Research Article

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Gle/Pib treatment in patients with CHC

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

Serkan Yaras[1], Mehmet Demir[2], Sezgin Barutcu[3], Abdullah Emre Yildirim[4], Selim Gurel[5], Enver Ucbilek[1], Ilkce Akgun Kurtulmus[6], Meral Akdogan Kayhan[7], Sezgin Vatansever[8], Haydar Adanir[9], Nilay Danis[10], Serkan Duman[11], Ilker Turan[12], Derya Ari[7], Sukran Kose[13], Huseyin Alkim[14], Muhsin Murat Harputluoglu[15], Feyza Dilber[16], Murat Akyildiz[17], Arif Mansur Cosar[18], Serdar Durak[18], Goktug Sirin[19], Ayse Kefeli[20], Hale Gokcan[21], Ufuk Avcioglu[22], Talat Ayyildiz[22], Orhan Sezgin[1], Mesut Akarsu[23], Dinc Dincer[24], Fatih Guzelbulut[25], Fulya Gunsar[12], Ulus Salih Akarca[12], Ramazan Idilman[21]

[1]Department of Gastroenterology, Mersin University, School of Medicine, Mersin, Turkiye; [2]Department of Gastroenterology, Mustafa Kemal University, School of Medicine, Hatay, Turkiye; [3]Department of Medical Sciences, Gaziantep University, School of Medicine, Gaziantep, Turkiye; [4]Department of Gastroenterology, Memorial Bahcelievler Hospital, Istanbul, Turkiye; [5]Department of Internal Medicine, Uludag University, School of Medicine, Bursa, Turkiye; [6]Department of Internal Medicine, Ege University, School of Medicine, Izmir, Turkiye; [7]Division of Gastroenterology, Department of Internal Medicine, Faculty of Health Sciences, Ankara City Hospital, Ankara, Turkiye; [8]Department of Gastroenterology, Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkiye; [9]Department of Internal Medicine, Akdeniz University, School of Medicine, Antalya, Turkiye; [10]Division of Gastroenterology and Hepatology, Department of Medicine, Johns Hopkins University, Baltimore, USA; [11]Department of Gastroenterology, Toros State Hospital, Mersin, Turkiye; [12]Department of Gastroenterology, Ege University, School of Medicine, Izmir, Turkiye [13]Department of Infectious Diseases and Clinical Microbiology, Dokuz Eylul University, School of Medicine, Izmir, Turkiye; [14]Department of Gastroenterology, Sisli Etfal Training and Research Hospital, Istanbul, Turkiye; [15]Department of Internal Medicine, Inonu University, School of Medicine, Malatya, Turkiye; [16]Department of Gastroenterology, Marmara University, School of Medicine, Istanbul, Turkiye; [17]Department of Gastroenterology, Koc University, School of Medicine, Istanbul, Turkiye; [18]Department of Gastroenterology, Karadeniz Technical University, School of Medicine, Trabzon, Turkiye; [19]Department of Gastroenterology, Kocaeli University, School of Medicine, Kocaeli, Turkiye; [20]Department of Gastroenterology, Tokat Gaziosmanpasa University, School of Medicine, Tokat, Turkiye; [21]Department of Gastroenterology, Ankara University, School of Medicine, Ankara, Turkiye; [22]Department of Gastroenterology, Ondokuz Mayis University, School of Medicine, Samsun, Turkiye; [23]Department of Gastroenterology, Dokuz Eylul, School of Medicine, Izmir, Turkiye; [24]Department of Gastroenterology, Akdeniz University, School of Medicine, Antalya, Turkiye; [23]Departments of Gastroenterology and Pathology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkiye

Abstract

Background and Aim: The aims of the present study were to evaluate the real-life efficacy and tolerability of glecaprevir (GLE)/pibrentasvir (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/PIB combination from 21 participating centers in Turkiye, were enrolled in the study.

Results: All patients were Caucasian, and their median age was 56 years. At the start of GLE/PIB 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/PIB 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 Turkiye 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 Turkiye. These two combinations have been widely used, as effective and tolerable treatments for patients with CHC with/without cirrhosis.[8] However, these two combinations have genotype-limited efficacy, especially in patients infected with HCV genotypes 2 and 3.[9,10]

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Corresponding author: Serkan Yaras; Mersin Universitesi Tip Fakultesi, Gastroenteroloji Anabilim Dali, Mersin, Turkiye
Phone: +90 324 241 00 00 / 21552; **e-mail:** drserkan1975@hotmail.com

Table 1. Baseline characteristics of all CHC patients treated with GLE/PIB

	Total (n=686)	Non-cirrhosis (n=621)	Cirrhosis (n=65)	p
Age years	53.6±18.3	52.3±18.1	60.3±14.3	0.020
Gender (M/F)	419/267	383/238	36/29	0.350
Median HCV RNA level (log10 IU/mL)	6.74	6.75	6.65	0.524
Disease duration (years)	3.3±5.1	3.0±4.7	5.6±7.1	0.000
Genotype 1a (%)	8.1	8.3	6.3	
Genotype 1b (%)	52,8	50.9	70.3	
Genotype 1 (%)	1.9	1.9	3.1	
Genotype 2 (%)	14.0	15.0	4.7	
Genotype 3 (%)	16.6	17.3	9.4	
Genotype 4 (%)	3.4	3.4	3.1	
Miscellaneous (%)	3.2	3.2	3.1	
Serum ALT level (range, U/L)	78.1±109.2	67.5±58.0	79.2±113.2	0.422
Serum AST level (range, U/L)	67.7±91.7	67.5±95.4	70.0±45.1	0.843
Total bilirubin level (mg/dL)	1.0±1.4	1.0±1.4	1.3±1.2	0.074
WBC	7.3±2.5	7.4±2.5	6.1±2.9	<0.001
Platelet counts	215.8±87.9	225,0±84.7	130.5±70.1	<0.001
INR	1.06±0.18	1.05±0.17	1.20±0.24	<0.001
Serum creatinine level (mg/dL)	0.96±1.0	0.81±0.3	0.98±1.0	0.255

GLE: Glecaprevir; PIB: Pibrentasvir; M: Male; F: Female; HCV: Hepatitis C Virus; ALT: Alanine aminotransaminase; AST: Aspartate aminotransferase; WBC: White blood cell; INR: International normalized ratio.

New pan-genotypic DAAs 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 genotype 1–6.[5,11] 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).[12] 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.[11] Early real-world experience studies demonstrated a high SVR rate in CHC patients treated with GLE/PIB treatment.[11,12] Further real-world studies including heterogeneous groups, represent all genotypes and determine potential drug-drug interactions are needed. Since 2019, GLE/PIB combination treatment has been available in Turkiye. To determine and present the real-life experience in Turkiye, we aimed to determine the efficacy of GLE/PIB treatment in CHC patients with/without cirrhosis and to analyze the tolerability of GLE/PIB treatment in such patients.

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 Turkiye 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.

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.[8]

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.

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 test 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

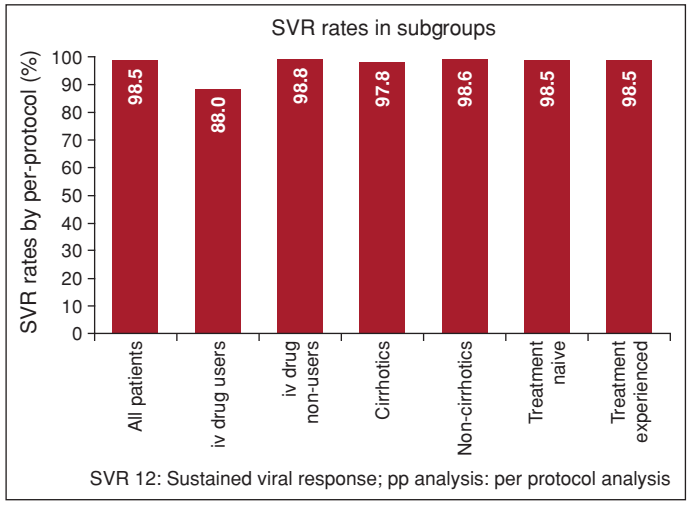

Figure 1. The SVR12 rates in patients with CHC.

variables. Descriptive analyses were presented using medians and interquartile range (IQR) for the non-normally distributed variables (HCV RNA levels). A $p<0.05$ was considered to show a statistically significant result. All statistical analyses were performed using the Statistical Package for Social Sciences software version 20.0 (IBM Corp.; Armonk, NY, USA).

Results

A total of 686 patients with CHC were enrolled in the study. All patients were Caucasian, and their median age was 56 years (range: 18–88 years). Their gender was predominantly male (61.1%). Among 686 patients, 553 received GLE/PIB treatment for 8 weeks, 96 received it for 12 weeks, and 37 received it for 16 weeks. At the start of treatment, the median serum HCV RNA and serum alanine amino transaminase (ALT) levels were 6.74 log10 IU/mL, 47 U/L (range: 6–1178 U/L), respectively. Of the available 652 patients, 52.8% were infected with genotype 1b, 16.6% with genotype 3, and 14.0% with genotype 2 (Table 1). Genotype 3 was frequently seen in patients with intravenous (i.v.) drug users (44.0%). Diabetes mellitus (n=58, 8.5%) and arterial hypertension (n=47, 6.9%) were the more common concomitant diseases. Overall, 29.3% of the patients (n=201) received at least one co-medication. Two patients had HBV co-infection. Sixty-five patients had CC. The median follow-up period was 19 months (range: 4–36 months). The baseline characteristics of the CHC patients are given in Table 1.

An SVR12 was achieved in 91.4% with intent-to-treat analysis, while SVR12 was achieved in 98.5% with per protocol (PP) analysis. An SVR was not different among cirrhotic and non-cirrhotic patients (97.8% vs. 98.6%, p=0.408), among treatment-naïve and treatment-experienced patients (98.5% vs. 98.5%, p=0.98), among patients who were infected with different genotypes ($p > 0.05$). There was a statistically significant difference between the patients who were i.v. drug users and non-user (88.0% vs. 98.8%, respectively, p=0.025) (Fig. 1).

From baseline to SVR12, serum ALT levels and Model for End-Stage Liver Disease (MELD) scores were significantly improved in patients with SVR12. The mean serum ALT levels significantly decreased from 78.1±109.2 U/L to 28.4±56.4 U/L ($p<0.001$). In cirrhotics, the mean MELD scores significantly decreased from 13.9±6.5 to 10.1±3.8 from the baseline to SVR12 (p=0.014).

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 Turkiye. 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-naïve 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/without advanced liver disease.[13–15]

GLE/PIB treatment is recommended for treatment-naïve and experienced CHC patients with or without CC, infected with any HCV genotypes.[7,16,17] However, HCV genotype 2 and 3 infections have been the most difficult genotype to treat.[18] 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.[5,19] In Europe, it is estimated that around two-thirds of the HCV infection arise from i.v. drug users.[20] A shorter antiviral treatment duration has the advantage of enhanced treatment adherence, especially for patients with low compliance (substance users, prisoners, and psychiatric patients).[13,21–23] 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.[22] 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

CHC patients with advanced liver disease treated with DAAs.[24] 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 Turkiye. 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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