
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 Canada (AMBER)

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)

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 Canada 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 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 evaluate the influence of adherence on treatment outcome in routine clinical practice
4. To describe the tolerability of the ABBVIE REGIMEN ± RBV
5. To document the effect of the ABBVIE REGIMEN ± RBV on PROs and work productivity in the Canadian population
6. To determine the impact of the ABBVIE REGIMEN ± RBV on healthcare resource utilization
7. 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 Canada. 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 39 medical centers in Canada experienced in the treatment of CHC. First patient entered the study on 13 October 2015, last patient last visit was on 20 December 2017.

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

In total, 565 patients were enrolled into the study. The safety population (SP) comprised 534 patients since treatment was never started in 28 patients and further no start of treatment was documented for another 3 patients who withdrew consent. One cirrhotic patient with genotype 1a did not receive RBV and 2 patients with genotype 1 received 2DAA instead of 3DAA regimen, thus 531 of the 534 patients remained in the core population (CP) which included patients who started recommended treatment regimens. Forty two patients were excluded from the CP to form the core population with sufficient follow-up data regarding SVR12 (CPSFU12) (n=489): 34 patients did not return, 4 patients withdrew consent and 4 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)
- 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 (\pm Dasabuvir, \pm RBV, intended and actual combination, dose and duration)
- Adherence

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- Serious (SAEs) and non-serious adverse events (AEs) and pregnancy occurrences
 - Questionnaires on PROs: EuroQol 5 dimension 5 level (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 and 24 weeks after EoT
 - Patient activation measure (PAM)-13, beliefs medication questionnaire (BMQ) and PSP satisfaction and utilization questionnaires
 - Healthcare resource utilization

Results

Median age of the CP was 57 years, 66.5% of participants were male, ethnic origin was White/Caucasian (79.8%), Asian (5.3%), Native American/ American Indian (4.7%), Black (3.6%) and other (6.6%). The most prevalent HCV genotype was genotype 1a (50.8%), followed by genotype 1b (41.4%) and genotype 4 (5.1%). Cirrhosis was present in 20.0% of patients and 7.5 % had transition to cirrhosis. Treatment experienced patients accounted for 14.3% of the population.

Co-morbidities and/or co-infections were present in 72.5 % of the CP; cardiovascular disease (24.7%), psychiatric disorders (19.2%) and diabetes mellitus (11.5%) prevailed. HIV co-infection was documented for 3.8% of patients and HBV co-infection for 1.3%.

In the safety population (SP) 72.3% of patients were receiving concomitant medications. The most frequently taken classes of concomitant medications were analgesics (21.7%), drugs for peptic ulcer and gastro-esophageal reflux disease (17.8%), drugs used in addictive disorders (16.9%), antidepressants (13.3%) and benzodiazepine derivatives (12.5%).

The planned treatment duration was 12 weeks for the vast majority of patients in this study. The 3 direct-acting antiviral agents (DAA) combination of paritaprevir/r plus ombitasvir plus dasabuvir with RBV was prescribed for 55.9% of the CP and without RBV for 39.4%, while 4.7% of patients were prescribed the 2 DAA regimen of paritaprevir/r plus ombitasvir in combination with RBV. One patient was prescribed the 3 DAA regimen without RBV for 8 weeks (genotype 1b without cirrhosis) and 3 patients with RBV for 24 weeks (all genotype 1a with cirrhosis); for all other patients the planned treatment duration was 12 weeks. In line with the local label and international recommendations, 98.9% of genotype 1a patients took the 3DAA regimen with RBV, whereas 93.6% of patients with genotype 1b received the 3DAA regimen without RBV. All genotype 4 patients were treated with the 2DAA regimen with RBV except two patients who received the 3DAA regimen with RBV. Of note 3 patients were excluded from the CP due to inadequate treatment regimen: 1 cirrhotic patient with

genotype 1a did not receive RBV and 2 patients with genotype 1 received 2DAA instead of 3DAA regimen.

SVR12 was achieved in 86.6% of the CP and in 94.1% of the CPSFU12. For genotype 1a the respective response rates were 82.4% and 92.1%, for genotype 1b 91.8% and 96.7%, for genotype 4 they were 88.9% and 92.3%. In patients with cirrhosis, SVR12 was achieved in 82.1% of the CP and in 91.6% of the CPSFU12. Please note that in the CP, patients with missing data were considered as non-responders. Reasons for virological failure 12 weeks after EoT were on-treatment virological failure in 1.3%, relapse in 2.1% and insufficient virological response in 0.6% of patients. One further patient who was a SVR12 responder relapsed in the SVR24 time window.

The association between adherence and SVR12 was investigated by univariate logistic regression and multivariable logistic regression (MLR) methods. Patients with lower adherence and those with cirrhosis, genotype 1a and a lower AST ratio showed lower SVR12 rates compared to patients with higher adherence, without cirrhosis, genotype 1b and a higher AST ratio, respectively.

Patient well-being during and after treatment was assessed by EQ-5D-5L and WPAI Hep C questionnaires. There was a statistically significant improvement of quality of life from baseline to EoT as well as 12 and 24 weeks after EoT as assessed by EQ-5D-5L for 3DAA regimens with or without RBV. The WPAI also showed slight improvement of work productivity 12 and 24 weeks after EoT as compared to baseline and of total activity for all time points. There was no relevant change of PAM-13 and BMQ scores during treatment.

Around one third of patients used the PSP during treatment and generally deemed the tool as useful.

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

The assessment of liver function tests for the SP revealed an improvement from baseline to EoT and to 12 weeks after EoT for alanine-aminotransferase (ALT), ALT ratio, aspartate-aminotransferase (AST), AST ratio, gamma-glutamyltransferase (γ -GT) while there was no change in median total bilirubin, albumin, creatinine and creatinine clearance. Very few patients had Grade 3 or 4 laboratory abnormalities. The analysis revealed two Grade 3 and one Grade 4 ALT increases, one Grade 3 AST increase, four Grade 3 low hemoglobin values, and four Grade 3 and four Grade 4 low creatinine clearance values post-baseline (the analysis includes patients with chronic kidney disease as co-morbidity).

Overall 37.5% of the patients reported at least one treatment-emergent AE. The most common AEs occurring in $\geq 3\%$ of patients of the overall SP were fatigue (13.5%), headache (9.2%), nausea (8.4%), anemia (7.1%), insomnia (4.5%), diarrhea (3.7%) and pruritus (3.4%). Treatment emergent SAEs were reported by 4.7% of patients. Two patients died within the AE reporting time window of up to 30 days post EoT: 1 each due to overdose and chronic kidney disease. Two patients died more than 30 days after EoT (cardiac arrest and one death with unknown cause). None of these cases was deemed related to treatment.

Nine patients (1.7%) of the SP terminated the ABBVIE REGIMEN prematurely due to an AE, including hyperbilirubinemia (n=2), hepatic failure, overdose, toxicity to various agents, nausea, sinusitis, chronic kidney disease and maculo-papular rash.

Discussion

Currently there are limited country specific data available in Canada 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, 94.1% overall, 92.1% for genotype 1a, 96.7% for genotype 1b and 92.3% for genotype 4, in line with results from the pivotal trials, including cirrhotic patients with 91.6% SVR12. There was a low percentage of virological failures. Results from the CP were lower (SVR12 overall 86.6%) e.g. due to missing values which reflects the non-interventional character of this study.

Analysis of the PRO instruments revealed an improvement in HRQoL by EQ-5D-5L and a decrease in total activity impairment as assessed by WPAI with the ABBVIE REGIMEN to EoT and post treatment timepoints which was statistically significant for the former. 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 1.7% of patients discontinuing the ABBVIE REGIMEN prematurely due to adverse events. 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 Canadian CHC population.