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 Ireland

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), Short Form 36 (SF-36v2)

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 Ireland 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 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 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 collect information on co-morbidities and concomitant medication in the Irish population
6. To describe the tolerability of the ABBVIE REGIMEN ± RBV
7. To document the effect of the ABBVIE REGIMEN ± RBV on PROs in the Irish population
8. To determine the impact of the ABBVIE REGIMEN ± RBV on healthcare resource utilization
9. To evaluate the contribution of the patient support program (PSP) to disease control, treatment continuation over time, patient satisfaction and PSP utilization
10. To describe the effect of the ABBVIE REGIMEN ± RBV on metabolic profile

Study Design

This was a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN ± RBV in Ireland. 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 hospitals in Ireland experienced in the treatment of CHC. First patient entered the study on 05 November 2015, last patient last visit was on 29 November 2017.

Subjects and Study Size, Including Dropouts

The target 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 prior to inclusion into the study.

In total, 101 patients were enrolled into the study and were taking the ABBVIE REGIMEN in line with recommendations. Thus all 101 patients were in the core population (CP) of this study. Due to failure to return, one patient of the CP was excluded from the core population with sufficient follow-up 12 weeks after EoT (CPSFU12).

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 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: EuroQol 5 dimension 5 level (EQ-5D-5L) questionnaire and Short-Form 36 (SF-36) prior to treatment initiation, at EoT as well as 12 and 24 weeks after EoT
- PAM (Patient Activation Measure)-13 and PSP satisfaction and utilization questionnaires

- Metabolic laboratory profile prior to treatment initiation, and at all subsequent visits
- Healthcare resource utilization

Results

Median age was 58 years, 66.3% of participants were female and almost all patients were White (94.1%). The most prevalent HCV genotype was genotype 1b (69.3%) followed by genotype 1a (30.7%). Compensated cirrhosis was present in 12.9% of patients and 9.9 % had transition to cirrhosis. Treatment experienced patients accounted for 16.8% of the population.

Co-morbidities and/or co-infections were present in 78.2 % of patients, cardiovascular disease (18.8%), psychiatric disorders (14.9%), hypothyroidism (13.9%) and lipid disorders (11.9%) prevailed. Co-infections were only documented for two patients (one HIV, one hepatitis B). Psychoactive substance dependency was reported for 15 patients (14.9%), all of whom were on opiate substitution therapy.

Concomitant medications were taken by 82.2% of patients. The most frequently (>10%) reported classes of concomitant medications were analgesics (27.7%), antibacterials (15.8%), anti-inflammatory and antirheumatic products (15.8%), hypnotics and sedatives (15.8%), drugs used in addictive disorders (14.9%), thyroid therapy (13.9%), drugs for peptic ulcer and gastro-esophageal reflux disease (11.9%), antidepressants (10.9%), antihistamines (10.9%) and corticosteroids (10.9%).

The planned treatment duration was 12 weeks for all patients except two in this study. The ABBVIE REGIMEN without RBV was prescribed for the majority of patients (65.3%) and in combination with RBV for 32.7% for 12 weeks. Two patients were taking the regimen with RBV for 24 weeks. In line with the local label and international recommendations, 94.3% of patients with genotype 1b received the ABBVIE REGIMEN without RBV, whereas all genotype 1a patients took the regimen with RBV .

SVR12 was achieved in 97.0% (95% CI: [91.6, 99.0]) of the CP (N=101) and in 98.0% (95% CI: [93.0, 99.4]) of the CPSFU12 (N=100). All patients with genotype 1b were responders (100%). For patients with genotype 1a SVR12 was 90.3% (n/N=28/31) in the CP (3 patients did not achieve response: 2 of them discontinued treatment early and one patient was lost to follow-up) and 93.3% (n/N=28/30) in the CPSFU12. In patients with cirrhosis SVR12 was 92.3% (n/N=12/13) in the CP (which is identical to the CPSFU12).

It was not feasible to investigate the impact of baseline factors and adherence on SVR 12 with univariate logistic regression methods since more than 95% of patients achieved SVR12.

Patient well-being during and after treatment was assessed by EQ-5D-5L and SF-36 questionnaires. EQ-5D-5L index scores increased in the total CP at EoT and 12 weeks after EoT as compared to baseline, mean changes from baseline for these time points were 0.045 and 0.030 and median changes were 0.012 and 0.006. Overall patients treated with the ABBVIE REGIMEN ± RBV experienced a small mean increase of the mental and physical component summary scores of the SF-36 instrument and of all SF-36 domains by EoT as well as 12 weeks after the EOT as compared to baseline, while median change from baseline was zero for the domains of physical functioning, role physical, bodily pain, social functioning and role emotional. The subgroup of patients treated with the ribavirin-free ABBVIE REGIMEN reported a slight increase in HRQoL during therapy as assessed by the SF-36 tool while patients receiving RBV experienced less improvement and in some domains even a decline of scores. However, this effect on HRQoL outcomes associated with ribavirin did not persist in the post-treatment period. Results from EQ-5D-5L did not reveal such trends in relation to RBV.

Only 26 patients participated in the PSP, thus no meaningful conclusions can be drawn.

The assessment of liver function tests revealed an improvement from baseline to EoT and to 12/24 weeks after EoT in alanine-aminotransferase (ALT), ALT ratio, aspartate-aminotransferase (AST), AST ratio and gamma-glutamyltransferase (γ-GT) while total bilirubin increased slightly from baseline during treatment and dropped to values below baseline after EoT. There was no relevant change in median creatinine and creatinine clearance. Very few patients had Grade 3 or 4 laboratory abnormalities: two Grade 3 ALT values and one Grade 4 Hb decrease were reported.

Assessment of the metabolic profile was available for very few patients in this real-world study preventing further conclusions.

Overall 83.2% of the patients reported at least one treatment-emergent AE. The most common AEs occurring in more than 5% of patients were fatigue (39.6%), headache (20.8%), nausea (16.8%), diarrhea (11.9%), lower respiratory tract infection (8.9%), pruritus (7.9%), rash (6.9%), insomnia (6.9%), sleep disorder (5.9%), depressed mood (5.9%), dry skin (5.9%), cough (5.0%), anemia (5.0%) and constipation (5.0%). Only one patient reported a SAE, no patient died. Two patients (2.0%) terminated the ABBVIE REGIMEN and RBV prematurely due to an AE (increased bilirubin in a cirrhotic patient and increased ALT in a non-cirrhotic patient).

Discussion

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

Very high SVR12 rates were achieved in the CPSFU12, 98.0% overall, 100% for genotype 1b and 93.3% for genotype 1a, mirroring response rates observed in pivotal trials, including cirrhotic patients with 92.3% SVR12. Results from the CP were slightly lower due to missing values which reflects the non-interventional character of this study.

Treatment was well tolerated with only one SAE reported and 2 patients (2.0%) 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 Irish CHC population.

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