Research Article
Viral Hepatitis

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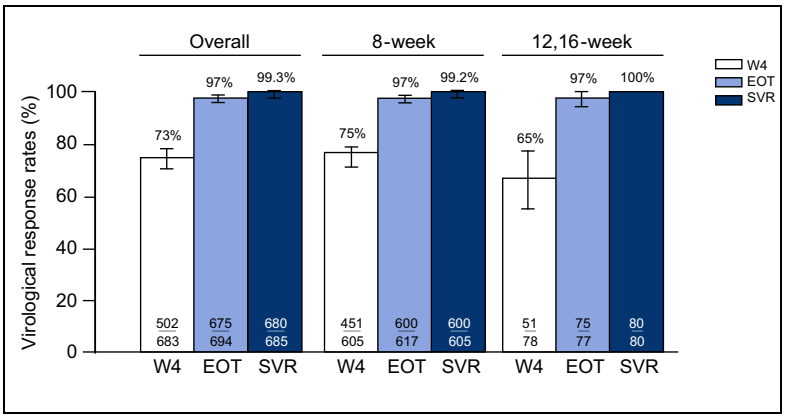
Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C

Graphical abstract



Highlights

- Glecaprevir/pibrentasvir combination has demonstrated excellent SVR rates (99.2%) in this real-world study in Italy.
- Male gender (0.022) and HCV genotype 3 (0.046) were associated with the lowest rates of SVR after 8-week G/P treatment.
- 8.3% of the patients reported mild adverse events and 0.7% of them prematurely withdrew antiviral treatment.

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Lay summary

A large number of patients with hepatitis C virus have been treated with glecaprevir/pibrentasvir (G/P) within the NAVIGATORE-Lombardia Network, in Italy. This is the first real-world study evaluating effectiveness and safety of G/P in patients with hepatitis C virus treated according to international recommendations. This study demonstrated excellent effectiveness (with sustained virological response rates of 99.3%) and safety profiles.

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Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C

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Background and Aims: The efficacy and safety of glecaprevir/pibrentasvir (G/P) for patients infected with hepatitis C virus (HCV) have only been investigated in clinical trials, with no real-world data currently available. The aim of our study was to investigate the effectiveness and safety of G/P in a real-world setting.

Methods: All patients with HCV consecutively starting G/P between October 2017 and January 2018 within the NAVIGATORE-Lombardia Network were analyzed. G/P was administered according to drug label (8, 12 or 16 weeks). Fibrosis was staged either histologically or by liver stiffness measurement. Sustained virological response (SVR) was defined as undetectable HCV-RNA 12 weeks after the end of treatment.

Results: A total of 723 patients (50% males) were treated with G/P, 89% for 8 weeks. The median age of our cohort was 58 years, with a median body mass index of 23.9 kg/m^2, and median liver stiffness measurement of 6.1 kPa; 84% were F0-2 and 16% were interferon-experienced. Median HCV-RNA was 1,102,600 IU/ml, and 49% of patients had HCV genotype 1 (32% 1b), 28% genotype 2, 10% genotype 3 and 13% genotype 4. The median estimated glomerular filtration rate was 90.2 ml/min, platelet count 209x10^3/mm^3 and albumin 4.3 g/dl. The SVR rates were 94% in intention-to-treat and 99.3% in per protocol analysis (8-week *vs.* 12 or 16-week: 99.2% *vs.* 100%). Five patients failed therapy because of post-treatment relapse; a post-treatment NS5A resistance-associated substitution was detected in 1 case. SVR rates were lower in males (p = 0.002) and in HCV genotype-3 (p = 0.046) patients treated for 8 weeks, but independent of treatment duration, fibrosis stage, baseline HCV-RNA, HIV co-infection, chronic kidney disease stage and viral kinetics. Mild adverse events were reported in 8.3% of the patients, and 0.7% of them prematurely withdrew treatment. Three patients died of drug-unrelated causes.

Conclusions: In a large real-world cohort of Italian patients, we confirmed the excellent effectiveness and safety of G/P administered for 8, 12 or 16 weeks.

Lay summary: A large number of patients with hepatitis C virus have been treated with glecaprevir/pibrentasvir (G/P) within the NAVIGATORE-Lombardia Network, in Italy. This is the first real-world study evaluating effectiveness and safety of G/P in patients with hepatitis C virus treated according to international

Keywords: HCV; DAA; Glecaprevir; Pibrentasvir; RAS; SVR; Real-life; Effectiveness; Safety.
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recommendations. This study demonstrated excellent effectiveness (with sustained virological response rates of 99.3%) and safety profiles.

Introduction

Chronic infection with hepatitis C virus (HCV) still remains a leading cause of morbidity and mortality worldwide, with more than 70 million individuals infected despite recent improvements in antiviral therapies.[1,2] In the last years, direct-acting antivirals (DAA) have dramatically revolutionized this scenario, since the availability of potent interferon (IFN)-free regimens has led to an increase in sustained virological response (SVR) rates, especially among patients in whom IFN-based antiviral therapies were previously contraindicated.[2,3]Moreover, because of the lack of tolerability issues, treatment indications have been widely extended to include patients with milder liver diseases, thus contributing to the goal of HCV eradication.[1]

More recently, several efforts have been made to further simplify anti-HCV therapies in order to optimize treatment management and improve patient adherence. Glecaprevir/pibrentasvir (G/P) is a pangenotypic regimen recently approved for the treatment of chronic HCV infection. Glecaprevir is a non-structural (NS) protein 3/4 A protease inhibitor, which is co-formulated with the NS5A inhibitor pibrentasvir. In phase II and III registration trials, SVR rates >95% were achieved when this combination was administered for 8 to 16 weeks, without safety issues.[4–11] However, in clinical trials, restricted inclusion and exclusion criteria for the targeted patients may influence outcomes. In fact, patients who receive treatment in the real-world can differ from those enrolled in clinical trials due to older age, more advanced stages of fibrosis, and higher prevalence of co-morbidities and co-medications, all conditions potentially affecting SVR rates.

To assess the effectiveness and safety of the G/P combination in a real-world setting, we assessed both SVR rates as well as safety and tolerability data in a large cohort of Italian patients with HCV enrolled in a retrospective-longitudinal study.

Material and methods

This is a retrospective-longitudinal multicenter study evaluating the antiviral efficacy of the G/P combination in a real-world setting. Data were collected through the NAVIGATORE-Lombardia Network web-based platform, which is based on REDCap (Research Electronic Data Capture; http://project-redcap.org) and includes data from all DAA-treated patients starting from December 2014 in Lombardy, Northern Italy. All patients with HCV consecutively starting G/P between October 2017 and January 2018 were analyzed. Informed consent was obtained from each patient included in the study. The study protocol was approved by the Institutional Board of our Department (Ethical Committee Milan Area 2) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Assessments

Demographic, clinical and virological data were available throughout G/P administration and after the end of treatment (EOT). Below the lower limit of quantification (LLOQ), and according to HCV-RNA assays, HCV-RNA was defined unquantified but detected (<LLOQ) or not detected (ND). An EOT response was defined as HCV-RNA <LLOQ or ND at the time of treatment completion; a sustained virological response (SVR) was defined as <LLOQ or ND HCV-RNA 12 weeks after treatment completion.[2]

Chronic kidney disease (CKD) stage was assessed according to the KDIGO (Kidney Disease: Improving Global Outcomes) classification as follows: stage 1 (normal) if estimated glomerular renal function (eGFR) ≥90 ml/min/1.73 m^2, stage 2 (mild decrease) if eGFR 60–89 ml/min/1.73 m^2, stage 3 (moderate decrease) if eGFR 46–59 (stage 3a) or 30–45 (stage 3b) ml/min/1.73 m^2, stage 4 (severe decrease) if eGFR 15–29 ml/min/1.73 m^2, stage 5 (end-stage renal disease) if eGFR <15 ml/min/1.73 m^2.[12]

Next generation sequencing was conducted on plasma samples collected from patients with a virological failure at baseline (when available), and the presence of polymorphisms in NS3 and NS5A was evaluated with the use of a 15% detection threshold. Substitutions (relative to baseline HCV sequence) that arose during treatment were analyzed.

Fibrosis stage was determined either histologically or non-invasively, by transient elastography (TE). According to the European Association for the Study of the Liver recommendations, advanced fibrosis was defined as METAVIR F3 or as a liver stiffness measurement (LSM) between 10 and 12.9 kPa. Cirrhosis was defined as METAVIR F4 or LSM ≥13 kPa.[2,13,14] These cut-offs were also endorsed by the Italian Medicines Agency (AIFA, *Agenzia Italiana del Farmaco*) to classify patients to be treated with any DAA regimen. In the NAVIGATORE-Lombardia platform, adverse events (AE) were also reported, at the discretion of treating physicians. Adherence to treatment was based on pharmacy refill data as well as on patients' reports.

Study endpoints

The primary endpoint of the study was effectiveness of G/P regimen, *i.e.* rates of SVR at week 12 after treatment completion. Secondary endpoints of the study were: rates of treatment discontinuation due to drug-related adverse events and/or drug-related deaths; incidence of drug-related adverse events; rates of week 4 on-treatment response (HCV-RNA <LLOQ or undetectable 4 weeks after treatment start) and rates of EOT response (HCV-RNA <LLOQ or undetectable at EOT assessment)

Statistical analysis

Categorical variables were reported as frequencies (percentages) and continuous variables as median (range). Categorical variables were compared using the χ^2 or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U*- test or the Kruskal-Wallis test, when appropriate. All tests were 2-sided and used a significance level of 0.05. Data handling and analysis were performed with Stat-View package (SAS Institute Inc., Cary, NC).

Results

Between 26 October 2017 and 31 January 2018, 723 HCV patients were treated with G/P in 32 centers in Lombardy. Three-hundred and sixty-one (50%) of them were males, with a median age of 58 (21–89) years. Baseline LSM was 6.1 (2.5–43) kPa; 601 (83%) patients had F0-F2 fibrosis, and 65 (9%) had F3 fibrosis. Cirrhosis had been previously diagnosed in 57 (8%) patients and was compensated (Child-Pugh A) in all cases.

A total of 352 (49%) patients had HCV genotype 1, 203 (28%) had genotype 2, 74 (10%) had genotype 3 and 91 (13%) had genotype 4. Pre-treatment HCV-RNA was 1,063,109 (153–38,300,000) IU/ml. The median baseline creatinine value was 0.80 (0.46–10.0) mg/dl, with 18 (3%) patients having an eGFR below 30 ml/min/1.73 m^2. One-hundred and sixteen (15%) patients were IFN-experienced, whilst no patients had failed any previous DAA-based regimen. Complete patient characteristics are provided (Table 1).

Treatment duration was 8 weeks in 639 (88%), 12 weeks in 78 (11%) and 16 weeks in 6 (1%) patients. Patients treated with 8-week G/P were younger ($p = 0.04$), more frequently females ($p = 0.03$), with milder liver disease ($p < 0.0001$), lower alanine aminotransferase ($p = 0.002$), platelet ($p < 0.0001$) and creatinine ($p = 0.05$) values, and a lower prevalence of co-morbidities ($p < 0.0001$) (Table 2). During treatment, 3 patients died of drug-unrelated causes (*see below*), and 35 (5%) were lost at follow-up; therefore, per protocol (PP) efficacy analysis has been carried out on 685 (95%) patients, treated for 8 (n = 605), 12 (n = 75) and 16 (n = 5) weeks.

Treatment effectiveness

Overall, 502/683 (73%) patients achieved an on-treatment virological response at week 4, independently of treatment duration (8-week *vs.* 12 or 16-week: 75% *vs.* 65%, $p = 1.00$) (Fig. 1). Among them, HCV-RNA was <LLOQ in 175 (26%) and undetectable in 327 (48%). In patients with detectable HCV-RNA, median values were 27 (12–349) IU/ml. A higher baseline HCV-RNA was associated with a lack of week 4 on-treatment response ($p = 0.0002$) (Table 2).

An EOT response was achieved by 675/694 (97%) patients, without differences between patients treated for 8 weeks *vs.* 12 or 16 weeks (97% *vs.* 97%, $p = 1.00$) (Fig. 1). Overall, HCV-RNA was <LLOQ in 105 (15%) and undetectable in 570 (82%) of them. In patients who tested positive at EOT, median HCV-RNA value was 19 (12–43) IU/ml. The achievement of a week 4 on-treatment response was the only factor associated with an EOT response ($p < 0.0001$), whilst no baseline predictors were identified (Table 2).

Overall, an SVR was achieved by 680 patients, with corresponding SVR rates of 94% (95% CI 92%–96%) at intention-to-treat (ITT) and 99.3% (95% CI 98.6%–99.9%) at PP analysis, respectively (Fig. 1). At PP analysis, SVR rates were lower in males (males *vs.* females; 98.5% [95% CI 97.1%–99.8%] *vs.* 100%; $p = 0.027$), but independent of treatment duration (8-week *vs.* 12 or 16-week; 99.2% [95% CI 98.5%–99.9%] *vs.* 100%; $p = 1.00$), HCV genotype (3 *vs.* non-3; 97.1% [95% CI 92.9%–100%] *vs.* 99.5% [95% CI– 98.9%–100%]; p = 0.08), fibrosis stage (F0-F2 *vs.* F3-F4; 99.1% [95% CI 98.3%–99.9%] *vs.* 100%; $p = 1.00$], baseline HCV-RNA (<800,000 IU/ml *vs.* 800,000–6,000,000 IU/ml *vs.* >6,000,000 IU/ml; 99.6% [95% CI: 98.8%–99.9%] *vs.* 99.2% [95% CI: 97.9%–100%] *vs.* 98.4% [95% CI: 94.5%–100%]; $p = 0.55$), body mass index (BMI) (<30 *vs.* ≥30 kg/m^2; 99.1% [95% CI: 98.1%–100%] *vs.* 100%; $p = 1.00$] or CKD stage (1–3 *vs.* 4,5; 99.1% [95% CI 98.3%–99.9%] *vs.* 100%, $p = 1.00$) (Fig. 1, Fig. 2). Moreover, SVR rates were not influenced by centers patients' capability (≥30 *vs.* <30 patients; 99.2% [95% CI 98.3%–99.9%] *vs.* 99.5% [95% CI: 98.6%–100%]; $p = 1.00$) or on-treatment viral kinetics, being similar in patients with or

Table 1. Baseline characteristics of the 723 patients included in the study.

Characteristics	All patients (n = 723)	8-week group (n = 639)	12,16-week group (n = 84[§])	*p* value[**]
Age, years	58 (21–89)	58 (21–89)	60 (32–87)	0.04
Males	361 (50%)	310 (49%)	51 (61%)	0.03
BMI, kg/m^2	24.0 (15.8–39.7)	23.7 (15.8–39.7)	24.6 (17.6–37.0)	0.19
IFN-experienced	106 (15%)	92 (14%)	13 (15%)	0.74
LSM, kPa	6.1 (2.5–43.0)	6.0 (2.5–19.8)	10.9 (2.7–43.0)	<0.0001
Fibrosis				<0.0001
F0–F2	601 (83%)	575 (90%)	26 (31%)	
F3	65 (9%)	59 (9%)	6 (8%)	
F4	57 (8%)	5 (1%)	52 (61%)	
HCV genotype				<0.0001
1[*]	352 (49%)	321 (50%)	31 (37%)	
2	203 (28%)	183 (29%)	20 (24%)	
3	74 (10%)	53 (9%)	21 (25%)	
4	91 (13%)	79 (12%)	12 (14%)	
n.a.	3 (0)	3 (0)	0	
HCV-RNA, IU/ml	1,063,109 (153–38,300,000)	1,055,046 (153–38,300,300)	1,092,837 (3,171–22,800,00)	0.59
ALT, U/L	50 (8–568)	49 (8–568)	63 (9–546)	0.02
PLT, 10^3/mm^3	209 (25–691)	213 (46–691)	178 (25–367)	<0.0001
Albumin, g/dl	4.2 (2.3–5.9)	4.2 (2.3–5.9)	4.0 (2.9–5.7)	0.15
INR	1.0 (0.4–3.2)	1.00 (0.40–3.20)	1.03 (0.90–2.50)	0.71
Creatinine, mg/dl	0.80 (0.46–10.0)	0.80 (0.46–10.0)	0.87 (0.50–9.60)	0.05
CKD stage 4–5	18 (3%)	11 (2%)	7 (8%)	0.004
AH	172 (24%)	139 (22%)	33 (39%)	<0.0001
Diabetes	37 (5%)	23 (4%)	14 (17%)	<0.0001
Co–medications	311 (43%)	256 (40%)	55 (65%)	<0.0001
HIV/HBV	50 (7%)/3 (0.4%)	43 (7%)/3 (0.5%)	7 (8%)/0	0.83/1.00

AH, arterial hypertension; ALT, alanine aminotransferase; BMI, body mass index; CKD, chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; INR, international normalized ratio; LSM, liver stiffness measurement; n.a., not available; nc, not classified; PLT, platelets 46). Categorical variables were reported as frequencies (percentages) and continuous variables as median (range). Categorical variables were compared using the χ^2 or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U*- test or the Kruskal-Wallis test, when appropriate.
[*]HCV genotype: 1b 233 (32%), 1a 113 (16%), 1nc 6 (1%).[§]6 patients underwent 16-week G/P.[**]8 weeks *vs.* 12 or 16 weeks.

Table 2. Factors associated with week 4 and EOT virological responses.

	Week 4 response (n = 502)	Non-week 4 response (n = 181)	*p* value	EOT response (n = 675)	Non-EOT response (n = 19)	*p* value
Age, years	58 (18–89)	58 (21–87)	0.37	58 (18–89)	59 (34–87)	0.72
Males	260 (52%)	85 (47%)	0.29	336 (50%)	8 (42%)	0.64
BMI, kg/m^2	24.0 (17.3–38.9)	23.5 (16.8–39.7)	0.49	24.0 (16.8–39.7)	23.1 (18.7–26.9)	0.20
IFN-experienced	67 (13%)	35 (19%)	0.07	97 (14%)	4 (21%)	0.50
LSM, kPa	6.1 (2.8–43.0)	5.8 (2.5–27.0)	0.16	6.1 (2.8–43.0)	5.7 (4.1–9.7)	0.97
Fibrosis			0.19			0.74
F0–F2	423 (84%)	149 (82%)		557 (83%)	19 (100%)	
F3	46 (9%)	13 (7%)		64 (10%)	0	
F4	33 (7%)	19 (11%)		51 (7%)	0	
HCV genotype*			<0.0001			0.62
1	247 (49%)#	87 (48%)°		326 (49%)§	11 (58%)^	
2	152 (30%)	38 (21%)		191 (28%)	4 (21%)	
3	52 (11%)	15 (8%)		66 (10%)	0	
4	48 (10%)	41 (23%)		86 (13%)	4 (21%)	
HCV-RNA, IU/ml	879,655 (324–22,800,000)	1,076,727 (5,726–38,300,000)	<0.0001	1,076,727 (153–38,300,000)	684,870 (43,445–8,730,379)	0.86
ALT, U/L	45 (29–76)	54 (9–215)	0.56	50 (8–568)	40 (23–201)	0.50
PLT, 10^3/mm^3	209 (25–333)	207 (60–812)	0.46	207 (25–812)	208 (151–262)	0.81
Albumin, g/dl	4.2 (2.3–5.2)	4.3 (2.9–5.2)	0.55	4.2 (2.3–5.9)	4.3 (3.7–4.7)	0.90
INR	1.00 (0.40–3.16)	1.00 (0.80–2.46)	0.84	1.00 (0.40–3.16)	0.98 (0.88–1.50)	0.07
Creatinine, mg/dl	0.82 (0.46–10.00)	0.80 (0.49–8.60)	0.35	0.80 (0.46–9.60)	0.91 (0.59–4.99)	0.37
CKD stage 4–5	14 (3%)	4 (2%)	0.79	17 (3%)	1 (5%)	0.40
AH	114 (23%)	43 (25%)	0.84	158 (24%)	7 (37%)	0.18
Diabetes	23 (5%)	10 (6%)	0.69	33 (5%)	1 (5%)	1.00
Co–medications	211 (42%)	81 (85%)	0.54	291 (43%)	9 (47%)	0.82
HIV	35 (8%)	11 (6%)	0.73	48 (7%)	2 (11%)	0.64
Treatment duration			0.15			1.00
8-week	451 (89%)	154 (85%)		600 (89%)	17 (89%)	
12-week	48 (10%)	24 (13%)		70 (10%)	2 (11%)	
16-week	3 (1%)	3 (2%)		5 (1%)	0	
Week-4 response	–	–	–	489 (72%)	0	<0.0001

AH, arterial hypertension; ALT, alanine aminotransferase; BMI, body mass index; CKD, chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; INR, international normalized ratio; LSM, liver stiffness measurement; n.a., not available; PLT, platelets.
Categorical variables were reported as frequencies (percentages) and continuous variables as median (range). Categorical variables were compared using the χ^2 or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U*- test or the Kruskal-Wallis test, when appropriate.
*HCV genotype available in 681 (99.7%) patients with week 4 response assessment and in 691 (99.6%) patients with EOT assessment. #1a in 76, 1b in 168, nc in 3. °1a in 31, 1b in 54, nc in 2. §1a in 101, 1b in 222, nc in 5. ^1a in 7, 1b in 4.

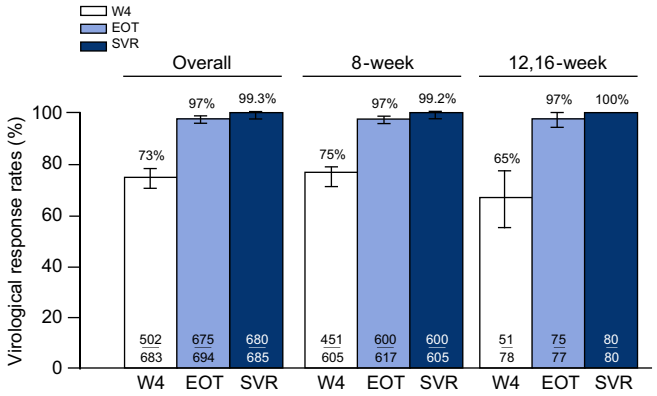

Fig. 1. Rates of virological response with G/P treatment. Rates of on-treatment (week 4 and EOT) and off-treatment (SVR) virological response overall, and according to G/P treatment schedule (PP analysis). Note: values are expressed as frequencies (%) and the 95% CI has been calculated. Categorical variables have been compared using the χ^2 or the Fisher's exact tests. EOT, end of treatment; G/P, glecaprevir/pibrentasvir; PP, per protocol; SVR, sustained virological response.

without a virological response at both week 4 (yes *vs.* no; 99.2% [95% CI 98.3%–99.9%] *vs.* 99.4% [95% CI 98.3%–100%]; $p = 1.00$) and EOT [yes *vs.* no: 99.2% [95% CI 98.6%–99.9%] *vs.* 100%; $p = 1.00$) (Fig. 2). In patients treated with 8-weeks of G/P, both male gender (p = 0.022) and infection with HCV genotype 3 (p = 0.046) were independent predictors of treatment failure (Fig. 3, Table 3).

Overall, 5 (0.7%) patients had a virological relapse, 1 at week 4 and at week 12 of follow-up; 1 patient who did not attend the week 4 post-treatment visit tested positive 12 weeks after treatment completion (Table 4). They were all males, non-cirrhotic, treatment-naïve, infected with genotype 2 (3 patients) or 3 (2 patients) and without co-morbidities. In all cases, HCV genotype was retested at the time of relapse, and did not differ from that assessed before treatment. Resistance-associated substitutions (RASs) were found at the time of virological relapse in the patient infected with HCV genotype 3 (Y93H and L31I), but not in those infected with HCV genotype 2.

Compliance to G/P label

Overall, compliance to the G/P label was excellent across all centers. Only 10 (1.4%) patients were undertreated, being treated for only 8 weeks despite the presence of cirrhosis (2 genotype 1a, 2 genotype 2, 1 genotype 4) or previous failure of a genotype 3 infection (4 F1, 1 F3). Nine of them achieved an SVR, with 1 F4 patient lost to follow-up, after the EOT.

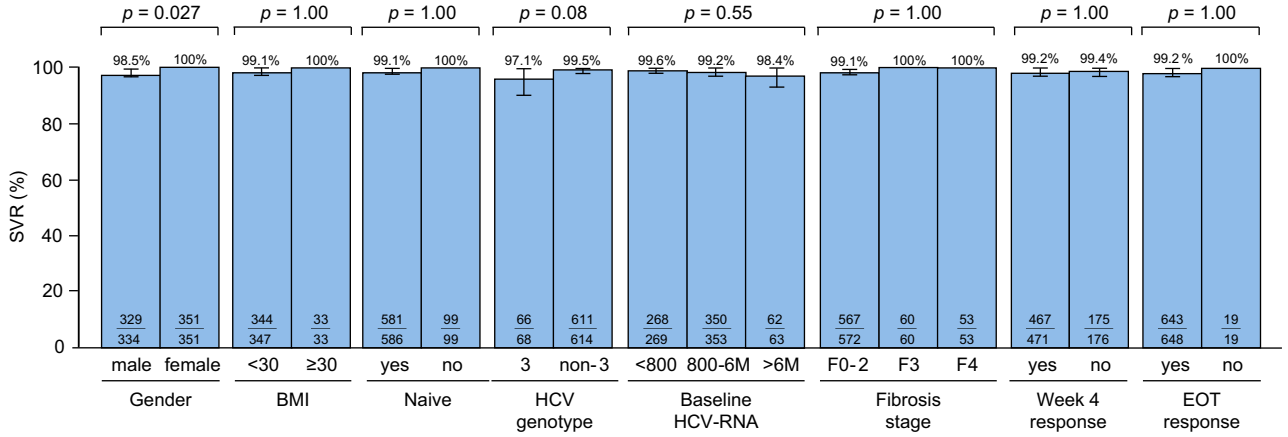

Fig. 2. Rates of SVR according to the most important features in 685 patients with HCV treated with any duration of G/P (PP analysis). Note: values are expressed as frequencies (%) and the 95% CI has been calculated. Categorical variables have been compared using the χ^2 or the Fisher's exact tests. G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; PP, per protocol; SVR, sustained virological response.

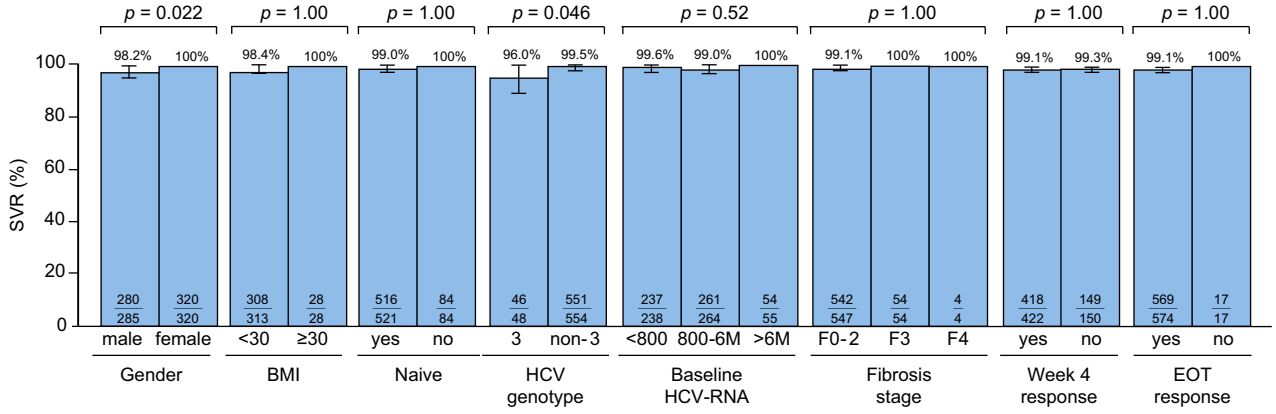

Fig. 3. Rates of SVR according to the most important features in 600 patients with HCV treated with 8-week G/P (PP analysis). Note: values are expressed as frequencies (%) and the 95% CI has been calculated. Categorical variables have been compared using the χ^2 or the Fisher's exact tests. G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; PP, per protocol; SVR, sustained virological response.

Thirty-one (4.3%) patients underwent longer than recommended treatment. Thirty (4.2%) non-cirrhotic patients were treated for 12 weeks. Fibrosis stage was F0 in 3 patients, F1 in 13, F2 in 8 and F3 in 6; all F3 patients had an LSM below 12 kPa and normal platelet count. Among those patients there were 7 genotype 3, non-cirrhotic (F1 in 1, F2 in 5 and F3 in 1), treatment-naïve patients. All these patients achieved an SVR. In addition, G/P was successfully administered for 16 weeks to a single naïve cirrhotic patient with genotype 3 infection, who had developed both hepatocellular carcinoma and variceal bleeding prior to DAA start.

Safety and tolerability

Sixty (8.3%) patients reported at least 1 adverse event, which was considered by physicians to be treatment-related. Among them, pruritus (2.5%), fatigue (2%), nausea (1.5%) and headache (1.0%) were the most frequently reported. Four (0.5%) patients had to discontinue G/P due to an AE (nausea in 2, pruritus in 1 and jaundice [total bilirubin 12 mg/dl] in 1): all of them were infected with genotype 2 and 3 of them were cirrhotic. Median time to discontinuation was 8 (5–8) weeks, despite that, all achieved an SVR. The single patient who prematurely withdrew antiviral therapy at week-8 (*vs.* week-12) due to poor adherence, also achieved an SVR. Three (0.4%) patients (F4 in 2, F1 in 1) died due to treatment unrelated causes (cerebral stroke, septic shock and disseminated intravascular coagulation) before the EOT (Table 5).

Discussion

This is the first real-world study demonstrating excellent SVR rates in a large real-world cohort of patients with HCV treated with G/P for 8 to 16 weeks. So far, only data from registration trials were available, reporting SVR rates ≥95% in selected HCV-infected patients treated with the G/P combination.[4–10] Indeed, after G/P EMA approval in July 2017, Italy was among the first countries in Europe to have G/P commercially available for the treatment of chronic HCV infection.

In our study, 723 patients were consecutively treated with G/P in 32 centers in Lombardy, and mostly underwent the shorter 8-week treatment duration. As per drug label, and according to international recommendations,[2] 8-week G/P is indicated for the treatment of any non-cirrhotic patients without genotype 3 infection, and for treatment-naïve non-cirrhotic genotype 3 patients. Therefore, the large number of patients treated with the shorter G/P duration in our cohort was not unexpected,

Table 3. Per protocol analysis of clinical factors associated with an SVR following 8-week G/P.

	SVR (n = 600)	Non-SVR (n = 5)	*p* value
Age, years	58 (18–89)	56 (27–72)	0.53
Age >65 years	206 (34)	2 (60%)	1.00
Males	280 (47%)	5 (100%)	0.02
BMI*, kg/m^2	23.7 (15.8–39.7)	24.7 (23.4–25.9)	0.41
BMI* >30 kg/m^2	28 (5%)	0	1.00
IFN-experienced	84 (14%)	0	1.00
LSM, kPa	5.9 (2.5–19.8)	6.3 (4.6–9.6)	0.99
Fibrosis Stage			
F3	54 (9%)	0	1.00
F3–F4	4 (0.6%)	0	1.00
HCV genotype**			0.02
1	307 (51%)	0	
2	173 (29%)	3 (60%)	
3	46 (8%)	2 (40%)	
4	71 (12%)	0	
HCV genotype 3	46 (8%)	2 (40%)	0.047
HCV-RNA***, IU/ml	1,077,364 (153–38,300,000)	3,600,000 (193,662–8,722,885)	0.18
Baseline HCV-RNA***, IU/ml			
≥800,000	315 (57%)	4 (80%)	0.40
≥6,000,000	54 (10%)	1 (20%)	0.41
ALT, U/L	49 (8–568)	39 (17–188)	0.94
PLT, 10^3/mm^3	214 (46–812)	196 (127–349)	0.37
Albumin, g/dl	4.3 (2.7–5.9)	4.3 (4.1–4.5)	0.72
INR	1.00 (0.40–3.16)	1.00 (1.00–1.20)	0.28
Creatinine, mg/dl	0.80 (0.46–8.60)	0.98 (0.70–1.20)	0.24
eGFR**** ml/min/1.73 m^2	83 (4–221)	84 (60–119)	0.82
CKD**** stage			
<60 ml/min/1.73 m^2	58 (12%)	0	1.00
<30 ml/min/1.73 m^2	10 (2%)	0	1.00
AH °	135 (43%)	0	0.08
Diabetes	22 (7%)	0	1.00
Concomitant medications°°°	247 (56%)	0	0.02
Detectable HCV-RNA			
Week 4 §	149 (26%)	1 (20%)	1.00
EOT§§	17 (3%)	0	1.00

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EOT, end of treatment; HCV, hepatitis C virus; IFN, interferon; INR, international normalized ratio; LSM, liver stiffness measurement; PLT, platelets; SVR, sustained virological response.
Numbers are expressed as n (%).
Categorical variables were reported as frequencies (percentages) and continuous variables as median (range). Categorical variables were compared using the χ^2 or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U*- test or the Kruskal-Wallis test, when appropriate.
*BMI available in 341; **HCV genotype available in 602; ***HCV-RNA available in 557; ****eGFR/CKD available in 497; °AH data available in 132; °°Diabetes data available in 313. °°°Concomitant medication data available in 443; §Week 4 assessment available in 567; §§EOT assessment available in 586.

since in Italy the majority of cirrhotics had already been treated during the first period after DAA approval (December 2014), as defined by former AIFA reimbursement rules.[15] Not surprisingly, demographic and clinical features of those patients significantly differed from those displayed by patients undergoing longer treatment duration. In fact, the former displayed features commonly associated with milder stages of fibrosis, such as younger age, low prevalence of genotype 3 infection as well as of other co-morbidities. Not unexpectedly, they were quite similar to those showed by patients included in registration trials according to HCV genotype.

In our cohort, we obtained overall excellent SVR rates (99.3%) across all genotypes, since only 5 patients (3 genotype 2 and 2 genotype 3) failed to achieve viral eradication because of post-treatment virological relapse. These high SVR rates are in line with those reported in registration trials, ranging between 95% and 100%.[4–10] In contrast to the data reported in registration trials, we observed lower SVR rates among males, both in the overall population ($p = 0.027$) and in the 8-week treatment group ($p = 0.022$). Not surprisingly, in this latter subgroup of patients, genotype 3 was associated with the lowest chances (96%) of achieving an SVR ($p = 0.046$), whilst the other genotypes did not impact on treatment outcome. Whether these results reflect the lower effectiveness of G/P in these specific subgroups of patients requires further investigation, due to the overall very high SVR rates obtained in our study. Meanwhile, our results mirror those reported in trials including non-cirrhotic patients treated for 8 weeks, where at PP analysis this treatment schedule led to SVR rates of 100% in genotype 1 and 4,[7,9] 96.2% in genotype 2[9] and 96.2% in naïve genotype 3[7] patients. Also, in these studies relapses accounted for most of the treatment failures observed among genotype 2 and 3 patients. However, unlike what we observed in our study, all those patients had failed a previous course of antiviral therapy, displayed high baseline viral load (≥6 $\log_{10}$) as well as RAS emergence at failure assessment. In our study, the 5 patients who failed G/P did not show any of the clinical features usually associated with a poor treatment outcome, which was surprising, and adherence was not an issue. An emergent NS5A-associated RAS (L31I) was detected in only 1 case. However, it has never been associated with failure on G/P treatment or other DAA regimens.

Table 4. Clinical and virological characteristics of patients with post-treatment relapse.

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Age, years	69	72	51	56	27
Gender	male	male	male	male	male
BMI, kg/m^2	25.0	23.4	23.6	25.9	24.7
HCV genotype	2	2	3a	3	2c
HBV/HIV co–infection	no	no	no	no	no
LSM, kPa	6.4	6.3	4.6	9.6	4.8
eGFR, ml/min/mm^3	60	75	119	100	84
Treatment history	naive	naive	naive	naive	naïve
G/P duration, weeks	8	8	8	8	8
Adherence	excellent	excellent	excellent	excellent	probably suboptimal
HCV-RNA, IU/ml					
Baseline	8,722,885	1,310,660	193,662	3,600,000	4,730,000
Week 4	<12	undetected	undetected	undetected	17
EOT	undetected	undetected	undetected	undetected	<12
SVR4	<12	n.a.	237,605	undetected	<12
SVR12	773,839	1,259,750	297,879	24,500,000	862,650
RAS					
NS3 variants					
Baseline	n.a.	n.a.	none	n.a.	n.a.
At relapse	none	none	none	none	none
NS5A variants					
Baseline	n.a.	n.a.	Y93H	n.a.	n.a.
At relapse	none	none	Y93H, L31I	none	none

BMI, body mass index; eGFR: estimated glomerular filtration rate; G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; LSM, liver stiffness measurement; n.a., not available; RAS, resistance-associated substitutions; NS, non-structural.

Table 5. Prevalence of AE according to G/P treatment schedule.

Adverse Events	8 week (n = 639)	12 weeks (n = 84)
Patients with any AEs	46 (7%)	14 (17%)
AEs		
Fatigue	12 (2%)	2 (<0.5%)
Nausea	8 (1%)	3 (4%)
Pruritus	7 (1%)	6 (7%)
Headache	6 (1%)	1 (1%)
Insomnia	4 (0.5%)	1 (1%)
Vomiting	1 (<0.5%)	1 (1%)
Hypertensive crisis*	3 (<0.5%)	0
Depression	2 (<0.5%)	0
Jaundice	0	1 (1%)
AEs leading to G/P discontinuation**	1 (<0.5%)	3 (3.5%)
Deaths***	1 (<0.5%)	2 (2.4%)

AEs, adverse events; DIC, disseminated intravascular coagulation; G/P, glecaprevir/pibrentasvir.
Categorical variables were reported as frequencies (percentages) and were compared using the χ^2 or the Fisher's exact tests.
*Both patients with poorly controlled arterial hypertension at baseline. **Nausea (n = 2), pruritus (n = 1), jaundice (n = 1). ***DIC, cerebral stroke, septic shock (not drug-related). No patients in the 16-week group reported any AE. Values are expressed as n (%).

In our study, only a restricted subgroup of patients underwent 12 or 16 weeks of G/P, with overall SVR rates of 100%. Again, these data are in line with those reported in phase III trials. In fact, in the EXPEDITION-1 study, all cirrhotics but 1 with HCV genotype 1a achieved an SVR.[10] Also, in the Surveyor-II (part 3) study, G/P administered for 12 weeks to naïve genotype 3 cirrhotics led to 100% SVR rates at PP analysis.[8] In the same study, genotype 3 patients who had previously failed on the combination of pegylated-interferon ± ribavirin ± sofosbuvir achieved SVR rates of 95% (non-cirrhotics) and 96% (cirrhotics) when treated with 16 weeks of G/P.[8]

Interestingly, even in the relatively limited subgroup of patients carrying clinical features usually associated with lower chances of achieving an SVR (*i.e.* infection with genotype 1a and 3 with advanced fibrosis, high HCV-RNA, high BMI) G/P treatment resulted in optimal effectiveness.

We found that SVR rates were independent of either baseline HCV viral load or on-treatment viral kinetics in all treatment duration groups. Indeed, although in our study baseline viral load influenced on-treatment viral kinetics (*i.e.* high on-treatment week 4 responses in low baseline HCV-RNA and high EOT rates in patients with faster viremia decline), we found that SVR rates were independent of these parameters. Unexpectedly, some patients (2.5%) were still viremic at the time of EOT assessment, independently of baseline HCV-RNA ($p = 0.86$) and treatment duration ($p = 1.00$). Interestingly, all of them achieved an SVR. Similar results were observed in the larger subgroup of patients (15%) where HCV-RNA was detected but <LLOQ. This is in line with what emerged from a recently presented pooled analysis of phase II and III clinical studies, including non-cirrhotic patients treated with 8-week G/P, which reported 100% SVR rates among 36/942 (4%) patients with HCV-RNA LLOQ at treatment week 4.[16] Similarly, no baseline clinical factors emerged as predictors of treatment failure from a recent integrated efficacy analysis of 2,041 patients with genotype 1–6 infections without cirrhosis treated for either 8 or 12 weeks with G/P.[11]

In our study compliance to G/P label was very high across all network centers. In particular, the rate of under-treatment was very low (1.4%), and all patients treated with an off-label shortened treatment duration achieved an SVR at PP analysis. Moreover, the additional 4 patients who prematurely discontinued G/P for tolerability or safety reasons remained HCV-RNA undetectable after treatment withdrawal. Meanwhile, patients over-treated for up to 12 or 16 weeks eventually achieved an SVR. As expected based on the real-world setting and multicenter design of the study, some patients were lost to follow-up. However, they accounted for a very limited subgroup of patients and data lost did not significantly modify study results.

Although safety was not the primary endpoint of this study, since safety data collection was not among the main objectives of the NAVIGATORE-Lombardia web-based platform, we were able to obtain some meaningful information. Indeed, in our real-world study, the rates of AE were extremely low, and most of them were of mild intensity, with safety and tolerability profiles quite similar to those reported in registration trials.[11] The most frequently reported events were fatigue, nausea and pruritus, without differences between treatment durations. Four patients reported moderate to severe AEs (pruritus, nausea and jaundice) which finally led to G/P discontinuation, and 1 poorly compliant patient prematurely discontinued antiviral treatment. No treatment-related deaths were observed.

We acknowledge that our study suffers from some limitation strictly related to its real-world design. First of all, some clinical information might have been under-reported. Indeed, the prevalence of co-morbidities, co-medications and mild AEs, for example, have been likely underestimated if compared with the available national epidemiological data.[17,18] However, we strongly believe that all severe AEs (either related or not to G/P administration) have been carefully recorded by the treating centers. Secondly, despite the real-world setting, in our study the number of F3 patients was quite limited, since they had been mostly treated during the first months after DAA approval, as well as cirrhotics, according to former AIFA reimbursement rules.[15] Similarly, on-treatment viral kinetic data are not available for all patients included in the study, due to changes in mandatory on-treatment testing required by AIFA. Lastly, patients' loss at follow-up is not unexpected in a real-world setting, however their very limited number should not significantly affect our study conclusions. We rather believe that these intrinsic limitations are fully counterbalanced by some peculiar strengths of the study: indeed, the strict AIFA reimbursement criteria have generally granted for a homogeneous characterization of HCV patients eligible for antiviral treatment, thus limiting the interpretation bias related to the multicenter design of the study. Moreover, all patients had been consecutively enrolled in the NAVIGATORE-Lombardia web-based platform, thus further limiting any other selection bias. Finally, although we occasionally faced a few deviations from G/P label and international recommendations this aspect further reinforces our study results, with particular reference to G/P antiviral potency.

In conclusion, we demonstrated for the first time the excellent effectiveness and safety of the G/P combination in a large cohort of patients with HCV treated in an Italian real-world setting.

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Conflict of interest

Roberta D'Ambrosio: Speaker: AbbVie, Gilead, MSD; Advisory Board: AbbVie, Gilead; Research Grants: Gilead; Luisa Pasulo: Advisory Board: AbbVie; Massimo Puoti: Speaker's bureau and Advisory: AbbVie, BMS, Boehringer Ingelheim, Janssen, Gilead, MSD, Roche; Reasearch Grant: Gilead, MSD; Maria Vinci: Advisory Board: AbbVie; Grant: AbbVie; Alessandro Soria: Consultation fees: AbbVie; Alessio Michele Aghemo: Speaker's bureau and Advisory: AbbVie, Gilead, Janssen, MSD; Maria Grazia Rumi: Speaker: AbbVie, Gilead, MSD; Advisory Board: AbbVie; Lorenzo Morini: Speaker: AbbVie; Alessia Giorgini: Speaker: AbbVie, MSD, Gilead; Advisory Board: AbbVie; Paolo Del Poggio: Speaker: MSD; Caterina Uberti-Foppa: Consultation fees: AbbVie, MSD; Paolo Bonfanti: Speaker: MSD, Gilead; Advisory Board MSD, Gilead; Natalia Terreni: Advisory Board: AbbVie; Andrea Gori: Consultation fees, Speaker's bureau, Research Grants: AbbVie, Astellas, BMS, Boehringer Ingelheim, Gilead, Janssen, MSD, Novartis, Pfizer, Roche, Viiv; Pietro Lampertico: Speaker's bureau and Advisory: AbbVie, BMS, Gilead, GSK, Janssen, MSD, Roche; Stefano Fagiuoli: Speaker's bureau and Advisory for AbbVie, Bayer, Gilead, MSD, Kedrion, Novartis. All other authors have nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

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The NAVIGATORE-Lombardia Network – Appendix

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.11.011.

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