to improve healthcare retention of drug users have been described, such as place OAT and DAA

therapy in the same location,[19] peer support or a helping hand from people in recovery,[20] and cash incentives.[21]

Another possible reason for the lower SVR rates in drug users, in addition to dropouts, could be the higher proportion of individuals with HCV genotype 3 infection.[22] In the SURVEYOR-II trial the efficacy of G/P was 91.7% in treatment-experienced patients with genotype 3 infection without cirrhosis.[23] In our study, HCV genotype 3 was more frequent in drug users. This could be expected given the high prevalence of HCV genotype 3 among PWID globally.[24] Lower rates of SVR in genotype 3-infected patients could explain the response rates found for active drug users. However, there were no virologic failures among active drug users in our study. In addition, active drug use independently associated with response after adjustment by HCV genotype 3.

G/P is recommended for individuals without cirrhosis or with compensated cirrhosis and contraindicated for patients with decompensated cirrhosis.[25, 26] In agreement with previous reported meta-analysis of G/P treatment,[27, 38] in clinical practice we found no difference in SVR rates according to cirrhosis status, even though SVR rates were slightly higher in individuals without cirrhosis. There was only one of interruption due to adverse effects in the cohorts in a cirrhotic patient HCV with genotype 3 infection and Child-Pugh Score B7, treated with G/P by decision of his physician. Despite of this, high response rates were found for cirrhotic patients in this study.

In this study we report the efficacy and safety of G/P in patients included in real-world multicenter cohorts. The overall efficacy of G/P among drug users

found in a previous meta-analysis was replicated in this real-world sample of patients.[18] However, this study may have certain limitations. First, drug use was self-reported and thus, it was likely underestimated. Second, reinfections were not systematically evaluated and might have gone unnoticed in the study population. However, reinfections were recently analyzed in these same cohorts finding a frequency lower than 0.2% for the period of DAAs administration.[2] Therefore, we assume that unnoticed reinfections should not change substantially the conclusions of this study.

In conclusion, G/P is effective in individuals with and without active drug use. Spain was on track to meet the 2030 HCV elimination targets by WHO, before the SARS-CoV-2 pandemic. To attain the national HCV elimination goal, specific strategies designed to increase the retention in care of active drug users are needed. G/P as a short treatment with high SVR rates in active drug users could be particularly beneficial in this scenario.

Abbreviations

Sustained virological response (SVR), direct-acting antiviral (DAA), Glecaprevir/Pibrentasvir (G/P), intention-to-treat analysis (ITT), per-protocol (PP), hepatitis C virus (HCV), opioid agonist therapy (OAT), people who inject drugs (PWID).

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Authorship

AGS and JM performed the acquisition, analysis, or interpretation of data for the work. JAP and JM designed the research study. ACG, FT, JC, LMR, RG, ARJ, JHQ, DM, RP, MJR and AC contributed essential reagents or tools. AGS and JM analyzed the data and wrote the paper.

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Conflict of interest

A.C.-G. has received lecture fees from Gilead. J.M. has been an investigator in clinical trials supported by Bristol-Myers Squibb, Gilead and Merck Sharp & Dome and has received lecture fees from Gilead, Bristol-Myers Squibb and Merck Sharp & Dome and consulting fees from Bristol Myers- Squibb, Gilead and Merck Sharp & Dome. J.A.P. has received consulting fees from Bristol-Myers Squibb, AbbVie, ViiV Healthcare, Gilead, MSD and Janssen Cilag, has received research support from Bristol-Myers Squibb, AbbVie, ViiV Healthcare, Janssen Cilag, MSD and Gilead and has received lecture fees from AbbVie, Bristol-Myers Squibb, Janssen Cilag, ViiV Healthcare, MSD and Gilead. All other authors: none to declare.

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460 **Tables:**

461

462 **Table 1.** Baseline characteristics of the patients (N = 644)

Characteristic	Never used drugs (n=229)	Past drug use (n=333)	Active drug use (n=82)	p-value
Male sex, n (%)	127 (55.5)	194 (58.3)	59 (59)	0.031
Age[a] , years	51.5 (46-57.8)	50.5 (46.2-54.5)	49.6 (45.2-53.3)	<0.001
HIV infection, n (%)	30 (13.1)	79 (23.7)	23 (28)	0.002
PWID, n (%):	0 (0)	310 (93.1)	65 (79.3)	<0.001
OAT, n (%):	0 (0)	90 (27)	26 (31.7)	<0.001
HCV genotype 3, n (%):	26 (11.5)	73 (22.9)	20 (26)	0.001
Cirrhosis[b], n (%):	11 (4.8)	34 (10.2)	8 (9.8)	0.063
G/P scheduled for 8 weeks, n (%):	214 (93.4)	289 (86.8)	73 (89)	0.041
Retreatment[c], n (%)	24 (11.8)	42 (12.7)	8 (9.9)	0.785
Liver stiffness[a], KPa	6.6 (5.3-8.8)	6.7 (5.3-8.6)	6.5 (5.2-8.4)	0.038
Baseline HCV RNA, IU/ml	1.3×10^6	1.5×10^6	1.6×10^6	0.222

463 [a]Median (Q1-Q3); [b]Cirrhosis was diagnosed with a liver biopsy showing fibrosis
464 stage 4, or with liver stiffness ≥12.5 kPa, or with a previous decompensation of
465 cirrhosis; [c]Previous treatment with peg-interferon plus ribavirin; OAT: opioid
466 agonist therapy; PWID: people who inject drugs.

Table 2. Virological and non-virological outcomes (N=644)

Outcome, n (%)	Never used drugs (n=229)	Past drug use (n=333)	Active drug use (n=82)	p-value
Discontinuation due to adverse events	1 (0.4)	0 (0)	0 (0)	0.404
Dropouts	4 (1.7)	16 (4.8)	15 (18.3)	<0.001
Viral breakthrough	0 (0)	0 (0)	0 (0)	-
Viral relapse	1 (0.4)	1 (0.3)	0 (0)	0.829
SVR ITT, n (%):	223 (97.4)	320 (96.1)	70 (85.4)	<0.001

Three patients with active drug use and four patients with past drug use achieved SVR despite voluntarily discontinuing treatment.

470 **Table 3.** Factors associated with sustained virological response (ITT) to direct-acting antiviral drug combinations

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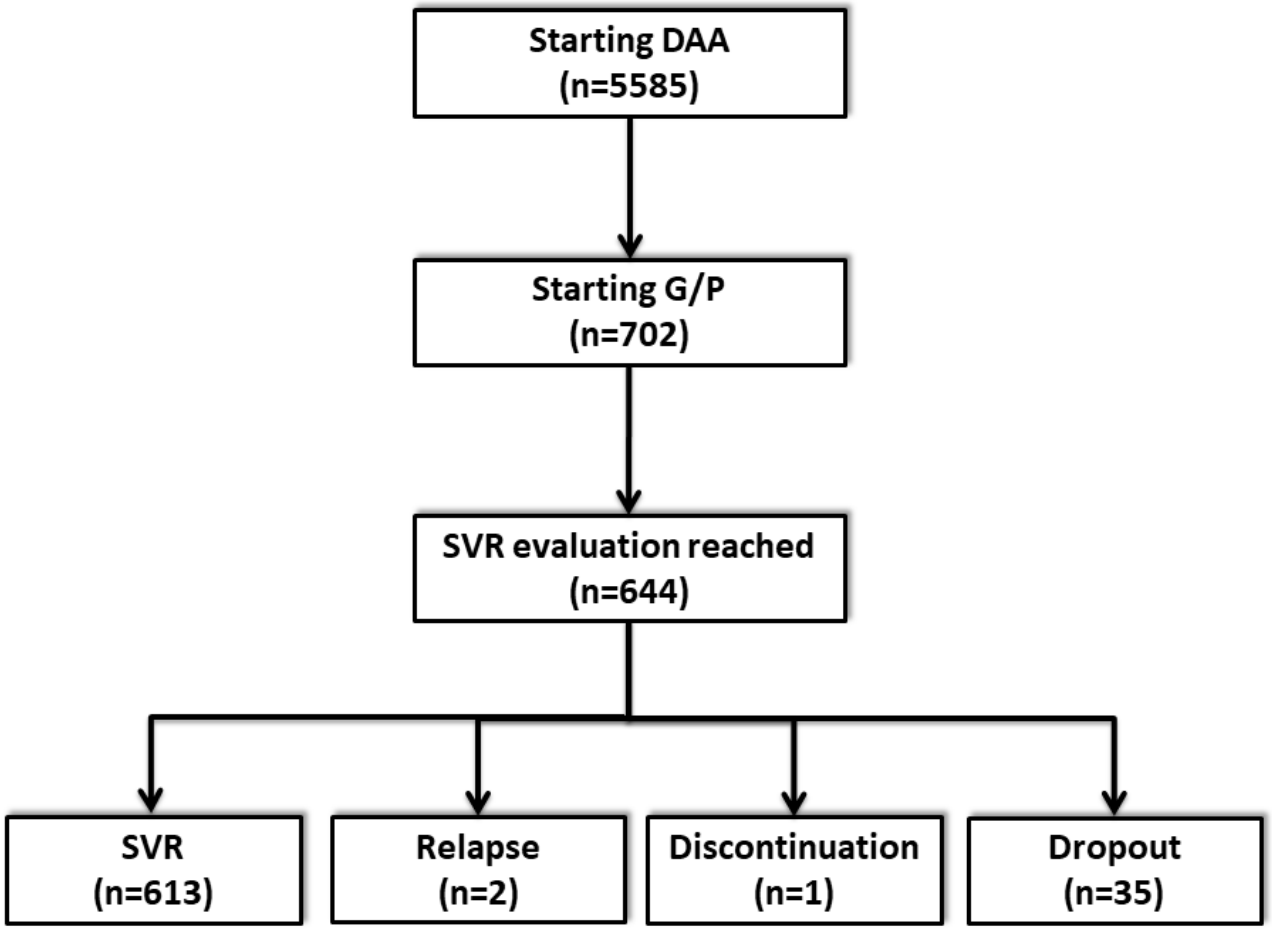
Variable		N	SVR, %	Univariate p-value	Adjusted odds ratio (95% CI[a])	Multivariate p-value
Sex:	Male	380	94.5	0.311	1.04 (0.45-2.40)	0.925
	Female	264	96.2			
Age:	> 51 years	299	96.3	0.210	1.02 (0.98-1.7)	0.327
	≤ 51 years	345	94.2			
Drug use:	Never	229	97.4	<0.001	Reference category	0.049
	Past	333	96.1		0.81 (0.26-2.51)	0.717
	Active	82	85.4		0.29 (0.09-0.99)	0.048
OAT:	Yes	116	91.4	0.034	0.44 (0.18-1.09)	0.075
	No	528	96			
PWID:	Yes	375	94.7	0.467		
	No	269	95.9			

HIV infection:	Yes	132	95.5	0.872		
	No	512	95.1			
HCV genotype 3:	Yes	119	91.6	0.043	0.53 (0.22-1.24)	0.141
	No	503	96			
Cirrhosis[b]:	Yes	53	92.5	0.311		
	No	591	95.4			
G/P for 8 weeks:	Yes	576	95.7	0.126		
	No	68	91.2			
Baseline HCV RNA:	< 1.5 x 10^6 IU/ml	390	94.1	0.175		
	≥ 1.5 x 10^6 IU/ml	232	96.6			
Liver stiffness	≤7.6 kPa	376	94.9	0.895	1.03 (0.95-1.11)	0.548
	7.7-9.4 kPa	105	95.2			
	9.5-14 kPa	69	97.1			
	>14 kPa	44	95.5			

Univariate p-values refer to the chi-square test. Multivariate p-values correspond to multivariate logistic regression analysis; [a]95%CI: 95% confidence interval; [b]Cirrhosis was diagnosed with a liver biopsy showing fibrosis stage 4, or with

liver stiffness ≥12.5 kPa, or with a previous decompensation of cirrhosis; OAT: opioid agonist therapy; PWID: people who inject drugs. Age and liver stiffness were entered as continuous variables into the linear regression model.

478 **Figure 1.** Flow-chart of patients



479

Figure 2. Global SVR rates to G/P