1.0 Abstract

Title

Real World Evidence of the Effectiveness of Paritaprevir/r – Ombitasvir, ± Dasabuvir, ± Ribavirin and Patient Support Program in Patients with Chronic Hepatitis C - An Observational Study in Israel (CITRINE STUDY)

Keywords

Chronic hepatitis C (CHC), non-interventional study, paritaprevir, ombitasvir, dasabuvir, ribavirin, sustained virological response (SVR), Patient Support Program (PSP)

Rationale and Background

The interferon-free combination regimen of paritaprevir/ritonavir (r) – ombitasvir with or without dasabuvir (ABBVIE REGIMEN) ± ribavirin (RBV) for the treatment of chronic hepatitis C (CHC) has been shown to be safe and effective in randomized controlled clinical trials with strict inclusion and exclusion criteria under well controlled conditions.

This observational study is the first effectiveness study examining the ABBVIE REGIMEN ± RBV, used according to local label, under real world conditions in Israel in a clinical practice patient population outside of a strict clinical study setting.

The rationale for this observational study was to determine how the efficacy and safety of the ABBVIE REGIMEN as demonstrated in pivotal trials translates into real world.

Research Question and Objectives

What is the effectiveness of the interferon-free regimen of Paritaprevir/r – Ombitasvir, ± Dasabuvir, ± Ribavirin and Patient Support Program and its influence on patients with CHC in a real life setting across clinical practice patient populations?

Primary Objective

1. To describe in routine clinical practice the effectiveness of the interferon-free ABBVIE REGIMEN ± RBV in patients with CHC as evidenced by sustained virological response at 12 weeks after end of treatment (SVR12)

Secondary Objectives

2. To provide real world evidence for predictive factors of virological response

3. To describe the safety and tolerability of ABBVIE REGIMEN ± RBV

4. To describe the pattern of real world use of the ABBVIE REGIMEN ± RBV with respect to different patient and treatment characteristics

5. To evaluate the contribution of the patient support program (PSP) to disease control, treatment continuation over time, patient satisfaction and PSP utilization

6. To describe the effect of the ABBVIE REGIMEN ± RBV on metabolic profile

7. To evaluate the effect of the ABBVIE REGIMEN ± RBV on extrahepatic manifestations and associated diseases like cryoglobulinemia/cutaneous vasculitis or porphyria cutanea tarda

Study Design

This was a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN ± RBV in Israel. The prescription of a treatment regimen was at the discretion of the physician in accordance with local clinical practice and label, was made independently from this observational study and preceded the decision to offer the patient the opportunity to participate in this study. Follow-up visits, treatment, procedures and diagnostic methods followed physicians' routine clinical practice. Data to be documented was those closest to the following time windows: baseline, early on-treatment visit, mid-treatment visit (for patients with a treatment duration of 24 weeks), end of treatment, early post- treatment and 12 weeks after the end of treatment (representing SVR12).

Setting

This observational study was conducted in 15 medical centers in Israel experienced in the treatment of CHC. First patient entered the study on 07 July 2016, last patient last visit was on 21 October 2018.

Subjects and Study Size, Including Dropouts

The target population comprised adult male or female patients with confirmed CHC, genotype 1, treatment-naïve or treatment-experienced, receiving combination therapy with the interferon-free ABBVIE REGIMEN ± RBV according to standard of care and in line with the local label who voluntarily signed and dated an informed consent prior to inclusion into the study.

In total, 256 patients were enrolled into the study and 228 patients were taking the ABBVIE REGIMEN in line with recommendations. Thus 228 patients were in the core population (CP) of this

study. Due to failure to return, withdrawal of consent and other not further specified reason, 60 patients of the CP were excluded from the core population with sufficient follow-up 12 weeks after EoT (CPSFU12).

Variables and Data Sources

Primary Variable

- The percentage of patients achieving SVR12 in the CP and CPSFU population (HCV RNA <50 IU/mL 12 weeks [i.e. ≥70 to 126 days] after the last actual dose of the ABBVIE REGIMEN)

Secondary Effectiveness Variables

- The percentage of patients with virological response (HCV RNA <50 IU/mL) at EoT, defined as last intake of ABBVIE REGIMEN or RBV)
- The percentage of patients with relapse (defined as HCV RNA <50 IU/mL at EoT followed by HCV RNA ≥50 IU/mL)
- The percentage of patients with breakthrough (defined as at least one documented HCV RNA <50 IU/mL followed by HCV RNA ≥50 IU/mL during treatment)

Further Secondary Variables

- Number and percentage of subjects administered each type of treatment regimen (± Dasabuvir, ± RBV, intended and actual combination, dose and duration)
- Changes from baseline in PAM (Patient Activation Measure)-13 total score and number and percentage of subjects using PSP • Changes in metabolic laboratory profile prior to treatment initiation, and at all subsequent visits
- Number and percentage of patients with treatment emergent serious and non-serious AEs and increases in laboratory parameters of interest

Results

Median age was 56 years, 57.5% of participants were male and all patients were white. The most prevalent HCV genotype in the CP was genotype 1b (94.7%) followed by genotype 1a (1.8%). Cirrhosis was present in 13.2% of patients and 15.8 % had transition to cirrhosis. Treatment experienced patients accounted for 21.9% of the population.

Co-morbidities and/or co-infections were present in 67.5 % of the patients. The most common categories of co-morbidities were cardiovascular disease (33.3%), diabetes mellitus (13.6%) and psychiatric disorders (9.2%). Co-infections were only documented for eight patients (five HIV, three hepatitis B).

Psychoactive substance dependency was reported for 9 patients (3.9%), all of whom were on opiate substitution therapy.

Concomitant medications were taken by 56.8% of patients. The most frequently (>5%) taken classes of concomitant medication were ACE inhibitors (14%), beta blockers (11.4%), analgesics (10.6%), drugs for peptic ulcer and gastro-esophageal reflux disease (10.2%), blood glucose lowering drugs (9.3%), antidepressants (7.2%), calcium channel blockers (7.2%), angiotensin II antagonists (7.2%),benzodiazepine derivatives (7.2%), vitamins (6.8%), drugs used in addictive disorders (5.1%), thyroid therapy (5.1%), and HMG COA reductase inhibitors (5.1%).

The planned treatment duration was 24 weeks for 1.3% of the patients, 12 weeks for 79.4% patients and 8 weeks for 19.3% patients. The 3DAA regimen of paritaprevir/r plus ombitasvir plus dasabuvir without RBV for 8 weeks and 12 weeks was prescribed for the majority of the CP (93.9%) and in combination with RBV for 4.8% for 12 weeks and 1.3% for 24 weeks. Three patients were prescribed the 3 DAA regimen with RBV for 24 weeks (all three patients had genotype 1a, two with and one without cirrhosis).

SVR12 was achieved in 70.6% of the CP and in 95.8% of the CPSFU12 and SVR24 was 93.8% in the CPSFU24. Please refer to Table 20 Virological Response Rates by Genotype and Cirrhosis Status - CP/CPSFU - Israel for confidence intervals (CI).
Data on SVR24 were missing in 56 patients since following for SVR24 is no longer considered standard of care. The CPSFU24 includes only 112 patients of the CPSFU12 (N=168), because no data were available at 24 weeks post-treatment in the remaining 56 patients (which are all SVR12 responders). Therefore, it is not possible to get a robust estimation of the actual virological response 24 weeks post-treatment.

137 patients (60.1%) of the CP participated in the PSP or intended to take part at baseline (Table 26 PSP Utilization and Satisfaction Until 12 weeks after EoT in Patients Taking Part in PSP by Treatment Regimen and Cirrhosis Status - CP - Israel). Of those patients only 14.6% used at least one component. During early treatment patients were mainly using personal support (70.0%) educational

information material, printed (65.0%) or additional digital and mobile resources reminders (65.0%), several times per week or less. At EoT, compared to baseline more patients used at least one of the PSP components.

Patients were asked to report their satisfaction with the PSP. In general it seems that the tool was deemed useful; however, due to very small sample size, no meaningful conclusions can be drawn.

The assessment of liver function tests of ALT, AST, Albumin, Gamma-GT and Total Bilirubin revealed an improvement in median values from baseline to EoT, and to 12 and 24 weeks after EoT. At 24 weeks after EoT laboratory values were generally available for less than half of the patients only but resembled those 12 weeks after EoT.

Assessment of the metabolic profile was available for very few patients in this real-world study preventing further conclusions.

Overall 21.2% of the patients reported at least one treatment-emergent AE and 2.5% of the patients at least one treatment-emergent SAE. At least one AE possibly related to the ABBVIE REGIMEN was reported in 13.6% of patients, at least one AE possibly related to RBV was documented for 21.4% of patients receiving RBV. One patient died due to atrial fibrillation, which was reported as having no reasonable possibility of being related to the ABBVIE REGIMEN. Six patients had SAEs due to toxicity to various agents, upper limb fracture, atrial fibrillation, ascites, hepatic failure, synovial cyst, hepatic encephalopathy or dyspnea.

Discussion

At the time the ABBVIE REGIMEN was authorized in Israel, there was limited country specific data available in Israel on the real world effectiveness of the ABBVIE REGIMEN. The present study was set up to close this data gap.

High SVR12 rates were achieved in the CPSFU12, 95.8% overall, 96.2% for genotype 1b and 90.0% for genotype 1a, mirroring response rates observed in pivotal trials, including cirrhotic patients with 95.8% SVR12. Results from the CP were slightly lower due to missing values which reflects the non-interventional character of this study.

Treatment was well tolerated with only 8 SAEs reported (2.5%) and 8 patients discontinuing the ABBVIE REGIMEN prematurely for safety reasons (3.4%). No new safety signals were detected from the study.

Overall the present study provides evidence for the high effectiveness and good tolerability of the ABBVIE REGIMEN under real world conditions in the Israeli CHC population.

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