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 Colombia (outCome)

Keywords

Chronic hepatitis C (CHC), non-interventional study, paritaprevir, ombitasvir, dasabuvir, ribavirin, sustained virological response (SVR), Patient Reported Outcome (PRO), EuroQol 5 dimension 5 level (EQ-5D-5L), Work Productivity and Activity Impairment (WPAI), Patient Activation Measure (PAM) -13

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 one of the first effectiveness studies examining the ABBVIE REGIMEN ± RBV, used according to local label, under real world conditions in Colombia 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 and to assess the impact on patient reported outcome (PRO) and work productivity.

Research Question and Objectives

Research Question

What is the effectiveness and PRO and work productivity and healthcare resource utilization 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 describe the pattern of real world use of the ABBVIE REGIMEN ± RBV with respect to different patient and treatment characteristics
3. To collect information on co-morbidities and concomitant medication in the Colombian population
4. To document the effect of the ABBVIE REGIMEN ± RBV on PROs and work productivity in the Colombian population
5. To determine the impact of the ABBVIE REGIMEN ± RBV on healthcare resource utilization
6. To evaluate the contribution of the patient support program (PSP) to disease control, treatment continuation over time, patient satisfaction and PSP utilization in the Colombian population

Study Design

This was a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN ± RBV in Colombia. 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 5 medical centers in Colombia experienced in the treatment of CHC. First patient entered the study on 23 February 2017, last patient last visit was on 30 August 2018.

Subjects and Study Size, Including Dropouts

The eligible 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 form prior to inclusion into the study.

In total, 66 patients were enrolled into the study. Since treatment was never started in 1 patient, the safety population (SP) comprised 65 patients and the core population (CP) as well. Three patients were excluded from the CP to form the core population with sufficient follow-up data regarding SVR12 (CPSFU12) (n=62): 2 patients were lost to follow-up and 1 patient 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)
- 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)
- Co-morbidities and concomitant medication
- Questionnaires on PROs: EuroQol 5 dimension 5 level (EQ-5D-5L) questionnaire, work productivity and activity impairment - hepatitis C (WPAI Hep C) questionnaire and patient activation measure (PAM) -13
- Serious (SAEs) and non-serious adverse events (AEs) and pregnancy occurrences

Results

Median age of patients in the CP was 63 years, 69.2% of participants were female, ethnic origin was other (95.4%), White/Caucasian (3.1%) and native American/American Indian (1.5%). The most prevalent HCV genotype was genotype 1b (78.5%) and 20.0% had genotype 1a; in 1 patient (1.5%) with genotype 1 the subtype was unknown. Cirrhosis was present in 38.5% of patients and 6.2 % had transition to cirrhosis. Treatment experienced patients accounted for 20.0% of the population.

Co-morbidities and/or co-infections were present in 89.2 % of the patients. The most common classes of not liver related co-morbidities were cardiovascular disease (43.1%), hypothyroidism (26.2%), diabetes mellitus (21.5%), chronic kidney disease (10.8%), lipid disorders (6.2%), psychiatric disorders (4.6%) and kidney transplantation (4.6%). HIV co-infection and HBV co-infection were documented for 1 patient each.

Concomitant medications were taken by 84.6% of patients. The most frequently reported classes of concomitant medications were beta blockers (27.7%), thyroid therapies (26.2%), vitamins (24.6%), angiotensin II antagonists (23.1%), drugs for peptic ulcer and gastro-esophageal reflux disease (20.0%), blood glucose lowering drugs (16.9%), diuretics (16.9%), analgesics (13.8%) and calcium channel blockers (12.3%).

The planned treatment duration was 12 weeks for the vast majority of patients in this study. The 3 direct acting antiviral (DAA) regimen of paritaprevir/r plus ombitasvir plus dasabuvir without RBV was prescribed for 73.8% of the CP for 12 weeks and for 1.5% for 8 weeks (all genotype 1b). The 3DAA regimen in combination with RBV was prescribed for 13.8% of patients for 12 weeks and for 10.8% of patients for 24 weeks. The vast majority of patients with genotype 1b (96.1%) received the 3DAA regimen without RBV and all patients with genotype 1a took the 3DAA regimen with RBV.

SVR12 was achieved in 87.7% of the CP and in 91.9% of the CPSFU12. For genotype 1a the respective response rates were 71.4% and 76.9% and for genotype 1b 92.2% and 95.9%. In patients with cirrhosis SVR12 was achieved in 84.0% of the CP and in 87.5% of the CPSFU12. Please note that patients with missing data were considered as non-responders. Reasons for virological failure among SVR12 non-responders were on-treatment virological failure in one patient (1.5%) and relapse in a second patient (1.5%).

Patient well-being during and after treatment was assessed by EQ-5D-5L, WPAI Hep C and PAM-13 questionnaires. Overall, there was no change of quality of life from baseline to EoT as assessed by the

index score and the VAS of the EQ-5D-5L questionnaire and a slight improvement from baseline to 12 weeks after the EoT. The total work productivity impairment (TWP) component of the WPAI showed hardly any change during and after treatment regarding work productivity in employed patients as compared to baseline. The total activity impairment (TAI) score in the whole study population - either working or not – showed improvement in health-related quality of life (HRQoL) at EoT and 12 weeks after the EoT compared to baseline. There was no change from baseline in PAM-13 scores until end of treatment.

Health care resource utilization was documented during the 4 weeks prior to starting the ABBVIE REGIMEN and during the total treatment duration. Outpatient appointments were recorded for 23 (35.4%) patients prior to treatment and a hospitalization for one patient. During treatment 19 patients (30.2%) attended outpatient consultations and there were 4 hospitalizations.

The assessment of liver function tests revealed an improvement from baseline to EoT and to 12 weeks after EoT for alanine-aminotransferase (ALT), ALT ratio, aspartate-aminotransferase (AST), AST ratio and gamma-glutamyltransferase (γ-GT) while there was no relevant change in median total bilirubin, albumin, creatinine and creatinine clearance. Few patients had Grade 3 or 4 laboratory abnormalities. Two Grade 3 and 2 Grade 4 low creatinine clearance values were reported, for 3 of these patients, chronic kidney disease and kidney transplant were reported at baseline as co-morbidity and diabetes mellitus for 1 patient.

Overall, 40.0% of the patients reported at least one treatment-emergent AE. The most common AEs occurring in ≥3% of patients were pruritus (6.2%), diarrhea (4.6%) and anemia (4.6%). Treatment emergent SAEs were reported by 10.8% of patients, no patient died.

Three patients (4.6%) terminated the ABBVIE REGIMEN prematurely due to 4 AEs including hyperbilirubinemia, jaundice, bacterial peritonitis and insomnia. Two patients (12.5%) of those taking RBV had their RBV permanently withdrawn due to anemia.

Discussion

Currently there is limited country specific data available in Colombia on the real world effectiveness of the ABBVIE REGIMEN. The outCome study was set up to close this data gap.

SVR12 was achieved in 91.9% of the CPSFU12 overall, in 76.9% for genotype 1a, in 95.9% for genotype 1b and in 87.5% for cirrhotic patients. There was a low number of virological failures.

Results from the CP were lower (SVR12 overall 87.7%) e.g. due to missing follow-up information which reflects the non-interventional character of this study.

Analysis of the PRO instruments shows that treatment does not negatively impact HRQoL overall and that there is an improvement after the EoT. Results of the outCome study regarding PROs are 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.

There does not seem to be an increase in healthcare resource utilization during treatment with the ABBVIE REGIMEN compared to the 4 weeks prior to treatment.

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

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

Marketing Authorisation Holder(s)

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