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ORIGINAL ARTICLE

Glecaprevir/Pibrentasvir is safe and effective in Italian patients with chronic hepatitis C aged 75 years or older: A multicentre study

Nicola Pugliese[1,2] | Vincenza Calvaruso[3] | Mario Masarone[4] | Roberta D'Ambrosio[5] | Sara Battistella[6,7] | Anna Licata[8] | Marcello Persico[4] | Maria Paola Anolli[5] | Marco Distefano[9] | Salvatore Petta[3] | Francesco Paolo Russo[6,7] | Vito Di Marco[3] | Alessio Aghemo[1,2]

[1]Division of Internal Medicine and Hepatology, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Rozzano, Italy

[2]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

[3]Section of Gastroenterology and Hepatology, PROMISE, University of Palermo, Palermo, Italy

[4]Internal Medicine and Hepatology Unit, Department of Medicine, Surgery and Dentistry, "Scuola Medica Salernitana", University of Salerno, Salerno, Italy

[5]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[6]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy

[7]Gastroenterology and Multivisceral Transplant Unit, Azienda Ospedale-Università di Padova, Padua, Italy

[8]Internal Medicine Unit, Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy

[9]UOC Malattie Infettive, Ospedale Umberto I di Siracusa, ASP Siracusa, Siracusa, Italy

Correspondence
Alessio Aghemo, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy.
Email: alessio.aghemo@hunimed.eu

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Abstract

Background: Glecaprevir and Pibrentasvir (G/P) determine high rates of sustained virological response (SVR) with optimal safety profile in patients with chronic hepatitis C virus (HCV) infection. The efficacy and safety of G/P in Caucasian patients aged 75 years and older have not been widely analysed.

Methods: This is a retrospective multicentre real-world study enrolling all consecutive patients 75 years and older who received G/P between October 2017 and January 2022 at five referral centres in Italy. SVR was analysed by intention-to-treat (ITT) and per-protocol analyses (PP).

Results: A total of 570 patients met the inclusion criteria and were analysed: mean age was 80 (75–97) years, 356 (62%) were females, 52% (298/570) had HCV-1, 44% (252/570) had HCV-2 and 137 (24%) patients had liver cirrhosis. Four hundred and sixty-three (81%) patients were taking at least one concomitant drug, with 144 (25%) taking ≥5 concomitant drugs. G/P was given for 8 weeks in 488 patients (86%). During treatment, 48 patients (8%) reported side effects, with 10 (2%) patients discontinuing treatment prematurely. Two patients developed treatment-unrelated serious adverse events. Overall, the SVR rate was 97.9% (558/570) by ITT analysis and 99.6% (558/560) by PP analysis. SVR rates remained consistently high among subgroup analysis stratified by genotype, treatment duration, fibrosis stage and concomitant medications.

Conclusions: Treatment with G/P achieved 97.9% SVR rates in HCV patients older than 75 years of age. Safety was optimal with only 2% of patients discontinuing early.

KEYWORDS
antiviral therapy, drug–drug interactions, elderly, G/P, Glecaprevir, HCV, Pibrentasvir, tolerability, viral hepatitis

1 | INTRODUCTION

Chronic infection with hepatitis C virus (HCV) affects nearly 57 million people worldwide and is among the leading causes of liver-related mortality, hepatocellular carcinoma (HCC) and liver transplantation.[1] HCV epidemiology is heterogenous worldwide with the virus spreading to the general population mainly through wide use of unsafe blood and medical products until 1990 and intravenous substance abuse starting from the 1970s.[2] Some countries such as Japan and Southern Europe have been mainly impacted by HCV transmission through parenteral procedures before 1990, while others such as the US, Northern Europe and Australia attribute most cases of HCV to intravenous substance use.[3] This translates to the former group of countries being mostly characterized by HCV patients older than 65 years of age with a decreasing HCV incidence and prevalence, while the latter group of countries is characterized by younger HCV patients and increasing rates of HCV-related complications.[4] HCV elimination has been made possible by the introduction of effective and safe directly acting antiviral agents (DAAs) that allow high rates of sustained virological response (SVR) and have little to no contraindications to treatment.[1,4–6] DAAs are safe and effective independently from HCV genotype, age, disease severity and concomitant comorbidities. Pangenotypic regimens such as Sofosbuvir/Velpatasvir (SOF/VEL) and Glecaprevir/Pibrentasvir (G/P) are at the core of the European association for the study of the Liver guidelines (EASL) as they have well-standardized treatment schedules, do not require treatment monitoring and have few well-characterized drug-drug interactions (DDIs).[7,8] The combination of G/P includes a protease inhibitor, a drug class which is contraindicated in patients with decompensated disease, has more DDIs than other DAA classes and is perceived by most clinicians as being slightly more difficult to manage in fragile/complex patients.[9] For this reason, the efficacy and safety of G/P in elderly patients have been reported in relatively small studies coming mostly from referral centres in Asia.[10–12] A recent real-life study from Italy in HCV patients >80 years of age found that G/P achieved SVR rates of 100% with no significant side effects; however, G/P was given only to 25% of the total cohort of patients, with most patients receiving SOF-based regimens.[13] With the aim to describe the efficacy and the safety of G/P in HCV patients aged >75 years, we designed a retrospective multicentre study enrolling all consecutive HCV patients who received treatment from 2017 to 2022 in five referral liver centres in Italy.

Lay Summary

In order to achieve HCV elimination, treatment of special populations appears to be essential. Access to antiviral therapy for elderly patients should be ensured after appropriate evaluation. Glecaprevir/Pibrentasvir is a safe and effective option in this group of patients.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a multicentre, retrospective, observational cohort study including all HCV patients aged ≥75 years who received interferon (IFN)-free combination treatment with G/P between October 2017 and January 2022 in five Hepatology Units located in Italy. HCV infection was defined by positive serum antibody to HCV and detectable HCV-RNA by commercial quantitative PCR tests.

Before starting treatment, AST to Platelet Ratio Index (APRI) and Charlson Comorbidity Index (CCI) were calculated for each patient. Moreover, all patients underwent vibration-controlled transient elastography (VCTE) by Fibroscan, manufactured by Echosens. VCTE was performed by expert physicians following the manufacturer's guidelines. A success rate higher than 70% was achieved for all patients included in the study. Different probes were used according to the patient's BMI: patients with a BMI <30 kg/m^2 were evaluated with M probe, while patients with a BMI >30 kg/m^2 were evaluated with XL probe.

Clinical evidence of cirrhosis was defined by a liver stiffness measurement (LSM) ≥12.5 kPa as measured by VCTE and/or by the presence of at least one feature among laboratory signs of portal hypertension (platelet count <150 × 10^3/μL), endoscopic evidence of oesophageal/gastric varices and/or portal hypertensive gastropathy and/or ultrasound evidence of irregular hepatic edge, liver surface nodularity, dilated portal vein and/or splenomegaly.

LSM values equal to or higher than 25 kPa associated with a platelet count <150 × 10^3/μL were selected to identify patients with clinically significant portal hypertension.[14]

The study was carried out in accordance with the principles of the Helsinki Declaration, and with local and national laws. Approval was obtained from the hospital's Internal Review Boards and their Ethics Committees and written informed consent for the study was obtained from all patients.

2.2 | Treatment

G/P was given for 8–12 weeks following both EASL and AISF treatment recommendations.[7,15] Patients were followed up every 4 weeks during treatment to monitor side effects, to assess adherence and to dispense G/P, and every 12 weeks after treatment completion, to assess SVR.

2.3 | Safety monitoring and efficacy

Serum biochemical tests including HCV-RNA levels, liver function tests and haematological tests were performed according to standard methods and collected at baseline and at week 12 of follow-up.

Co-administered medications were examined and DDI with G/P was verified by consulting the Liverpool Interaction Checker at https://www.hep-druginteractions.org.[16]

Safety data were recorded during treatment. Changes in chronic medications, severe adverse events (SAEs), adverse events (AEs) and adherence were also collected. The primary measure of efficacy was SVR defined as negative HCV-RNA at 12 weeks after treatment completion (SVR12).

2.4 | Statistical analysis

We performed a descriptive analysis for all variables. We reported continuous variables using means ± standard deviations or median (range). For categorical variables, we report the percentage. We performed correlation analyses (Chi-squared test, Pearson coefficient) to establish relations between the SVR and clinical, laboratory and demographic factors. A p-value <0.05 was considered statistically significant.

SVR was assessed as patients who achieved SVR12 on an intention-to-treat (ITT) analysis and on a per-protocol (PP) analysis (i.e. excluding patients who were lost to follow-up or discontinued treatment).

3 | RESULTS

3.1 | Characteristics of patients

This study included 570 patients who consecutively received G/P. Table 1 shows the characteristics of the entire cohort enrolled in this study. Median age was 80 (range 75–97) years and the majority of patients were female (62%). Sixty-nine patients (12%) were treatment experienced to IFN-based therapies; no patient was previously treated with DAAs. HCV genotypes 1 (52%) and 2 (44%) were the most commonly found, with only six patients having HCV genotype 3. Compensated cirrhosis at baseline was diagnosed in 137 (24%) patients. Treatment duration with G/P was 8 weeks in 488 patients (86%) and 12 weeks in the remaining 14% of cases. Among patients with liver cirrhosis, treatment duration with G/P was 8 weeks in 89 patients (65%).

Concomitant comorbidities were common, with only 58 patients (10%) reporting no comorbidities at baseline, while 330 (58%) had ≤2 and 182 (32%) reported ≥3 comorbid conditions. The most frequently represented were arterial hypertension (68%), diabetes mellitus (17%), cardiovascular or cerebrovascular major disease (17%) and obesity (10%). The CCI was >5 in 380 patients (67%). Two patients had primary biliary cholangitis, while no patient had HBV or HIV coinfection.

Concomitant drugs at baseline were common in our cohort with 463 patients (81%) taking at least one medication and 144 (25%) taking ≥5 concomitant drugs (Figure 1). The most common drugs were antihypertensive drugs (54.9%), proton pump inhibitors (29.1%) and statins (9%).

TABLE 1 Characteristics of 570 patients enrolled in the present study.

Characteristics	$n = 570$
Age, mean (range)	80 (75–97)
Females, *n* (%)	356 (62)
Genotype, *n* (%)	
GT 1a/1b	298 (52)
GT 2	252 (44)
GT 3	6 (1)
GT 4/5/6	14 (3)
Platelet count, *n* (%)	
<150 000/mm^3	109 (19%)
>150 000/mm^3	461 (81%)
APRI score, *n* (%)	
<0.5	242 (42)
0.5–1.5	290 (51)
>1.5	38 (7)
Liver cirrhosis, *n* (%)	137 (24)
Treatment duration, *n* (%)	
8 weeks	488 (86)
12 weeks	82 (14)
Comorbidities, *n* (%)	
No comorbidities	58 (10)
≤2 comorbidities	330 (58)
≥3 comorbidities	182 (32)
Concomitant drugs, *n* (%)	
≥1 drug	463 (81)
≥5 drugs	144 (25)
Charlson Comorbidity Index	
≤5	190 (33)
>5	380 (67)

Abbreviation: APRI, AST to Platelet Ratio Index.

Overall, 41 patients (7%) had to modify their concomitant medications due to significant DDIs with G/P treatment. The drug classes most often involved in potential interactions were statins (17 patients), anticoagulants (12 patients) and anti-arrhythmic (6 patients).

3.2 | Treatment safety and adherence

In total, 48 (8%) patients experienced treatment-related AEs. Pruritus, headache and fatigue were the most commonly reported AEs. In total, 10 (2%) patients discontinued prematurely G/P treatment for side effects. In eight patients (2%), G/P treatment was discontinued prematurely due to AEs including pruritus (four patients), vomiting (three patients) and headache (one patient). In two patients, antiviral therapy was stopped due to treatment-unrelated SAEs: one patient had a car accident and the other one had an acute myocardial infarction (Table 2).

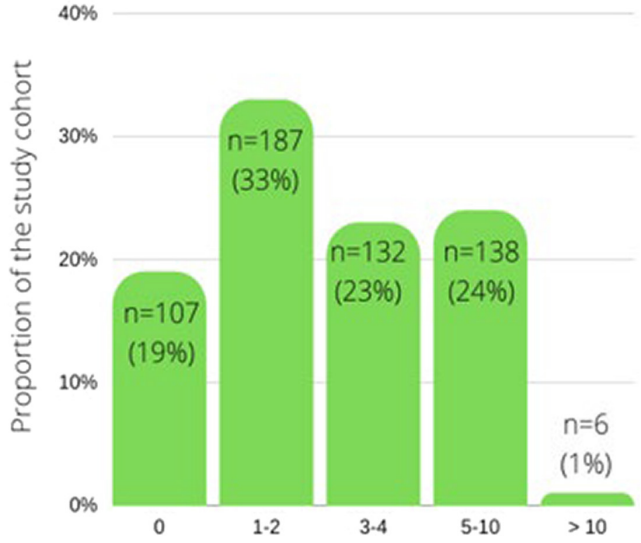

FIGURE 1 Number of concomitant drugs.

TABLE 2 Adverse events (AEs).

Patients with AEs	
Any AE, *n* (%)	48 (8)
Serious AEs, *n* (%)	2 (0.3)
AE leading to discontinuation of G/P, *n* (%)	8 (1.4)
Any drug-related serious AEs, *n*	0
Common AEs	
Pruritus, *n* (%)	21 (3.7)
Fatigue, *n* (%)	18 (3.1)
Headache, *n* (%)	5 (0.9)
Other	4 (0.7)

Considering the patients who experienced AEs, 22 (45%) were taking more than five concomitant drugs and eight (16.6%) were found to have at least three comorbidities. Only four of them were cirrhotic.

4 | VIROLOGICAL RESPONSE TO GLECAPREVIR AND PIBRENTASVIR TREATMENT

Treatment efficacy was analysed by ITT and PP analyses. ITT analysis included all patients who started G/P treatment and considered as treatment failures those who discontinued treatment prematurely ($n = 570$ patients; ITT). PP analysis included only patients who completed G/P treatment ($n = 560$; PP) (Figure 2).

The overall SVR12 rate was 97.9% (558/570) and 99.6% (558/560) in the ITT and PP analysis respectively. By ITT, SVR12 rates in patients with HCV genotypes 1, 2 and 3 were 98.3%, 99.2% and 100% respectively. Further, ITT SVR12 rates were not significantly influenced by gender, treatment duration, prior IFN-based therapies or presence of liver cirrhosis. For selected special patient populations including patients with ≥5 concomitant medications, platelets count <150000/μL, liver stiffness values >25 kPa or both platelets count <150000/μL and liver stiffness values by TE > 25 kPa, SVR12 rates were 98.6% (142/144), 99% (108/109), 100% (9/9) and 100% (7/7) respectively (Figure 2).

Considering the ITT analysis, 12 (2.1%) patients did not achieve SVR12. Among them, 10 were patients who stopped treatment prematurely, eight for treatment-related AEs and two for treatment-unrelated SAEs. All patients received at least 4 weeks of treatment. Although these 10 patients were classified as treatment failures, an SVR was achieved in nine of them. The remaining two patients experienced a posttreatment virological relapse at the week 12 follow-up visit. Both patients achieved undetectable HCV-RNA at the end of therapy evaluation. One was an 81-year-old treatment naïve woman with genotype 2 infection, with a concomitant diagnosis of primary biliary cholangitis without other major significant comorbidities. The other patient was a treatment naïve 85-year-old woman with genotype 1 infection and without any major comorbidities. None of the patients had cirrhosis.

5 | DISCUSSION

This multicentre, retrospective, observational cohort study was conducted to assess the safety and efficacy of G/P in elderly people (aged 75 years or older) with chronic hepatitis C. The results show that G/P for 8 or 12 weeks is a safe, well-tolerated and highly efficacious in this subgroup of patients with chronic HCV infection. By ITT analysis, 97.9% of patients achieved an SVR, with the efficacy not being impacted by gender, treatment duration, prior IFN-based therapies or liver disease staging. G/P was generally well tolerated by elderly patients as most AEs were mild to moderate in severity and the few SAEs (.3%) were not treatment related. Moreover, 98% of patients were able to complete the predetermined treatment schedule. Furthermore, although adherence to antiviral therapy was not precisely evaluated and was self-reported by patients, the high SVR rates exclude that it played a major role in treatment efficacy. To our knowledge, this study describes the largest European cohort of patients aged 75 years or older undergoing G/P. At present, only few studies aimed to assess the efficacy and safety of G/P in elderly patients involving Japanese cohorts. In particular, Watanabe and colleagues analysed a cohort ($n = 59$) of patients aged >75 years or older undergoing G/P, showing overall SVR12 rates of 98.3% and 100%, in the ITT and PP analyses respectively.[10] Moreover, they compared the SVR12 rates between patients >75 years of age and those <75 years of age finding similar SVR rates, even after stratification for liver status, prior DAA treatment, duration of treatment, gender, history of HCC and FIB4 index >3.25.[10] The recent analysis of another Japanese cohort by Komaki and colleagues showed similar results with SVR12 rates of 95.8% and 98.6% in the ITT and PP analysis, respectively, in a group of patients aged over 75 undergoing treatment with G/P for 8 or 12 weeks.[11] Our study is in line with

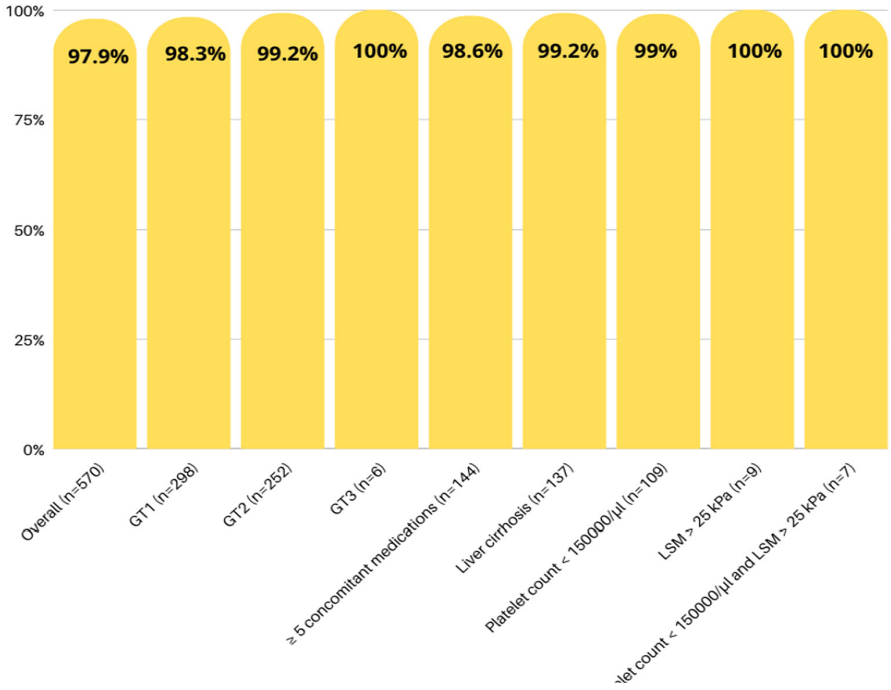

FIGURE 2 Rates of sustained virological response stratified by subgroups. LSM, liver stiffness measurement.

these study results and further supports the efficacy and safety of G/P in this population. Also in line are data coming from Europe, which, however, derive from subgroup analysis of retrospective studies, as none of these studies was focused solely on G/P. In a multicentre real-life study from Italy aimed at evaluating the efficacy and safety of DAAs in patients aged 80 and over, 43/170 (25.3%) received G/P for 8 or 12 weeks with SVR12 rates of 100%, in the absence of SAEs or premature discontinuations.[13] Similarly, De Santis and colleagues,[17] who evaluated the efficacy and safety of multiple DAA regimens in patients older than 70 years found that in this cohort of 138 patients, of whom 34 (24.6%) received G/P for 8 or 12 weeks, SVR12 was achieved in 98% of patients. Interestingly, the authors found a higher incidence of itching in patients treated with G/P than those treated with other regimens (17% vs 3%), with G/P confirmed to be a risk factor for itching (odds ratio 3.6, $p=0.03$) by logistic regression analysis.[17]

Taken altogether all the literature is unanimous in emphasizing the efficacy and safety of G/P for the treatment of chronic HCV infection in elderly patients. We are, however, aware that most studies, ours included, might be influenced by a selection bias caused by the perception that SOF-based regimens might be safer in fragile HCV patients. This might have caused more advanced/sick patients to receive SOF-based regimens, thus artificially boosting the efficacy and safety of G/P in retrospective cohorts. While this bias can be excluded only by a randomized trial design, we think that our cohort is reflective of the elderly HCV-compensated population as 32% of the patients had more than two concomitant comorbidities, while 25% of our patients were taking at least five concomitant medications and lastly 24% had liver cirrhosis. These figures are similar to those reported by other Italian studies focusing on treatment with DAAs in elderlies, where SOF-based regimens were the most commonly used DAAs.[13,17,18] We are also aware of the limitations stemming from the inclusion of patients managed in expert tertiary referral centres; however, this was not the consequence of a flawed study design but rather than treatment in Italy is still restricted to specialist care. Another limitation is the absence of patients infected with unusual HCV genotypes such as 1l, 4r, 3b, 3g, 6u and 6v, which have been shown to be prevalent in some regions of Asia and Africa and among migrants from these areas that, however, are extremely rare in Italy.[19,20] Lastly, given the few HCV-3 patients with advanced disease included in our study, we are not able to confirm data deriving from the CREST study, that is, that 8 weeks of treatment with G/P allow high SVR rates in elderly patients with cirrhosis. Once again, the reason for the small number of HCV-3 patients included can be explained by the Italian epidemiology where this genotype circulated mostly from the 1970s in persons who inject drug (PWID), this being extremely uncommon in patients older than 75 years of age.[21]

In conclusion, we think that our study provides solid evidence on the safety and efficacy of G/P in patients older than 75 years of age. This result coupled with studies suggesting that HCV cure in elderly patients can improve quality of life and life expectancy, strongly supports universal DAA treatment and excludes that age per se should be considered as a barrier to treatment.[22] In addition, from a Public health standpoint, treatment of elderly patients should not be considered trivial as it is key to the achievement of HCV elimination.[23,24]

FUNDING INFORMATION

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CONFLICT OF INTEREST STATEMENT

AA reports Grant and research supports Abbvie and Gilead; advisory board: Abbvie, Gilead, MSD, Mylan, Intercept, Sobi and Takeda. RDA: Advisory Board: AbbVie, Gilead and Takeda; Speaking and teaching: AbbVie and Gilead; Research support: AbbVie and Gilead.

SP acted as speaker/advisor for Abbvie, Echosens, Gilead, Intercept, MSD, Novonordisk and Pfizer. VC acted as speaker/advisor for Abbvie, Echosens, Intercept and Ipsen. FPR acted as speaker/advisor for Abbvie and Gilead.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Nicola Pugliese https://orcid.org/0000-0001-6466-1412
Vincenza Calvaruso https://orcid.org/0000-0002-0287-1059
Mario Masarone https://orcid.org/0000-0003-0550-8201
Roberta D'Ambrosio https://orcid.org/0000-0003-0019-1153
Anna Licata https://orcid.org/0000-0003-0383-6121
Marcello Persico https://orcid.org/0000-0002-1399-6498
Salvatore Petta https://orcid.org/0000-0002-0822-9673
Francesco Paolo Russo https://orcid.org/0000-0003-4127-8941
Vito Di Marco https://orcid.org/0000-0001-6397-4206
Alessio Aghemo https://orcid.org/0000-0003-0941-3226

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