
1.0 Abstract

Title

Real World Evidence of the Effectiveness of Paritaprevir/r – Ombitasvir, \pm Dasabuvir, \pm Ribavirin in Patients with Chronic Hepatitis C -
An Observational Study in France (OPALE)

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), Fatigue Impact Scale (FIS), Beliefs Medication Questionnaire (BMQ), Patient Activation Measure (PAM)-13

Rationale and Background

The interferon-free combination regimen of paritaprevir/ritonavir (r) – ombitasvir with or without dasabuvir (ABBVIE REGIMEN) \pm 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 \pm RBV, used according to local label, under real world conditions in France 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).

Research Question and Objectives

Research Question

What is the effectiveness of the interferon-free ABBVIE REGIMEN \pm 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 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 French population
5. To determine the impact of the ABBVIE REGIMEN ± RBV on healthcare resource utilization

Study Design

This was a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN ± RBV in France. 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 69 medical centers in France experienced in the treatment of CHC. First patient entered the study on 15 December 2015, last patient last visit was on 29 March 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, 735 patients were enrolled into the study. Since treatment was never started in 7 patients, the safety population (SP) comprised 728 patients. The core population (CP) comprised 720 patients (1 patient did not have confirmed CHC and 7 patients did not receive recommended treatment regimens). Thirty six patients were excluded from the CP to form the core population with sufficient follow-up data regarding SVR12 (CPSFU12) (n=684): 27 patients did not return, 2 patients withdrew consent and 2 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 or reinfection (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
- Serious (SAEs) and non-serious adverse events (AEs) and pregnancy occurrences
- Questionnaires on PROs: EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire, Work Productivity and Activity Impairment - Hepatitis C (WPAI Hep C), Fatigue Impact Scale (FIS) questionnaire, Beliefs Medication Questionnaire (BMQ) and Patient Activation Measure (PAM-13)
- Healthcare resource utilization
- Co-morbidities and concomitant medication

Results

Median age of patients in the CP was 56 years, 51.3% of participants were female, reported ethnic origins were White/Caucasian (79.4%), Black (12.2%), other (4.3%), Asian/Oriental (3.9%) and native American/American Indian (0.1%). The most prevalent HCV genotype was genotype 1b (59.3%), followed by genotype 4 (29.0%) and genotype 1a (10.6%). Cirrhosis was present in 15.3% of patients and 13.3% had transition to cirrhosis. Treatment experienced patients accounted for 32.8% of the population.

Co-morbidities and/or co-infections were present at baseline in 53.5% of the patients. The most common classes of not liver related co-morbidities were cardiovascular disease (23.3%), psychiatric disorders (8.3%), diabetes mellitus (6.9%), hypothyroidism (6.3%) and lipid disorders (3.1%). Human immunodeficiency virus (HIV) co-infections were documented for 1.7% of patients and Hepatitis B virus (HBV) co-infections for 1.0%.

Concomitant medications were taken by 48.2% of the SP. The most frequently reported classes of concomitant medications were beta blockers (8.2%), analgesics (8.0%), thyroid therapy (6.3%), drugs for peptic ulcer and gastro-esophageal reflux disease (6.2%), benzodiazepine derivatives (5.5%), ACE inhibitors (5.4%) and diuretics (5.1%).

The planned treatment duration was 12 weeks for the vast majority of patients in the OPALE study (86.6%), for 95 patients (13.2%) the planned treatment duration was 8 weeks and for 2 patients 24 weeks. The 3-direct-acting antiviral agent (DAA) regimen of paritaprevir/r plus ombitasvir plus dasabuvir without RBV was prescribed for 46.3% of the CP for 12 weeks and for 13.2% for 8 weeks. The 3DAA regimen in combination with RBV was prescribed for 11.5% of patients for 12 weeks and for 2 patients for 24 weeks. The 2DAA regimen of paritaprevir/r plus ombitasvir in combination with RBV for 12 weeks was prescribed for 28.8% of patients. For the vast majority of patients with genotype 1b (97.7%), the 3DAA regimen without RBV was prescribed, whereas for most of the genotype 1a patients (84.5%) it was the 3DAA regimen with RBV. All genotype 4 patients (n=209) except two were prescribed the 2DAA regimen with RBV for 12 weeks and the remaining two patients received the 3DAA regimen with RBV for 12 weeks.

SVR12 was achieved in 90.7% of the CP and in 95.5% of the CPSFU12. For genotype 1a the respective response rates were 84.5% and 89.9%, for genotype 1b 93.0% and 95.7% and for genotype 4 they were 88.5% and 97.4%. In patients with F4, SVR12 was achieved in 90.8% of the CP and in 94.0% of the CPSFU12. Patients with missing data were considered as non-responders in the

calculation of SVR12 rates. In the CPSFU12, patients with no HCV RNA data ≥ 70 days post treatment were excluded from the SVR12 analysis unless data was missing for reasons related to efficacy or safety.

In patients who completed treatment with the ABBVIE REGIMEN, SVR12 was 93.6% in the CP and 97.3% in the CPSFU12.

In patients with a planned treatment duration of 8 weeks (all but 2 patients had genotype 1b), SVR12 was achieved in 92.6% of the CP and in 95.7% of the CPSFU12. In non-cirrhotic patients with a planned treatment duration of 12 weeks the respective response rates were 91.3% and 96.1%.

In the overall CP, there was no relevant difference in virological response between treatment-naïve and treatment-experienced patients.

Reasons for virological failure among SVR12 non-responders were on-treatment virological failure for 11 patients (1.5%), relapse for 7 patients (1.0%) and insufficient virological response for 3 patients (0.4%). One further patient who was a SVR12 responder relapsed in the 48-week time window.

Patient well-being during and after treatment was assessed by EQ-5D-5L, WPAI, FIS, BMQ and PAM-13 questionnaires. Overall, there was an improvement of quality of life and fatigue from baseline to EoT as well as from baseline to 12 and 24 weeks after the EoT as assessed by EQ-5D-5L and FIS questionnaires. At 12 and 24 weeks after the EoT, there was an improvement of work productivity and activity as assessed by the WPAI questionnaire as compared to baseline, while there was no relevant change during treatment. There was no change of BMQ and PAM-13 scores during treatment.

The assessment of liver function tests revealed an improvement from baseline to EoT and to 12 weeks after EoT for alanine-aminotransferase (ALT), aspartate-aminotransferase (AST 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. The analysis revealed two Grade 3 ALT increases, two Grade 3 AST increases, one Grade 3 low hemoglobin (Hb) value, and four Grade 3 and ten Grade 4 low creatinine clearance values post-baseline (the analysis includes patients with chronic kidney disease as co-morbidity).

Overall, 22.4% of the patients reported at least one treatment-emergent AE. The most common AEs occurring in $>1\%$ of patients of the overall SP were asthenia (5.4%), anemia (3.7%), fatigue (3.0%),

headache (1.9%), pruritus (1.8%), insomnia (1.8%), nausea (1.5%) and dry skin (1.1%). In total, 8 patients died. Two patients died within 30 days after EoT, one due to carotid aneurysm rupture and one due to myocardial infarction and one patient died about 2 months after the EoT (myocardial infarction). Another 5 patients died 3 to 6 months after the EoT (encephalopathy, death in a patient with cardiac failure, death in a patient with metastatic breast cancer, and 2 completed suicides). All these 5 patients had achieved SVR12 and/or SVR24. None of these cases of death were deemed related to treatment.

Fifteen patients (2.1%) terminated the ABBVIE REGIMEN prematurely due to AEs and 7 patients (2.4%) of those taking RBV had their RBV permanently withdrawn due to AEs.

Discussion

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

High SVR12 rates were achieved in the CPSFU12, 95.5% overall, 89.9% for genotype 1a, 95.7% for genotype 1b, 97.4% for genotype 4, 94.0% for patients with F4 and 95.7% in patients with a planned treatment duration of 8 weeks, resembling results from the clinical trials. Results from the CP were lower (SVR12 overall 90.7%) e.g. due to missing follow-up information which reflects the non-interventional character of this study.

This is one of the first studies showing results for the 8-week treatment duration of the ABBVIE REGIMEN in a real-world setting. Virological response rates of non-cirrhotic patients with genotype 1b who were treated for 8 or 12 weeks are almost identical.

Analysis of the PRO instruments shows that treatment with the ABBVIE REGIMEN does not negatively impact HRQoL overall and that there is an improvement after the EoT. Results of the OPALE 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.

Treatment was well tolerated with a low number of SAEs and only 2.1% of patients discontinuing the ABBVIE REGIMEN prematurely for safety reasons. 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 French CHC population.