

Glecaprevir/ Pibrentasvir in the Treatment of Chronic Hepatitis C Patients – A Real-World Nationwide HCV Registry Program (TACR) in Taiwan

Chung-Feng Huang

Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

Hsing-Tao Kuo

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chi Mei Medical Center.

Te-Sheng Chang

Division of Hepatogastroenterology, Department of Internal Medicine, ChiaYi Chang Gung Memorial Hospital and College of Medicine, Chang Gung University.

Ching-Chu Lo

Division of gastroenterology, department of Internal medicine, St. Martin De Porres Hospital.

Chao-Hung Hung

Division of Hepatogastroenterology, Department of Internal Medicine, ChiaYi Chang Gung Memorial Hospital.

Chien-Wei Huang

Division of Gastroenterology, Kaohsiung Armed Forces General Hospital.

Lee-Won Chong

Division of Hepatology and Gastroenterology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital.

Pin-Nan Cheng

Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University.

Ming-Lun Yeh

Department of Internal Medicine, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

Cheng-Yuan Peng

Center for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital; School of Medicine, China Medical University.

Chien-Yu Cheng

Division of Infectious Diseases, Department of Internal Medicine, Taoyuan General Hospital, Ministry of Health and Welfare.

Jee-Fu Huang

Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

Ming-Jong Bair

Division of Gastroenterology, Department of Internal Medicine, Taitung Mackay Memorial Hospital.

Chih-Lang Lin

Liver Research Unit, Department of Hepato-Gastroenterology and Community Medicine Research Center, Chang Gung Memorial Hospital at Keelung, Chang Gung University, College of Medicine.

Chi-Chieh Yang

Department of gastroenterology, Division of internal medicine, Show Chwan Memorial Hospital.

Szu-Jen Wang

Division of Gastroenterology, Department of Internal Medicine, Yuan's General Hospital.

Tsai-Yuan Hsieh

Division of Gastroenterology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center.

Tzong-Hsi Lee

Division of Gastroenterology and Hepatology, Far Eastern Memorial Hospital.

Pei-Lun Lee

Chi Mei Medical Center, Liouying Division of Gastroenterology and Hepatology, Department of Internal medicine.

Wen-Chih Wu

Wu Wen-Chih Clinic.

Chih-Lin Lin

Department of Gastroenterology, Renai branch, Taipei City Hospital.

Wei-Wen Su

Department of Gastroenterology and Hepatology, Changhua Christian Hospital.

Sheng-Shun Yang

Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital.

Chia-Chi Wang

Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and School of Medicine, Tzu Chi University.

Jui-Ting Hu

Liver center, Cathay General Hospital.

Lein-Ray Mo

Tainan Municipal Hospital(Managed by Show Chwan Medical Care Corporation Division of Gastroenterology).

Chun-Ting Chen

Division of Gastroenterology, Department of Internal Medicine Tri-Service General Hospital Penghu Branch, National Defense Medical Center.

Yi-Hsiang Huang

Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital; Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei.

Chun-Chao Chang

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical University Hospital.

Chia-Sheng Huang

Yang Ming Hospital.

Guei-Ying Chen

Penghu Hospital, Ministry of Health and Welfare.

Chien-Neng Kao

National Taiwan University Hospital Hsin-Chu Branch .

Chi-Ming Tai

Department of Internal Medicine, E-Da Hospital.

Chun-Jen Liu

Hepatitis Research Center and Department of Internal Medicine, National Taiwan University Hospital.

Mei-Hsuan Lee

Institute of Clinical Medicine, National Yang Ming Chiao Tung University.

Pei-Chien Tsai

Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

Chia-Yen Dai

Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

Jia-Horng Kao

Hepatitis Research Center and Department of Internal Medicine, National Taiwan University Hospital.

Han-Chieh Lin

Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital; Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei.

Wang-Long Chuang

Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

Chi-Yi Chen

Division of Gastroenterology and Hepatology, Department of Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital.

Kuo-Chih Tseng

Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi; School of Medicine, Tzuchi University.

Ming-Lung Yu (✉ fish6069@gmail.com)

Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

Research Article

Keywords: DAA, CHC, HCV, efficacy, SVR, HCRU, RWD, G/P, GLE/PIB, pangenotypic

Posted Date: September 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-882398/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background/Aims

The study evaluated the real-world treatment outcomes of Glecaprevir/pibrentasvir (GLE/PIB) including effectiveness, safety and healthcare resource utilization based on a nation-wide registry in Taiwan.

Methods

The Taiwan HCV Registry (TACR) is a nation-wide platform organized and supervised by the Taiwan Association for the Study of the Liver. Data were analyzed for patients treated with GLE/PIB, including 3,144 patients who had treatment outcome available. The primary endpoint was sustained virological response (SVR12, undetectable HCV RNA throughout 12 weeks of end-of-treatment).

Results

The overall SVR12 rate was 98.9% (3110/3144), with 98.8%, 99.4% and 100% in patients receiving 8 weeks, 12 weeks, and 16 weeks of GLE/PIB respectively. The SVR12 rate in the treatment-naïve cirrhotic patients receiving 8 weeks of GLE/PIB was 98.2% (108/110). The most common AEs were fatigue (7.5%), pruritus (6.7%) and dizziness (1.5%). The mean number of outpatient visits during the GLE/PIB was 5.94 visits for patients treated with 8 weeks, significantly different from the patients treated with 12 weeks of GLE/PIB (6.90 visits).

Conclusions

The results support the effectiveness and safety of GLE/PIB treatment in real-world clinical practice, and provide further evidence that the shorter, 8-week GLE/PIB regimen is effective and cost-saving.

Introduction

Hepatitis C virus (HCV) infection is recognized as a global health threat, affecting approximately 71 million patients worldwide.[1] In Taiwan, HCV is endemic with an estimated prevalence ranged from 3.28% among the general population to more than 10% in hyperendemic areas. [2, 3] One of the five core interventions identified by the World Health Organization (WHO) toward eliminating viral hepatitis is to enhance and expand the response of the oral, well-tolerated direct-acting antivirals (DAAs) for people with chronic hepatitis C virus (CHC) infection, which can achieve cure rates of over 90% and thereafter avoid further transmission and reduce HCV-related complications, including decompensated cirrhosis, liver transplantations and death. [1, 4].

Among the all-oral DAAs recommended by the regulations of the Health and Welfare Department of Taiwan [5] and regional guidelines [6, 7], the regimen of glecaprevir/pibrentasvir (GIE/PIB) provides the opportunity for shortening CHC therapy to 8 weeks in the majority of patients.[8] GLE/PIB is a once daily, ribavirin-free, fixed-dose combination of two pan-genotypic DAAs: glecaprevir (a HCV NS3/4A protease

inhibitor) and pibrentasvir (a NS5A inhibitor), indicated for CHC patients for a duration of 8, 12 or 16 weeks.[9] The efficacy and safety data of GLE/PIB for the indicated CHC patients have been demonstrated in registrational phase II and phase III clinical trials [8, 9, 10, 11]; however, there are only limited data evaluating the efficacy of GLE/PIB in real-world, non-clinical trial settings. Since the Taiwan National Health Insurance (NHI) program started to reimburse GLE/PIB in August 2018, several real-world data regarding the effectiveness and safety of DAAs including GLE/PIB have been reported. [12–15] As nation-wide data of GLE/PIB, especially from special populations, are scarce, the aim of the present study was to evaluate the real-world efficacy and safety of GLE/PIB in adult patient with CHC infection enrolled in the Taiwan Association for the Study of the Liver HCV Registry (TACR).

Methods

Patients and study design

The TASL HCV Registry (TACR) is an ongoing, non-interventional, prospective, observational nationwide cohort study organized and funded by the Taiwan Association for the Study of the Liver (TASL), which set up and manages the database and biobank of HCV patients who receive DAA therapy in Taiwan, as previously described. [15] The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital, which conformed to the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients had to provide written informed consent before being enrolled in the registry. Inclusion criteria for the registry were: 20 years of age or older, chronic HCV infection with detectable HCV ribonucleic acid (RNA) and prescribed with DAA-containing regimens. Individual patient records were reviewed, and data were extracted and validated using a standardized case report form and a unified coding dictionary for the pre-defined patient (e.g., demographics, previous HCV treatment, comorbidities, and cirrhotic status) and virological characteristics (e.g., HCV genotypes, viral loads and treatment outcomes) before and after antiviral treatment. In this registry, the choice of DAA was at the discretion of the treating physician taking into account the recommendations [6,7] and the regulations of the Health and Welfare Department of Taiwan. [5] The current analysis included patients with CHC infection who received 1 or more dose of GLE/PIB according to the label at the time of registration and had treatment outcome available as of 31 October 2020.

Assessments and endpoints

Demographics and clinical characteristics were assessed at baseline, including age, gender, HCV genotype, viral load, liver cirrhosis status, history of previous HCV treatment, comorbidities and history of drug abuse. Liver cirrhosis was defined by any of the following: liver histology, transient elastography (FibroScan®, Echosens, Paris, France, > 12 kPa), acoustic radiation force impulse (> 1.98 m/s), fibrosis-4 index (> 6.5) or the presence of clinical, radiological, endoscopic, or laboratory evidence of cirrhosis and/or portal hypertension, as previously described. [15] Hepatocellular carcinoma (HCC) was confirmed by histological or clinical diagnosis, and patients with inactive HCC were defined as those who were subjected to surgical resection, local alcohol injection, radiofrequency ablation or liver transplantation

and without imaging evidence of recurrence within 3 months prior to receiving DAA treatment [12]. Patients with chronic kidney disease (CKD) included dialytic patients and patients with a decreased estimated glomerular filtration rate (eGFR, < 60 ml/min/1.73 m²) or kidney function damage (e.g., presence of proteinuria) for more than 3 months. [16]

Efficacy outcome was the overall rate of sustained virological response (SVR12, defined as undetectable HCV RNA level < lower limit of quantification at off-therapy week 12). SVR12 rates in the following subgroups of interest were evaluated: HCV genotypes (GTs), liver cirrhosis status (no cirrhosis or compensated cirrhosis), previous HCV treatment history (treatment naïve or treatment experienced), comorbidities including hepatitis B virus (HBV)-coinfection, human immunosuppressant virus (HIV)-coinfection, HCC, or CKD, GLE/PIB treatment duration (8, 12, or 16 weeks), adherence (defined as the percentage of actual dosage being taken divided by the anticipated DAA dosage throughout the treatment course in each subject) and history of drug abuse (patient who inject drugs, PWID).

Safety outcomes were the percentages of patients with adverse events (AEs), serious AEs (SAEs) and common AEs (occurring in ≥ 1% of patients). Healthcare resource utilization (HCRU) was defined as the number of clinic visits from GLE/PIB initiation to the SVR12 survey visit.

Statistical analyses

Descriptive statistics including mean (± standard deviation, SD) or frequency (percentage) were used to summarize baseline demographics, clinical characteristics and HCRU for each treatment duration. For efficacy outcomes, the overall and stratified viral response rates (SVR12) were shown in numbers and percentages with 95% confidence interval (CI). Frequencies were compared between groups using the χ^2 test with the Yates correction or Fisher's exact test. Group means were compared using analysis of variance and Student's *t*-test or the nonparametric Mann-Whitney U test when appropriate. Stepwise logistic regression analysis was performed to determine factors associated with treatment failure by analyzing the covariates with a *p* value <0.1 in the univariate analysis. The overall safety profiles were shown in numbers and percentages as appropriate. The statistical analyses were performed using the SPSS 12.0 statistical package (SPSS, Chicago, IL, USA). All statistical analyses were based on two-sided hypothesis tests with a significance level of *p*<0.05.

Results

Patient characteristics

Patient data of a total of 27,265 CHC patients were collected from 48 sites and registered in TACR platform as of 31 October 2020. Among the 3,209 patients treated with GLE/PIB, 21 patients were excluded because of documented decompensated cirrhosis at baseline (12 patients) or previous exposure to NS3/4A protease inhibitor and/or NS5A inhibitor-containing DAAs (9 patients), in accordance with the Taiwan Food and Drug Administration (TFDA)-approved label. Of the remaining 3,188 patients, 3,144 patients with the treatment outcome at post-treatment week 12 available were included in the

present analysis (Figure 1). The mean age was 58.9 years, and females accounted for 49.3% of the population. The dominant viral genotype was HCV genotype 2 (GT2, 56.8%), followed by GT1 (27.5%), GT6 (8.5%) and GT3 (4.6%). Six hundred and eight patients (19.3%) had baseline HCV RNA > 6,000,000 IU/ml. The majority of patients were treatment naïve (92.0%) and had no liver cirrhosis (85.1%). One hundred and seventeen (3.7%) had history of HCC (active, 2.9%, inactive, 0.9%) before DAA treatment, 248 (7.9%) and 154 (4.9%) patients were dually infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV), respectively, 830 (26.4%) patients had chronic kidney disease (CKD). For high-risk behaviors, 41 patients (1.3%) were documented with a history of intravenous drug abuse. The majority of patients (2,601, 82.7%) received GLE/PIB for 8 weeks (Table 1).

Treatment responses

For the primary efficacy outcome, the overall SVR12 rate was 98.9% (3,110/3,144). The proportion of SVR12 was 98.8% (2,570/2,601), 99.4% (519/522), and 100% (21/21) in patients receiving 8, 12 and 16 weeks of treatment, respectively (Figure 2a). The SVR12 rate was 98.9% (2,459/2,487), 99.0% (400/404), 99.5% (187/188) and 98.5% (64/65) in treatment-naïve noncirrhotic, treatment-naïve cirrhotic, treatment-experienced noncirrhotic and treatment-experienced cirrhotic patients, respectively (Figure 2b). When stratified according to HCV genotype, the proportion of SVR12 was 99.4% (2,971/2,998) in GT1, 99.0% (1,767/1,785) in GT2, 95.2% (139/146) in GT3, 100% (1/1) in GT4, 100% (1/1) in GT5, 98.5% (262/266) in GT6 and 100% (81/81) in mixed or unclassified genotype (Figure 3a). Noteworthy, the SVR12 rate was 98.2% (108/110) for the treatment-naïve cirrhotic patients who received GLE/PIB for 8 weeks (Figure 2b).

Subgroup analysis for SVR12

For the SVR rate in selected subgroups of special interest, it was 97.9% (595/608) for patients with baseline HCV RNA level > 6,000,000 IU/mL, 96.1% (148/154) for HIV-coinfection patients, 98.8% (245/248) for HBV-coinfection patients, 90.2% (37/41) for people who inject drugs (PWID), and 100% (6/6) for patients with adherence < 80% (Figure 3b). The treatment responses in patients with different HCV genotypes stratified by treatment duration are shown in Supplementary Table 1.

Univariate and subsequent multivariate logistic regression analyses showed that age, GLE/PIB treatment duration, treatment adherence, prior antiviral treatment failure, liver cirrhosis, or comorbidities such as HBV or HIV co-infection, HCC, or CKD were not associated with GLE/PIB treatment outcomes. It is also noted that albeit the male gender (odds ratio [OR]/95% confidence intervals [CI]: 3.25/1.31-8.07, P=0.01), baseline HCV RNA levels (OR/CI: 1.88/1.19-2.99, P<0.01), HCV GT3 (OR/CI: 2.96/1.20-7.29, P=0.02) and intravenous drug abuse (OR/CI: 5.51 /1.44-21.0, P=0.01) were associated with a low rate of SVR12, the SVR12 rates for all patient subgroups were similarly high (> 95%) with the sole exception for PWID (Table 2).

Safety

As shown in Table 3, 864 patients (27.5%) experienced AEs. The most common AEs ($\geq 1\%$ of total patients) were fatigue (7.5%), pruritus (6.7%) and dizziness (1.5%). Eight patients (0.3%) had documented serious AEs (eye ptosis, arrhythmia, upper gastrointestinal tract bleeding, acute on chronic kidney disease, hepatic nodule, HCC, dizziness, recurrent HCC, and colon cancer). The proportion of abnormal liver function were also displayed. The causality of the adverse events and laboratory abnormalities were not presented as its assessment was not mandatory according to the TACR database.

Health care resource utilization

The mean number (mean \pm SD) of outpatient visits during the GLE/PIB treatment (from GLE/PIB initiation to SVR 12 survey visit) was 6.11 ± 1.00 visits for all patients, with 5.94 ± 0.88 visits for patients receiving 8-week regimen, 6.90 ± 1.16 visits for patients receiving 12-week regimen, and 6.77 ± 1.07 visits for patients receiving 16-week regimen. There was a statistically significant difference in the number of visits between the patients receiving 8-week and 12-week regimens ($p < 0.0001$).

Discussion

Real-world data and the results from clinical studies are complementary to each other, both provide valuable information in routine clinical practice. The result of this nation-wide, large-scaled study indicates that GLE/PIB is an effective and well-tolerated pangenotypic DAA for Taiwanese patients with CHC infection irrespective of host or viral diversities in the real-world setting.

The characteristics of this patient cohort were generally representative, as the majority of the 3,144 patients were non-cirrhotic (85.1%) and had not undergone other HCV treatment prior to GLE/PIB (92.0%). In accordance with the TFDA-approved label at the time of enrollment, 2,601 (82.7%) of the patients received 8-week treatment regimen. Similar to the previous real-world reports of GLE/PIB, a large part (56.8%) of the current cohort had GT2 infection, in contrast to the overall genotype distribution in Taiwan, which was dominant by GT1. [13, 14] The preponderance of GT2 CHC in GLE/PIB reports reflected the evolution of DAAs, that the treatments of GT1 CHC were licensed earlier than the treatments of other genotypes. [14]

The overall SVR12 rate of 98.9% was comparable with the registrational phase II and III clinical studies [10, 11] and previously published real-world reports. [13, 14, 15, 17] Even when stratified according to cirrhosis status and treatment experience, GLE/PIB demonstrated a similarly high SVR12 rate of 98.5% in the more difficult-to-treat patients who were cirrhotic and had exposed to previous HCV treatment.

In addition, this study reinforced the effectiveness of GLE/PIB in several subpopulations of interest, including patients with HIV or HBV dual infections or with comorbidities such as HCC or CKD. The favorable treatment outcome in CHC patients dually infected with HIV has been previously proven in clinical trials and real-world reports. [10, 13] Unlike most western countries, both HBV and HCV are endemic in Taiwan [18]. However, the treatment efficacy of GLE/PIB in patients with HBV/HCV dual infection has rarely been validated on a large population basis [13, 19]. In the present cohort, the SVR12

rate of the 248 patients (7.9%) with HBV/HCV dual infection was equally high (98.8%) as in the HCV mono-infected patients (98.9%).

It has been previously reported that patients with active HCC are prone to encounter DAA treatment failure[15, 20], yet the information is scarce with patients who received GLE/PIB. Ninety patients (2.9%) of the present cohort had documented active HCC, and the SVR12 rate of 97.8% was comparable to the patients without a history of HCC (98.9%) or with inactive HCC (100%). As for the 830 patients (26.4%) with renal impairment, the high SVR12 rate of 99.5% was also in line with the previous observations of GLE/PIB. [13, 17, 21] The results of the univariate and subsequent multivariate logistic regression analyses in this study also indicated that the comorbidities of HCC or CKD were not associated with the efficacy outcome of GLE/PIB.

It is important to report the potential factors associated with a lower SVR12 rate. In contrast to the data reported in registration trials [10], lower SVR rates were observed to be associated with males, high baseline HCV RNA levels, HCV GT3 and intravenous drug abuse in the current study. Other large-scaled real-world reports and post marketing observational studies for GLE/PIB have reported conflicting results of the predicting factors including the male gender [22, 23], HCV viral load at baseline [23, 24], GT3 [24, 25] and people who use drugs. [22, 25] It is worth noting that the SVR12 rates remained high (> 95%) for all subgroups analyzed, excepting a numerically lower SVR12 rate of 90.2% for PWID, but it might have been affected by the small number of patients (41, 1.3%).

The phase 3 EXPEDITION-8 trial reported that for the treatment-naïve patients with compensated cirrhosis, 8 weeks of GLE/PIB achieved a high SVR12 rate of 99.7%. [8] Based on this trial, an 8-week GLE/PIB regimen for treatment of cirrhotic patients who received no prior HCV treatment was approved by TFDA in April 2020. It is hoped that reducing treatment duration may help to address remaining gaps in the cascade of care of HCV [4], yet there have only been very limited real-world studies of the effect of the 8-week GLE/PIB regimen on the treatment-naïve patients with compensated cirrhosis [23, 26, 27]. The present study demonstrated that 8 weeks of GLE/PIB achieved a high SVR12 rate (98.2%) in 110 treatment-naïve Taiwanese patients with compensated cirrhosis, supporting the results of EXPEDITION-8. [8]

No specific safety issues were observed from GLE/PIB initiation to the SVR12 survey visit, and the common adverse events were similar to what had been reported in clinical studies [11] or real-world publications. [17, 27]

Compared with the 12-week regimen, 8-week GLE/PIB was associated with a reduction in healthcare resource utilization (5.94 visits vs. 6.90 visits), determined by the number of clinic visits. In consistence with previous reports, the shorter, 8-week treatment with GLE/PIB can reduce healthcare resource use, which may further reduce the health and cost burden of the disease. [28]

Real-world observational studies such as this have inherent limitations. Firstly, the treatment outcomes for certain populations may be inconclusive due to limited patient numbers, such as patients who

injected drugs, with HCV GT 4 or 5 infection, or receiving 16-week regimen. Secondly, for the treatment naïve patients with compensated cirrhosis, the 8-week treatment emerged only very recently, and thus only a small portion of such patients were treated for the shorter course. Lastly, the information of drug abuse and data of adverse events were subject to reporting biases, and the causal relationships between the AEs and the treatment could not be fully established.

In conclusion, the result of this study demonstrated that based on the first and largest real-world, nationwide registry in Taiwan, GLE/PIB was highly effective and safe in treating CHC patients across viral genotypes and special subgroups including treatment-experienced or cirrhotic patients. This study also adds to the growing body of evidence supporting that the shorter, 8-week GLE/PIB regimen may be an effective and cost-saving pangenotypic treatment option for the majority of patients with CHC infection.

Abbreviations

CHC, chronic hepatitis C; DAA, direct-acting antiviral agents; GLE, glecaprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PIB, Pibrentasvir; SAE, serious adverse event; SVR, sustained virological response.

Declarations

Acknowledgments

The authors would like to thank the Taiwan Association for the Study of the Liver (TASL), the TASL Foundation and Taiwan Liver Research Foundation for grant support and the TACR study group for data collection. We also thank the Center for Medical informatics and Statistics of Kaohsiung Medical University for providing administrative and funding support.

Funding

The study was supported by grants from Kaohsiung Medical University (100CM-KMU-09, KMU-KI110002, MOST 108-2314-B-037 -066 -MY3, KMU-TC109B05 [Center for Liquid Biopsy and Cohort Research], KMU-TC109A04 [Center for Cancer Research]) and Kaohsiung Medical University Hospital (KMUH109-9R06, KMUH-DK(C)110011, KMUH-DK(C)110004, KMUH109-9R05).

Conflict of interest:

Ming-Lung Yu

Research support from Abbvie, Abbott, BMS, Gilead, Merck and Roche.

Consultant for Abbvie, Abbott, Ascletis, BMS, Gilead, J&J, Merck, Novartis, Pharmaessential and Roche.
Speaker for Abbvie, Abbott, Ascletis, BMS, Gilead, Merck, Pharmaessential and Roche.

Chung-Feng Huang

Speaker for Abbvie, BMS, Gilead, Merck, and Roche.

Contributions of authors:

Conception and design: MLY

Acquisition of data: CFH, HTK, TSC, CCL, CHH, CWH, LWC, PNC, MLY, CYP, CYC, JFH, MJB, CLL, CCY, SJW, TYH, THL, PLL, WCW, CLL, WWS, SSY, CCW, JTH, LRM, CTC, YHH, CCC, CSH, GYC, CNK, CMT, CJL, MHL, PCT, CYD, JHK, HCL, WLC, CYC, KCT

Data analysis and interpretation: CFH, PCT and MLY.

Manuscript drafting and critical revision: CFH and MLY.

Approval of the final version of the manuscript: MLY.

References

1. World Health Organization, Global Health Sector Strategy on Viral Hepatitis 2016-2021. WHO, <https://apps.who.int/iris/bitstream/handle/10665/246177/WHO?sequence=1> (accessed on 27th June 2021).
2. Yu ML, Yeh ML, Tsai PC, et al. Huge gap between clinical efficacy and community effectiveness in the treatment of chronic hepatitis C: a nationwide survey in Taiwan. Medicine 2015, 94:e690.
3. Yang JF, Lin CI, Huang JF, et al. Viral hepatitis infections in southern Taiwan: a multicenter community-based study. The Kaohsiung journal of medical sciences 2010, 26:461-9.
4. Yu ML and Chuang WL. Path from the discovery to the elimination of hepatitis C virus: honoring the winners of the Nobel Prize in Physiology or Medicine 2020. The Kaohsiung Journal of Medical Sciences 2021, 37(1):7-11.
5. https://www.nhi.gov.tw/Content_List.aspx?n=A4EFF6CD1C4891CA&topn=3FC7D09599D25979 (accessed on 10th February 2021)
6. Yu ML, Chen PJ, Dai CY, et al. 2020 Taiwan consensus statement on the management of hepatitis C: part (I) general population. Journal of the Formosan Medical Association 2020, 119:1019-40.
7. Yu ML, Chen PJ, Dai CY, et al. 2020 Taiwan consensus statement on the management of hepatitis C: Part (II) special populations. Journal of the Formosan Medical Association 2020, 119(7):1135-1157.
8. Brown RS, Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1–6 and compensated cirrhosis: The EXPEDITION-8 trial. Journal of Hepatology 2020, 72(3):441-449.
9. AbbVie Inc. MAVIRET (glecaprevir/pibrentasvir) summary of product characteristics. <https://www.ema.europa.eu/en/medicines/human/EPAR/maviret> (accessed on 10 February 2021)

10. Puoti M, Foster GR, Wang S, et al. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: an integrated analysis of HCV genotype 1–6 patients without cirrhosis. *Journal of Hepatology* 2018;69(2):293-300.
11. Gane E, Poordad F, Zadeikis N, et al. Safety and pharmacokinetics of glecaprevir/pibrentasvir in adults with chronic genotype 1–6 hepatitis C virus infections and compensated liver disease. *Clinical Infectious Diseases* 2019;69(10):1657-1664.
12. Huang CF, Yeh ML, Huang CI, et al. Equal treatment efficacy of direct-acting antivirals in patients with chronic hepatitis C and hepatocellular carcinoma? A prospective cohort study. *BMJ open* 2019; 9:e026703.
13. Liu CH, Liu CJ, Hung CC. Glecaprevir/pibrentasvir for patients with chronic hepatitis C virus infection: Real-world effectiveness and safety in Taiwan. *Liver international : official journal of the International Association for the Study of the Liver* 2020; 40:758-68.
14. Hsu SJ, Chiu MC, Fang YJ, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in Asian patients with chronic hepatitis C. *Journal of the Formosan Medical Association* 2019;118(8):1187-1192
15. Chen CY, Huang CF, Cheng PN, et al. Factors associated with treatment failure of direct-acting antivirals for chronic hepatitis C: A real-world nationwide hepatitis C virus registry programme in Taiwan. *Liver International* 2021; doi: 10.1111/liv.14849.
16. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3:1–15.
17. Lampertico P, Carrió JA, Curry M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: A meta-analysis. *Journal of Hepatology* 2020; 72(6):1112-1121.
18. Chen DS, Kuo GC, Sung JL, et al. Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. *The Journal of Infectious Diseases* 1990;162(4):817–822.
19. Park YJ, Woo HY, Heo J, et al. Real-life effectiveness and safety of glecaprevir/pibrentasvir for Korean patients with chronic hepatitis C at a single institution. *Gut and Liver* 2020. doi: 10.5009/gnl19393.
20. Huang CF, Yu ML. Unmet needs of chronic hepatitis C in the era of direct-acting antiviral therapy. *Clin Mol Hepatol* 2020; 26:251-60.
21. Gane E, Lawitz , Pugatch D, et al. Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment. *New England Journal of Medicine* 2017; 377:1448-1455.
22. Persico M, Aglitti A, Milella M, et al. Real-life glecaprevir/pibrentasvir in a large cohort of patients with hepatitis C virus infection: The MISTRAL study. *Liver International* 2019;39(10):1852-1859.
23. Zarębska-Michaluk D, Jaroszewicz J, Pabjan P, et al. Is an 8-week regimen of glecaprevir/pibrentasvir sufficient for all hepatitis C virus infected patients in the real-world experience? *Journal of*

Gastroenterology and Hepatology 2020. doi: 10.1111/jgh.15337.

24. D'Ambrosio R, Pasulo L, Puoti M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. *Journal of Hepatology* 2019;70(3):379-387.
25. Aghemo A, Alberti A, Andreone P, et al. Effectiveness and safety of glecaprevir/pibrentasvir in chronic hepatitis C patients: Results of the Italian cohort of a post-marketing observational study. *Digestive and Liver Disease* 2020 Sep 8;S1590-8658(20)30401-1.
26. Lampertico P, Mauss S, Persico M, et al. Real-world clinical practice use of 8-week glecaprevir/pibrentasvir in treatment-naïve patients with compensated cirrhosis. *Advances in Therapy* 2020;37(9):4033-4042.
27. Wedemeyer H, Erren P, Naumann U, et al. Glecaprevir/pibrentasvir is safe and effective in hepatitis C patients with cirrhosis: Real-world data from the German Hepatitis C-Registry. *Liver International* 2021;41(5):949-955.
28. Gschwantler M, Hametner S, Maierov A, et al. Health related quality of life and healthcare resource utilization in chronic HCV patients under the glecaprevir/pibrentasvir regimen: interim-analysis of the Austrian CONFIRMATION study. *Zeitschrift fur Gastroenterologie* 2019;57(05):e159.

Tables

Table 1. Baseline characteristics

Characteristics	All patients (n=3,144)	8-week (n=2,601)	12-week (n=522)	16-week (n=21)
Age (years), mean±SD	58.9±13.1	58.1±13.2	63.4±12.1	54.7±10.8
Age > 65 y, n(%)	1,141 (36.3)	876 (33.7)	260 (49.8)	5 (22.7)
Male,n(%)	1,595 (50.7)	1,315 (50.6)	267 (51.2)	13 (61.9)
HCV genotype				
1, n (%)	864 (27.5)	741 (28.5)	112 (21.5)	11 (50.0)
2, n (%)	1,785 (56.8)	1,456 (56.0)	329 (63.0)	0 (0.0)
3, n (%)	146 (4.6)	105 (4.0)	31 (5.9)	10 (47.6)
4, n (%)	1 (0.03)	0 (0.0)	1 (0.2)	0 (0.0)
5, n (%)	1 (0.03)	1 (0.04)	0 (0.0)	0 (0.0)
6, n (%)	266 (8.5)	239 (9.2)	27 (5.2)	0 (0.0)
Mixed, n (%)	51 (1.6)	35 (1.4)	16 (3.1)	0 (0.0)
Unclassified, n (%)	30 (1.0)	24 (0.9)	6 (1.2)	0 (0.0)
HCV RNA, log ₁₀ IU/mL, mean±SD	5.9±1.1	5.9±1.1	5.9±1.0	6.2±0.7
HCV RNA > 6,000,000 IU/ml, n (%)	608 (19.3)	506 (19.5)	97 (18.6)	5 (23.8)
Prior antiviral retreatment				
Naïve, n(%)	2,891 (92.0)	2,428 (93.3)	458 (87.7)	5 (23.8)
IFN-based Experienced, n(%)	253 (8.0)	173 (6.7)	64 (12.3)	16 (76.2)
Liver Cirrhosis				
No, n (%)	2,675 (85.1)	2,478 (95.3)	188 (36.0)	9 (42.9)
Yes, n (%)	469 (14.9)	123 (4.7)	334 (64.0)	12 (57.1)
HBV coinfection ,n(%)	248 (7.9)	195 (7.5)	52 (9.9)	1 (4.6)
HIV coinfection, n(%)	154 (4.9)	148 (5.7)	5 (1.0)	1 (4.8)
History of HCC				
No HCC, n (%)	3,027 (96.3)	2,561 (98.5)	448 (85.8)	18 (85.7)
Active HCC, n (%)	90 (2.9)	33 (1.3)	54 (10.3)	3 (14.3)
Inactive HCC, n(%)	27 (0.9)	7 (0.3)	20 (3.8)	0 (0.0)

CKD				
No	2,314 (73.6)	1,987 (76.4)	310 (59.4)	17 (81.0)
Yes	830 (26.4)	614 (23.6)	212 (40.6)	4 (19.1)
PWID, n (%)	41 (1.3)	38 (1.5)	3 (0.6)	0 (0.0)

Note: HBV, hepatitis B virus; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; CKD, chronic kidney disease; PWID, patients who inject drugs.

Table 2. Univariate and multivariate logistic regression analysis for predicting factors associated with SVR12

Predictor	SVR12, n/N(%)	Unadjusted OR (95% CI)	P- value	Adjusted OR (95% CI)	P- value
Age		1.05 (1.02-1.07)	<0.01	1.03 (1.00- 1.06)	0.08
Gender					
Female	1,543/1,549 (99.6)	Ref.		Ref.	
Male	1,567/1,595 (98.2)	0.22 (0.09-0.53)	<0.01	0.31 (0.12- 0.76)	0.01
Prior HCV treatment					
No	2,859/2,891 (98.9)	Ref.			
Yes	251/253 (99.2)	1.40 (0.33-5.90)	0.64		
HBV coinfection					
No	2,865/2,896 (98.9)	Ref.			
Yes	245/248 (98.8)	0.88 (0.27-2.91)	0.84		
HIV coinfection					
No	2,962/2,990 (99.1)	Ref.		Ref.	
Yes	148/154 (96.1)	0.23 (0.10-0.58)	<0.01	0.95 (0.31- 2.94)	0.94
History of HCC					
No	2,995/3,027 (98.9)	Ref.			
Active HCC	88/90 (97.8)	0.47 (0.11-1.99)	0.31		
Inactive HCC	27/27 (100.0)	-	-		
Liver Cirrhosis					
No	2,646/2,675 (98.9)	Ref.			
Yes	464 /469 (98.9)	1.02 (0.39-2.64)	0.97		
HCV RNA, log		0.48 (0.30-0.77)	<0.01	0.53 (0.33- 0.84)	<0.01
<= 6,000,000	2,515/2,536	Ref.			

IU/ml	(99.2)					
> 6,000,000 IU/ml	595/608 (97.9)	0.38 (0.19-0.77)	<0.01			
HCV genotype						
Non-GT3	2,971/2,998 (99.1)	Ref.		Ref.		
GT3	139/146 (95.2)	0.18 (0.08-0.42)	<0.01	0.34 (0.14-0.83)	0.02	
PWID						
No	3,073/3,103 (99.0)	Ref.		Ref.		
Yes	37/41 (90.2)	0.09 (0.03-0.27)	<0.01	0.18 (0.05-0.69)	0.01	
CKD						
No	2,284/2,314 (98.7)	Ref.				
Yes	826/830 (99.5)	2.71 (0.95-7.72)	0.06			
Treatment Duration						
8 week	2,570/2,601 (98.8)	Ref.				
12 week	519/522 (99.4)	2.09 (0.64-6.85)	0.23			
16 week	21/21 (100.0)	-	-	-		
Adherence						
>80%	3,104/3,138 (98.9)	-	-	-		
<80%	6/6 (100.0)	-	-	-		

Note: HBV, hepatitis B virus; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; CKD, chronic kidney disease; PWID, patients who inject drugs; GT, genotype.

Table 3. Patients with adverse events (AEs)

Event, n (%)	All patients (n=3,144)	8-week (n=2,601)	12-week (n=522)	16-week (n=21)
Any adverse event	864 (27.5)	636 (24.5)	225 (43.1)	3 (14.3)
Serious adverse event	8 (0.3)	6 (0.2) ^a	2 (0.4) ^b	0 (0.0)
Adverse event occurring in $\geq 1\%$ of total patients				
Fatigue	237 (7.5)	181 (7.0)	56 (10.7)	0 (0.0)
Pruritus	210 (6.7)	156 (6.0)	53 (10.2)	1 (4.6)
Dizziness	48 (1.5)	38 (1.5)	10 (1.9)	0 (0.0)
Total Blood bilirubin increased ¹				
Grade 1	15 (0.5)	9 (0.4)	6 (1.2)	0 (0.0)
Grade 2	74 (2.4)	58 (2.2)	16 (3.1)	0 (0.0)
Grade 3	9 (0.3)	5 (0.2)	4 (0.8)	0 (0.0)
Alanine aminotransferase increased ²				
Grade 1	23 (0.7)	16 (0.6)	7 (1.3)	0 (0.0)
Grade 2	26 (0.8)	19 (0.7)	7 (1.3)	0 (0.0)
Grade 3-4	20 (0.6)	15 (0.6)	5 (0.9)	0 (0.0)
Aspartate aminotransferase increased ²				
Grade 1	31 (1.0)	26 (1.0)	4 (0.8)	1 (4.8)
Grade 2	9 (0.3)	6 (0.2)	3 (0.6)	0 (0.0)
Grade 3-4	21 (0.7)	16 (0.6)	5 (1.0)	0 (0.0)

a:1 patient Rt eye ptosis ; 1 patient Arrhythmia; 1 patient Upper gastrointestinal tract bleeding, acute on Chronic kidney disease;1 patient Liver nodule;1 patient Hepatocellular carcinoma;1 patient dizziness

b: 1 patient Hepatocellular carcinoma recurrent; 1 patient Colon cancer

Adverse Events graded based on CTCAE 5.0

¹ Total Blood bilirubin increased: Grade1: 1.0 ULN -1.5x ULN if baseline was normal; >1.0–1.5 x baseline if baseline was abnormal ; Grade2: >1.5–3.0 x ULN if baseline was normal; >1.5–3.0 x baseline if

baseline was abnormal ; Grade3: $>3.0 - 10.0 \times \text{ULN}$ if baseline was normal; $>3.0 - 10.0 \times \text{baseline}$ if baseline was abnormal

²Alanine aminotransferase/ Aspartate aminotransferase increased: Grade1: $>1.0 - 3.0 \times \text{ULN}$ if baseline was normal; $>1.5 - 3.0 \times \text{baseline}$ if baseline was abnormal; Grade2: $>3.0 - 5.0 \times \text{ULN}$ if baseline was normal; $>3.0 - 5.0 \times \text{baseline}$ if baseline was abnormalGrade3: $>5.0 - 20.0 \times \text{ULN}$ if baseline was normal; $>5.0 - 20.0 \times \text{baseline}$ if baseline was abnormal; Grade4: $>20.0 \times \text{ULN}$ if baseline was normal; $>20.0 \times \text{baseline}$ if baseline was abnormal

Figures

Figure 1

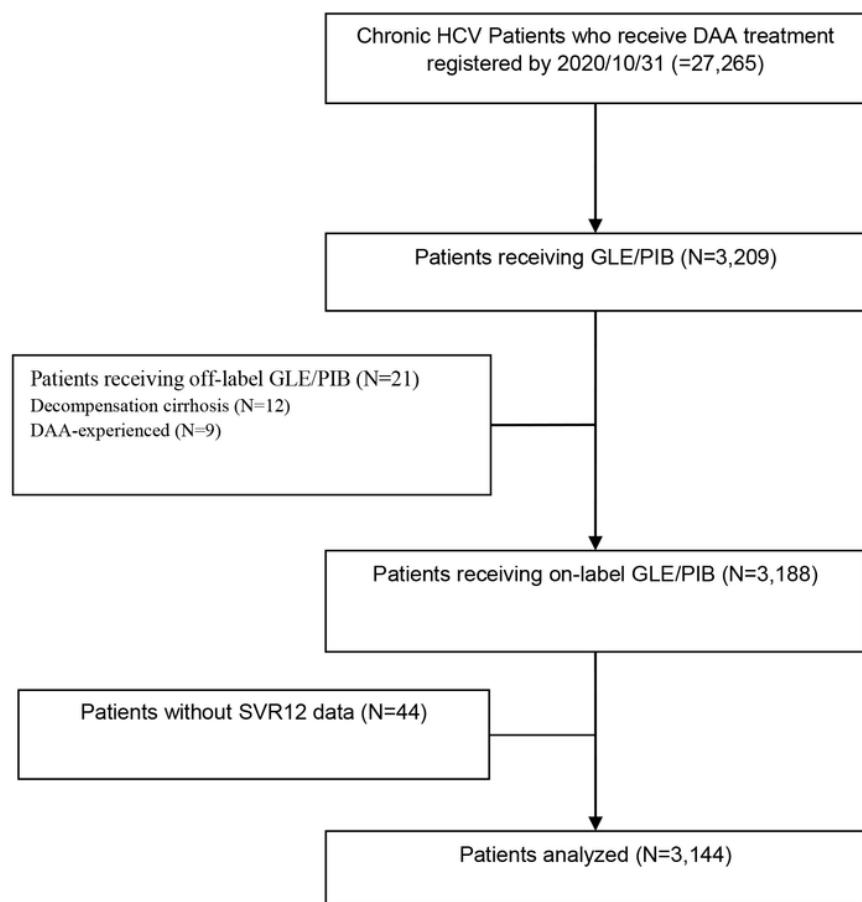


Figure 1

Study Flow

Figure 2

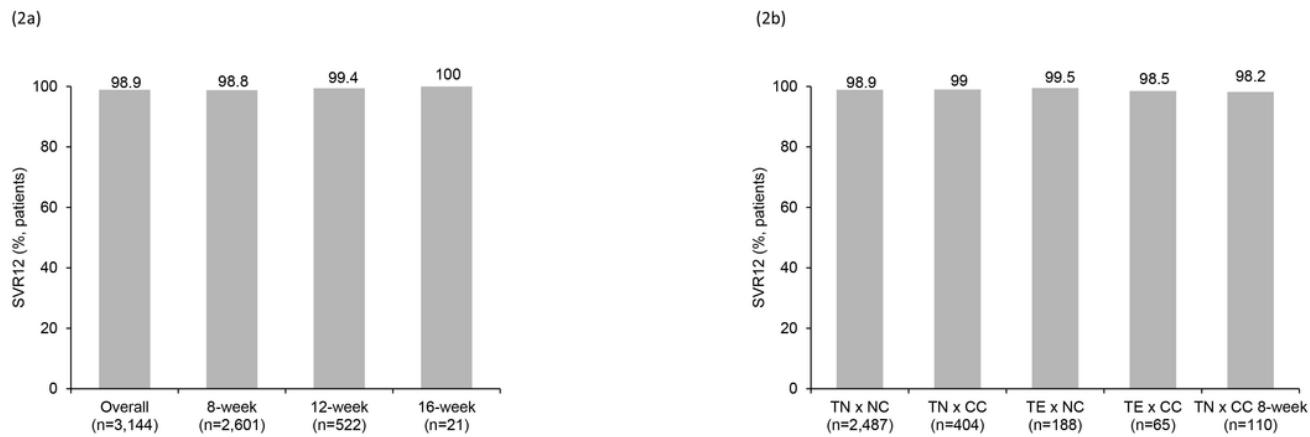


Figure 2

Rate of SVR12 stratified by different treatment durations (2a), or combinations of previous treatment history and liver cirrhosis status (2b) (TE, treatment experienced, TN, treatment naïve, CC, compensated cirrhosis, NC, non-cirrhotic)

Figure 3

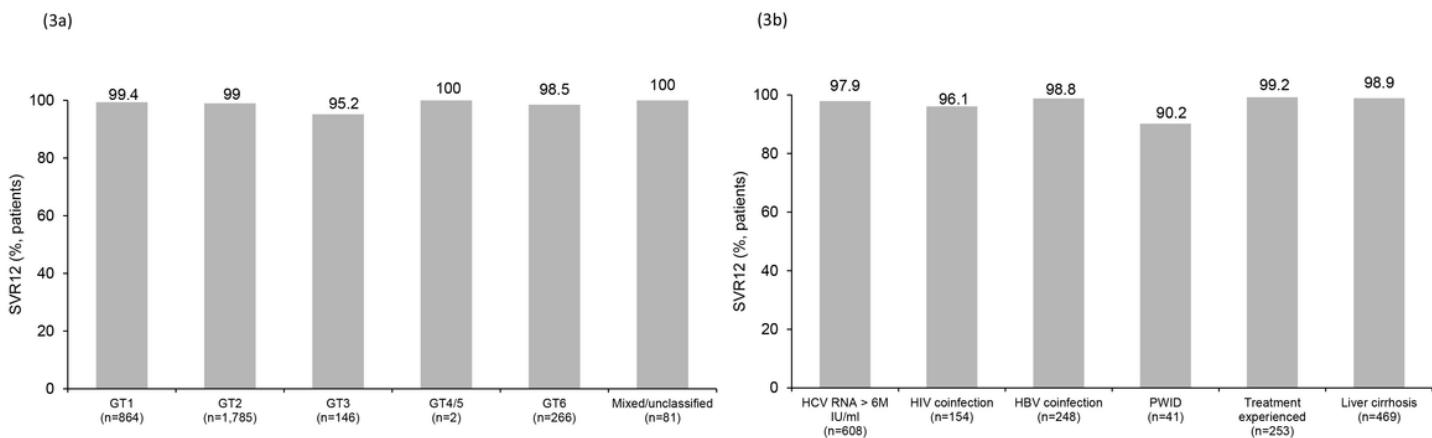


Figure 3

Rate of SVR12 stratified by different genotypes (3a), or in patient subgroups of interest (3b) (GT, genotype, PWID, people who inject drugs, HBV, hepatitis B virus, HIV, human immunodeficiency virus)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable.pdf](#)