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 Greece

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 Greece 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, PROs and pattern of the real world use, as well as adherence, work productivity and evaluation of the patient support program (PSP) associated with 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 document the effect of the ABBVIE REGIMEN ± RBV on PROs and work productivity in the Greek population
5. To evaluate the contribution of the 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 Greece. 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 22 medical centers in Greece experienced in the treatment of CHC. First patient entered the study on 05 April 2016, last patient last visit was on 31 October 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 an informed consent form prior to inclusion into the study.

In total, 216 patients were enrolled into the study, all of whom started treatment and were thus part of the safety population (SP) and fulfilled the criteria of the target population. Three patients were excluded due to inadequate treatment regimen: 1 cirrhotic patient with genotype 1a did not receive RBV and 2 patients with genotype 4 were not prescribed RBV. Thus 213 patients were in the core population (CP). Ten patients were excluded from the CP to form the core population with sufficient follow-up 12 weeks after EoT (CPSFU12): 6 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 (and not related to efficacy 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)]

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 onedocumented 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
- 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 weeks after EoT
- PAM (Patient Activation Measure)-13 and PSP satisfaction and utilization questionnaires
- Co-morbidities and concomitant medication
- Serious (SAEs) and non-serious adverse events (AEs) and pregnancy occurrences

Results

Median age of patients in the CP was 56 years, 53.1% of participants were male and almost all patients were White (97.7%). The most prevalent HCV genotype was genotype 1b (55.4%), followed by genotype 4 (29.6%) and genotype 1a (13.1%). Cirrhosis was present in 50.7% of patients and 32.9 % had transition to cirrhosis. Treatment experienced patients accounted for 63.4% of the population. Thus study participants can be regarded as a difficult-to-treat population.

Co-morbidities and/or co-infections were present in 68.5 % of the CP, cardiovascular disease (25.4%), psychiatric disorders (16.9%) and diabetes mellitus (15.5) prevailed. Co-infection was only documented for one patient (hepatitis B).

In the SP, 55.6% of patients were receiving concomitant medications. The most frequently taken classes of concomitant medications were beta blockers (14.8%), thyroid therapy (11.1%), angiotensin II antagonists (10.2%) and blood glucose lowering drugs (9.7%).

The planned treatment duration was 12 weeks for all patients except one in this study. The 3 direct-acting antiviral agents (3-DAA) combination of paritaprevir/r plus ombitasvir plus dasabuvir without RBV was prescribed for the majority of the CP (50.2%). The 3-DAA regimen in combination with RBV was prescribed for 20.2%, while 29.1% of patients were prescribed the 2-DAA regimen of paritaprevir/r plus ombitasvir in combination with RBV for 12 weeks. One patient was taking the 3-DAA regimen with RBV for 24 weeks (genotype 1a with cirrhosis). The vast majority of patients with genotype 1b (89.8%) received the 3-DAA regimen without RBV, whereas 93.8% of genotype 1a patients took the 3-DAA regimen with RBV. In the CP, all genotype 4 patients were treated with the 2-DAA regimen with RBV except one patient who received the 3DAA regimen with RBV. One cirrhotic patient with genotype 1a and two patients with genotype 4 not receiving RBV were excluded from the CP.

SVR12 was achieved in 91.1% of the CP (95% CI: [86.5, 94.2]) and in 95.6% of the CPSFU12 (95% CI: [91.8, 97.7]). For genotype 1a, the respective response rates were 90.6% and 93.5%; for genotype 1b, they were 93.2% and 97.3%; for genotype 4, they were 87.3% and 93.2%. In patients with cirrhosis, SVR12 was achieved in 90.7% of the CP and in 93.3% of the CPSFU12. In the CP, patients with missing data were considered as non-responders.

Reasons for virological failure among SVR12 non-responders were on-treatment virological failure for one patient, insufficient virological response for 3 patients and relapse for 2 patients; 5 of these patients had cirrhosis.

Patient well-being during and after treatment was assessed by EQ-5D-5L and WPAI Hep C questionnaires. There was a statistically significant but small improvement of quality of life from baseline to EoT as well as 12 and 24 weeks after EoT as assessed by EQ-5D-5L. The WPAI also showed improvement of work productivity and total activity for all time points and treatment regimens.

Only 7 patients of the CP participated in the PSP, thus no meaningful conclusions can be drawn.

The assessment of liver function tests for the SP revealed a clinically important improvement from baseline to EoT and to 24 weeks after EoT for alanine-aminotransferase (ALT), ALT ratio, aspartate-aminotransferase (AST), AST ratio, gamma-glutamyltransferase (γ-GT) and total bilirubin while there was no relevant change in median creatinine and creatinine clearance. Very few patients had Grade 3 or 4 laboratory abnormalities. The analysis revealed one Grade 3 hemoglobin decrease, and one Grade 3 and two Grade 4 decreases in creatinine clearance post-baseline (the analysis includes patients with chronic kidney disease as co-morbidity).

Overall 9.7% of the patients reported at least one treatment-emergent AE. The most common AEs occurring in more than 1% of patients of the overall SP were anemia

(3.7%) and pruritus (1.4%). Treatment-emergent SAEs were reported by 7 patients (3.2%); no patient died. Three patients (1.4%) of the SP terminated the ABBVIE REGIMEN prematurely due to an AE, including vomiting, hepatic failure and blood bilirubin increased. Three patients (2.8%) of those taking RBV had their RBV permanently withdrawn due to anemia, vomiting and pruritus, respectively.

Discussion

Currently there is limited country specific data available in Greece 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, 95.6% overall, 93.5% for genotype 1a and 97.3% for genotype 1b, resembling results from the clinical trials, including cirrhotic patients with 93.3% SVR12. There was a low number of virological failures (1 on-treatment failure, 3 insufficient virological responses and 2 relapses). Results from the CP were slightly lower (SVR12 overall 91.1%) due to missing values which reflects the non-interventional character of this study.

Analysis of the PRO instruments revealed an improvement in HRQoL already during treatment with the ABBVIE REGIMEN and also from baseline to SVR12/24 for EQ-5D-5L and WPAI. 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 3 patients (1.4%) discontinuing the ABBVIE REGIMEN prematurely for safety reasons. As compared to pivotal studies, the overall AE rate reported in this observational study was very low, however, data on safety and adverse clinical outcomes may be limited by underreporting in the real world setting of the present study. 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 Greek CHC population.

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