1 Abstract

Title

Real World Evidence of the Effectiveness of Paritaprevir/r – Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients with Chronic Hepatitis C -
An Observational Study in Belgium

Keywords

Chronic hepatitis C (CHC), non-interventional study, paritaprevir, ritonavir (r), ombitasvir, dasabuvir, ribavirin (RBV), sustained virological response (SVR), patient reported outcome (PRO), patient activation measure (PAM-13), beliefs medication questionnaire (BMQ)

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 research examining the ABBVIE REGIMEN ± RBV, used according to local label, under real world conditions in Belgium 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

Research Question

What is the effectiveness and the influence of adherence on treatment outcome of the interferon-free ABBVIE REGIMEN ± RBV in 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 pattern of real world use of the ABBVIE REGIMEN ± RBV with respect to different patient and treatment characteristics
4. To evaluate the influence of adherence on treatment outcome in routine clinical practice
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 assess viral resistance patterns

Study Design

This was a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN ± RBV in Belgium. 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 were 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 (EoT), early post- treatment and 12 and 24 weeks after the end of treatment (representing SVR12 and SVR24).

Setting

This observational study was conducted in 20 medical centers in Belgium experienced in the treatment of CHC. First patient entered the study on 6 October 2015, last patient last visit was on 12 February 2018.

Subjects and Study Size, Including Dropouts

The eligible population comprised adult male or female patients with confirmed CHC, genotype 1 or 4, 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 form prior to inclusion into the study.

In total, 314 patients were enrolled. The safety population (SP) comprised 311 patients since for 2 patients treatment start date was missing and 1 patient withdrew consent and no start of treatment was documented. Three patients with genotype 4 did not receive RBV, thus 308 of the 311 patients remained in the core population (CP) which included patients who started recommended treatment regimens. Twenty patients were excluded from the CP to form the core population with sufficient follow-up data regarding SVR12 (CPSFU12) (n=288): 12 patients did not return, 1 patient withdrew consent and 7 patients had no HCV RNA measurement ≥70 days after EoT due to other reasons, not further specified (but not related to virological response or safety).

Variables and Data Sources

Primary Variable

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

Main 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)

Further Secondary Variables

- Type of treatment regimen (± Dasabuvir, ± RBV, intended and actual combination, dose and duration)
- Adherence
- PSP satisfaction and utilization questionnaires
- Viral resistance
- Patient activation measure (PAM)-13 and beliefs medication questionnaire (BMQ)
- Serious (SAEs) and non-serious adverse events (AEs) and pregnancy occurrences
- Co-morbidities and concomitant medication

Results

Median age of the CP was 61 years, 52.9% of participants were male. The most prevalent HCV genotype was genotype 1b (73.1%), followed by genotype 4 (19.2%) and genotype 1a (7.5%). Cirrhosis was present in 36.7% of patients and 22.7 % had transition to cirrhosis. Treatment experienced patients accounted for 41.2% of the population.

Co-morbidities and/or co-infections were present in 85.4 % of the CP, cardiovascular disease (45.8%), diabetes mellitus (18.8%), psychiatric disorder (15.6%), hypothyroidism (11.7%) and lipid disorders (10.7%) prevailed. HIV co-infection was documented for 4.9% of patients and HBV co-infection for 1.9%.

In the SP 79.4% of patients were receiving concomitant medications. The most frequently taken classes of concomitant medications were analgesics (27.3%), drugs for peptic ulcer and gastro-esophageal reflux disease (26.4%), beta blockers (23.5%), calcium channel blockers (14.8%), benzodiazepine derivatives (12.9%), blood glucose lowering drugs (12.5%), antidepressants (11.3%), thyroid therapy (10.9%), ACE inhibitors (10.6%) and diuretics (10.6%).

The 3 direct acting antiviral agents (DAA) regimen of paritaprevir/r plus ombitasvir plus dasabuvir with RBV was prescribed for 12 weeks for 15.3% of the CP and for 24 weeks for 2.3% of the CP. The 3DAA regimen without RBV was taken by 62.7% of patients for 12 weeks and by 0,6% of patients for 8 weeks. The 2DAA regimen of paritaprevir/r plus ombitasvir in combination with RBV was prescribed for 15.3% and 3.9 % of patients for 12 and 24 weeks, respectively.

SVR12 was achieved in 87.7% of the CP (95% CI: [83.5, 90.9]) and in 93.8% of the CPSFU12 (95% CI: [90.3, 96.0]). For genotype 1a the respective response rates were 83.3% and 95.2%, for genotype 1b 90.7% and 96.2%, for genotype 4 they were 78.0% and 83.6%. In patients with cirrhosis SVR12 was achieved in 87.6% of the CP and in 94.3% of the CPSFU12. Please note that patients with missing data were considered as non-responders. Reasons for virological failure 12 weeks after EoT were on-treatment virological failure for 5 patients (1.6%), relapse for 6 patients (1.9%) and insufficient virological response for 1 patient (0.3%).

Univariate and MLR methods were used for the CP to investigate the impact of various explanatory covariates (patient and disease characteristics) at baseline on SVR12. Less years since diagnosis of HCV infection and genotype 4 were associated with a lower likelihood of achieving SVR12.

The association between adherence and SVR12 was also investigated by univariate logistic regression and MLR methods. Patients with lower adherence and those with less years since diagnosis of HCV infection showed lower SVR12 rates compared to patients with higher adherence and more years since diagnosis of HCV infection, respectively.

Analysis of the PRO instruments revealed no relevant change during treatment as assessed by PAM and BMQ.

Just 9 patients participated or intended to participate in the PSP at baseline, thus a meaningful evaluation of the tool is not possible within the scope of this study.

No data were reported on viral resistance.

Overall 50.2% of the patients reported at least one treatment-emergent AE. The most common AEs were fatigue (16.7%), pruritus (10.6%), anemia (7.1%), headache (5.8%) and asthenia (5.1%). Treatment-emergent SAEs were reported by 4.8% of patients.Three patients died (sudden death, death with unknown cause and cerebral hemorrhage, the two latter cases occurred more than 30 days after EoT).

In the SP 3.5% of patients discontinued the ABBVIE REGIMEN due to AEs and in patients receiving RBV 5.3% experienced AEs leading to discontinuation of RBV.

Discussion

Currently there is limited country specific data available in Belgium 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, 93.8% overall, 95.2% for genotype 1a, 96.2% for genotype 1b and 83.6% for genotype 4, mirroring results from the pivotal trials, including cirrhotic patients with 94.3% SVR12. There was a low number of virological failures. Results from the CP were lower (SVR12 overall 87.7%) due to missing values which reflects the non-interventional character of this study.

PROs remained generally unaltered by the ABBVIE REGIMEN ± RBV with no evidence of unfavorable impact.

Treatment was well tolerated, no new safety signals were detected.

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

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