Original Article

Efficacy and safety of glecaprevir and pibrentasvir in Saudi patients with chronic hepatitis C virus infection at a major tertiary hospital

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ABSTRACT

الأهداف: تقييم فعالية ومأمونية دواء قليكابرڤير/ بيبيرينتاسڤير في مرضى التهاب الكبد الوبائي سي، والتحقق من مدى التزام الأطباء بتوصيات هيئة الغذاء والدواء بشأن مدة العلاج الصحيحة.

المنهجية: الدراسة نُفذت بتصميم حشديه تراجعية لمرضى التهاب الكبد الوبائي سي المزمن لمن هم أكبر من أو يساوي 18 عام، بوجود تليف الكبد أو بدونه، ممن خضعوا للعلاج من قبل او بدونه، وبوظائف كلى طبيعية أو بقصور فيها بما في ذلك مرضى غسيل الكلى بمدينة الأمير سلطان الطبية العسكرية من فبراير 2020م إلى مارس 2021م. كانت نقطة نهاية الفعالية الأولية هي معرفة عدد ونسبة المرضى الذين حققوا الاستجابة الفيروسية المستمرة، الفشل والانتكاس الفيروسي. تم التحقق من مأمونية الدواء لكلٍ من الآثار السلبية الخطرة وغير الخطرة.

النتائج: إجماليا، تم تسجيل 92 مريضاً في هذه الدراسة. من بينهم 52 (56.5%) الإناث، وعدد 84 (91.3%) لم يستخدموا علاج الكبد الوبائي سي و45 (48.9%) لديهم نمط وراثي رابع. حققت الاستجابة الفيروسية المستمرة 91 (98.9%؛ CI:94-99.8). فقط مريض واحد (1.1%؛ فترة الثقة CI: 0.2-5.9) اكتسب انتكاسة فيروسية تحت ثقة 95%. لم تتوفر بيانات للتحقق من الفشل الفيروسي. بشكل عام، لوحظت آثار سلبية غير خطيرة في 26 (28.5%) ولم تسجل أي آثار سلبية خطيرة أدت إلى وقف استخدام الدواء. قرابة، 75% من المرضى تلقوا علاجاً لمدة غير مناسبة (8 مقابل 12 أسبوعاً)، الغالبية منهم تم وصفها من قبل الأطباء الأخصائيين 40 (p<0.022; 58%).

الخلاصة: دواء قليكابرڤير/ بيبيرينتاسڤير فعال وآمن في المرضى السعوديين لمن لديهم الكبد الوبائي سي.

Objectives: To evaluate the effectiveness and safety of glecaprevir/pibrentasvir (GLE/PIB) in chronic hepatitis C (HCV) patients, and to assess the prescribers' adherence to Food and Drug Administration recommendations on treatment duration.

Methods: A retrospective cohort study was carried out on chronic HCV patients of ≥18 years, with or without cirrhosis, naive or experienced, and with normal kidney function or chronic kidney disease (including dialysis patients) at Prince Sultan Military Medical City in Riyadh, Saudi Arabia, between February 2020 and March 2021. The primary effectiveness end-point was the number and percentage of patients who achieved a sustained virologic response (SVR12), virologic failure, and non-response. Safety was determined considering both serious and non-serious adverse events.

Results: A total of 92 patients were enrolled in this study. Among patients, 52 (56.5%) were female, 84 (91.3%) were naive, and 45 (48.9 %) had HCV genotype 4. The SVR12 was achieved in 91 (98.9%, 95% CI: [94-99.8]) patients. Only one patient (1.1%, 95% CI: [0.2-5.9]) developed virologic non-response and there were missing data on virologic failure. Overall, non-serious adverse events were observed in 26 (28.5%) patients, and none of them had serious adverse events that led to treatment discontinuation. Approximately 75% of the patients received an inappropriate treatment duration (12 weeks vs. the recommended 8 weeks) and most (n=40, 58%; p<0.022) of the exceedingly long treatments were prescribed by registrars.

Conclusion: The GLE/PIB was highly effective and safe in chronic HCV Saudi patients.

Keywords: hepatitis C virus, direct-acting antiviral agent, chronic kidney disease, glecaprevir, pibrentasvir, Saudi Arabia

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Hepatitis C virus (HCV) infection is considered an international health issue affecting 71 million people worldwide.[1] In Saudi Arabia, it is estimated that approximately 101,000 people are infected with HCV.[2] Thereby, the Saudi national operational strategy aims to attain the eradication of HCV in Saudi Arabia in accordance with the guidelines of the World Health Organization (WHO) by diagnosing 90% of HCV-infected people and treating 80% of them.[3] Patients with HCV are at a potential risk of developing liver fibrosis, which may progress to liver cirrhosis and hepatocellular carcinoma.[4] Moreover, HCV may cause extrahepatic manifestations including accelerated progression of chronic kidney disease (CKD), cryoglobulinemic vasculitis, B-cell lymphoproliferative disease, insulin resistance, neurocognitive, and cardiovascular disorders.[5] The prevalence of HCV in patients with CKD or end-stage renal disease (ESRD) has historically been higher than in the general population, and the incidence is substantially increased in those who have undergone hemodialysis.[6,7] Thereby, antiviral therapy is recommended for treating chronic HCV patients to attain unpredictable serum or plasma HCV RNA 12 weeks post-treatment.[8]

The advent of interferon-free direct-acting antiviral therapies has revolutionized the treatment landscape of HCV because these agents possess a wide variety of features including the targeting of HCV viral replication, high sustained virologic response (SVR) rates, and few adverse events (AE).[9] According to the guidelines of the American Association for the Study of Liver Disease, the most recommended direct acting antivirals for chronic HCV in CKD patients, including those on hemodialysis, are elbasvir/grazoprevir and glecaprevir/pibrentasvir (GLE/PIB). However, in November 2019, the Food and Drug Administration of the United States (FDA) revised the labeling for sofosbuvir based-regimens to allow its use in patients with renal impairment, including those with an estimated glomerular filtration rate (eGFR) of ≤30 mL/minute (min) and patients on dialysis.[10]

Glecaprevir/pibrentasvir are oral interferon-free agents in a pan-genotypic fixed co-formulated regimen with a high resistance barrier and potent antiviral activity. These agents obtained FDA approval on August 2017 and marketing authorization was granted in Saudi Arabia on September 2019 for the treatment of chronic HCV patients with or without cirrhosis, including naive and experienced patients.[11,12] The approved treatment duration is 8 weeks for naive patients with or without cirrhosis. For experienced patients, treatment ranges from 8-16 weeks depending on the HCV genotype, previous HCV treatment experience, and cirrhosis status.[13,14] The aim of this study was to evaluate both the effectiveness and safety of GLE/PIB across all chronic HCV Saudi populations who had been treated in a single tertiary hospital.

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Methods. A retrospective cohort study was carried out at a single tertiary hospital in Riyadh, Saudi Arabia. The aim of this study was to evaluate both the effectiveness and safety of this co-formulated medication (GLE/PIB) in all chronic HCV adult patients with HCV genotypes 1-6 (GT1-6) between February 2020 and March 2021. Patients who were naive or experienced, without cirrhosis or with compensated cirrhosis, CKD patients including those in stages 3b, 4, and 5 (with or without hemodialysis), and those with normal renal function were included. Clinical and demographic variables including age, gender, body weight, fibrosis stage, HCV genotype, Child-Pugh score, presence of comorbidities, renal and liver function tests, CKD stages, and mode of dialysis were obtained from the hospital's electronic system.

The stage of liver fibrosis was determined with either a liver biopsy or FibroScan prior to treatment initiation. The CKD stage was evaluated according to the kidney disease: improving global outcomes categorization, as follows: stage 1: if eGFR is ≥90 mL/min/1.73 m^2; stage 2: if eGFR is 89-60 mL/min/1.73 m^2, stage 3a: if eGFR is 59-46 mL/min/1.73 m^2; stage 3b: if eGFR is 45-30 mL/min/1.73 m^2; stage 4: if eGFR is 29-15 mL/min/1.73 m^2; and stage 5: (as ESRD) if eGFR is <15 mL/min/1.73 m^2.

All enrolled patients met the following criteria: adult (≥18 years) with a chronic HCV GT1-6 infection (including mixed GTs); positive plasma HCV antibody and viral load of ≥1000 IU/mL; with or without fibrosis (F0-F3 by FibroScan), with compensated cirrhosis (F4 by FibroScan and Child-Pugh score of <6), or decompensated cirrhosis (Child-Pugh score of ≥7); normal renal function or CKD including dialysis patients; naive or experienced patients who had received HCV treatment with interferon or pegylated interferon (PegIFN; with or without ribavirin [RBV]) or sofosbuvir (SOF) plus RBV (with or without PegIFN). Hepatitis C virus/HIV coinfected patients except those who were treated with efavirenz, etravirine, nevirapine, and ritonavir containing antiretroviral regimen, and

HCV/HBV coinfected patients. However, none of the patients were co-infected with HBV or HCV.

Patients were excluded if they fulfilled any of the following criteria: I) history of drug or alcohol abuse as this may interfere with medication adherence and thus affect the study's outcomes; II) patients who had not completed the full course of treatment; and III) those whom missed the serum or plasma HCV RNA 12 test weeks post-treatment.

The primary effectiveness end-point was to determine the number and percentage of patients who attained a sustained virologic response, defined as HCV RNA of <30 IU/mL, 12 weeks after the last dose of GLE/PIB. The secondary end-points were: I) the percentage of patients who developed virological failure, defined as a confirmed elevation in the HCV RNA level of at least 100 IU/mL after measurement, HCV RNA of <30 IU/mL during the treatment, or HCV RNA of ≥30 IU/mL at 6 or more weeks after the end of the treatment; II) the percentage of virologic non-response among all treated patients was defined as HCV RNA of ≥30 IU/mL, 12 weeks after the last administered dose.

The prescribers' adherence to FDA-approved labeling recommendations on appropriate treatment duration (8 vs. 12 weeks) was assessed for both naive and experienced patients. The approved treatment duration was 8 weeks for naive cirrhotic and non-cirrhotic patients. However, for experienced patients who had previously been exposed to a regimen containing Peg (interferon), ribavirin, or sofosbuvir, the duration was 8 weeks for non-cirrhotic patients and 12 weeks for those with compensated cirrhosis. For experienced patients with genotypes 1 and 3, the duration was extended to 16 weeks for both cirrhotic and non-cirrhotic patients.

The safety of GLE/PIB was evaluated by reviewing laboratory abnormalities and AE as documented in the patient's file during the treatment period. Moreover, the severity of all AE and serious adverse events (SAE) was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 of the National Cancer Institute.

Statistical analysis. Descriptive statistics, such as frequencies and percentages (%), were calculated to summarize nominal data, while the mean and median were used to describe numerical variables. Inferential statistics such as a 95% confidence interval (CI) were calculated for the main outcomes and a Chi-squared test was carried out to evaluate the association between the determinants and the outcome variables. Ethical approval was obtained from the Institutional Review Board of Prince Sultan Military Medical City, Riyadh, Saudi Arabia (Ref. no.: 1584, August 23, 2021). Statistical analyses were carried out using the Statistical Package for the Social Sciences, version 26 (IBM Corp., Armonk, NY, USA). Any *p*-value of <0.05 was considered a significant association or difference.

Results. Of a total of 95 patients who received GLE/PIB, only 92 patients met the inclusion criteria, and 3 patients were excluded from this study (missing data on a single patient due to lack of HCV RNA test 12 weeks post treatment, another was a drug abuser who did not complete the course of treatment, and one died during the treatment period [received a 3-week of therapy] due to a road traffic accident). More than half of the patients were female (56.5%). The patients' ages ranged from 21-89 years (mean age: 59.7±15 years; Table 1).

At the baseline, the HCV RNA mean was 2.9×10^6 IU/mL, total bilirubin was 13.6 mcmol/L, and albumin was 38.4 g/L. A total of 76 (82.6%) patients had comorbidities. Most (n=63, 68.5%) had stages 0-III liver fibrosis, while 29 (31.5%) patients had stage VI liver fibrosis. Furthermore, 78 (84.8%) had a Child-Pugh score of A, while 4 (4.3%) were classified as having Child-Pugh scores of B, and 10 (10.9%) were classified as having Child-Pugh scores of C. A total of 73 (79.4%) patients were between stages 1-4 of CKD, 19 (20.6%) had stage 5 CKD, and 17 (18.5%) of them were on regular hemodialysis. Almost half of the patients (n=45, 48.9%) were infected with genotype 4 of HCV alone, followed by genotype 1 subtype b (n=11, 12%; Table 2). Moreover, 8 (8.7%) patients had experienced HCV therapy with either pegIFN (with or without RBV), or SOF plus RBV (with or without pegIFN).

Table 1 - Demographic general health characteristics of the respondents (n=92).

Characteristics	n (%)
Gender	
Male	40 (43.5)
Female	52 (56.5)
Age	
≤30	3 (3.3)
31-50	20 (21.7)
51-70	45 (48.9)
>70	24 (26.1)
Comorbidities	
No	16 (17.4)
Yes	76 (82.6)
Type of patient	
Naive	84 (91.3)
Experience	8 (8.7)

Values are presented as numbers and precentages (%).

Table 2 - Distribution of the clinical characteristics related kidney and liver status.

Characteristics	n (%)
Stages of liver fibrosis	
F 0	36 (39.1)
F I	10 (10.9)
F II	10 (10.9)
F III	7 (7.6)
F IV	29 (31.5)
Kidney stage	
G 1	30 (32.3)
G 2	28 (30.1)
G 3a	9 (9.7)
G 3b	3 (3.2)
G 4	3 (3.2)
G 5	19 (20.4)
On hemodialysis	
Yes	17 (18.5)
No	75 (81.5)
HCV genotype	
Not carried out	13 (14.1)
GT I	3 (3.3)
GT I (a)	6 (6.5)
GT I (b)	11 (12.0)
GT 1 & 4	5 (5.4)
GT 2	5 (5.4)
GT 2 & 3	1 (1.1)
GT 3	3 (3.3)
GT 4	45 (48.9)
Child-Pugh class	
A	78 (84.8)
B	4 (4.3)
C	10 (10.9)
Duration of treatment	
8 weeks	23 (25.0)
12 weeks	69 (75.0)

Values are presented as numbers and precentages (%). G: grade, F: stage of fibrosis, GT: genotype

Table 3 - Effectiveness and adherence of glecaprevir/pibrentasvir among Saudi population at a single tertiary hospital.

Outcomes	n (%)	95% CI
Overall SVR12	91 (98.9)	94-99.8
Virologic non-response	1 (1.1)	0.2-5.9
Virologic failure		
Yes	0 (2.2)	-
No	0 (94.6)	-
Missing data	92 (3.3)	-
Appropriate duration of treatment (8 vs 12 weeks)		
Yes	23 (25.0)	16.6-35.1
No	69 (75.0)	65.2-83
SVR12 achievement according to duration of treatment		
8 weeks	23 (100)	85-100
12 weeks	68 (98.5)	92.2-99.7

Values are presented as numbers and precentages and 95% confidence interval (CI). SVR12: sustained virologic response

Most patients had hypertension (60%), diabetes mellitus (45.6%), and dyslipidemia (15.6%). Other comorbidities were distributed with a lower prevalence among the patients.

Overall, 91 (98.9%, 95% CI: [94-99.8]) of all enrolled HCV patients with or without renal impairment achieved SVR12 post-treatment (Table 3). However, this was achieved in all 22 (100%) CKD patients at stages 4 and 5, including those on hemodialysis. Only one patient experienced a virologic non-response, which accounts for 1.1% of the total. Furthermore, the virologic failure was not assessed due to the lack of HCV RNA test results during the treatment course.

The adherence to the FDA approval recommendation on treatment duration was poor, as 69 (75%, 95% CI: [65.2-83]) patients received an inappropriate duration of 12 weeks instead of 8 weeks and no difference was identified between patients who received 8 or 12 weeks in terms of SVR12 rate achievement (Table 3). Most inappropriate prescriptions were issued by registrars (n=40, Chi-square: 5.2; $p<0.022$) compared to consultants (Table 4). Moreover, 14 (15.2%) of patients have decompensated liver cirrhosis and received inappropriate GLE/PIB as contraindicated in these group of patients by FDA labeling recommendation, 11 (12%) were issued by registrars and 3 (3.2%) by consultants (Chi-square: 4.9; $p<0.026$).

The safety of GLE/PIB was assessed during therapy and 4 weeks after treatment completion. Serious and non-serious AE were included. Post-baseline hepatic laboratory abnormalities and non-serious adverse events (NSAE) were detected in 26 (28.5%) patients. The alanine aminotransferase (ALT) mean during treatment was high (53.6±92.3 U/L), but it notably decreased after 4 weeks of treatment (25.8±27.5 U/L). According to the CTCAE, ALT was grade 0 in 91.2% of patients, and it was grade I in 6.6% of patients, and II in 2.2% of patients.

The bilirubin concentration was 14.5±17 during treatment and 12.9±16.1 after 4 weeks of treatment. According to CTCAE, 90.1% of patients had grade 0, while 4.4% had grade I, 2.2% had grade II, and 3.3% had grade III AE. The mean of the aminotransferase enzyme (AST) was 46.2 during treatment and 30.2 after 4 weeks of treatment. Based on CTCAE, 91.3% of patients had grade 0, while 5.4% had grade I, 2.2% had grade II, and 1.1% had grade III AE. Only one patient developed skin itching, which was considered a grade I adverse event by CTCAE (Table 5). Moreover, none of the patients experienced serious AE that were attributed to GLE/PIB or led to treatment interruptions.

Table 4 - Distribution of physicians who prescribed appropriate and inappropriate duration, either 8 or 12 months, according to FDA recommendation.

Physicians' grade	Appropriate duration according to FDA recommendation (8 vs 12 weeks)		Chi-square test	*P*-value
	Yes	No		
Registrars	7 (15.0)	40 (85.0)	5.2	0.022
Consultants	16 (36.0)	29 (64.0)		

Values are presented as numbers and precentages (%). FDA: US Food and Drug Administration

Table 5 - Safety of glecaprevir/pibrentasvir among Saudi population at a single tertiary hospital.

Outcomes	n (%)	95% CI
Elevation in ALT		
Grade 0	83 (91.2)	82.2-95.4
Grade I	6 (6.6)	2.4-13.7
Grade II	2 (2.2)	0.3-7.6
No data	1 (1.1)	-
Elevation in bilirubin		
Grade 0	82 (89.1)	80.9-94.7
Grade I	4 (4.3)	1.2-10.8
Grade II	2 (2.2)	0.3-7.6
Grade III	3 (3.3)	0.7-9.2
No data	1 (1.1)	-
Elevation in AST		
Grade 0	84 (91.3)	83.6-96.2
Grade I	5 (5.4)	1.8-12.2
Grade II	2 (2.2)	0.3-7.6
Grade III	1 (1.1)	-
Skin itching		
Grade I	1 (1.1)	-

Values are presented as numbers and precentages and and 95% confidence interval (CI). ALT: alanine aminotransferase, AST: aspartate transferase

Discussion. Glecaprevir/pibrentasvir is characterized as a pan-genotypic, ribavirin-free, and interferon-free regimen approved for chronic HCV patients. This co-formulated medication has demonstrated excellent effectiveness in a wide variety of clinical trials with negligible side effects, and a shorter duration of 8 weeks for naive or compensated cirrhotic patients.[15,16]

In this study, the enrolled population represented a high proportion of patients with comorbidities (82.6%), and more than half of them (60%) were known to have hypertension at baseline. Furthermore, among Saudi patients who were infected with HCV GT 1-6 including CKD patients with or without dialysis, GLE/PIB was effective and resulted in a high SVR rate 12 weeks post-treatment in 98.9% of all the enrolled population. Only one patient had virologic non-response, (a 70-year-old female who has a known case of hypertension, CKD stage 5 on hemodialysis, hypothyroidism, and liver cirrhosis with GT 4). Moreover, she had received inappropriate 3 months of therapy because she was naive). High SVR was achieved regardless of the host or viral factors, including GT status, degree of fibrosis, HCV RNA viral load, renal impairment, and patients' comorbidities. Remarkably, GLE/PIB was well tolerated, as none of the patients developed SAE that necessitated treatment discontinuation.

Most patients received an inappropriately long 12-week duration instead of 8 weeks. Registrars demonstrated a higher rate of extended duration (12 weeks) prescriptions, followed by consultants. Thereby, providing continuous education on proper treatment duration and implementing a hard-stop alert during order entry is encouraged as GLE/PIB is considered a high-cost burden medication.

In the EXPEDITATION-8 trial, SVR12 was demonstrated in 97.7% of all intention-to-treat patients, which is similar to our findings. Only one patient developed virologic relapse, whereas 2% developed SAE.[17] In another prospective, multicenter study, which enrolled chronic HCV Japanese patients infected with GTs1-3 and severe renal impairment, including those on hemodialysis, the SVR12 was 99.3% and only 3 (7.2%) patients had an AE that led to treatment discontinuation.[18] In EXPEDITATION-4, pruritis was the most common AE, with NSAE accounting for 21% (n=20/104).[19] In the present study, none of the patients had grade 3 or higher elevation in AST, ALT, or bilirubin as a post-baseline laboratory abnormality, which is consistent with the findings from the phase-3 multicenter study on Japanese patients.[20]

The NS3/4A or NS5 variants, which can lead to treatment-emergent resistance, was not analyzed for a patient who had a virologic failure due to a lack of documentation. As per our extensive literature review revealed, Saudi patients were not included in any of the previous original studies regarding the use of GLE/PIB. However, the high SVR12 achievement reported here is similar to that of other globally carried out clinical trials.

Study limitations. Including non-comparative design, carried out in a single tertiary hospital, and small

number of enrolled patients. Another limitation of the study is that, GT status was not evaluated in 13 (14.1%) patients. However, because GLE/PIB is a pan-genotypic drug, the SVR was achieved in all GT-untested patients. Furthermore, a few enrolled patients had GT 1, 2, and 3. However, these results reflect the low prevalence of these genotypes across Saudi Arabia.[21]

In conclusion, GLE/PIB was effective and safe among all enrolled Saudi patients who had chronic HCV with GT 1-6, with or without renal impairment, including those undergoing hemodialysis. An elevation in liver enzymes (ALT, AST, and bilirubin) was the most common laboratory abnormality detected as a non-serious adverse event. Optimizing the selection, duration of treatment, and providing a continuous education program for prescribers is tremendously encouraged.

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