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Real-World Effectiveness and Safety of Glecaprevir/Pibrentasvir for the Treatment of Chronic Hepatitis C: A Prospective Cohort Study in Portugal

Efetividade e Segurança de Glecaprevir/Pibrentasvir para Tratamento de Hepatite C Crónica: Um Estudo de Coorte Prospetiva em Portugal

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ABSTRACT

Introduction: Information about pan-genotypic treatments for hepatitis in Portugal is scarce. We aimed to evaluate the effectiveness and safety of glecaprevir plus pibrentasvir (GLE/PIB) treatment for hepatitis C virus (HCV) infection in real-world clinical practice.

Methods: An observational prospective study was implemented in six hospitals with 121 adult HCV patients who initiated treatment with GLE/PIB between October 2018 and April 2019, according to clinical practice. Eligible patients had confirmed HCV infection genotype (GT) 1 to 6 and were either treatment-naïve or had experience with interferon-, ribavirin- or sofosbuvir-based regimens, with or without compensated cirrhosis. Baseline sociodemographic and safety data are described for the total population (N = 115). Effectiveness [sustained virologic response 12 weeks after treatment (SVR12)] and patient-reported outcomes are presented for the core population with sufficient follow-up data (n = 97).

Results: Most patients were male (83.5%), aged < 65 years (94.8%), with current or former alcohol consumption (77.3%), illicit drug use (72.6%), and HCV acquisition through intravenous drug use (62.0%). HIV co-infection occurred in 22.6% of patients. The prevalence of each GT was: GT1 51.3%, GT2 1.7%, GT3 30.4%, GT4 16.5%, and GT5.6 0%. Most patients were non-cirrhotic (80.9%) and treatment-naïve (93.8%). The SVR12 rates were 97.9% (95% CI: 92.8 - 99.4), and > 95% across cirrhosis status, GT, illicit drug use, alcohol consumption, and HCV treatment experience. The adverse event rate was 2.6%, and no patient discontinued treatment due to adverse events related to GLE/PIB.

Conclusion: Consistent with other real-world studies and clinical trials, treatment with GLE/PIB showed high effectiveness and tolerability overall and in difficult-to-treat subgroups (ClinicalTrials.gov: NCT03303599).

Keywords: Genotype; Glecaprevir; Hepatitis C, Chronic/drug therapy; Pibrentasvir; Portugal; Treatment Outcome

RESUMO

Introdução: A informação sobre os tratamentos pan-genotípicos da hepatite em Portugal é escassa. Pretendeu-se avaliar a efetividade e segurança do glecaprevir+pibrentasvir (GLE/PIB) para tratamento da infeção por vírus da hepatite C (VHC), na prática clínica habitual em Portugal.

Métodos: Estudo prospetivo observacional em seis hospitais, com 121 adultos com hepatite C que iniciaram GLE/PIB entre outubro 2018 e abril 2019, conforme a prática clínica habitual. Os doentes elegíveis tinham infeção por VHC de genótipo (GT) 1 a 6, independentemente de ter ou não cirrose compensada e tratamento prévio. Os dados sociodemográficos e de segurança foram descritos para a população total (N = 115). As taxas de resposta virológica sustentada às 12 semanas (RVS12) foram apresentadas para a população com seguimento completo (n = 97).

Resultados: A maioria dos doentes eram homens (83,5%), < 65 anos (94,8%), consumo atual ou anterior de álcool (77,3%) e de substâncias ilícitas (72,6%), e infeção VHC adquirida por agulha contaminada/uso de substâncias intravenosas (62,0%); 22,6% era co-infetado com VIH. A prevalência de GT1 foi de 51,3%, GT2 1,7%, GT3 30,4%, GT4 16,5% e GT5,6 0%. A maioria não tinha cirrose (80,9%) nem tratamento prévio (93,8%). As taxas de RVS12 foram de 97,9% (IC de 95%: 92,8 - 99,4) no geral e > 95% nos subgrupos com cirrose, GT3, uso de substâncias ilícitas, alcoolismo e tratamento prévio. A taxa de eventos adversos foi de 2,6% e nenhum doente interrompeu o tratamento devido a eventos adversos. A qualidade de vida, produtividade e fadiga melhoraram após tratamento.

Conclusão: Em linha com outros estudos, o tratamento com GLE/PIB mostrou alta eficácia e tolerabilidade, no geral e por subgrupos de doentes de difícil tratamento (ClinicalTrials.gov: NCT03303599).

Palavras-chave: Genótipo; Glecaprevir; Hepatite C Crónica/tratamento farmacológico; Pibrentasvir; Portugal; Resultado do Tratamento

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease and liver-related mortality.[1] By 2015, approximately 71 million people were living with HCV infection worldwide, with a higher prevalence in the Eastern Mediterranean (2.3%) and European (1.5%) regions.[2,3] Globally, the most prevalent genotypes (GT) are GT1 (44%), GT3 (25%), and GT4 (15%).[2] About 10% to 20% of individuals with chronic HCV develop extensive fibrosis and cirrhosis over 20 to 30 years, and untreated cases may evolve into hepatic decompensation, liver failure or hepatocellular carcinoma (HCC).[4,5] Treatment of HCV, along with improved access to diagnosis and care,

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prevents both disease progression and transmission and is fundamental to achieve the World Health Organization (WHO) targets of 80% reduction in HCV incidence and 65% reduction in HCV-related mortality by 2030.[4,6]

Initial chronic HCV treatments were based on interferon, did not have high cure rates, could not be used to treat all genotypes, and had considerable drug-related adverse events. Therefore, these regimens raised concerns regarding patient adherence, particularly among vulnerable populations such as incarcerated persons and people who inject drugs (PWID).[4,7] Currently, HCV can be treated using pan-genotypic direct-acting antivirals (DAAs), which achieve sustained virological responses post-treatment week 12 (SVR12) over 90%, have a well-established safety profile, and have a treatment duration between eight and 16 weeks.[8]

The combination of glecaprevir (GLE, a NS3/4A protease inhibitor) plus pibrentasvir (PIB, a NS5A inhibitor) is a once-daily, oral, interferon- and ribavirin-free DAA regimen, approved in 2017 for the treatment of HCV GT 1-6 infection. GLE/PIB is the pan-genotypic agent with the shortest treatment duration (i.e., eight weeks) for treatment-naïve patients without cirrhosis or with compensated cirrhosis. Initially, this treatment duration was approved only for naïve non-cirrhotic patients; however, the EXPEDITION-8 study demonstrated that eight-week treatment duration had an overall SVR12 of 97.7% among GT1-6 treatment-naïve patients with compensated cirrhosis.[8,9]

Both clinical trials and real-world evidence (RWE) consistently support GLE/PIB treatment as it has high SVR12 rates and is well tolerated. Indeed, a pooled analysis of phase II and phase III trials evaluating the GLE/PIB regimen in treatment-naïve patients, reported overall SVR12 rates of 97.6% (1218/1248) in the intention to treat (ITT) population and 99.3% (1218/1226) when excluding patients with non-virologic failure (modified ITT). This analysis also showed that only 2.4% of patients reported serious adverse events (AEs) and less than 1% of patients had an AE that led to GLE/PIB discontinuation.[10] Similarly, and according to a pooled analysis from post-marketing observational studies across nine countries (between 13th November 2017 and 31st January 2020), GLE/PIB had a SVR12 of 96.7% in the overall analysis population (N = 1648), and higher than 95% across subgroups of interest including PWID, alcohol users, and those with psychiatric diseases. In addition, DAA-related serious AEs were reported for 0.9% of patients, and the rate of DAA-related AEs leading to treatment discontinuation was 0.3% (N = 2036).[11]

Portugal endorsed the European Union HCV Elimination Manifesto[12] and is one of the first countries in the world to allow universal access to HCV treatment, with relevant health gains in the first year of the program (2015 - 2016).[13] HCV epidemiological data for Portugal are scarce, with estimates for 2015 suggesting a viremic prevalence of 0.8%, and a higher proportion of GT1 (68.1%) followed by GT3 (17.9%) and GT4 (12.5%).[2] Importantly, in 2017 a very high HCV seroprevalence (67.6%) was reported among attendees of a low-threshold methadone program, particularly in the PWID subgroup (94.2%).[14] The INFARMED (Portuguese Authority of Medicines and Health Products) reported that 30 086 treatments had been recorded in the national registry by January 2022.[15] There are no robust data about the current number of untreated HCV infections in Portugal, but experts have recently estimated this number to be around 40 000.[16]

There are no published studies regarding the safety and effectiveness of GLE/PIB in routine clinical practice in Portugal. In addition, data characterizing HCV patients treated in Portuguese hospitals are also sparse. The objective of this prospective observational study is to provide data on the effectiveness and safety of GLE/PIB treatment in specific cohorts of HCV patients in Portugal.

METHODS

Study design and participants

This observational, multicenter, prospective cohort study was conducted to examine the treatment of chronic HCV with GLE/PIB in routine clinical practice in Portugal. The study was part of an international post-marketing project (clinicaltrials.gov: NCT03303599) and was implemented in six hospitals with recognized experience in HCV management from two mainland regions: north (Centro Hospitalar Universitário Porto; Centro Hospitalar Vila Nova de Gaia/Espinho) and south (Centro Hospitalar Barreiro-Montijo; Hospital Garcia de Orta; Centro Hospitalar Universitário Lisboa Central; Centro Hospitalar Universitário Lisboa Norte). The study followed the ethical principles described in the Declaration of Helsinki, was approved by the Ethics Committees of the participating centers and was conducted in compliance with Portuguese and European legislation. All study participants provided written informed consent prior to study procedures.

Eligible participants were adults with confirmed HCV infection GT1 to 6, who were treatment-naïve or treatment-experienced (with regimens based on interferon, ribavirin or sofosbuvir), with or without compensated cirrhosis, with no more than four weeks of GLE/PIB treatment at enrollment, and who provided written informed consent and were not enrolled in any interventional study.

Treatment

The treatment decision was made independently of study procedures and preceded the decision to invite the patient to the study. The prescription of the GLE/PIB regimen was at the discretion of the physician and in

accordance with local clinical practice, international guidelines and/or the summary of product characteristics. During the recruitment period of the study, the GLE/PIB recommended dosage was 300 mg GLE/120 mg PIB once daily for eight weeks (non-cirrhotic, treatment-naïve patients), 12 weeks (all cirrhotic, treatment-naïve patients), and 12 weeks (all treatment-experienced patients, except GT3, which required 16-weeks treatment duration).

The observational period for patients receiving eight weeks of GLE/PIB was approximately 20 weeks (eight weeks treatment and 12 weeks post-treatment), for patients receiving 12 weeks of GLE/PIB the observational period was approximately 24 weeks (12 weeks treatment and 12 weeks post-treatment), and for patients receiving 16 weeks of GLE/PIB the observational period was approximately 28 weeks (16 weeks treatment and 12 weeks post-treatment).

Study variables and endpoints

Demographic, clinical, virological, safety, and treatment-related variables were collected from clinical records. The protocol described five potential visits per patient, regardless of treatment duration: at baseline, during treatment, end of treatment, early post-treatment, and post-treatment week 12 to assess sustained virological response (SVR12). Nevertheless, the number of visits, laboratory tests, and other medical procedures were at the provider's discretion as per routine clinical practice.

HCV RNA tests for SVR12 assessment were performed using a sensitive polymerase chain reaction (PCR) test with a lower limit of quantification < 50 IU/mL, in accordance with the centers' practice. Cirrhosis status was determined by the investigator at baseline according to clinical practice. When available, the results of liver fibrosis assessment through transient elastography (FibroScan®, Echosens, Waltham, MA, USA), the aspartate aminotransferase to platelet ratio index (APRI), and the fibrosis-4 (FIB-4) scores were also collected.

The primary endpoint was the percentage of patients achieving SVR12, defined as HCV RNA detected via PCR test with a lower limit of quantification (LLoQ) of < 50 IU/mL 12 weeks after the last actual dose of GLE/PIB. This was analyzed in the overall population and subpopulations of interest: HCV genotypes, cirrhotic *versus* non-cirrhotic patients, treatment-experienced *versus* treatment-naïve, elderly (≥ 65 years) *versus* non-elderly (< 65 years), illicit substance users *versus* non-users. According to routine clinical practice, SVR12 rates were calculated considering the HCV RNA measurement performed within a time window of 70 to 126 days after the last GLE/PIB dose.

Safety endpoints included the number and percentage of patients with treatment-emergent serious and non-serious adverse events (AEs) and increases in laboratory parameters of interest, namely the hepatic function panel. Safety data were collected at each visit after baseline: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 21.1); laboratory parameters were performed as per routine practice.

Patient-reported outcomes (PROs) included the 36-Item Short-Form Health Survey (SF-36), the Work Productivity and Activity Impairment (WPAI) Questionnaire, and the Fatigue Severity Scale (FSS), and were collected at baseline, end of treatment, and SVR12 visit (final visit). The SF-36 consists of eight domains that result in the physical component summary (PCS) and the mental component summary (MCS) scores (range 0 - 100; higher scores indicate better health-related quality of life). The FSS is a nine-item scale that measures fatigue severity and its impact on daily activities and lifestyle. Each item is rated from 1 (completely disagree) to 7 (completely agree), and the FSS total score ranges from 1 (no fatigue) to 7 (very severe fatigue). Minimum clinically important differences (MCID) from baseline to SVR12 were defined as an increase of at least 2.5 points in the PCS or MCS scores and a decrease of at least 0.7 points in the FSS scores. The WPAI questionnaire is a six-item scale measuring work absenteeism, presenteeism, and daily activity impairment during the last seven days. The HCV-specific version, WPAI HepC Version 2.0 was used, and results were expressed as a percentage of overall work impairment due to HCV and percentage of general activity impairment due to HCV.

Statistical methods

Safety data and baseline characteristics were assessed for all patients who received at least one dose of GLE/PIB (total population). The effectiveness analysis (SVR12) was carried out in the core population with sufficient follow-up data (CPSFU), which included all patients who received a GLE/PIB regimen according to their disease characteristics, excluding those patients without an HCV RNA evaluation 70 days after the last dose due to other reasons not related to safety or efficacy (e.g., missing or lost to follow-up).

Comparison of patient characteristics (i.e., current drinkers, illicit drug use, patient on stable opioid substitution therapy) according to the geographical region was performed using the chi-square test with a significance level of 5%. In addition, the comparison of GT frequency by region was performed overall for GT1, GT3, and GT2/4 (chi-square test for independence), and by GT *versus* others (2 x 2 chi-square test except for GT4 *versus* other, where exact Fisher test was used since one expected value was < 5. For the primary SVR12 outcome, 95% confidence intervals (CIs) were provided for both the overall population and the main subgroups of interest. The inclusion of 120 patients would allow a width (i.e., from the lower limit to the upper limit of

the CI) of the 95% CI of the overall estimate of SVR12 of 8.2%, using Wilson's score method. Comparisons between groups with small sample sizes were only done descriptively.

RESULTS

Baseline characteristics

Between 28th September 2018 and 30th April 2019, 121 patients with chronic hepatitis C were enrolled in the study (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18876/15304), with patients receiving at least one dose of GLE/PIB and being included in the safety analysis, and 97 patients comprising the CPSFU and being included in the effectiveness analysis (Fig. 1).

Among the patients that initiated treatment, 94.8% were aged < 65 years and 83.5% were male (Table 1); 73.9% were followed up at centers in southern Portugal. Most patients (77.3%) reported current or former alcohol consumption. Current or former use of illicit drugs was reported by 72.6% of patients, with a significantly higher frequency among patients from the south region (77.6% *vs* 57.1% in the north region; $p = 0.035$, Fig. 2), and 60.2% were PWID (64.7% in the south *vs* 39.3% in the north region; $p = 0.014$). Most patients (62.0%) acquired HCV infection through intravenous (IV) drug use (67.9% in the south *vs* 31.3% in the north region; $p = 0.006$). HIV co-infection was reported in 26 patients (22.6%), of which six presented with an HIV load ≥ 20 copies/mL. There were no patients with chronic HBV infection at baseline.

The most frequent HCV genotype was GT1 (51.3%), followed by GT3 (30.4%), GT4 (16.5%), and GT2 (1.7%), while GT5 and GT6 were not identified in our patients. There were statistically significant differences in the distribution of HCV genotypes by Portuguese region ($p = 0.006$). GT1 was more prevalent in the south (56.5%) *vs* north (36.7%), and GT3 was more prevalent in the north (53.3%) *vs* south (22.4; $p = 0.002$). Overall, 80.9% of patients were non-cirrhotic and 106 patients (93.8%) were treatment-naïve. All cirrhotic patients had a Child-Pugh classification of 5 - 6. Among the seven patients with treatment experience (three patients GT1, two GT3 and two GT4), five had been previously treated with interferon/ribavirin-based regimens (three relapses and two null responses), one had been previously treated with sofosbuvir only (GT3 non-cirrhotic with relapse), and these data were missing for one patient. The mean (± standard deviation) HCV viral load at baseline was 6.0 ± 0.9 $\log_{10}$ IU/mL.

One patient had a history of esophageal varices, and one had ongoing hepatocellular carcinoma. Of 75 patients with available data on renal function, 69.3% had no renal impairment, 29.3% had minor renal impairment (defined as eGFR 60 - 90 mL/min/1.73 m^2) and 1.3% had moderate impairment (eGFR 30-60 mL/min/1.73m^2). Regarding other comorbidities, 10.4% (n = 12) had cardiovascular disease and 7.0% (n = 8) had diabetes mellitus or other metabolic

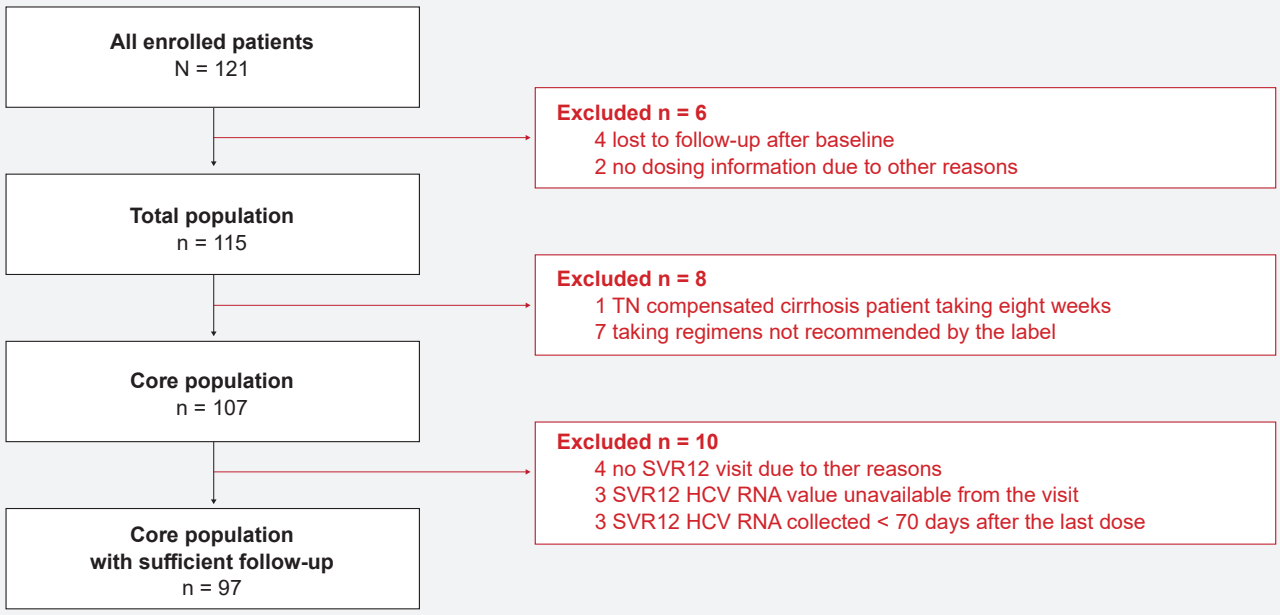

Figure 1 – Patient flowchart

Total population: all patients who received at least one dose of GLE/PIB; Core population: all patients who received a GLE/PIB regimen according to their disease characteristics; Core population with sufficient follow-up: all patients who received a GLE/PIB regimen according to their disease characteristics, excluding those patients without an HCV RNA evaluation 70 to 126 days after the last dose due to other reasons (e.g., missing or lost to follow-up) not related to safety or efficacy.
GLE/PIB: glecaprevir plus pibrentasvir; SVR12: sustained virological response 12 weeks after treatment; TN: treatment-naïve.

Table 1 – Baseline characteristics of the total population

	Total population (n = 115)
Male sex	96 (83.5)
Age (years), mean ± SD	50.6 ± 8.8
Age < 65 years	109 (94.8)
White	111 (96.5)
Current occupational status (n = 85)	
Employed	48 (56.5)
Unemployed	29 (34.1)
Retired/Homemaker	8 (9.4)
Current smoker (n = 84)	57 (67.9)
Any illicit substance use (n = 113)	82 (72.6)
Current use	12 (10.6)
≤ 12 months	7 (6.2)
> 12 months	62 (54.9)
People who inject drugs (current or past) (n = 113)	68 (60.2)
On stable opiate substitution therapy (n = 113)	25 (22.1)
Any history of regular alcohol consumption (n = 88)	68 (77.3)
Current alcohol consumption (any)	41 (46.6)
Current alcohol consumption > 4 drinks/day	16 (18.1)
HCV genotype	
GT1	59 (51.3)
GT2	2 (1.7)
GT3	35 (30.4)
GT4	19 (16.5)
GT5,6	0
Acquisition of HCV infection (n = 100)	
Contaminated needle or IV substance use (current/past)	62 (62.0)
Contact with an infected individual (other than vertical transmission)	4 (4.0)
Blood product transfusion	3 (3.0)
Vertical transmission (mother to child)	2 (2.0)
Surgical procedure	2 (2.0)
Unknown	27 (27.0)
Referral to the hospital for HCV treatment (n = 63)	
Primary care physician	30 (47.6)
Physician at substance dependence treatment center	18 (28.6)
Another physician	15 (23.8)
Years since HCV diagnosis (n = 98), mean ± SD	11.1 ± 9.2
Viral load - HCV RNA (log_{10} IU/mL) (n = 111), mean ± SD	6.0 ± 0.9
< 6.0	44 (39.6)
≥ 6 to < 6.3	15 (13.5)
≥ 6.3	52 (45.6)
Naïve to HCV treatment (n = 113)	106 (93.8)
No history of varices, decompensation, hepatorenal syndrome, or HCC	113 (98.3)
Cirrhosis	22 (19.1)
Liver fibrosis stage* (n = 79)	
F0 to F1	54 (68.4)
F2	3 (3.8)
F3	6 (7.6)
F4	16 (20.3)
APRI score (n = 79), median [min-max]	0.60 [0.17 - 19.48]
APRI > 1	25 (31.6)
FIB-4 score (n = 79), median [min-max]	1.65 [0.41 - 15.79]
Renal function (GFR) (n = 75)	
Normal (≥ 90 mL/min)	52 (69.3)
Mild impairment (≥ 60 to < 90 mL/min)	22 (29.3)
Moderate impairment (≥ 30 to < 60 mL/min)	1 (1.3)
Severe impairment (< 30 mL/min)	0

Data are n (%), except otherwise mentioned. Number of patients in the total population was 115 unless stated otherwise.
APRI: aspartate aminotransferase to platelet ratio index; GFR: glomerular filtration rate; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; SD: standard deviation.
*: Assessed by transient elastography (FibroScan®)

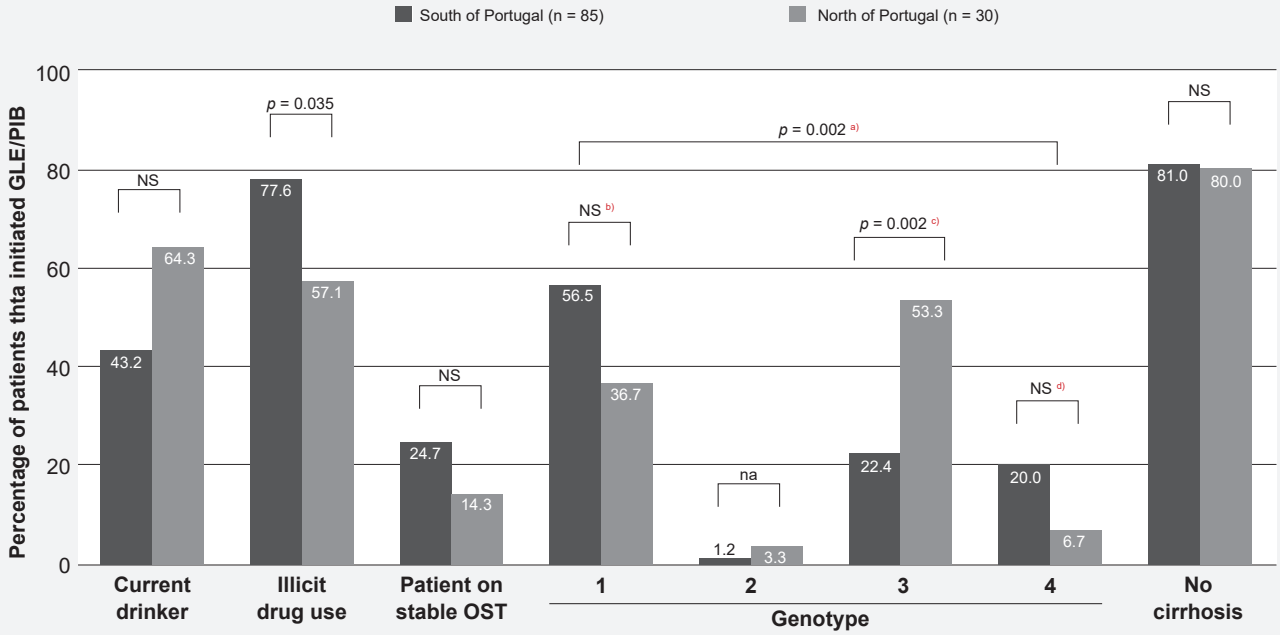

Figure 2 – Main characteristics of the total population (n = 115) at baseline, by Portuguese Region

NS: not statistically significant ($p > 0.05$); n/a: not applicable; OST: opioid substitution therapy.

[a] Chi-square test for independence, after grouping genotypes 2 and 4

[b] Comparison by region of GT1 *versus* other genotypes (chi-square test; *p*-value = 0.062)

[c] GT3 *versus* other (chi-square test; *p*-value = 0.002), and

[d] GT4 *versus* other (exact Fisher; *p*-value = 0.148).

Note: Differences in the number of patients with information available are reported for the following variables: 'Current drinker': north (n = 74) and south (n = 14); 'Illicit drug use': north (n = 28); and 'Patients on stable OST': north (n = 28).

disorders. In addition, 26.1% had a history of depression or suicide attempts/self-injury, 6.1% (n = 7) had depression or bipolar disorder, and 4.3% (n = 5) had a history of anxiety.

During the treatment period, a total of 123 concomitant medications were reported for 60 (52.2%) patients, of whom 43.9% were taking one medicine. The most frequent drug classes (≥ 5% of patients) were anti-HIV drugs (n = 25, 21.7%), drugs used in addictive disorders (n = 18; 15.7%), anxiolytics (n = 10; 8.7%), and antidepressants (n = 6; 5.2%).

Treatment exposure

One hundred and fifteen patients received at least one dose of GLE/PIB, and the most prescribed treatment duration was eight weeks (76.5%), followed by 12 weeks (23.5%). No patient received 16 weeks of treatment. The mean treatment duration was 56.7 ± 3.9 days for the eight-week duration and 82.4 ± 11.5 days for the 12-week regimen. Of the 27 patients with a 12-week regimen, 21 (77.8%) patients had cirrhosis and 15 (55.6%) had GT3 infection (of whom, 12 patients were treatment-naïve with compensated cirrhosis). Of the 35 patients with GT3 infection, 15 (42.9%) initiated a 12-week regimen.

When considering patients that initiated GLE/PIB on-label and according to their disease characteristics (n = 107), 80.4% were assigned to an eight-week treatment duration and 19.6% were prescribed a 12-week treatment. During the study, patients had a median of three in-office appointments (range 2 - 5) with healthcare professionals, including any office visits, emergency room visits, or hospitalizations (based on healthcare resource use data that was available for 88 patients initiating GLE/PIB).

Effectiveness

Of the 97 patients of the CPSFU, 95 (97.9%) achieved SVR12 (95% CI: 92.8% to 99.4%) as shown in Fig. 3. The two patients with virological failure had the following characteristics: < 65 years-old, APRI score ≥ 1, non-cirrhotic, treatment-naïve (HCV viral load ≥ 6.3 $\log_{10}$ IU/mL), history of illicit substance use, no comorbidities/co-infections, and no concomitant medications. Furthermore, one patient had GT1A, and the other patient presented GT3A. Both patients were non-responders due to relapse.

Of the 10 patients who initiated GLE/PIB but had no SVR12 data, nine had unquantifiable/negative HCV RNA at their last measures (five had their last measures during/at the end of treatment, and four had HCV RNA collected ≥ 53 days after the last dose); one patient had only the

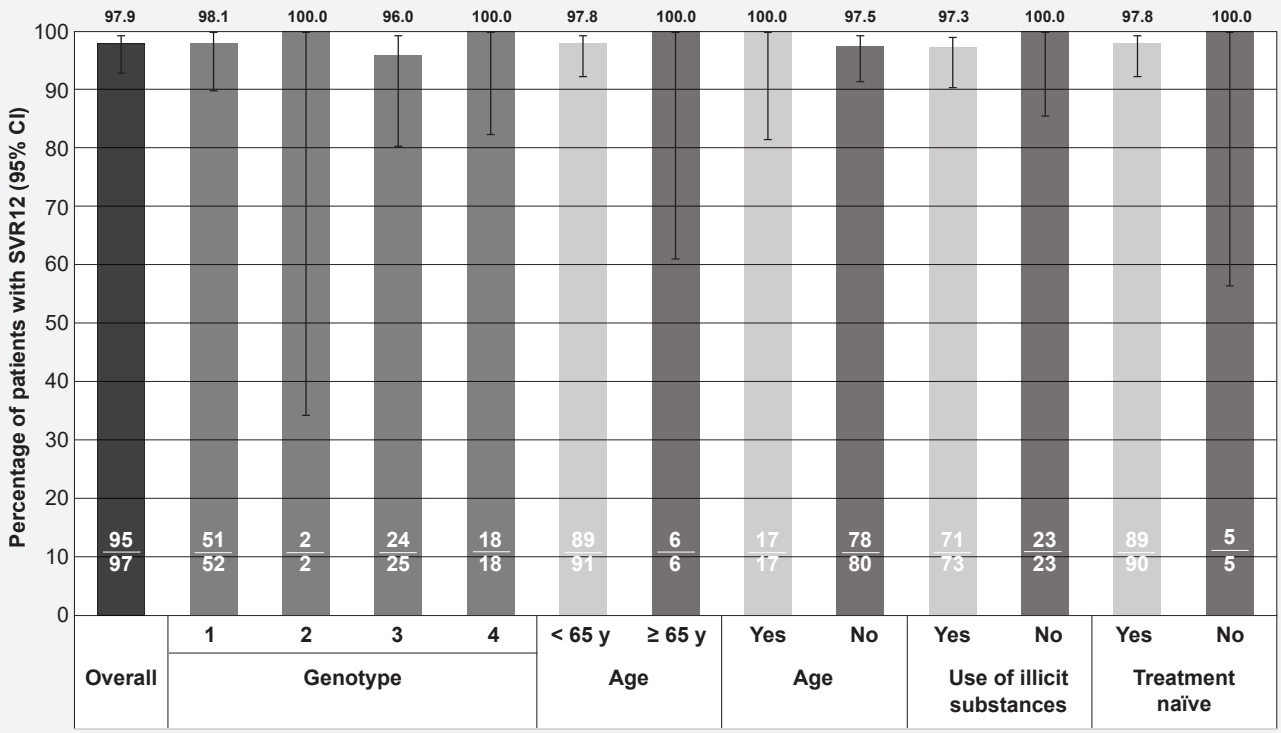

Figure 3 – SVR12 rates after GLE/PIB treatment in the core population with sufficient follow-up: overall and by subgroups of interest

pre-treatment assessment.

Safety evaluation

No serious adverse events were recorded, and the rate of any adverse events was 2.6% (Table 2), namely, headache (n = 2, both treatment-related and one severe), vomiting (n = 2, severe and treatment-related in one case), nausea (n = 1, not treatment-related) and fatigue (n = 1, not treatment-related). One patient discontinued treatment during the first month, after reporting nausea, vomiting, and fatigue (moderate severity and not treatment-related); two patients did not complete treatment and were lost to follow-up, with no reported adverse events. No patient had post-baseline increases of total bilirubin ≥ 2 times the upper limit of normal.

Patient reported outcomes

PROs improved from baseline to the SVR12 visit, presenting MCID in SF36 physical summary score (55% of patients), in SF36 mental summary score (48.3%), and in FSS (31.9%; Table 3).

DISCUSSION

To the best of our knowledge, this is the first observational study to evaluate the safety and effectiveness of GLE/PIB for the treatment of HCV infection in routine clinical practice in Portugal, and the first published study to provide real-world data on the use of pan-genotypic DAAs in this country. We observed an overall SVR12 rate of 97.9% and two virological failures due to relapse (2.1%). This rate is slightly lower than that estimated from the multinational analysis of the same study (98.0%)[17] and from an Italian cohort (99.4%),[18] but is consistent with the results from a Swiss cohort (96.9%),[19] as well as with the pooled analysis of other real-world studies (96.7%).[11] Prospective data of the German Hepatitis C registry (n = 552 patients; 53% GT1, 33% GT3; mostly treatment-naïve, non-cirrhotic and receiving the 8-week GLE/PIB regimen) showed an overall SVR12 rate of 96.7%, with one documented relapse and two HCV reinfections.[20] In our study, the majority of patients were also treatment-naïve and non-cirrhotic; the eight-week regimen was prescribed in more than 75% of cases and more than half of patients presented HCV GT1 infection. Likewise, the results are also similar to the 98% SVR12 reported in a pooled analysis of phase III studies for the GLE/PIB eight-week regimen.[21] When considering patient subgroups, SVR12 results were always higher than 95%, regardless of the cirrhosis status, previous treatment experience, genotype, or use of illicit substances. Even though GT3 infections are considered the most difficult to treat,[1] we observed a 96% SVR12 rate in a total of 25 patients with that genotype.

Table 2 – Adverse events and laboratory abnormalities during the study for the total population

	Total population n = 115
Subjects with AEs	
Any AE	3 (2.6)
Any AE possible related to GLE/PIB treatment*	2 (1.7)
Any AE with a grade of 3 or higher	1 (0.9)
Any treatment-related AE with a grade 3 or higher	1 (0.9)
Any serious AE	0
Any AE leading to treatment discontinuation or interruption	1 (0.9)
Deaths	0
Adverse events reported – preferred term	
Headache	2 (1.7)
Vomiting	2 (1.7)
Fatigue	1 (0.9)
Nausea	1 (0.9)
Laboratory abnormalities, no. of cases/patients evaluated	
Post-nadir ALT > 5x ULN	0/47
Total Bilirubin ≥ 2x ULN	0/47
Post-nadir ALT > 3x ULN and total bilirubin > 2x ULN	0/47

Data are n (%), except otherwise mentioned.
AE: adverse event; ALT: alanine aminotransferase; GLE/PIB: glecaprevir/pibrentasvir; ULN: upper limit of normal.
*: By investigator assessment.

GLE/PIB treatment was well tolerated in our study, with no serious AEs and only 2.6% of patients reporting any AE. This proportion is lower than observed in the Swiss cohort (20.6%) and another German study (26%),[20,21] closer to the 8.3% reported in an Italian real-world study,[22] and higher than the rate observed in the Italian cohort of the same international post-marketing study.[18] Headache was the most common AE as described in clinical trials, and there was no evidence of drug-induced liver injury. An improvement in patients' quality of life was observed during the study, with about half of the patients presenting clinically meaningful improvement in physical or mental dimensions of SF-36. Fatigue improvement (mean decrease of 0.3) was less evident than that observed in the Swiss cohort (mean decrease: 0.8) and in the multinational analysis of the same study.[17] Even so, about a third of patients showed a clinically meaningful improvement in fatigue from baseline to SVR12 visit.

The main study limitation is that the sample was not large enough (safety population: N = 115; evaluable for SVR12: n = 97) to allow robust subgroup analyses for effectiveness, namely for treatment-experienced (n = 5) or elderly (n = 6) patients. Like other real-world studies, safety data may have been underreported, particularly when compared with AE rates from clinical trials (63% for the eight-week duration and 68% for the 12-week duration).[21] Even so, real-world studies enable the evaluation of treatment effectiveness, safety, and prescribing patterns in routine clinical practice with more heterogenous populations, thus providing valuable information for healthcare decision-making. Furthermore, our study sample is likely to represent the Portuguese context, since its demographics are aligned with other national and European reports which described a higher incidence of HCV infection among men and high-risk groups such as PWID.[23-25] GT distribution is also similar to that observed in a larger genomic study in Portugal.[26]

Interestingly, there seem to be regional differences in HCV-infected patients, with a statistically significant higher prevalence rate of illicit drug use in the south and GT3 in the north. We hypothesize that this may result from a different epidemic curve between these regions since subjects with HCV in the south region reflect an older population of PWID associated with a higher frequency of GT1.[26] However, the north region (along with the Azores) presented the highest prevalence of recent and current consumption of any drug and, unless preventive, diagnostic and treatment strategies are reinforced, a rise in the number of patients living with HCV may be observed in this region.[27] A pan-genotypic approach like GLE/PIB has the potential to simplify treatment initiation, e.g., with point-of-care HCV RNA or core antigen testing without genotyping. The ease of use, good safety and tolerability, and short treatment duration may simplify

Table 3 – Summary of patient-reported outcomes during the study

	Baseline	End of treatment	SVR12 visit
SF36 Physical Component Summary score			
n	91	64	60
Mean score at baseline	44.7	44.5	44.0
Mean score at visit		46.9	46.4
Mean ± SD change from baseline		2.5 ± 7.3	2.4 ± 8.4
Increase from baseline ≥ 2.5 points, n (%)		33 (51.6)	33 (55.0)
SF36 Mental Component Summary score			
n	91	64	60
Mean score at baseline	42.6	42.8	43.2
Mean score at visit		46.1	44.6
Mean ± SD change from baseline		3.4 ±10.3	1.3 ±9.8
Increase from baseline ≥ 2.5 points, n (%)		35 (54.7)	29 (48.3)
Work productivity and activity impairment			
% Overall work impairment due to HCV			
n	48	29	24
Mean score at baseline	21.4	15.5	12.5
Mean score at visit		25.3	16.1
Mean ± SD change from baseline		9.8 ± 26.3	3.6 ± 26.4
% Daily activities impairment due to HCV			
n	105	80	64
Mean score at baseline	31.0	33.5	26.4
Mean score at visit		27.6	24.1
Mean ± SD change from baseline		-5.9 ±31.7	-2.3 ± 24.7
Fatigue Severity Scale (FSS) total score			
n	107	83	72
Mean score at baseline	4.4	4.4	4.2
Mean score at visit		3.9	3.9
Mean ± SD change from baseline		-0.4 ± 1.5	-0.3 ± 1.3
Decrease from baseline ≥ 0.7 points, n (%)		28 (33.7)	23 (31.9)

HCV: hepatitis C virus; SD: standard deviation; SF36: 36-Item Short Form Health Survey; SVR12: sustained virological response 12 weeks after completion of treatment.
All scores range from 0 - 100, except FSS total score which ranges from 1 (no fatigue) to 7 (very severe fatigue).

monitoring and reduce healthcare resource use while promoting treatment adherence and patient retention in the cascade of care.[6,9] The shorter GLE/PIB regimens may be particularly relevant in Portugal, considering the high HCV prevalence rate among the difficult-to-treat population of illicit substance users.

CONCLUSION

GLE/PIB administered for eight or 12 weeks was highly effective and well tolerated in the overall sample, regardless of genotype, HCV treatment experience, cirrhosis status, and illicit drug use. In addition, safety and effectiveness results were consistent with those observed in previous clinical trials and real-world studies.[11,21]

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PREVIOUS AWARDS AND PRESENTATIONS

Poster “EP-137 - Real World Evidence (RWE) of the Effectiveness and Clinical Practice Use of Glecaprevir Plus Pibrentasvir (G/P) in Patients with Chronic Hepatitis C

Genotypes 1 to 6 in Portugal – Final Results of the Response Study". Semana Digestiva 2020. November 2020.

DATA AVAILABILITY

AbbVie is committed to responsible data sharing, including access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. The study data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

AUTHOR CONTRIBUTIONS

JV: Acquisition and interpretation of data for the work; drafting the work; approval of the final version.

AG, DP, DS, FM, IP, LM, MM, MJV, MJM, PF, SL, TPG, VB, NM: Acquisition of data for the work; critical review; approval of the final version.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

AG has received support for training/congresses from AbbVie, and advisory boards fees from ViiV Healthcare;

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