1.0 Abstract

Title

Real World Evidence of the Effectiveness and Clinical Practice Use of Glecaprevir plus Pibrentasvir in Patients with Chronic Hepatitis C Genotypes 1 to 6 in Russian Federation

Keywords

Chronic hepatitis C, glecaprevir-pibrentasvir combination, observational study

Rationale and Background

The interferon- and ribavirin-(RBV) free combination regimen of glecaprevir plus pibrentasvir (GLE/PIB) for the treatment of genotypes 1 to 6 of chronic hepatitis C (CHC) viral infection has been shown to be safe and effective in randomized controlled clinical trials.
The rationale for this observational study was to determine how the efficacy and safety of GLE/PIB as demonstrated in pivotal trials translates into real world clinical settings, which means evaluating its effectiveness. Whereas efficacy can be defined as a measure of the capacity of a treatment to produce the desired effect in a controlled environment, as in a well-controlled setting as a randomized trial, effectiveness is the extent to which a drug achieves its intended effect in the real world. Effectiveness trials typically have limited exclusion criteria and will involve the broader patient populations in routine clinical practice which might have been underrepresented in pivotal trials. Examples of this in the CHC disease landscape will be those patients actively using drugs such as recreational and alcohol abuse, the elderly, patients with renal impairment, different ethnic groups, patients with heterogeneous compliance patterns due to socioeconomic factors and patients with significant comorbid conditions or extrahepatic manifestations. Effectiveness research allows for external patient-, provider-, and system-level factors and can therefore be more relevant for health-care decisions by both health care providers and policy-makers.

This observational study was the first effectiveness research examining the GLE/PIB regimen in Russia.
GLE/PIB is the first pangenotypic RBV-free regimen allowing for treatment duration as short as 8 weeks for all treatment-naïve patients with genotypes 1 to 6 without cirrhosis. However, the label of the GLE/PIB regimen recommends longer therapy (e.g. 12 or 16 weeks) for certain patient subpopulations. It was therefore relevant to understand and characterize the clinical practice use and whether variations have an effect on virological outcome.
With a pangenotypic approach, there is potential for treatment strategy simplification, e.g. therapy initiation without genotyping and with point-of-care hepatitis C virus (HCV) ribonucleic acid (RNA) testing, possibly resulting in a shift of CHC treatment to community based primary care physicians. The ease of use, favorable safety and tolerability profile (RBV-free) and short treatment duration might simplify monitoring during therapy and thus reduce healthcare resource utilization (HCRU) at the centers.
This observational study documented visit frequencies and laboratory assessments in light of varying clinical practice use of the GLE/PIB regimen and different patient subpopulations like cirrhotic vs non-cirrhotic patients.
In addition, this study provided data on the adherence to treatment in subpopulations of real world interest, which may help treating physicians, improve the management of patients under their care.
The aim of this observational study was to provide evidence of the effectiveness, clinical practice use and HCRU of the GLE/PIB regimen across a variety of patient populations in a real world clinical practice setting.

Research Question and Objectives

What is the effectiveness of the glecaprevir plus pibrentasvir (GLE/PIB) regimen in patients with chronic hepatitis C (CHC) in a real world setting across clinical practice patient populations in Russian Federation?

Primary Objective

To describe in routine clinical practice the effectiveness of GLE/PIB overall.

Secondary Objectives

1. To describe in routine clinical practice the effectiveness of GLE/PIB by subpopulations of interest: mono HCV infected and co-infected HCV/HIV patients, HCV genotype/subgenotype, cirrhotic and non-cirrhotic patients, treatment-experienced (prior treatment with pegIFN (or IFN), and/or RBV and/or sofosbuvir [PRS]) and treatment-naïve, elderly (≥ 65 years) and non-elderly (<65 years), people who use drugs (PWUD) and nondrug users, as evidenced by sustained virological response at 12 weeks (SVR12) after end of treatment (EoT).
2. To document the adherence to the prescribed GLE/PIB regimen overall and by subpopulations of interest.
3. To collect information on co-morbidities and concomitant medication.
4. To describe the safety and tolerability of GLE/PIB.
5. To collect HCRU information.

Study Design

This was a prospective, multi-center observational study in patients with CHC receiving the GLE/PIB regimen. The prescription of a treatment regimen was at the discretion of the physician in accordance with local clinical practice, international guidelines and/or label, was made independently from this observational study and preceded the decision to offer the patient the opportunity to participate in this study.

Setting

For purpose of this study, participants were recruited and observed in 11 national and regional hospital/outpatient services for treatment of infectious diseases, gastroenterology hospital/outpatients clinics and AIDS centers.

Subjects and Study Size, Including Dropouts

According to Zeuzem et al.[1] among 1208 HCV treated patients the rate of sustained virologic response at 12 weeks in sample of genotype 1–infected patients was 99.1% (95% CI, 98 to 100) in the 8-week group and 99.7% (95% CI, 99 to 100) in the 12-week group. Genotype 3–infected patients who were treated for 12 weeks had a rate of sustained virologic response at 12 weeks of 95% (95% CI, 93 to 98; 222 of 233 patients) with GLE/PIB; 8 weeks of treatment with GLE/PIB yielded a rate of 95% (95% CI, 91 to 98; 149 of 157 patients).
With 145 patients, and assumed estimation about 97% of SVR12, the width of the 95% confidence interval (CI) (from the lower limit to the upper limit of the CI) will be 6.0% using Wilson's score method.
With assumed approximate 10% of lost to follow-up at 12 weeks after treatment, number of recruited participants in this observational study constituted 161.

One hundred and sixty-one patients were enrolled into this study. One hundred and forty patients completed the study.

Variables and Data Sources

Primary Variable

The percentage of patients achieving SVR12 (defined as HCV RNA <lower limit of quantification/detection [LLoQ/D] 12 weeks [i.e. ≥70 days] after the last actual dose of GLE/PIB with a sensitive polymerase chain reaction [PCR] test with an LLoQ/D of <50 IU/mL or as described in a validated assay as used in the settings of the Russian Federation) overall.

[1] Zeuzem S, Foster GR, Wang S, et al. Glecaprevir/pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med 2018;378:354-69.

Secondary Variables

1. The percentage of patients achieving SVR12 (defined as HCV RNA <lower limit of quantification/detection [LLoQ/D] 12 weeks [i.e. ≥70 days] after the last actual dose of GLE/PIB with a sensitive polymerase chain reaction [PCR] test with an LLoQ/D of <50 IU/mL or as described in a validated assay as used in the settings of the Russian Federation) in subgroups of interest.
2. Number and percentage of patients with co-morbidities and taking concomitant medication.
3. Average percentage of GLE/PIB dose taken by patient report in relation to the prescribed target dose (number of pills taken out of the number that should have been taken).
4. Number and percentage of patients with treatment emergent serious and non-serious adverse events (AEs) and increases in laboratory parameters of interest overall and in subgroups of interest.
5. Average number of HCRU over time overall and by subpopulations of interest.

Note: the subpopulations of interest were: mono HCV and co-infected HCV\HIV patients, HCV genotype/subgenotype, cirrhotic and non-cirrhotic patients, PRS treatment-experienced and treatment-naïve, elderly (≥65 years) and non-elderly (<65 years), PWUD and non-drug users.

Data Sources:

Source documents were defined as original documents. The investigator documented patient data in his/her own patient files which had served as source data for the study.

Results

A prospective, multi-center observational study in patients with chronic hepatitis C genotypes 1 to 6 receiving the all oral GLE/PIB regimen was conducted to provide evidence of the effectiveness, clinical practice use and HCRU of the GLE/PIB regimen across a variety of patient populations in a real world clinical practice setting.

The GLE/PIB regimen was highly effective in the managing of chronic hepatitis C in patients with different HCV genotypes and co-morbidities in routine clinical practice. 99.2% (127/128) of patients included in the core population with sufficient follow-up data achieved SVR12 (defined as HCV RNA <lower limit of quantification/detection [LLoQ/D] 12 weeks [i.e. ≥70 days] after the last actual dose of GLE/PIB with a sensitive polymerase chain reaction [PCR] test with an LLoQ/D of <50 IU/mL or as described in a validated assay as used in the settings of the Russian Federation) overall. In the core population 88.2% (142/161) of patients achieved SVR12. Among patients who failed to achieve SVR12, none had a virologic failure. The most common reasons for not achieving SVR12 were patient was lost to follow-up or SVR data was missing.

All patients with HCV genotype 1a, 1b, 3, and other genotypes achieved SVR12. Among patients with HCV genotype 2 SVR12 was achieved in 91.7% (11/12) of patients. All cirrhotic patients and 98.9% of non-cirrhotic patients achieved SVR12. All patients for whom cirrhosis status was not known achieved SVR12. All of treatment-experienced patients and 99.1% of treatment-naïve patients achieved SVR12 ≥70 days after the last actual dose of GLE/PIB. All patients who use drugs 99.2% of non-drug users achieved SVR12. SVR12 was achieved in all patients older than 65 years. Among younger patients SVR12 was achieved in 99.2% of patients.

High compliance with prescribed therapy was observed in this study. Almost all patients took all prescribed GLE/PIB pills, and there were only 1.9% of patients who did not.

According to the results of key biochemistry, the improvement of the liver enzymes was observed at SVR12 Visit, and no clinically significant changes in the key laboratory parameters were revealed.

The GLE/PIB regimen was well tolerated. There were 3 patients with 3 AEs observed in this study: 2 cases were mild, and 1 case was severe and was evaluated as SAE.

A slight decrease of the health care resource utilization by decreasing the number of face-to-face visits and phone calls to the healthcare professionals was observed in this study. Median number of visits/touchpoints with a healthcare professional or designee in relation to HCV infection for all patients was 2 overall during the study.

Conclusion

The study demonstrated a high percentage of patients achieving SVR12, which allows one to conclude that the GLE/PIB combination is an effective treatment regimen in the population of patients with chronic hepatitis C. The results of this study regarding the effects of treatment of chronic hepatitis C are consistent with the published data. There are no new significant data on the safety of GLE/PIB combination in this population.

Marketing Authorisation Holder(s)

[redacted]

Names and Affiliations of Principal Investigators

Information is provided in **Section 3**.