1.0 Abstract

Title

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

Keywords

Chronic hepatitis C (CHC), non-interventional study, paritaprevir , ombitasvir, dasabuvir, ribavirin, sustained virological response (SVR), Health Economics and Outcomes Research (HEOR), Patient Reported Outcome (PRO), EuroQol 5 dimension 5 level (EQ-5D-5L), WPAI (Work Productivity and Activity Impairment)

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 Austria 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 everyday clinical settings and to assess the impact on PRO and work productivity.

Research Question and Objectives

Research Question

What is the effectiveness, PRO and work productivity 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 tolerability of the ABBVIE REGIMEN ± RBV
4. To document the effect of the ABBVIE REGIMEN ± RBV on PROs and work productivity in the Austrian population
5. To evaluate the contribution of the patient support program (PSP) to disease control, treatment continuation over time, patient satisfaction and PSP utilization

Study Design

This was a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN ± RBV in Austria. 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 10 medical centers in Austria experienced in the treatment of CHC. First patient entered the study on 06 October 2015, last patient last visit was on 12 January 2017.

Subjects and Study Size, Including Dropouts

The target 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 a patient authorization to use and disclose his/her anonymized health data prior to inclusion into the study.

In total, 173 patients were enrolled into the study. Two patients never started treatment, thus the safety population (SP, defined as enrolled patients who received at least one dose of the ABBVIE REGIMEN) included 171 patients. For 25 patients (14.6%) of the SP, there was no hepatitis C virus (HCV) ribonucleic acid (RNA) assessment performed at least 10 weeks post-treatment. Reasons were failure to return for 10 patients, insufficient virological response for 2 patients, one withdrawal of consent, one death, and for 11 patients no measurement was reported due to other reasons, not further specified.

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)

Secondary Effectiveness Variables

- The percentage of patients with virological response (HCV RNA <50 IU/mL) at end of treatment (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

- Type of treatment regimen (± Dasabuvir, ± RBV, intended and actual combination, dose and duration)
- Adherence
- Co-morbidities and concomitant medication
- Serious (SAEs) and non-serious adverse events (AEs) and pregnancy occurrences
- Questionnaires on PROs: EQ-5D-5L questionnaire and work productivity and activity impairment - hepatitis C (WPAI Hep C) questionnaire prior to treatment initiation, at EoT as well as 12 weeks after EoT
- PAM (Patient Activation Measure)-13 and PSP satisfaction and utilization questionnaires

Results

Median age of the core population (CP) was 53 years and 69.7% of participants were male. The most common races reported were White (95.8%) and Asian (2.4%). The most prevalent HCV genotype was genotype 1b (52.7%), followed by genotype 1a (41.8%) and genotype 4 (4.8%). Cirrhosis was present in 13.9% of patients and 8.5 % had transition to cirrhosis. Treatment experienced patients accounted for 37.6% of the population.

Co-morbidities and/or co-infections were present in 57.6 % of the CP, cardiovascular disease (23.0%) and psychiatric disorders (15.2%) prevailed. Co-infections were only documented for 3 patients, just one patient each (0.6%) had human immunodeficiency virus (HIV) co-infection, hepatitis B virus (HBV) co-infection and Schistosomiasis, respectively.

In the safety population (SP) 49.1% of patients were receiving concomitant medications. The most frequently taken classes of concomitant medications were analgesics (12.3%), antidepressants (11.7%), beta blockers (9.9%) and calcium channel blockers (8.8%).

The planned treatment duration was 12 weeks for all patients in the REAL study. The regimen of paritaprevir/r plus ombitasvir plus dasabuvir was prescribed for the majority of patients (63.6%) in the CP and in combination with RBV for 32.1%, while 4.2% of patients were prescribed paritaprevir/r plus ombitasvir in combination with RBV. In line with the local label and international recommendations, 96.6% of patients with genotype 1b received the 3 direct-acting antiviral agent (DAA) regimen without RBV, whereas 70% of genotype 1a patients took the 3DAA regimen with RBV. All but one genotype 4 patients in the CP were treated with the 2DAA regimen with RBV.

SVR12 was achieved in 84.8% of patients of the CP and in 95.9% of the core population with sufficient follow-up data regarding SVR12 (CPSFU12). In patients with genotype 1a, 1b and 4, SVR12 in the CP was 81.4%, 87.4% and 87.5%, whereas respective SVR12 rates in the CPSFU12 were 96.6%, 95.0% and 100%. For the 23 patients with cirrhosis SVR12 was 91.3% in the CP and 95.5% in the 22 respective patients in the CPSFU12. Please note that in the CP patients with missing data were considered as non-responders.

On-treatment virological failure was reported for 2 patients and insufficient virological response for 1 patient, none of these patients had cirrhosis and all 3 had genotype 1b. There was no report on relapse or viral breakthrough.

Multiple logistic regression (MLR) methods were used to investigate the impact of baseline factors on SVR 12. The type of the treating institute was the only statistically significant factor which stayed in the model for the CP. Treatment in general hospitals was found to be associated with a higher likelihood of SVR12 than treatment in university hospitals. The reason for this finding is probably that more patients treated in university hospitals were lost to follow-up.

Patient well-being during treatment and up to 12 weeks after the EoT was assessed by EQ-5D-5L and WPAI Hep C questionnaires. In general the analysis of both questionnaires showed comparable trends. Overall, patients experienced a small improvement of their quality of life from baseline to 12 weeks after EoT, during treatment there was almost no change. This trend was similar in cirrhotic and non-cirrhotic patients.

Only 26 patients (15.8%) of the CP participated in the PSP, due to small sample size no meaningful conclusions can be drawn regarding the impact of the PSP.

The assessment of liver function tests for the SP revealed a clinically important improvement from baseline to EoT and to 12 weeks after EoT for the median values of alanine-aminotransferase (ALT), ALT ratio, aspartate-aminotransferase (AST), AST ratio, gamma-glutamyltransferase (γ-GT), total bilirubin and albumin. Overall there was no relevant change in median creatinine and creatinine clearance. Very few patients had potentially clinically significant laboratory values. The analysis revealed 2 patients with very high ALT values, 1 patient with very high AST, 4 patients with very high creatinine and 2 patients with very low creatinine clearance (analysis includes patients with chronic kidney disease as co-morbidity).

In patients receiving RBV there was a decrease in hemoglobin (Hb) from baseline to EoT which recovered to near baseline values at 12 weeks after EoT.

Overall 22.8% of the patients reported at least one treatment emergent AE. The most common AEs occurring in more than 4% of patients of the overall SP were fatigue (8.2%), headache (4.7%), nausea (4.1%) and pruritus (4.1%).Treatment emergent SAEs were reported by 5 patients (2.9%), in 2 patients they were deemed related to the ABBVIE REGIMEN. Each type of SAE occurred only once. One patient died due to cardiac failure, the patient had cirrhosis and chronic kidney disease. Five patients (2.9%) of the SP terminated the ABBVIE REGIMEN prematurely due to an AE including pruritus, diarrhea, fatigue, hyperbilirubinemia and increased ALT and AST. Two patients (3.3%) of those taking RBV had their RBV permanently withdrawn due to fatigue and hyperbilirubinemia. No new safety signals were detected during this study.

Discussion

Currently there is limited country specific data available in Austria 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, 95.9% overall, 96.6% for genotype 1a and 95.0% for genotype 1b, resembling results from the pivotal trials, including cirrhotic patients with 95.5% SVR12. There was a low number of virological failures (2 on-treatment failures and 1 insufficient virological response) and no relapse or break-through. Results from the CP were lower (SVR12 overall 84.8%) due to missing values which reflects the non-interventional character of this study.

PRO instruments revealed a trend for an improvement in health-related quality of life (HRQoL) from baseline to 12 weeks after EoT, while there was no change during treatment. This is in contrast to well-known assessments of HRQoL in patients receiving interferon-based therapies where usually a clinically important deterioration of HRQoL occurred during treatment.

Treatment was well tolerated with a low number of SAEs and 5 patients (2.9%) discontinuing the ABBVIE REGIMEN prematurely for safety reasons. No new safety signals were detected during this study.

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

Marketing Authorisation Holder(s)

AbbVie Ltd

[redacted]

United Kingdom

AbbVie GmbH

[redacted]

Austria