Safety and Efficacy of Glecaprevir/Pibrentasvir in Chronic Kidney Disease, Compensated Cirrhosis and Non-Cirrhosis

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Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, if not treated promptly, can progress to potentially life-threatening complications of liver disease, including cirrhosis, hepatocellular carcinoma, liver failure, and death. There are 6 types of HCV genotypes globally: genotype 1 (1a and 1b), genotype 2, genotype 3, genotype 4, genotype 5 and genotype 6.
Exact data on the prevalence of HCV infection in Saudi Arabia is currently unavailable, as most HCV research was conducted over 10 years ago. The rate of Prevalence recorded for Saudi Arabia in various studies ranges from 0.22 - 1.1 %(1, 2). The most prevalent genotype (GT) is HCV GT4, followed by GT1(3). However, with advanced technologies, such as HCV gene sequencing, more genotypes will become evident.
Glecaprevir/Pibrentasvir (GLE/PIB) is a fixed-dose combination of (300 mg/120 mg once daily) 2 DAA therapies for the treatment of adult patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infections including treatment nieve and treatment experienced without cirrhosis or with compensated cirrhoisis, it is also approved for treatment of CKD pateints and those who are on dialysis (4) . Glecaprevir is an HCV NS3/4A PI, preventing the proteolytic cleavage of the HCV-encoded polyprotein into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins and thus preventing viral replication (5). Pibrentasvir is an HCV NS5A inhibitor, preventing viral RNA replication and virion assembly (6). However, there are no studies in saudi arabia

METHODS:

Study Design:

The study is a retrospective study which was conducted at King Fahad specialist Hospital, Buraidah between May 2019 and Aug 2022, in accordance with Good Clinical Practice guidelines and approved by regional institutional review boards and regulating agencies. Final manuscript was reviewed and approved by all the study authors. A fixed dose combination tablet containing Glecaprevir 100 mg once daily Pibrentasvir 40mg once daily ie 3 tablets at the same time with food was given to all participants

for 8 weeks or 12 weeks According to EASL practical guidelines on treatment of hepatitis C [(7)]

- Treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis and treatment experienced patients without cirrhosis should be treated without testing genotype/subtype with fixed-dose combination of glecaprevir and pibrentasvir for 8 weeks.
- Treatment-experienced patients with compensated (Child-Pugh A) cirrhosis should be treated without testing genotype/subtype fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks

Ptients with end stage renal disease are treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks [(8)]. Pateints with treatment failure or relapse after DAAs therapy are treated with sofospuvir 400 mg daily plus fixed dose combination of glecaprevir and pibren- tasvir for 12 weeks. [(9)] Drug drug interaction are reviewed through a key internet resource is www.hepdruginteractions.org where recommendations are regularly updated.

All participants were followed up for another 12 weeks to track their SVR status and monitor for side effects or adverse effects related to treatment. Dose modifications were not allowed. The study was terminated 12 weeks after completion of treatment.

Participants:

The participants included Male and female patients 18 years and older with HCV infection, any level of detectable HCV RNA, and a documented HCV infection. All cirrhotic participants were assigned a Child Pugh(CP) score based on clinical, laboratory data and MELD score based on laboratory data. Cirrhosis and non-cirrhosis was defined by clinical, radiological features and liver stiffness assessed by transient elastography with a value >12.5 kpa and <12.5 kpa respectively within six months of screening [(10-12)]. Patients with decompensated cirrhosis, co-infection with HBV or HIV, pregnancy or HCC were excluded from the study.

Assessment and Analysis:

The primary objective was to achieve SVR after 12 weeks of completing the treatment (SVR12), which is defined as HCV RNA <15 IU/mL (lower limit of quantitation; 15 IU/mL, lower limit of detection: 15 IU/mL). Efficacy is presented for the intention-to-treat population, which includes all participants who received ≥1 dose of the study medication.

The model for the end-stage liver disease (MELD) score and the CP score were analyzed at baseline and at follow-up during Week 24. Evaluation of safety was done by monitoring for adverse events and serious adverse events, with serious adverse events defined as events that may lead to treatment discontinuation or death. Analysis of laboratory abnormalities included grade 3/4 laboratory abnormality, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 5 times the upper limit of normal (ULN), and total bilirubin levels >2.6 mg/dL, and hemoglobin value of less than 8.9g/dl.

Statistical analysis was done using the Statistical Program for Social Analysis (SPSS version 22.0). Baseline patient characteristics are presented in numbers and percentages. A 95% confidence interval plot was plotted using the Clopper–Pearson method to assess the baseline patient characteristics that may affect SVR12. On-treatment and off-treatment viral response rates are presented in numbers and percentages. Confidence interval was calculated for changes in the CHILD and MELD scores, the safety profile summary is presented in numbers and percentages

RESULTS:

Sample Demography:

In our study, we assed data from 33 participants with HCV infection, of the 33 participants 14 were females and 19 were males. The mean age was 52.55+/-13.89 for all sample subjects, with predilection for a higher mean age in the cirrhotic subject at 57.6% . There were 26 cirrhotic participants with **CHILD A** and 7 non cirrhotic participants.

Three participants were relapse after treatment with 12 weeks of sofospuvir and daclatasvir. 17 patient's CKD out of which 4 patient's had CKD stage 1-3 and 13 patients' had CKD stage 4-5. Genotypes are done for all participants 16 were genotype 4, 12 were genotype 1a, 2 with genotype 1 b and 2 patients were genotype 2. single patient with genotype 3.

Pretreatment HCV RNA levels were >1000000 iu/ml in 19 participants (57.6%) and 14 participants have HCV RNA level of <1000000 iu/ml.

Treatment regimens:

Glecaprevir 300 mg, Pibrentasvir 120 mg was administered once daily to 30 patients for 8 weeks and 3 patients with relapse for 12 weeks. Twelve weeks after completion of treatment, 32 of the participants had

undetectable HCV RNA levels (100 % SVR rate in intention to treat population) and one patient lost for follow up.

Efficacy:

SVR was observed in 32 of participants and one patient in non-cirrhotic CKD patient stage 1-3 lost for follow up, at the end of 12 weeks of treatment.

Post treatment MELD score improved in 12 (46.2%) participants of the sample having a score less than 10, while 14 participants (53.8%) had a score more than 10.

CHILD SCORE: In the pretreatment group, 38.5% of the participants were CHILD A5 while after treatment completion, 76.9% of the participants were CHILD A5

Safety and tolerability:

Treatment related adverse events were noted in 5 participants in cirrhotic group, while no serious adverse events or laboratory abnormality that could result in treatment discontinuation was observed in any participant. There was no death or hepatic decompensation during treatment and on follow up. Single patient in cirrhotic reported fatigue and two patients in non-cirrhotic had itching and nausea. All treatment related adverse effects were subsided upon treatment discontinuation

Discussion:

In this open label, retrospective study, efficacy was demonstrated, with 99% of the study sample achieving SVR12 after completing the treatment course. Both cirrhotic and non-cirrhotic participants were equally responsive to the treatment regimen. Only 5 participants reported treatment-related adverse effects which disappeared on treatment completion. These findings provide evidence that the regimen is safe and effective.

The observed efficacy of the treatment regard to SVR12 with other studies are in compensated cirrhosis is as follows. In A total of 2169 CKD patients, 392 patients were stage 1, 413 patients were stage 2 and 17 patients were stage 3 SVR12 after 8 weeks of treatment was 96.4%, 98.5% and 94.1% respectively and SVR12 was 98.3% in 633stage 1 patients, 98% in593 stage 2 patients, 100% in 18 patients of stage 3 and 98.1% in stage 4-5 patients who ere treated for 12 weeks([13]) .

In a total of 141 CKD stage 4 and stage 5 patients, In 91 patients SVR 12 after 8 weeks was 98.9% and SVR 12 100% in 50patients who were treated for 12 weeks[(14)].

In a total of 343 compensated cirrhotic patients enrolled. The SVR12 rate observed in patients with GT1–6 was 99.7% [(15)]

A total of 386 compensated cirrhotic patients were included in the full analysis set (FAS), 375 patients completed the study, and 325 patients were included in the modified analysis set (MAS); Overall, in the MASandFAS,SVR12 was achieved in 99.1%and 84.2% of patients, respectively[(16)]

In a total of 301 compensated cirrhotic patients enrolled, 275 had SVR12 data. The SVR12 rate was 98.2% (270/275) in the modified intention-to-treat (mITT) population and 89.7% (270/301) in the intention-to-treat (ITT population) [(17)]

In a cohort study of 18,498 initiators of PI-based DAA therapy (paritaprevir/ritonavir/ombitasvir +/− dasabuvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir) matched 1:1 on propensity score to non-PI- based DAA initiators (sofosbuvir/ledipasvir, sofosbuvir/velpatasvir) the risk of severe hepatic dysfunction and hepatic decompensation did not differ between PI and non-PI-based DAA initiators in either FIB-4 group[(18)].

Our study has a more exclusive area of interest, as we assessed HCV responsiveness to a treatment protocol with a sample size of 35 compensated cirrhotic patients on dialysis. However, the limitations of the study are as follows, single center and it is retrospective and post treatment participants could not be observed for long term complication (relapse and HCC)

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Adverse Events during Treatment and Follow-Up

Variables	Noncirrhotic (n=7)	Cirrhotic (n=26)	All participants (n=33)	P Value
Adverse events (AEs)				
• Fatigue	1(14.3%)	2(7.7%)	3(9.1%)	0.697
• Itching	1(14.3%)	1(3.8%)	2(6.1%)	0.565
• Nausea	0(0%)	2(7.7%)	2(6.1%)	1.000
Treatment-related AEs				
• Serious AEs	0(0%)	0(0%)	0(0%)	
• Treatment discontinuation due to AEs	0(0%)	0(0%)	0(0%)	
Laboratory Abnormalities				
• ALT/AST elevation 1.1–2.5 × baseline	0(0%)	0(0%)	0(0%)	
Grade ¾ laboratory abnormalities				
• Total bilirubin elevation >2.6	0(0%)	0(0%)	0(0%)	
• ALT/AST elevation >5 ULN	0(0%)	0(0%)	0(0%)	
• Hemoglobin (< 8.9–7 g/dL)	0(0%)	0(0%)	0(0%)	
• Hemoglobin (<7 g/dL)	0(0%)	0(0%)	0(0%)	
• Death	0(0%)	0(0%)	0(0%)	

Chi-Square Test/Fisher Exact Test

NOTE: Values are presented as n (%), AEs (adverse events), ALT (alanine aminotransferase), AST

(aspartate aminotransferase).

Participants' Demographics and Baseline Characteristics

Characteristics	Noncirrhotic (n=7)	Cirrhotic (n=26)	All participants (n=33)	P Value
Gender				
• Female	4(42.9%)	10(42.3%)	14(42.4%)	0.937
• Male	3(42.9%)	16(61.5%)	19(57.6%)	
HCV GT				
• 1a	2(28.6%)	10(38.5%)	12(36.4%)	0.977
• 1b	1(14.3%)	1(3.8%)	2(6.1%)	
• 2	0(0%)	2(7.7%)	2(6.1%)	
• 3	0(0%)	1(3.8%)	1(3%)	
• 4	4(57.1%)	12(46.2%)	16(48.5%)	
Treatment status				
• Naïve	1(14.3%)	12(46.2%)	13(39.4%)	0.223
• Naïve CKD stage 1-3	3(42.9%)	1(3.8%)	4(12.1%)	
• Naïve CKD Stage 4-5	2(28.6%)	11(42.3%)	13(39.4%)	
• Treatment experienced	1(14.3%)	2(7.7%)	3(9.1%)	
Viral Load				
• <1000000	4(42.9%)	10(38.5%)	14(39.4%)	0.870
• >1000000	3(42.9%)	16(61.5%)	19(57.6%)	
Child-Pugh score				
• **A5**	0(0%)	10(38.5%)	10(30.3%)	1.000
• **A6**	0(0%)	16(61.5%)	16(48.5%)	
MELD Score				
• <10	0(0%)	10(38.5%)	10(30.3%)	1.000
• >10	0(0%)	16(61.5%)	16(48.5%)	

Chi-Square Test/Fisher Exact Test

SVR 12 w - distribution of patients

RESULT	Noncirrhotic	Cirrhotic
Negative	6(85.7%)	26(100%)
Positive	1(14.3%)	0(0%)

P=0.212, Not Significant, Fisher Exact Test

Pre and post-treatment Child Pugh scores

CP Class	Pre–treatment	Post – treatment	% Difference
A5	10(38.5%)	20(76.9%)	38.4%
A6	16(61.5%)	6(23.1%)	-38.4%
Total	26(100%)	26(100%)	-

P=0.031*, Significant, Paired Proportional Test

Pre and post -treatment MELD scores

MELD Score	Pre treatment MELD score	Post treatment MELD score	% Difference
<10	10(38.5%)	12(46.2%)	7.7%
>10	16(61.5%)	14(53.8%)	-7.7%
Total	26(100%)	26(100%)	-

P=0.336, Not Significant, Paired Proportional Test

Table 2: Sustained virolgical response SVR 12 (95% Confidence Interval)

Variables	n/N	% Confidence Interval
All	32/33	98% (90-100)
Gender		
• Female	14/14	100%(89-100)
• Male	18/19	95%(77-100)
HCV genotype		
• 1a	12/12	100%(89-100)
• 1b	2/2	100%(89-100)
• 2	2/2	100%(89-100)
• 3	1/1	100%(89-100)
• 4	15/16	98%(90-100)
Treatment status		
• Naïve	1/1	100%(89-100)
• Naïve CKD stage 1-3	2/3	98%(90-100)
• Naïve CKD Stage 4-5	2/2	100%(89-100)
• Treatment experienced	1/1	100%(89-100)
Baseline HCV RNA level		
• <1000000 IU/ml	13/13	100%(69-100)
• >1000000 IU/ml	19/20	98%(88-100)
Child-Pugh score		
• 5	19/19	100%(59-100)
• 6	7/7	100%(48-100)
MELD score		
• <10	10/10	100%(54-100)
• >10	15/16	88%(47-100)