The efficacy and tolerability of glecaprevir/pibrentasvir treatment in a real-world chronic hepatitis C patients cohort

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Abstract
Background and Aim: The aims of the present study were to evaluate the real-life efficacy and tolerability of glecaprevir/pibrentasvir (GLE/PIB) in the treatment of patients with chronic hepatitis C (CHC).

Materials and Methods: Between May 2019 and May 2022, 686 patients with CHC, treated with GLE/PB combination from 21 participating centers in Turkey, were enrolled in the study.

Results: All patients were Caucasian, and their median age was 56 years. At the start of GLE/PB treatment, the median serum Hepatitis C virus RNA and serum alanine amino transaminase (ALT) levels were 6.74 log10 IU/mL and 47 U/L, respectively. Fifty-three percent of the patients were infected with genotype 1b, followed by genotype 3 (17%). Diabetes was the more common concomitant disease. The sustained virological response (SVR12) was 91.4% with intent-to-treat analysis and 98.5% with per protocol analysis. The SVR12 rates were statistically significant differences between the patients who were i.v. drug users and non-user (88.0% vs. 98.8%, p=0.025). From the baseline to SVR12, the serum ALT levels and Model for End-Stage Liver Disease score were significantly improved (p<0.001 and p=0.014, respectively). No severe adverse effect was observed.

Conclusion: GLE/PB is an effective and tolerable treatment in patients with CHC.

Keywords: Chronic hepatitis C; glecaprevir-pibrentasvir; real-life experience.

Introduction
Hepatitis C virus (HCV) is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC).[1] Globally, approximately 58 million individuals have chronic hepatitis C (CHC), with around 1.75 million new infections occurring annually.[2,3] The prevalence of anti-HCV antibody positivity in Turkey is about 1% in the adult population.[4] The main goals of HCV treatment are to eradicate the HCV, prevent the disease progression to cirrhosis, decompensation, and HCC, and improve survival and quality of life.[5,6]

Direct-acting agents (DAA) have replaced interferon-based therapy because of their limited efficacy and many side effects.[7] DAAs are effective in the antiviral treatment of CHC patients with chronic hepatitis, compensated cirrhosis (CC), and decompensated cirrhosis pre/post-liver transplantation. In 2016, Ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir/dasabuvir (± ribavirin) were the first two interferon-free DAA regimens approved in Turkey. These two combinations have been widely used, as effective and tolerable treatments for patients with CHC with/without cirrhosis.[8,9] However, these two combinations have genotype-limited efficacy, especially in patients infected with HCV genotypes 2 and 3.[9,10]
New pan-genotypic DAAAs have evolved and became treatment options in the late 2010s. Glecaprevir (GLE), an inhibitor of the NS3/4A protease/pibrentasvir (PIB), an NS5A inhibitor, were combined as a once-daily regimen approved for the treatment of HCV infection with genotypes 1–6. This combination is interferon-free, ribavirin-free, and has a high barrier to resistance and potent antiviral activity with high rates of sustained virologic response (SVR). GLE/PIB treatment has well-tolerated safety profiles. Biliary excretion is the primary route of elimination for these drugs. GLE/PIB treatment has insignificant renal elimination and a promising drug-drug interaction profile. Early real-world experience studies demonstrated a high SVR rate in CHC patients treated with GLE/PIB treatment. Further real-world studies including heterogeneous groups, represent all patients [NS5A inhibitors]) based on physicians’ discretion. A specific electronic case report form (CRF) was designed for data collection and recording. Each center entered the relevant data in the CRF. The study was approved by Mersin University Ethical Committee for Clinical Research, with the number 2022/59 and the date of January 26, 2022.

Serum HCV RNA levels were measured using the Roche (Pleasanton, CA) COBAS AmpliPrep/CoBAS TaqMan HCV Test, version 2.0. HCV genotype and subtypes were determined by diverse methods due to the different setups of the participating centers as previously described. The sustained virological response (SVR12) was defined as the absence of measurable HCV RNA levels in serum at 12 weeks after the end of the GLE/PIB treatment.

Patients were regularly seen in an outpatient clinic during the treatment and follow-up periods. A physical examination and biochemical, serological, and virological tests were performed at each visit. Safety and tolerability analyses of the GLE/PIB treatment were based on assessing adverse effects (AE), serious AE, drug discontinuation owing to AEs, laboratory abnormalities, and deaths.

### Materials and Methods

This was a retro-prospective, observational study with a large-scale patient population. Between May 2019 and May 2022, a total of 686 CHC patients from 21 different participating centers in Turkey were enrolled in the study. Cirrhosis was defined based on the clinical, laboratory, or histological findings when available. Patients received GLE 300 mg and PIB 120 mg in a fixed standard-dose combination tablet once daily for either 8 weeks (for non-cirrhotic treatment naïve and experienced patients [except NS5A inhibitors], and treatment naïve CC patients) or 12 weeks (for treatment-naïve and experienced patients CC patients [except NS5A inhibitors]) or 16 weeks (for treatment-experienced CC patients [NS5A inhibitors]) based on physicians’ discretion. A specific electronic case report form (CRF) was designed for data collection and recording. Each center entered the relevant data in the CRF. The study was approved by Mersin University Ethical Committee for Clinical Research, with the number 2022/59 and the date of January 26, 2022.

### Statistical Analyses

The proportions of the patients with CHC were presented by gender, HCV genotype, and the presence of SVR 12 achievement using cross-tabulations. The Chi-square test or Fisher’s exact test (when Chi-square assumptions do not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups. A p < 0.05 was considered to show a statistically significant result. The continuous variables were investigated using histograms and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk’s Test) to determine whether they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed...
Before the starting GLE/PIB treatment, 11 patients (male/female ratio: 8/3, median age: 68 years) had a history of previous HCC. CHC patients with a history of HCC were older than patients without HCC (63.2±14.7 years versus 53.7±17.2 years, p=0.039). Ten of them successfully reached SVR, and the SVR12 was achieved in 90.9%. HCC recurrence was not observed in any patients with a history of previously treated HCC during or after the antiviral treatment. Of note, no newly diagnosed HCC was detected.

### Safety

GLE/PIB treatment was generally well tolerated. Fatigue was the most common adverse effect, followed by dyspepsia, headache, and nausea. Ascites developed in one patient with CC. The patient responded well to diuretic treatment. No HBV reactivation was observed based on elevated serum ALT and HBV DNA levels in two HCV and HBV co-infected patients. No hepatitis flare was observed during GLE/PIB treatment in one CHC patient with concomitant autoimmune hepatitis. Psoriatic-like skin lesion was developed during the GLE/PIB treatment and healed with topical steroid treatment.

### Discussion

This study provides the first real-life data on the efficacy and tolerability of GLE/PIB for the treatment of patients with CHC from nearly all geographical regions across Turkey. The SVR rate was consistently high, with 98.5% with PP analysis. SVR rates were not significantly different among patients infected with different genotypes, patients with treatment-naive and treatment-experienced, patients with and without cirrhosis, and patients with or without a history of previous HCC. This result confirms previous studies demonstrating that the SVR rates of the GLE/PIB treatment were high for CHC patients with or without advanced liver disease.

GLE/PIB treatment is recommended for treatment-naive and experienced CHC patients with or without CC, infected with any HCV genotypes. However, HCV genotype 2 and 3 infections have been the most difficult genotype to treat. Today, sharing needles, syringes, or any other equipment used to prepare and inject drugs is the most common contagious way of HCV infection. The prevalence of HCV infection is about 40% among individuals who are actively i.v. drug users. In Europe, it is estimated that around two-thirds of the HCV infection arise from i.v. drug users. A shorter antiviral treatment duration has the advantage of enhanced treatment adherence, especially for patients with low compliance (substance users, prisoners, and psychiatric patients).

A meta-analysis study reported that an SVR was 87.7% among individuals with recent injecting or non-injecting drug users, while it was 90.7% among individuals receiving opioid substitution therapy. In the present study, HCV genotype 3 infection was more frequently seen in i.v. drug users (44%). An SVR rate was 88.0% in such individuals, and the SVR difference was significant between the patients who are i.v. drug users and non-users (p=0.025). GLE/PIB treatment was generally tolerable in such individuals. This study indicates that GLE/PIB treatment was effective and tolerable in CHC patients with i.v. drug users. High virological response rates and shorter treatment duration are promising among unstable substance users supporting broadening access in this population, preventing patients’ loss in follow-up, and gaps in the cascade care. Eleven patients had a history of previous HCC before starting GLE/PIB treatment. An SVR12 was achieved in 91.0% of these patients. Previous studies reported conflicting data on HCC development in patients with CHC.
During the median 19 months of the follow-up period, HCC recurrence was not observed in any patients with a history of previously treated HCC. Notably, no newly diagnosed HCC was detected.

GLE/PIB treatment was well tolerated in the present study. A few patients experienced minor AE, such as fatigue, headache, nausea, and dyspepsia. No liver enzyme flare-ups were observed. No significant AEs attributed to the GLE/PIB treatment were observed. Decompensation occurred in one cirrhotic patient during the therapy. The patients with ascites were treated with diuretics. No HBV reactivation was observed during the GLE/PIB treatment.

There are some limitations of our study. A specific electronic CRF was designed for data collection and recording in the present study. Each center entered the relevant data in the CRF. The heterogeneous data recruited from hospital patients’ charts are limited. In addition, patients with CHC treated with GLE/PIB between May 2019 and May 2022 were enrolled in the present study. The COVID-19 pandemic started on March 2020 in Türkiye. The COVID-19 pandemic negatively affected outpatient clinic visits for all-cause of chronic diseases.

Conclusion
GLE/PIB treatment was effective and tolerable in CHC patients with/without advanced liver disease. HCV eradication with GLE/PIB treatment was associated with improved liver function.

Ethics Committee Approval: The Mersin University Clinical Research Ethics Committee granted approval for this study (date: 26.01.2022, number: 2022/59).

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